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BIENNIAL REPORT

1994–1995

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Introduction

This Biennial Report covers the period from 1 July 1993 to 31 December 1995. Thus, most of the scientific projects reported were initiated under the direction of my predecessor, Dr Lorenzo Tomatis, who retired at the end of 1993 after 26 years of loyal and enthusiastic service to the Agency. During his twelve years as Director, important new initiatives were taken, in the areas of both laboratory research and cancer epidemiology. Building upon the solid foundation laid by the Agency's first Director, Dr John Higginson, he further increased the standing of the Agency within the international cancer research community and enhanced its role as one of the world's leading centres focusing on cancer etiology and prevention.

This report breaks with tradition insofar as it covers a 2½-year period. Technical progress in publishing has enabled us to markedly reduce production time and the introduction of an automated bibliographic system allowed us to include publications which appeared as late as December 1995. In future, the coverage of the IARC Biennial Report will, therefore, coincide with the calendar years and the biennial budget.

Expansion of the scientific programme

Progress in biomedical research consists of a continuous acquisition of new research data and their dissemination in the scientific community. The pace at which this occurs has greatly accelerated in the past decade. The rapid progress in molecular cancer genetics, in particular the identification of transforming genes and tumour-suppressor genes and the elucidation of their roles in the regulation of cell growth and differentiation, have profoundly changed our view of the process of malignant transformation. We can now begin to understand aspects of the etiology of human cancer which until recently were very difficult to approach, in particular gene–environment interactions, including genetic susceptibility to neoplasms associated with environmental carcinogens, hormonal imbalance and dietary factors. This development has also stimulated ever-closer collaboration between epidemiologists and laboratory scientists, and the majority of IARC's epidemiological studies now include serum and tissue sampling. While in the past this collaboration concentrated on the correlation between tumour incidence and exposure to environmental carcinogens, it has recently become evident that mutations in transformation-associated genes often reflect the etiological agent or exposure, making human tumours a primary source of information on cancer etiology. Many of the new aspects of cancer research have been introduced into IARC projects, mainly in the units of Mechanisms of Carcinogenicity and the Unit of Multi stage Carcinogenesis, but to allow the Agency to participate more fully in these research areas and to ensure its competitiveness in the mainstream of cancer research, new scientific units focusing on molecular genetic aspects of tumour development have been established during 1995.

New research units

On 1 February 1995, a new Unit of Molecular Pathology was established, which is focusing its attention on the pathogenesis of brain tumours and stomach cancer. It is headed by Dr Hiroko Ohgaki, who studied veterinary medicine at the Tokyo University

of Agriculture and Technology and in 1980 joined the Biochemistry Division of the National Cancer Research Institute, Tokyo. Under the direction of Dr Takashi Sugimura, she made significant contributions to understanding the carcinogenicity of heterocyclic amines, a class of mutagenic carcinogens produced during the heating of food. She also pioneered work on the genetic susceptibility of certain strains of rats to induction of stomach cancer by MNNG. After postdoctoral periods in the Institute of Toxicology and the Department of Pathology, University of Zurich, she worked with Dr. S. Thorgeirsson at the National Cancer Institute, Bethesda. During her stay in Zurich, Dr Ohgaki and I began a collaboration on molecular genetic aspects of human brain tumours which we are continuing at IARC.

A new Unit of Genetic Cancer Susceptibility, set up on 1 April 1995, is examining familial cancer and complex genetic traits that influence individual susceptibility to environmental carcinogens. This unit is headed by Dr Giovanni Romeo, previously chief of the Clinical Genetics Unit at the Istituto Gaslini, one of the leading paediatric hospitals in Italy. Dr Romeo graduated in medicine at the University of Bologna in 1965. After research periods in the Department of Pediatrics at John Hopkins Medical School, Baltimore, and with Dr. L. Cavalli-Sforza in Stanford, he joined the Laboratory of Human Genetics at the International Institute of Genetics and Biophysics in Naples. In 1986 he was appointed Professor of Human Genetics at the University of Genoa.

A new Unit of Genetic Cancer Epidemiology will be established in January 1996. This is headed by Dr David Goldgar, previously at the University of Utah. Dr Goldgar's previous achievements and the programme of his unit will be outlined in the next Biennial Report.

Restructuring of research units and programmes

The departure in 1993 of Dr Helmut Bartsch, Chief of the Unit of Environmental Carcinogens and Host Factors and the retirement at the end of 1994 of Dr Rodolfo Saracci, Chief of the Unit of Analytical Epidemiology, made necessary a restructuring of the respective research units. This was taken as an opportunity to put several young scientists with a proven record of scientific accomplishments in charge of a unit or research programme. IARC's laboratory research on molecular epidemiology (i.e. the quantitative determination of carcinogen adducts in DNA and proteins as biomarkers of exposure) was combined in a new Unit of Environmental Carcinogenesis, headed by Dr Christopher Wild, previously a staff scientist in the Unit of Mechanisms of Carcinogenesis. A Programme of Molecular Toxicology was established which concentrates on the genetics and regulation of the cytochrome P450 enzymes, heavily involved in bioactivation of xeno biotics. Polymorphism and individual expression of P450 genes play a role in the determination of genetic susceptibility to environmental carcinogens. This programme, headed by Dr Matti Lang, is attached to the Unit of Mechanisms of Carcinogenesis. Nutrition and Cancer, previously a programme within the Unit of Analytical Epidemiology, is now an independent unit, headed by Dr Elio Riboli. Cancer epidemiology concentrating on environmental carcinogens, in particular occupational cancer, is concentrated in the new Unit of Environmental Cancer Epidemiology, headed by Dr Paolo Boffetta, previously responsible for this research area within the dissolved Unit of Analytical

Epidemiology. Dr Annie Sasco heads a new Programme of Epidemiology for Cancer Prevention which focuses on the adverse effects of smoking and on breast cancer prevention. Dr Elisabeth Cardis is responsible for the Programme of Radiation and Cancer. Her work concentrates on the consequences of low-level exposure to ionizing radiation and on increased cancer risks following the nuclear accident in Chernobyl.

A new evaluation programme on chemoprevention

While the best form of cancer prevention remains the avoidance of exposure to carcinogenic agents (notably tobacco), a range of compounds are now recognized as having cancer-protective effects and are being increasingly promoted as 'anti-carcinogens'. Such chemopreventive agents are of particular interest for populations at high risk for cancer, for example because of a high level of exposure to carcinogens or genetic susceptibility to a familial cancer syndrome. In order to assess the potential for cancer prevention in such high-risk groups, the Agency has initiated a new evaluation programme on cancer chemoprevention. Like the successful programme producing the IARC Monographs on Carcinogenenic Risks to Humans, this will be based on working group meetings during which external experts and IARC staff scientists will evaluate compounds for evidence of cancer-preventive activity in humans and experimental animals, for associated toxicity and for any carcinogenic risks. The scientific information and the working group's conclusions will be published in a new book series, the IARC Handbook of Cancer Prevention. An international meeting on Principles of Chemoprevention held in November 1995 provided guidelines for this programme and the first working group meeting is scheduled for late 1996.

Reallocation of space and the new EPIC building

The space in the tower was reallocated during the summer of 1994 and this resulted in each research unit being consolidated on one floor. The sixth floor was converted from office to laboratory space, enabling scientists working in the old prefabricated laboratories to return to the main building. In October 1995, a new building for the cryopreservation of large numbers of serum and cell samples was completed. This building was necessary to meet the requirements of the European Prospective Investigation into Cancer and Nutrition and the building has, therefore, been given the name 'EPIC'. On the first floor, it contains office space for the Unit of Nutrition and Cancer, and it also houses the Programme on Radiation and Cancer.

In 1995, the four main lifts in the IARC tower were replaced. The willingness of the city of Lyon to supervise and to bear the costs of this work is greatly appreciated.

Calum Muir

In June 1995, Dr Calum S. Muir, world-renowned epidemiologist and IARC staff member for 23 years, died from a neoplastic disease. He joined the Agency in 1967 and was Deputy Director from 1986 to 1990. He then retired but continued to work on cancer epidemiology in his native Scotland. Dr Muir will be remembered for the promotion of cancer registration worldwide as well as for his many scientific contributions, including those to the landmark book series Cancer Incidence in Five Continents. In memory of his achievements and warm-hearted personality, the meeting room in the ground floor of the tower building has been named the Calum Muir Lounge.

Computers and scientific instruments

Over recent years, the Agency fell behind in maintaining a high level of quality and sophistication in scientific instruments, due to budgetary restrictions. During its 1994 and 1995 sessions, the Governing Council granted extra financial resources to reverse this trend. This has enabled the Agency to acquire 30 additional personal computers (including some with high-power processors for statistical analysis), improving secretarial and administrative work-flow. We were further able to purchase an automated DNA sequencer and a phosphor-image analyser, laboratory instruments badly needed by the research units involved in genetic analysis.

Restructuring of personnel and resources

With the approval of the Governing Council, 13 general service staff positions were abolished during 1994, but the negative social impact of these changes was significantly reduced by mutual separation agreements in most cases. Major reduction in expenditure was also made in the area of service contracts. The savings resulting from these measures have been redirected towards the Agency's research programmes and allowed the expansion of the scientific programme outlined above. I wish to thank the staff, and in particular the representatives of the Staff Association, for their loyalty and co-operation during this difficult period of adjustment.

IARC Press

The .IARC Monographs on the Evaluation of Carcinogenic Risks to Humans and IARC Technical Reports are distributed by WHO headquarters in Geneva, while the IARC Scientific Publications are distributed by Oxford University Press (OUP). However, visitors to the Agency indicated that in many countries, obtaining IARC publications was often slow and difficult. We therefore decided to open an additional channel of distribution directly from the Agency. This division, IARC Press, sells our publications on terms similar to those of WHO and OUP, but aims specially to ensure speed of delivery, by mailing publications within 48 hours of receipt of an order. IARC Press started its activity on 1 April 1995 and is responsible for both the promotion and distribution of IARC publications.

IARC Day

Collaboration with the local scientific and medical communities has been increased, culminating in an annual 'IARC Day'. On this occasion, scientists, physicians, health organizations and political representatives are invited to visit the Agency and this is combined with the annual Professor Sohier lecture. In order to allow Governing Council members to attend, this event takes place immediately before the Council's spring meeting. In 1994, the Sohier lecture was presented by Dr Guy de Thé, on 'Epidémiologie Moléculaire des Rétrovirus Oncogènes'. In 1995, Dr Richard Peto presented extensive epidemiological data on the theme of 'The Avoidance of Premature Death'.

Extrabudgetary funds

Competing for research grants is part of a scientist's life, and is encouraged at IARC as in other scientific institutions. We appreciate contributions from a wide variety of granting agencies and charities. Special thanks are due to the National Cancer Institute, Bethesda, USA, for their continued support to the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. The Italian Government, the Autonomous Region of Valle d'Aosta, Italy, and the Swedish Medical Research Council

generously support the Gambia Hepatitis Intervention Study. We also appreciate funding of many of our projects by the European Union, in particular the European Prospective Investigation into Cancer and Nutrition (EPIC). The Swiss Government generously provided seed money for our new chemoprevention programme, and for several collaborative projects between Swiss and IARC scientists. The US Department of Defense provided a major grant for the programme for early detection of breast cancer in the Philippines. Finally, we are grateful for the many donations and legacies from ordinary citizens in France, which have enabled us to initiate and sustain several important projects and to construct the new EPIC building.

Scientific Council

Collaboration with the Scientific Council, which evaluates the Agency's programme and reports to the Governing Council, has been excellent. Council members are scientists with an international reputation in the field of cancer research and we appreciate their willingness to sacrifice some of their precious time. On the behalf of the Agency's scientists, I should like to thank those members whose term finished during the past biennium: Drs K. Alitalo (Helsinki), P. A. Cerutti (Lausanne), C. C. Harris (Bethesda), H. Marquardt (Hamburg), F. Mitelman (Lund), G.R. Mohn (Bilthoven), P. Pasquini (Rome) and T. Sanner (Oslo). Members of the Scientific Council elected for the period 1994 to 1998 are Drs J.C. Barrett (Research Triangle Park), D. Kromhout (Bilthoven), E. Lynge (Copenhagen) and U.A. Meyer (Basel), and for 1995 to 1999 Drs H.E. Blum (Freiburg i. Br.), E. Dybing (Oslo), I. Ernberg (Stockholm), T. Hakulinen (Helsinki) and P. Vineis (Turin).

My special thanks go to the Chairmen of the Scientific Council, Dr Tore Sanner, (1994–1995) and Dr Adèle Green, Brisbane, (1996). Both have played very active roles not only in the evaluation of our scientific programme, but also in providing invaluable advice to the Director in the exploration of new research openings.

Governing Council

IARC Governing Council has continued to provide generous support to the Agency. Despite budgetary restraints in most of our member states, the Governing Council in 1995 provided an increase in the regular budget for the biennium 1996-1997 which largely offsets the adverse effects of the currency changes. The guidance and support from the Council as a whole and many of its individual members in the restructuring of personnel and resources as well as in the expansion of the scientific programme is highly appreciated. The entire staff of the Agency is committed to maintaining the status of the Agency as one of the leading cancer research institutes world-wide.

Paul Kleihues, M.D.
Director

PART 1. CANCER OCCURRENCE AND OUTCOME

Knowledge of the size and nature of the cancer problem in the world is fundamental in planning and evaluating appropriate control measures, and the Agency's work on this subject represents an essential complement to the work of WHO Headquarters.

Studies of the variation in the risk of different cancers according to geographical location continue to provide important clues as to possible etiology. Changes in risk over time and between different population subgroups (defined in the terms of ethnicity, socio-economic status, birthplace etc.) provide additional dimensions which enhance the interpretation of the geographical patterns. These descriptive epidemiological studies constitute a major component of the work of the Agency.

Since the value of the descriptive studies depends upon their completeness and quality of the data-sets used, considerable effort is also put into improvement of cancer registration world-wide.

1.1 Support to cancer registries

Cancer registries are the source of information on the incidence of, and survival from, cancer, as well as providing a focus for epidemiological studies. In many parts of the world, they constitute the only available cancer information system. The comparative value of the statistics produced depends on the adoption of common methods and definitions, so that international collaboration in this area has a very important role.

1.1.1 International Association of Cancer Registries

D.M. Parkin and S.L. Whelan; in collaboration with A. Hanai, Osaka, Japan; and C.S. Muir, Edinburgh, UK

The International Association of Cancer Registries (IACR), a non-governmental organization in official relations with WHO since 1979, has been supported by a secretariat within IARC since 1973, which provides a link between registries situated in many different countries in the world.

In mid-1995 the Association included 389 members in 102 countries, 75% of them cancer registries. Thirty-eight new registries, from 36 countries, have become members during the two years covered in this report.

Members collaborate with the Agency in publications on cancer morbidity, such as the *Cancer Incidence in Five Continents* series (Section 1.2.1), and in studies such as the ECLIS study of childhood leukaemia incidence in relation to the Chernobyl accident (Section 2.5.2.3). One of the basic aims of the Association is to improve quality of data and comparability between registries by standardizing methods of registration, definitions and coding, and the Association also contributes to the preparation of publications and technical reports on cancer registration methodology, such as *Comparability and Quality Control in Cancer Registration* [443] (Section 1.1.3.1).

Annual reports from cancer registries as well as publications presenting features of interest in their data are collected by the secretariat in a library, now comprising over 1500 publications. Each report is abstracted,

and the reference and keywords are kept in a bibliographic database.

A scientific meeting lasting two to three days is held each year. The 1993 meeting was held in Bratislava, Slovakia, preceded by a symposium sponsored by the US National Institute on Aging, which addressed the problem of the increase to be expected in the world cancer burden with ageing of the world's populations. The IACR programme addressed environmental pollution and cancer; the central position of the registry in prevention and control of cancer; and methodological issues in cancer registration.

The 1994 meeting, held in Bangalore, India, took place immediately before the XVIth UICC International Cancer Con gress in Delhi. The keynote topic was cancer in women, and the programme inclu ded cancer control; molecular epidemiology of cancer; smokeless tobacco and cancer; screening and registration methodology.

The 1995 meeting, in Rio de Janeiro, Brazil, had as its main theme causes and prevention of cancer in developing countries. A seminar on cancer registration for Latin American countries, sponsored by IACR, the IARC and UICC, was held in Spanish before the meeting.

1.1.2

European Network of Cancer Registries (ENCR)

D.M. Parkin, R.J. Black, J. Ferlay, E. Démaret and J. Estève; in collaboration with F. Berrino, Milan, Italy; F. Ménégoz, Meylan, France; C. Navarro, Murcia, Spain; R. Otter, Groningen, Netherlands; D. Pheby, Bristol, UK; H.H. Storm, Copenhagen, Denmark; and H. Tulinius, Reykjavik, Iceland

The European Network of Cancer Registries was established in 1989 with the support of the 'Europe Against Cancer' programme of the European Commission. The Network aims to improve the quality and comparability of cancer registry data in Europe, to establish a basis for the monitoring of cancer incidence and mortality information and to promote the use of this information for research and planning. There are 85 general, population-based cancer registries in European Union (EU) countries which are full members of the Network. In addition, associate member ship is offered to 'specialist' registries which collect information on a limited range of cancers, for example childhood cancers, and to general registries in non-EU countries in the European continent. The Network is directed by a Steering Com mittee of nominees of the cancer registry associations of Europe, with IARC providing the secretariat.

The main activities of the Network are:

(*a*) Surveys of cancer registration methods. These have been conducted by the Danish Cancer Registry and have revealed important differences in the coding and classification practices of member registries.

(*b*) Establishing standards and definitions. The survey results have led to the formation of small working groups to establish recommendations to be disseminated to registries throughout Europe. The first set of recommendations, covering definitions of date of incidence, multiple primary tumours and guidelines for the registration of bladder tumours, have been completed by Dr D. Pheby (UK), Dr L. Schouten (Netherlands) and Dr M. Roumagnac (France).

(*c*) Training in cancer registration methods. A standard set of training materials has been established based on the surveys of registration methods and a course for supervisors of cancer registry staff held in Copenhagen in January 1994. These materials were translated into Spanish for the second training course, held in Granada, Spain, in January 1995. A course in French is to be held in Toulouse, France, during early 1996. Courses in statistical methods

for cancer registries are also organized by the Network (see Section 1.2.2).

(*d*) Fellowships. Ten 'mini-fellowships' per year are offered to cancer registry personnel so that they can attend a course or make a short visit to a cancer registry or other cancer organization in order to learn technical aspects of registration or data analysis.

(*e*) Consultancy. Cancer registries, particularly those in development, can request a consultant visit by an experienced person to advise on cancer registration methodology or specific local problems.

(*f*) Publications. Information about cancer is disseminated through EUROCIM (see Section 1.2.2) and other publications. *Facts and Figures of Cancer in the European Community* [161] was published in 1994, providing basic information on cancer in Europe. A more detailed analysis of cancer in the European Union is in preparation. An information diskette, for use with 'Windows' software, has been prepared. In addition, the Network secretariat regularly provides information to researchers and policy-makers. For example, the European Commission has updated the 'European Code Against Cancer' using data from ENCR member registries. At the request of the Commission, a brochure publicizing the activities of the Network has been prepared and is being translated into four major European languages, for publication in 1995 by the Commission.

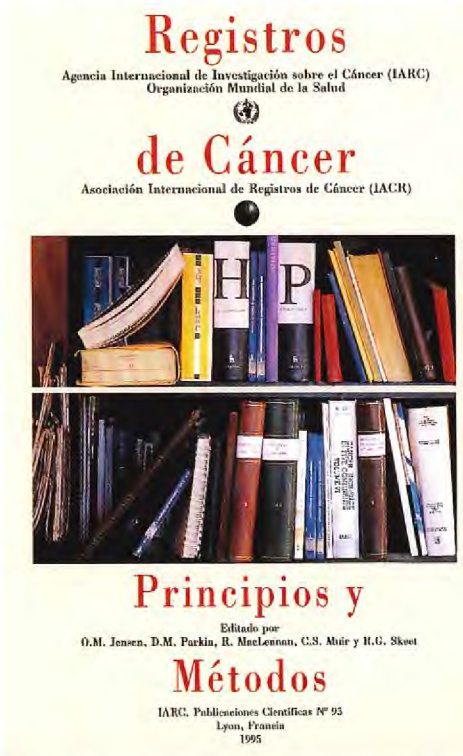


Figure 1. The Spanish edition of Cancer Registration: Principles and Methods

1.1.3 Reliability and validity of cancer registry data

Cancer Registration: Principles and Methods (Jensen *et al.*, 1991, IARC Scientific Publications No. 95) provided guidance on the techniques required to collect, store, analyse and interpret data on individuals with cancer. A Spanish edition was published in 1995 (Figure 1), and a French edition is planned for 1996.

1.1.3.1 Comparability and quality control in cancer registration

D.M. Parkin, S.L. Whelan and J. Ferlay; in collaboration with V. Chen, New Orleans, USA; J. Galceran, Tarragona, Spain; and H.H. Storm, Copenhagen, Denmark

The IARC Technical Report No. 19 *Comparability and Quality Control in Cancer Registration* [443] is a practical guide, presenting the techniques available to ensure completeness of coverage of the population in the registration area, and to check the accuracy and detail of the information collected. A comprehensive review of the literature is included. A diskette of the IARC-CHECK program, originally designed to check data

contributed to Volume VI of *Cancer Incidence in Five Continents*, accompanies the book (see Section 1.1.4.3).

Comparability and Quality Control in Cancer Registration was published in Spanish in 1995 and is being translated into French for publication in 1996.

1.1.3.2

Coding and comparability

D.M. Parkin and S.L. Whelan

Cancer registries must distinguish between a new primary cancer and an extension or recurrence of an existing cancer. The increasingly intensive investigation and follow-up of the cancer patient, the use of treatments which are of themselves carcinogenic, and the prolongation of survival have led to the more frequent recognition of multiple primary tumours in the same individual. For the purpose of comparison between registries, it is essential that similar rules be applied. For this reason the IARC, in collaboration with the International Association of Cancer Registries, has developed a set of rules for use in comparative studies, presented in IARC Internal Report No. 94/003.

1.1.3.3

Training manual for cancer registry personnel

S.L. Whelan and D.M. Parkin; in collaboration with D. Esteban and A.V. Laudico, Manila, Philippines; D. Badger, Ottawa, Canada; S. Gravestock, Liverpool, UK; and A.L. Maya, Miami, USA

Existing training and procedure manuals for clerical and technical registry personnel are often far too complex and specialized for the needs of cancer registration in developing countries. A manual was published as an IARC Technical Report. The book covers the various stages in the process of cancer registration, from where to find data on cancer patients and how to recognize and abstract the appropriate information, to simple analysis and understanding of results. The manual emphasizes the techniques required for registration in developing countries, where the registry personnel have to go out and seek information from the different sources of data rather than process reports received.

1.1.4
Computer software for cancer registries

D.M. Parkin, J. Ferlay, S. Olivier and A. Cooke

1.1.4.1

CANREG

This is an integrated suite of computer programs designed to meet the needs of population-based cancer registries in developing countries and in smaller registries elsewhere. It is easily adapted to meet the requirements of each registry, in terms of what tumour/patient data is collected, whilst remaining easy to use for people with little computing experience. Rigorous data verification is performed automatically at the point of entry to ensure good quality and accuracy. Numerical code tables are provided to ease data entry—both standard ones (e.g., ICD codes), and locally required ones (e.g., region).

Specialized tools for analysis and data presentation allow the production of tables of incidence rates by site with comparison with world standardized rates, user-designed formatted reports of selected records, and integration into an existing statistics package (Epi-Info).

IARC manages the original set-up and installation of the system. Training of users is conducted via structured group courses in various countries, and by fellowships and visits of registry staff to the Agency.

Figure 2. Locations of CANREG installations

Figure 2 shows sites where CANREG is in full operation and producing live data. It has been installed in more than fifty sites worldwide, and has been translated into many languages.

1.1.4.2 CONVERT

The two main classification systems used in analysis of cancer statistics are the International Classification of Diseases (ICD), based primarily on the site of the cancer, and the International Classification of Diseases for Oncology, 1st Edition (ICD-O), based on the combination of topography and morphology. New versions of each of these have been published recently—the tenth revision of the ICD (ICD-10, 1992), superseding the 9th revision of the ICD (1977), and ICD-O 2nd edition (1990) superseding the first edition (1976).

A conversion program [168] allows registry personnel to convert data easily from one ICD classification system to another, thus allowing comparison of data from different sources.

1.1.4.3 CHECK

The IARC CHECK program [443] performs various validity checks both on individual data items and on consistency between items. It produces a report file for each validity check, and indicates whether the case is impossible or unlikely, highlighting, for example, invalid sex/site/morphology combinations, or unlikely age/site/morphology combinations.

1.1.4.4

International Classification for Childhood Cancer (ICCC)

As an independent activity in connection with *International Incidence of Childhood Cancer*, volume 2 (see Section 1.4.1), an IARC Technical Report is being prepared, with a set of programs for conversion between ICD-O and the International Classification for Childhood Cancer (ICCC). Also included will be standardized check programs for validity and consistency of the data. These will be based on the CHECK program (see Section 1.1.4.3) with modifications for age/tumour and site/morphology combinations specific to childhood cancer.

1.1.5

Cancer registration and cancer epidemiology in Latin countries

J. Estève and A. Rivoire; in collaboration with F. Berrino, Milan, Italy; L. Cayolla da Motta and E. Limbert, Lisbon, Portugal; M.J. Michelena Esteveste, San Sebastian, Spain; J. Faivre, Dijon, France; M. Geddes, Florence, Italy; F. Levi, Lausanne, Switzerland; L. Raymond, Geneva, Switzerland; H. Sancho-Garnier, Montpellier, France; P. Schaffer, Strasbourg, France; B. Terracini and R. Zanetti, Turin, Italy; and A. Tuyns, Lyon, France

IARC provides support to the "Groupe pour l'Enregistrement du Cancer dans les Pays de Langue Latine" by participating in its Steering Committee and supporting several of its activities. The annual meeting was held in 1994 at the School of Public Health in Granada (Spain) at the invitation of Dr Carmen Martinez, and in 1995 at IARC at the invitation of the Director of the Agency. Methodological workshops were organized as usual on the day preceding the annual meeting: the interpretation and estimation of prevalence were discussed in Granada and the methods of descriptive data analysis with the EUROCIM software were discussed in Lyon. The book on statistical methods in descriptive epidemiology, based on the seminars organized in this group, is now available in English [160].

1.1.6

Support to specific cancer registries

D.M. Parkin, P. Pisani, R. Sankaranarayanan, S.L. Whelan, A. Cooke and S. Olivier

Advice is given both to organizations wishing to set up cancer registries, and to established registries on the methodology of registration and the analysis of data. Staff of the Unit of Descriptive Epidemiology have made visits to several cancer registries in the course of the biennium, and many individuals working in cancer registries have visited the unit for training or discussion.

Collaborating cancer registries in Europe and Asia have assisted with training of registry personnel. They include the Mersey Regional Cancer Registry (Dr E. Williams and Mrs S. Gravestock) and East Anglian Cancer Registry (Dr T. Davies and Mrs M. Paige) in the UK, the cancer registries of Bas-Rhin (Dr P. Schaffer) and Isère (Dr F. Ménégoz) in France, the cancer registry of Tarragona (Dr J. Galceran) in Spain, the Geneva Cancer Registry (Dr L. Raymond) in Switzerland, the Danish Cancer Registry (Dr H. Storm), the Madras Cancer Registry (Dr V. Shanta) and the Barsi Cancer Registry (Ms. K. Jayant) in India.

The Unit of Descriptive Epidemiology also provides more direct support and encouragement for cancer registration activities in Africa, Asia, Central and South America, and Oceania, often in the form of collaborative research agreements between the registry and IARC.

1.1.6.1

Africa

Algeria:

Setif (H. Cherif): Support to the registry continued through a collaborative research agreement. Cancer incidence data for the period 1990–93 are being analysed.

Alger (D. Hammouda): Following training of two registry clerks in Lyon, the registry began operations on 1 January 1993. Results for the first year have been published.

Batna (M. Bouhidel): The principal investigator spent a four-week training period in Lyon and Strasbourg to develop plans for population-based cancer registration in Batna.

Burundi (V. Bigirimara and L. Ngendahayo): The principal investigator spent a six-week training period in Lyon, Oxford (UK) and Grenoble, learning epidemiological methods and registration tech niques.

Cameroun (A. Mbakop, A. Moune and G. Enow-Orok): Following a visit during 1994, the pathology-based cancer registry in Yaoundé was expanded to become population-based. The registry supervisor spent a period of training at IARC and in Strasbourg, and a research agreement was concluded to provide logistic support.

Congo, Brazzaville (C. Gombe-Mbalawa): With the support of WHO Regional Office, plans were made to initiate population-based cancer registration for the city of Brazzaville from January 1996.

Ivory Coast (A. Echimane and A. Ahnoux): The registrar received a four-week training at IARC and Grenoble in 1994, and data collection for that year was commenced on his return.

Gabon (F.E. Nze-Nguena and D. Minko-Mi-Etoua): A pathology registry has existed in the national laboratory of anatomical pathology for many years. Following a training period at IARC and Strasbourg, the principal investigator developed plans to move towards population-based registration initially for the Libreville area, and later for the whole country. Data collection began during 1995.

Guinea (M. Koulibaly and I. Kabba): The cancer registry began collecting data for the city of Conakry for the years 1991 onwards; first results have been analysed. The registry manager spent a four-week training period at IARC and the Anglian Cancer Registry (UK) in April 1994.

Malawi (L.T. Banda): Support for the registry continued, permitting active data collection from all hospitals in the Blantyre district. The registrar received training in Lyon and the East Anglian Cancer Registry in 1993.

Mali (S. Bayo and S. Kané): Data are now available for about eight years. An analysis of this material, including a review of possible time trends for certain cancers, was completed during a visit of the cancer registrar to Lyon in 1995.

Niger (H. Nouhou): The registry was equipped with a new computer. Initial results for 1994 suggest that registration remains incomplete.

Rwanda (B. Sindikubwabo, P.-L. Ngilimana and R. Newton (ICRF, Oxford, UK)): The registry continued to provide the framework for the studies of HIV-related cancers (Section 2.6.2) until all activity ceased with the events of April 1994. The results obtained before this date were submitted for publication.

Uganda (H. Wabinga and S. Nambooze): The cancer registry provides the framework for the studies of Kaposi's sarcoma in adults and children (Section 2.6.2), and surveillance of time trends in HIV-related cancers (Section 2.6.1). A second analysis of results will be carried out when data collection for 1994 is complete.

Zimbabwe (L. Levy, E. Chokunonga, B. Mauchaza and M. Bassett): The Harare registry has prepared its first complete results (for 1990–92) for publication. The staff have continued to provide training and support for the extension of registration activities to Bulawayo.

1.1.6.2

Asia

Bahrain (Y.T. Omar): Consultant advice was provided in 1993 to assist national authorities in establishing a population-based registry for the country.

India:

Ahmedabad (D.B. Balar and D.D. Patel): An agreement was concluded to provide new computer equipment and software to upgrade the activities of this registry.

Ambilikkai (J. Cherian and R. Rajkumar): Support to procure computing equipment and technical assistance was provided to encourage cancer registration covering a 400 000 rural population in Tamil Nadu. The principal investigator received three weeks' training in Madras and Barsi.

Barsi (B. Nene and K. Jayant). Support to encourage registration activities and analysis of data in this new registry serving a rural population in Maharashtra state was continued.

Bombay (D.J. Jussawala and B.B. Yeole): An agreement was established with the host institution of this registry to procure additional computing equipment and to provide technical support for the analysis of survival data.

Madras (V. Shanta and C.K. Gajalakshmi): An agreement was established with the host institution of this registry to increase computing facilities and to provide analytical support for the study of cancer survival in Madras. A statistician from this registry spent one month in Lyon to receive training in survival analysis.

Trivandrum (K. Nair and C. Varghese): Technical support was provided to establish a population-based registry covering a population of 1 million in the Trivandrum district, Kerala.

Indonesia (R. Mangunkusomo and Sarjadi): Technical support for the cancer registry in Semarang was continued, including assistance with interim analyses of the data. The registrar received four weeks' training in Madras Cancer Registry, India. A course in the use of the CANREG software (Section 1.1.4.1) was held for individuals likely to be responsible for the planned network of cancer registries, in April 1995 in Jakarta.

Laos (B. Bounxouei and P. Sithideth): Following a visit in 1995, local personnel spent one week studying registry methods in Thailand, and plans were drafted for a population-based registry for the city of Vientiane, to start in 1996.

Philippines (D. Esteban, A. Laudico, G. Martinez and B. Talaver): Data collection in the two registries serving the population of greater Manila was enhanced by employment of additional temporary staff. This will reduce the delay in identifying and registering cases—important for follow-up of the large cohort involved in the breast cancer screening project (Section 5.3.1). Visits were made to Cebu (where completeness of registration has improved) and Davao, where staffing problems have caused delays in the registry start-up.

Pakistan (R. Maher and M. Alam): At the request of WHO, a consultant visit was made to review how the existing cancer registry (involving selected hospitals and laboratories in five different cities) might be

replaced by a more productive system. An initial recommendation for population-based registration in the Rawalpindi–Islamabad population was not supported. Local initiative in Karachi has, however, resulted in establishment of a population-based registry for the southern part of the metropolis. The principal investigator (R. Maher) received training at IARC and technical support has been provided.

Thailand (N. Martin, S. Sontipong, S. Sriampom, H. Sriplung and V. Vatanasapt): The three established registries published their results in 1994 (Section 1.2.3.2). A further analysis of time trends in incidence in the longer-established registries is planned. Retrospective registration for a five-year period (1988–92) was completed for the northern province of Lampang, supervised by Chiang Mai registry staff. Planning continues for population registration in one of the provinces in the central region. Staff from Khon Kaen and Chiang Mai registries received training in survival analysis in Lyon.

Turkey (G. Aydemir): The Izmir Cancer Registry has not yet succeeded in reaching population coverage, although the majority of the hospitals and clinics contribute data. The registry was, however, able to provide data for the international study of childhood cancer (Section 1.4.1).

Viet Nam (Pham Hoang Ahn, Nguyen Chan Hung and Quoc Nguyen Manh): The registry in Hanoi produced a second report (1991–92) confirming the patterns noted previously [481], but suggesting some under-registration in earlier years.

The registry manager from the Cancer Institute in Ho Chi Minh City spent a period of training at IARC and in Grenoble during 1994. Progress in extending data collection to all hospitals and treatment centres in the city remains slow.

1.1.6.3

Americas

Argentina, Bahia Blanca (E. Laura and C. DiMartini): Continuing support has been provided for the registry. The first results have been published locally.

Barbados (R. Knight and P. Prussia): Plans for a population-based cancer registry for the island are well advanced, as part of an initiative of the regional office of PAHO. The principal investigator received a period of training in Lyon and at the East Anglian Cancer Registry (UK).

Brazil:

Rio de Janeiro (E. de Abreu): Central co-ordination of activities of the Brazilian cancer registries is provided through the Oncology Programme at the National Cancer Institute. The methods and results were reviewed in 1994.

Fortaleza (M. Gurgel da Silva) and Belem (A. Madeira Neto): The registries record cancer cases from their respective cities. Evaluation is difficult because of the inadequate data-handling and analysis methods.

Costa Rica (C. Bratti): CANREG software was installed to computerize the registry, which had functioned manually since its establishment in 1980. The loading of the system with the data from the registry archives is almost complete. The automation of the registry was promoted by the execution of several epidemiological projects which require efficient linkage with the incidence data provided by the registry.

Cuba (L. Fernandez): An agreement was established to provide technical support for cancer survival analysis and to increase computing facilities. A staff member spent one month in Lyon to receive training in statistical methods of survival analysis.

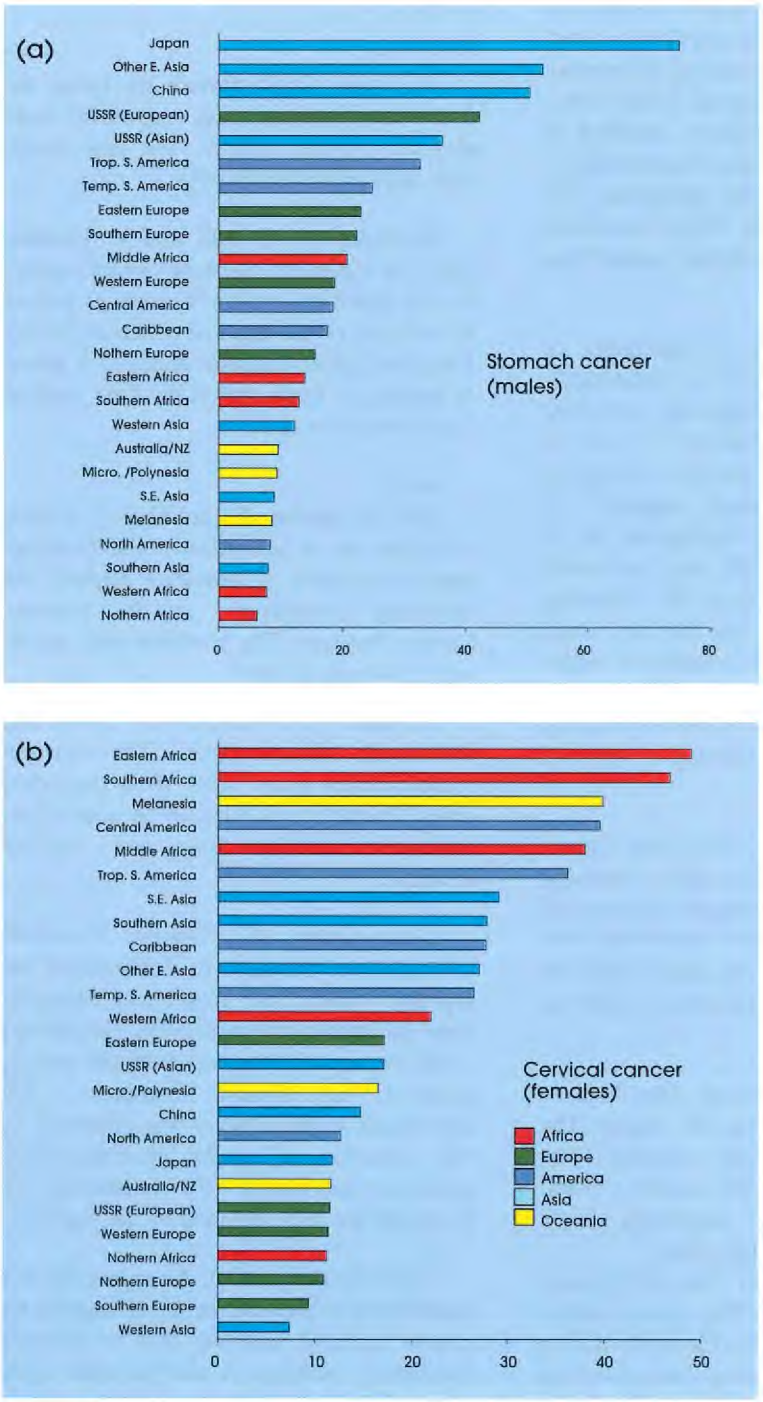


Figure 3. Examples of histograms to depict age-standardized incidence rates. (a) Stomach cancer in males; (b) cervical cancer in females.

Ecuador (F. Corral and P. Cueva): Technical advice was provided to the Quito registry. Overall quality is good, and an analysis of temporal trends in incidence is planned.

Peru (P.J. Albujar, E. Caceres and M. Almonte): Continuing support was provided for the registry in Trujillo, as well as technical advice for the cancer registry serving the population of metropolitan Lima. A comparative analysis of results has been completed (Section 1.2.3.3).

Trinidad (E. Quamina): A registry has been established covering initially the city of Port of Spain, with data collection starting in 1995. It is planned to extend coverage to the whole island. Technical support has been provided, and the CANREG system (Section 1.1.4.1) installed.

Uruguay (E. de Stefani): Continuing support for the registry (which covers the city of Montevideo) was provided. The results were prepared for publication by the principal investigator.

1.2 Geographic variation in cancer occurrence

The enormous variability in the occurrence of cancer in different populations has continued to provide a stimulus for research into the causes. Such data also give indications of priorities for cancer control. The collation, processing analysis and presentation of these data continue to be a major activity of IARC.

1.2.1 Cancer Incidence in Five Continents, Volume VII

D.M. Parkin, S.L. Whelan and J. Ferlay; in collaboration with L. Raymond, Geneva, Switzerland; and J. Young, Sacramento, USA

Data on the incidence of cancer worldwide for the years 1988–92 are being collected for the seventh volume of the *Cancer Incidence in Five Continents* series, to be published in 1997. Volume VI included data for 170 populations in 46 countries. More than 20 countries which have never presented data in the series have been invited to contribute to the seventh volume, and it is hoped that the final selection will include several new areas from Africa and from developing countries in Asia.

The methodology designed to condense the data from Volumes V and VI on diskette is being developed further, and the seventh volume will include a diskette with the published results (population figures and incidence at the ICD three-digit level).

A computer program, IARC-CHECK, to identify data errors and inconsistencies, notably wrong or unlikely combinations of site or morphology codes, has been distributed to cancer registries with the publication *Comparability and Quality Control in Cancer Registration* [443] (see Section 1.1.3.1), and the majority of contributors to Volume VII will have been able to verify their own data. Data will be accepted only on computer medium, in the form of a case-listing and including the histological diagnosis.

Over the years the editors have defined features of a data-set which can help to identify incomplete or invalid registration. Measures of quality include the proportion of cases for which the site of the primary is not known, the numbers of cases of unknown age, the percentages of histological

verification and of notifications based only on a death certificate, the ratio of mortality to incidence and significant changes in rates over time. New measures of quality are being introduced, for example childhood cancer rates (which are similar worldwide) outside the expected range, or unlikely changes in population structure over time.

This process is being automated for Volume VII, highlighting unexpected indices of quality, age-specific curves and changes in rates or in the structure of the population at risk. New background material, including histograms to illustrate average age-standardized incidence for major cancers and for all sites in different parts of the world (Figure 3), is being prepared.

1.2.2

European Cancer Incidence and Mortality Database (EUROCIM)

D.M. Parkin, R.J. Black, J. Ferlay, T. Valdivieso and J. Estève; in collaboration with F. Berrino, Milan, Italy; F. Ménégoz, Meylan, France; C. Navarro, Murcia, Spain; R. Otter, Groningen, Netherlands; D. Pheby, Bristol, UK; E. Schifflers and A. de Coninck, Namur, Belgium; H.H. Storm, Copenhagen, Denmark; and H. Tulinius, Reykjavik, Iceland

The EUROCIM package combines a database of cancer incidence and mortality data contributed by member registries of the European Network of Cancer Registries (see Section 1.1.2) and statistical software for the comparative analysis of these data. The latter was developed by an external contractor, while the management of the data and liaison with cancer registries are carried out at IARC. Version 1.0 of EUROCIM was distributed to contributing registries in 1994. The current version, EUROCIM 2.0, which was released in 1995, contains comparative data from 79 registries in Europe. The statistical software has been improved and the user manual completely revised.

EUROCIM permits access to incidence data at the level of 'epidemiological entities', which are histological types of tumours classified within anatomical site. The 730 entities permit more detailed analysis of population-based cancer incidence data than has been possible using the conventional classification of cancer by anatomical site only.

The EUROCIM package has provided the basis for training courses in statistical methods for cancer registries during 1994–95. The courses cover the theoretical basis for descriptive epidemiology, methods of calculation of rates, comparative methods and statistical modelling of rates. The first course was held in Lyon in March 1994 and the second, also in Lyon, was conducted in the French language in May 1995. A course in English was held in London in October 1995.

1.2.3

Analysis of data from collaborating cancer registries

Investigators working in cancer registries are assisted in analysing and presenting their data. Priority is given to data-sets of special interest, representing hitherto unpublished material, and to combined analyses from several registries within the same country.

1.2.3.1

Africa

D.M. Parkin, A. Vizcaino and J. Ferlay; in collaboration with L. Levy, M. Bassett and E. Chokunonga, Harare, Zimbabwe; M. Skinner, formerly Bulawayo, Zimbabwe; R. Newton, Oxford, UK; and B. Sindikubwabo and P.J. Ngilimana, Butare, Rwanda

The data collected over a fifteen-year period (1963–77) from the cancer registry of Bulawayo, Zimbabwe, were published as an IARC Technical Report [586] and in summarized form [453]. As well as the

descriptive epidemiology, the importance of certain environmental exposures (tobacco, alcohol, etc.) and personal variables (e.g., reproductive habits) in determining the risk of the major cancers (oesophagus, lung, bladder, breast, cervix, corpus uteri) was presented. The results for two sites, oesophagus [669] and bladder [668] have been published separately. For oesophageal cancer, tobacco smoking proved to be a more important determinant of risk than alcohol drinking, and there were clear geographical variations in risk. Bladder cancers were predominantly (71%) squamous cell tumours for which a past history of schistosomiasis, but not tobacco smoking, was an important risk factor.

More recent results from Zimbabwe have become available through a first analysis of the results from the cancer registry in Harare (1990–92). They confirm some familiar features in the black population of southern Africa—high rates of oesophagus and lung cancers in men, and cervix cancer in women, and also the new feature of Kaposi's sarcoma, now the most common cancer of men [31]. The white population has a completely different pattern, with very high incidence rates of skin cancers, as well as breast cancer (in women) and bladder and large bowel cancers [32].

The results obtained from the cancer registry in Butare, Rwanda, have also been prepared for publication, although partially incomplete. Surprisingly, Kaposi's sarcoma was less frequent in this population than other common cancers such as stomach in men, and cancers of the cervix and breast in women.

1.2.3.2

Asia

D.M. Parkin, P. Boffetta and J. Ferlay; in collaboration with N.C. Martin, Chiang Mai, Thailand; V. Vatanasapt and S. Sriamporn, Khon Kaen, Thailand; H. Sriplung, Songkhla, Thailand; S. Sontipong and K. Chindivijak, Bangkok, Thailand; L. Reyes and A. Laudico, Manila, Philippines; and H.A. Pham, Hanoi, Vietnam

Results from three cancer registries (Chiang Mai, Khon Kaen, Songkhla) and a cancer survey (in Bangkok) in Thailand were published as IARC Technical Report No. 16 [662], which presented national estimates of incidence and a review of epidemiological studies. The results were published in summary form [663] and a separate analysis of childhood cancers was concluded [593].

The first results from the new cancer registry in Hanoi, Vietnam, were published [481]. More recent results suggest some under-registration, and even higher incidence rates of lung and stomach cancers are now evident, but cervix cancer is clearly rare in this population, in contrast to the south of Vietnam, where high relative frequencies are reported.

The combined data from the two cancer registries in Manila, Philippines for the period 1983–87 were analysed by a visiting fellow, and published by the UICC [293].

1.2.3.3

South America

D.M. Parkin and J. Ferlay; in collaboration with E. Caceres and M. Almonte, Lima, Peru; and P. Albujár, Trujillo, Peru

The revival of the cancer registry in Lima, Peru, has provided new data for that population for the years 1990–91. The results have been analysed by a visiting fellow, and compared with those for the coastal city of Trujillo (1988–90), and the cancer surveys in the Andean cities of Huancayo and Cuzco. Stomach cancer is the most common cancer of men in all four cities; in women cervix cancer is the major cancer in the provincial cities, but incidence rates for breast cancer exceed those for cervix cancer in Lima.

1.2.3.4
General

D.M. Parkin, P. Boffetta, R. Sankaranarayanan and J. Ferlay; in collaboration with R. Newton, Oxford, UK; and A. Kricker, Sydney, Australia

The availability of cancer incidence and mortality databases at IARC permits the study of the epidemiology of different cancers with respect to geographical variation and time trends.

An overview of the patterns of cancer in developing countries [67] and an analysis of time trends for the major sites [440] indicate priority areas for cancer control in different areas of the world. Cancer registry data permit analyses of such patterns by cell type (as well as tumour site), which is particularly useful in evaluating possible etiological connections. Analyses for lung cancers [449] and for cholangiocarcinomas [444] have been completed. A study of the geographical patterns of the three major types of eye tumour (retinoblastoma, melanoma and squamous cell cancers of the conjunctiva) is in progress.

1.2.4
Worldwide burden of cancer

D.M. Parkin, P. Pisani and J. Ferlay

The measures of cancer burden have been extended to other indexes such as prevalence, age at onset and duration of the disease. Prevalence has been long recognized as a useful measure of cancer burden, indicating the number of patients alive who require medical care. There is no standard definition of a prevalent case of cancer, as this depends on the definition of a cured patient. A reasonable compromise is to include cancer patients who are still alive between 0 and 5 years after diagnosis, as this approximates to the period of active treatment. Prevalence of cases for 18 sites and all cancers, in five age groups, was obtained by combining the annual number of new cancer cases with their characteristic survivorship function. Figure 4(*a*) shows estimated world totals of prevalent cases by sex and site. The total number of cancer patients demanding care is estimated at 15.3 million: 40% men and 60% women. The most prevalent cancer sites are those which combine high incidence and good survival, namely breast and colorectal cancers in the more developed regions, and cervix and breast cancers in the less developed ones (Figure 4(*b*)).

Age at onset and duration of the disease, for the same cancer sites in the two sexes and five age groups, were obtained. These figures contribute to the calculation of indices such as disability-adjusted life years lost (DALY), and quality-adjusted life years lost (QALY), as used in the *World Development Report 1993: Investing in Health* of the World Bank (World Bank, 1993, New York, OUP; Murray and Lopez, eds, 1995, Geneva, WHO).

Estimates are now being prepared of the cancer burden which may be attributed to known causes. The proportion of all cancers attributable to tobacco smoking has been estimated as 15% or 1.1 million new cases per year (25% in men and 4% in women). In developing countries, the etiological fraction is 10%, compared to the 16% estimated for the 'western' countries [448]. A preliminary estimate of the etiological fraction due to infectious agents has also been prepared: 22% of all new cancer cases are due to infection with viruses, parasites or bacteria in developing countries; the corresponding figure in developed areas is estimated at 9%.

A project to quantify cause-specific attributable fractions of cancer incidence and mortality in the countries of the European Community has been initiated. The

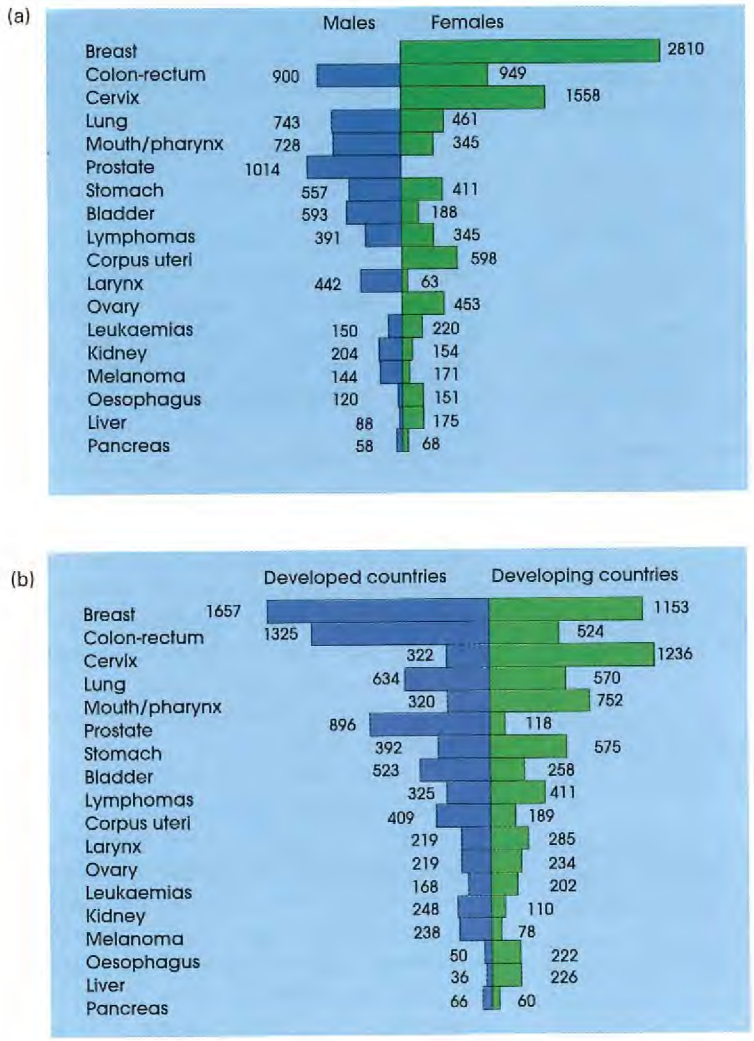


Figure 4. Number of 5-year prevalent cancer cases (thousands) (a) by sex and site, and (b) by site and level of economic development

numbers of deaths from, and numbers of new cases of, all cancers and specific cancers will be attributed to causes such as smoking, reproductive factors, dietary habits (including alcohol consumption), exposure to chemicals in the workplace, exposure to infectious agents, radiation, and drug use. Interactions among these factors and the potential of genetic predisposition are being taken into account.

1.2.5

The mapping of cancer mortality and incidence data

M. Smans and R. Winkelmann; in collaboration with P. Boyle, Milan, Italy; F. Levi, Lausanne, Switzerland; T. Men and D. Zaridze, Moscow, Russia; E. Pukkala, Helsinki, Finland; and J. Tyczynski and W. Zatonski, Warsaw, Poland

The *Atlas of Cancer Mortality in Central Europe* is now complete and publication will take place before the end of

1995. The geographical patterns and the differences in trends seen between countries for certain cancers show the scope for prevention and for improved treatment in some areas.

The geographical patterns of cancer mortality and incidence in the former USSR are being analysed, with a particular emphasis on the quality of registration.

The feasibility is being assessed of updating the existing databases used for the atlases of cancer mortality in nine countries of the European Economic Community and in nine central European countries, to cover a recent period, with the goal of producing a complete picture of the European continent.

1.2.6 Ecological studies

P. Pisani, D.M. Parkin and J. Reissigová; in collaboration with R. Prentice, D.B. Thomas and M.A. Rossing, Seattle, USA

Ecological studies are correlative epidemiological studies in which the group rather than the individual constitutes the basic statistical unit.

It is a well established principle that ecological studies cannot provide unequivocal evidence of a causal linkage between a factor and the risk of developing a disease; rather they suggest hypotheses to be tested through proper analytical studies. However, this study design has been undervalued in two instances: (1) as a means to quantify the impact of factors judged of causal nature in explaining geographical and temporal variation of the risk of the disease, and (2) when the exposure under study shows little variation within defined populations and it is difficult to measure with accuracy at the individual level. Two such instances can be recognized in the relationship between some reproductive factors and the incidence of gynaecological cancers, as well as between dietary habits and the risk of breast, colon and other cancers.

A systematic search for results from international surveys on women's reproductive habits and temporal trends of fertility has been undertaken. The most comprehensive and consistent data across countries, representing both developed and developing areas, are available through the UN World Fertility Survey programme, set up in the early 1970s for the purpose of monitoring population growth and determinants of changes. Historical data on parity and fertility rates by age of women are being assembled, for correlation with the mortality and, when possible, the incidence of cancers of the breast, uterus and ovary, allowing for cohort-specific changes in reproductive habits.

A large ecological study (the International Aggregate Data Study) has been planned by researchers at the University of Seattle, with IARC co-investigators. It aims to investigate the relationship between cancer incidence rates in 35 populations worldwide, and prevalence of exposure variables in random samples of the same populations. The main emphasis is upon dietary exposures, as measured by 24-hour recall interview and through measurements of blood nutrients, micronutrients and hormones; analysis will focus in particular upon cancers of the breast, prostate, colon-rectum and lung.

1.3 Description of cancer incidence and mortality in migrant populations

Studies of migrant populations are of particular value in estimating the relative contributions of genetic and environmental factors in cancer etiology. In such studies,

the risk of cancer in a migrant population is compared with that in persons of the same genetic background (living in the place of origin of the migrants), or with persons in the host country sharing a common external environment. The aim is to see how much the risk of cancer changes from that of the country of origin to that of the host country, and to determine how rapidly such changes occur. The results are useful in formulating hypotheses on the relative importance of environmental factors in etiology, and on the probable stage of carcinogenesis on which they act.

The emphasis in recent projects has been upon hitherto unstudied groups, and on exploiting data-sets which permit analysis of trends in risk by time since migration, or comparison between first-generation migrants and their offspring.

1.3.1
Cancer in migrants to France

D.M. Parkin; in collaboration with C. Bouchardy, Geneva, Switzerland; M. Khlat, Paris, France; and P. Wanner, Geneva, Switzerland

A large-scale analysis of cancer risks in the various migrant populations in France has been completed, using mortality data for the period 1979–85. Results for several migrant populations have been examined separately: Chinese and south-east Asian migrants, and migrants from North Africa and from sub-Saharan Africa (Bouchardy *et al.*, 1992, *Bull. Suisse Cancer*, **3**, 90–94; [79]).

1.3.2
Cancer in Polish migrant populations

D.M. Parkin; in collaboration with W. Zatonski, J. Tyczynski and W. Tarkowski, Warsaw, Poland; E. Matos, Buenos Aires, Argentina; A. Brancker, Ottawa, Canada; J. Iscovich, Jerusalem, Israel; and L. Bernstein, Los Angeles, USA

The objective of this study is to compare the risk of cancer in Polish migrant populations with that of the host countries. The countries studied include Argentina, Australia, Canada, England and Wales, France, Israel and the USA. For migrants to Australia, Israel and the USA, cancer risk will also be examined in relation to duration of residence in the host country; for Canada, the risk in first-generation migrants (born in Poland) is being compared with that in the Canada-born population of Polish parentage. The results for migrants to France and Australia have been published (Tyczynski *et al.*, 1992, *Bull. Cancer Paris*, **79**, 789–800; [632]).

1.3.3
Cancer in migrants to Canada

D.M. Parkin; in collaboration with L. Gaudette, Ottawa, Canada

Death registrations in Canada record not only the place of birth of the deceased, but also the parents' birthplaces. This permits the analysis of cancer risk in migrants, and in the offspring of migrants (the latter can be separated into individuals with mother, father or both born abroad).

An analysis of the Canadian data for Italian migrants and their offspring has been completed [23] and demonstrates how the risk of different cancers is modified between the generations (Figure 5).

A similar analysis has been completed for Polish migrants (see Section 1.3.2).

1.3.4
Cancer in Jewish migrants to Israel and their offspring

D.M. Parkin; in collaboration with J. Iscovich, Jerusalem, Israel

This study is examining the risk of cancer in the Jewish population born in Israel according to birthplace of parents, and comparing this with the risk among migrants. The population born in Israel is still

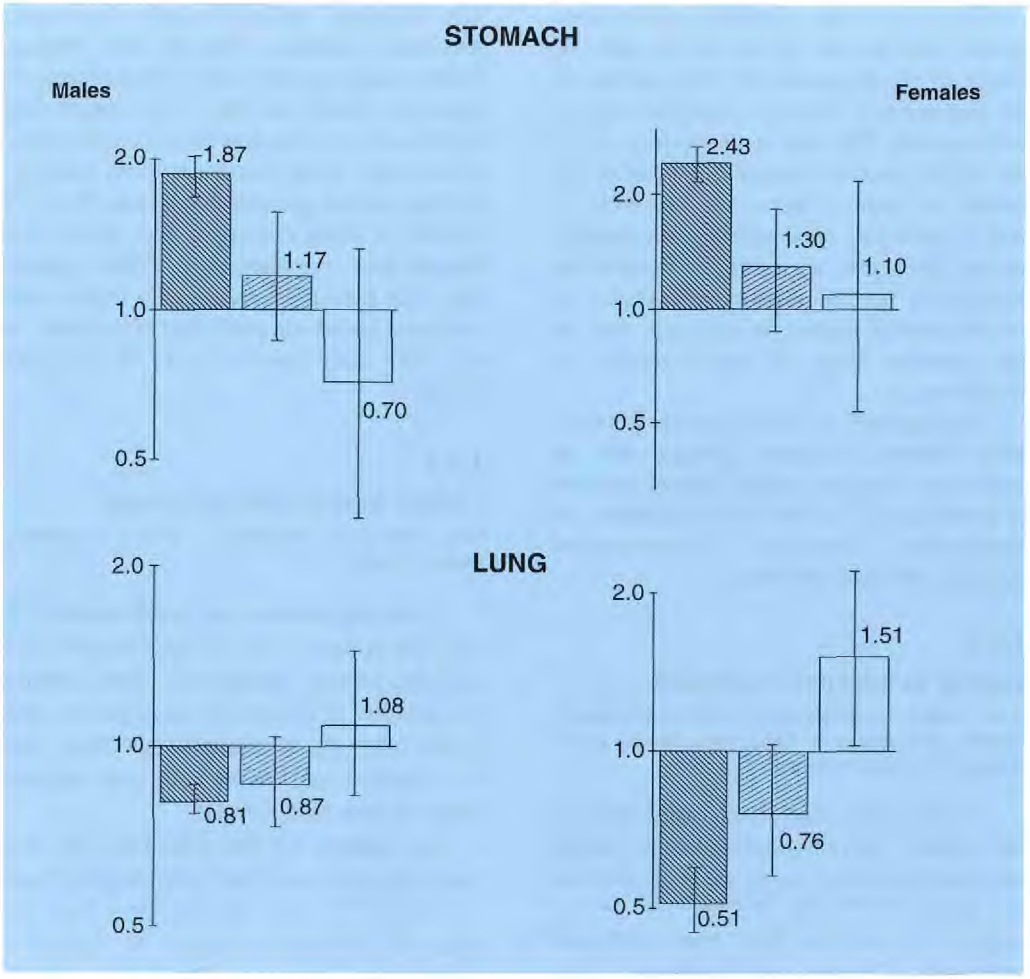


Figure 5. The risk of stomach and lung cancer in migrants to Canada from Italy and in their offspring born in Canada, relative to that in Canadians with local-born parents.

▨ Born in Italy; ▨ Born in Canada, two Italian parents; □ Born in Canada, one Italian parent

quite young, and for this and other technical reasons, the analysis is confined to cancers appearing in the young (before age 30). Earlier studies of Jewish migrants (Steinitz *et al.*, 1989, *Cancer Incidence in Jewish Migrants to Israel 1961–1981* , Lyon, IARC) showed large differences in incidence according to birthplace, and the persistence of a differential in the offspring of such migrants, compared with individuals whose parents were born in Israel, implies an important hereditary component in etiology.

The data comprise all records of cancer cases aged 0–29 years for the period 1961–89 (10 256 cases). Of these, 2660 are migrants, 6554 offspring of migrants, and the remainder 'third-generation' (Israel-born, with parents born in Israel).

The results are interesting in distinguishing between cancers for which distinctive risks in migrant population are retained in the second generation (e.g., nasopharynx, melanoma, non-Hodgkin lymphoma), and those for which the risks change towards those of the population with Israel-born parents (cervix, breast, thyroid).

1.4 Descriptive studies of childhood cancer

Careful analyses of large data-sets on childhood cancer to detect variations by age, sex, place of residence, ethnicity, time, etc. have been particularly useful in yielding clues to etiology and in deciding on the likely importance of environmental factors.

1.4.1 *International Incidence of Childhood Cancer*, Volume 2

D.M. Parkin, E. Kramárová and E. Masuyer; in collaboration with G.J. Draper, Oxford, UK; J. Michaelis, Mainz, Germany; J. Neglia, Minneapolis, USA; S. Qureshi, Islamabad, Pakistan; and C.A. Stiller, Oxford, UK

This publication will update in time and coverage the rates of childhood cancer, published in the first volume (Parkin *et al.*, 1988, *International Incidence of Childhood Cancer*, Lyon, IARC). The period covered will be approximately the decade 1980–89, depending on data availability and the period published in the first volume for a particular registry. A listing of all new cases that occurred during the reference period in patients aged 0–14 years has been requested from each registry, with identifiers, sex, age, date of diagnosis and the codes of site, morphology and behaviour of the neoplasm. The optional variables were laterality for tumours in bilateral organs (retinoblastoma and kidneys) and ethnic group.

Data collection is complete. About 150 centres in 60 countries are participating. Virtually all are population-based registries, with the exception of eight hospital-based registries operating in Africa or Asia. For countries where several regional registries are present, the data will be pooled and overall rates presented. Incidence trends will be presented for registries contributing to both volumes of this monograph.

The International Classification for Childhood Cancer (ICCC) published in the first volume of this monograph will be updated. The revisions were made on the basis of ICD-O-2 nomenclature and widely distributed for comments to those with interest and expertise in paediatric oncology or epidemiology.

This publication is to be produced under the auspices of IARC, the International Association of Cancer Registries (IACR) and the International Society of Pediatric Oncology (SIOP).

1.4.2 Descriptive studies of particular types of childhood cancer

D.M. Parkin, J. Ferlay and J. Nectoux; in collaboration with G.J. Draper and C.A. Stiller, Oxford, UK

The large database collected for the study of international incidence of childhood cancer (Parkin *et al.*, 1988, *International Incidence of Childhood Cancer*, Lyon, IARC) has been used to complete a detailed review of the geographical and ethnic differences of the common childhood cancers. During the biennium, the results of these analyses for childhood soft-tissue sarcomas [597], childhood brain tumours [596] and childhood carcinomas (Stiller, 1994, *Cancer*

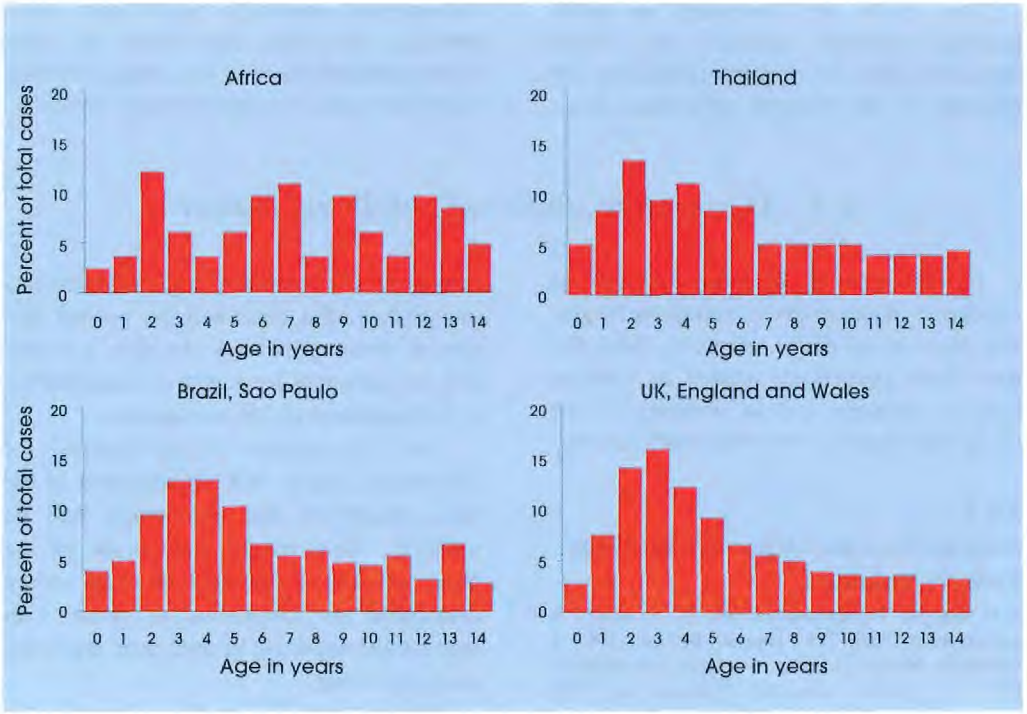


Figure 6. Percentage of cases of acute lymphocytic leukaemia at different ages in various regions of the world (African data are from Ibadan (Nigeria), Kampala (Uganda) and Bulawayo (Zimbabwe))

Epidemiol. Biomarkers Prev., **3**, 305–310) were published.

Soft-tissue sarcomas comprise 4–8% of cancers in children, with incidence rates rather lower in Asian populations than elsewhere. Most are rhabdomyosarcomas. Intracranial and intraspinal tumours are the second most frequent type of childhood cancer (after leukaemia), accounting for around 20% of cases in many areas. The most common types are astrocytomas (37% in England and Wales), medulloblastomas (20%) and ependymomas (12%). Low incidence rates in developing countries may be due to under-ascertainment. Differences in frequencies of the histological types between western countries and Japan, and between ethnic groups in the USA, suggest that genetic predisposition is important in determining risk.

A review of patterns of childhood cancer in developing countries has been completed [451]. The geographical, ethnic and temporal variations in incidence provide useful clues as to whether environmental exposures are significant in determining risk, as, for example, in the case of childhood acute lymphocytic leukaemia (Figure 6).

1.4.3 Neonatal tumours

A.J. Sasco, I. Gendre and O. Chatard; in collaboration with E. Robert, Lyon, France; and D. Satgé, Tulle, France

Since population-based information on the occurrence of both benign and malignant neonatal tumours is rare, we have explored all available data sources for the Rhône-

Alpes region of France. These include population-based general cancer registries, specialized paediatric cancer registries and registries of congenital malformations, as well as hospital sources, and our survey confirms the need for multiple sources of information in order to ensure complete coverage. Etiological research on neonatal tumours is poorly developed, in part due to their rarity. Both genetic and hormonal factors may be involved [570]. A case–control study of neonatal angiomas is being conducted in public obstetric units in Lyon to evaluate the role of maternal exposures during pregnancy.

1.5 Survival from cancer

Survival from cancer among a population is usually expressed in terms of the probability of surviving at a stated time (often one or five years) after diagnosis of the disease. Population-based cancer survival data are an important element of the evaluation of cancer control activities; geographical or other variations in survival from cancer of a given site may reflect differences in diagnostic and/or therapeutic practices in the populations concerned.

1.5.1 Survival from cancer in Europe

J. Estève; in collaboration with F. Berrino and M. Sant, Milan, Italy; R. Capocaccia and A. Verdecchia, Rome, Italy; J.W.W. Coebergh, Eindhoven, Netherlands; M.P. Coleman, Sutton, UK; J. Faivre, Dijon, France; T. Hakulinen, Helsinki, Finland; C. Martinez, Granada, Spain; and S. Wilson, Manchester, UK

A concerted action (designated EUROCARE), financed by the European Union, started in 1989, with the objective of evaluating survival from selected cancers. The first part of the study, published in 1995 as IARC Scientific Publications No. 132 [41], summarized the survival experience of about 800 000 cancer patients diagnosed during 1978–85 in 11 European populations covered by cancer registries. It shows that cancer survival rates are similar for most sites of cancer but reveals substantial differences for breast, large bowel, and stomach.

The Working Group is pursuing its efforts by collecting and analysing detailed data on stage, diagnostic methods, and treatment to help to understand the observed differences in survival probability between the populations of the study.

1.5.2 Survival from cancer in developing countries

R. Sankaranarayanan, R.J. Black, D.M. Parkin and J. Estève; in collaboration with M. Hamdi-Cherif, Setif-Wilaya, Algeria; Jian-Guo Chen, Qidong, China; Fan Jin, Shanghai, China; C. Bratti, San Jose, Costa Rica; M. Graupera and L. Fernandez, Havana, Cuba; A. Nandakumar and N. Anantha, Bangalore, India; K. Jayant, Barsi, India; B.B. Yeole and D.J. Jussawalla, Bombay, India; R. Swaminathan, C.K. Gajalakshmi and V. Shanta, Madras, India; M. Krishnan Nair, Trivandrum, India; S.C. Freni, Netherlands Antilles; D. Esteban, Manila, Philippines; N. Martin, Chiang Mai, Thailand; and S. Sriamporn and V. Vatanasapt, Khon Kaen, Thailand

Difficulties of data collection and follow-up have so far precluded the assessment of survival data from developing countries. Work is in progress to describe population-based cancer survival in countries such as Algeria, China, Costa Rica, Cuba, India, Philippines and Thailand. Fourteen population-based cancer registries, two of them national registries, are participating. A variety of methods such as matching with death certificates, scrutiny of hospital records, matching with national population registers, reply-paid postal

Table 1. Number of cases and five-year cumulative observed and relative survival rates by tumour site in Khon Kaen, Thailand

Site	Number of cases	Survival rate (%)	
		Observed	Relative [a]
Lip	111	70.4	84.1
Oral cavity	235	35.7	42.5
Nasopharynx	190	31.1	34.5
Stomach	220	20.3	23.4
Large bowel	421	36.8	41.9
Liver	3548	8.0	9.2
Lung	518	13.1	15.4
Breast	423	45.4	48.1
Cervix	857	56.6	60.1
Ovary	239	39.7	41.6
Bladder	127	47.3	56.9
Brain and other CNS	136	31.3	33.0
Thyroid	286	31.3	33.0
Non-Hodgkin lymphoma	218	30.2	32.5
Lymphoid leukaemia	112	31.4	28.8
Myeloid leukaemia	122	16.1	16.8
All cancer	10333	26.9	30.2

[a] Patient survival relative to survival among the general population.

enquiries and house visits have been used by these registries to collect information on vital status of incident cases. The results from Khon Kaen Registry in Thailand are shown in Table 1.

In addition to providing the first survival rates from developing countries [414, 592], the project aims to develop expertise within participating registries in methods of survival analysis, and statisticians from four participating registries have already been trained. A monograph discussing methodological issues, results and their potential application in cancer control is in preparation.

PART 2. ENVIRONMENTAL CAUSES OF CANCER

2.1 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

H. Vainio, H. Møller, D. McGregor, C. Partensky, I. Peterschmitt, J. Wilbourn and P. Webb. The following members of other units have contributed to the programme: B.K. Armstrong, P. Boffetta, J. Cabral, E. Cardis, M. Friesen, J. Estève, H. Fu, S. Franceschi, M. Kogevinas, V. Krutovskikh, J. Little, M. Lang, R. Montesano, V. Moreno, N. Muñoz, A. Mylvaganam, H. Nakazawa, H. Ohshima, I.K. O'Neill, B. Pignatelli, P. Pisani, E. Riboli, C.P. Wild and H. Yamasaki

The *IARC Monographs* programme aims to identify agents that increase the risk of cancer in exposed humans. Working Groups of invited experts in carcinogenesis follow guidelines established during several consultative meetings in formulating their evaluations. During the period 1 July 1993 to 31 December 1995, meetings were held to prepare volumes 60–65 of the *IARC Monographs*. Three ad-hoc meetings, on quantitative estimation and prediction of cancer risks, priorities for future IARC Monographs and peroxisome proliferation, were also organized.

2.1.1 Some industrial chemicals

(Volume 60, 15–22 February 1994)

A working group convened by IARC evaluated the carcinogenic risks to humans of 14 chemicals. Several of these chemicals are characterized by unsaturated bonds, which are important for their extensive use in the production of polymers and copolymers. Epoxides which can be formed during metabolic reactions at these bonds were also evaluated. Two of the chemicals (ethylene and isoprene) occur in human breath as a result of endogenous formation.

On the basis of limited human and sufficient experimental evidence of carcinogenesis as well as strong supporting genetic evidence, ethylene oxide was evaluated to be carcinogenic to humans (Group 1). The exposure was judged to be causally associated with human lymphatic and haematopoietic system malignancies. For all other chemicals, the human cancer evidence was inadequate for any judgement to be made. Acrylamide and styrene-7,8-oxide were evaluated as probably carcinogenic to man (Group 2A), on the basis of sufficient experimental evidence of carcinogenicity supported by strong genetic evidence. Isoprene, propylene oxide, 4-vinylcyclohexene and 4-vinylcyclohexene diepoxide were evaluated as possibly carcinogenic to humans (Group 2B) on the basis of sufficient experimental evidence of carcinogenicity. Although for styrene the experimental evidence was only limited, it too was evaluated as a possible human carcinogen, mainly on the basis of metabolic evidence of its conversion to styrene-7,8-oxide. The other six chemicals (2-ethylhexyl acrylate, *N*-methylolacrylamide, ethylene, propylene, methyl methacrylate and vinyl toluene) were not classifiable as to their carcinogenicity to humans (Group 3).

2.1.2 Schistosomes, liver flukes and *Helicobacter pylori*

(Volume 61, 7–14 June 1994)

A working group of scientists from 11 countries reviewed the role of certain parasitic and bacterial infections in human cancers.

It is estimated that about half of the world's population is infected with *Helicobacter pylori*, and there is evidence that this infection is the cause of most cases of chronic gastritis. The Working Group concluded that *H. pylori* plays a causal role in gastric carcinogenesis and reached the evaluation that infection with *H. pylori* is carcinogenic to humans (Group 1).

Infections with three species of schistosomes were evaluated. *Schistosoma haematobium* infection was judged to be causally associated with cancer of the urinary bladder: infection with *S. haematobium* is carcinogenic to humans (Group 1).

Infections with *S. japonicum* and *S. mansoni* have been linked with cancer of the liver and the gastrointestinal tract, but the Working Group found the evidence to be less strong: infection with *S. japonicum* is possibly carcinogenic to humans (Group 2B) and infection with *S. mansoni* is not classifiable as to its carcinogenicity to humans (Group 3).

Associations between infections with liver flukes and cholangiocarcinoma have been reported in various populations. The Working Group's evaluation was that infection with *Opisthorchis viverrini* is carcinogenic to humans (Group 1), infection with *Clonorchis sinensis* is probably carcinogenic to humans (Group 2A), while infection with *O. felineus* is not classifiable as to its carcinogenicity to humans (Group 3).

2.1.3

Wood dust and formaldehyde

(Volume 62, 11–18 October 1994)

A group of experts from 10 countries prepared monographs on wood dust and formaldehyde. Industries and occupations in which exposures to wood dust occur have been evaluated previously in Volume 25 and Supplement 7 of the *Monographs*. In the present monograph, the structure of wood, its production and uses and the industries in which it is used were described. There are few epidemiological studies in which wood types and levels of exposure were described; the primary data consisted of case–control studies of sinonasal cancer in various occupational situations where exposure to wood dust occurs. The database on animal carcinogenicity studies was limited and it is known that further long-term studies in rodents are in progress. The overall evaluation was that wood dust is carcinogenic to humans (Group 1). This evaluation was based on the observation of a marked increase in the occurrence of cancers of the nasal cavities and paranasal sinuses among workers exposed predominantly to hardwood dusts.

Formaldehyde, also evaluated previously in the *Monographs* series in 1982 and 1987, was considered at this meeting since in some wood-related industries, e.g. particle board manufacture, exposures to both agents occur. In spite of some new epidemiological data, it was concluded that there is still limited evidence in humans for the carcinogenicity of formaldehyde and sufficient evidence in experimental animals. Formaldehyde was classified as probably carcinogenic to humans (Group 2A).

2.1.4

Dry cleaning, some chlorinated solvents and other industrial chemicals

(Volume 63, 7–14 February 1995)

A working group convened by IARC evaluated the relationship between employment in dry cleaning and the occurrence of cancer, as well as the carcinogenic risks to humans of two important solvents, trichloroethylene and tetrachloroethylene, and of 13 other industrially significant chemicals.

Evaluation of numerous case–control studies and four cohort studies, two of which were restricted to dry cleaners and two of which addressed both laundry and dry cleaning workers, indicated that there

was limited evidence that the risks for cancers at two sites, the urinary bladder and the oesophagus, may be increased by employment in dry cleaning (Group 2B). The epidemiological evidence was also considered to be limited for both trichloroethylene and tetrachloroethylene. Experimental studies with rodents indicated increased tumour incidence at various sites after exposure to trichloroethylene and liver tumours in mice and kidney tumours and leukaemia in rats after exposure to tetrachloroethylene. The role of peroxisome proliferation in the carcinogenicity of these two compounds was considered, but could apply only to liver tumours. Consequently, it was considered that there was sufficient evidence of carcinogenicity, so the overall evaluations for both compounds were that they are probably carcinogenic to humans (Group 2A).

Other compounds that were evaluated as probably carcinogenic to humans (Group 2A) were 1,2,3-trichloropropane and vinyl fluoride. On the basis of experimental carcinogenicity studies, vinyl acetate, 1-chloro-2-methylpropene, furan and benzofuran were evaluated as possibly carcinogenic to humans (Group 2B). Chemicals which could not be classified as to their carcinogenicity to humans (Group 3) were chloral and chloral hydrate, dichloroacetic acid, trichloroacetic acid, 3-chloro-2-methylpropene, acrolein, crotonaldehyde and furfural.

2.1.5 Human papillomaviruses

(Volume 64, 6–13 June 1995)

The papillomaviruses, a genus within the Papovaviridae family, are a group of species-specific viruses that infect humans and a range of animals. To date, more than 70 types of human papillomavirus (HPV) have been identified and most of these fall into two main groups: the genital HPVs and the epidermodysplasia verruciformis (EV) HPVs. The viruses target epithelial cells causing papillomas and warts at a range of sites including the anogenital tract, upper respiratory tract, oral cavity, larynx and conjunctiva as well as on the skin. The genital types of HPV are transmitted primarily through sexual contact. EV is a rare disease characterized by a generalized cutaneous infection by a group of HPVs that are rarely found in normal immunocompetent individuals. EV patients develop widespread warts which frequently develop into squamous-cell carcinomas on sun-exposed areas of skin.

Many case–control studies have been conducted to investigate the association between HPV infection and the development of cervical and other anogenital cancers, while smaller studies in groups of immunosuppressed individuals and EV patients have evaluated the association with skin cancers. Detection methods for HPV infection and HPV DNA have improved considerably over the last few years and the early studies using less advanced techniques must be interpreted with caution. The working group convened concluded that HPV types 16 and 18 are carcinogenic to humans (Group 1), that HPV types 31 and 33 are probably carcinogenic to humans (Group 2A) and that some other HPV types are possibly carcinogenic to humans (Group 2B).

2.1.6 Printing processes and printing inks, carbon black and some nitro compounds

(Volume 65, 10–17 October 1995)

A number of epidemiological studies of cancer have reported increased risks of cancers of the lung, oropharynx, bladder, kidney and haematopoietic system in printing workers. Although certain occupations in the various printing processes, such as newspaper pressmen, have been associated with increased lung cancer risks, it was not generally possible to identify specific

processes associated with the increased cancer risks at other sites. The Working Group concluded that there is *limited evidence* that occupational exposures in printing processes are carcinogenic, that there is *inadequate evidence* for the carcinogenicity in humans of printing inks and that there is *inadequate evidence* for the carcinogenicity in experimental animals of printing inks. The overall evaluation was that occupational exposures in printing processes *are possibly carcinogenic to humans (Group 2B)*. Printing inks *are not classifiable as to their carcinogenicity to humans (Group 3)* .

Carbon black is widely used in rubber tyres, hoses, gaskets and coated fabrics; smaller amounts are used in printing inks, paints and plastics. Although one cohort study on carbon black production workers showed slight excesses of lung cancer, the totality of the epidemiology studies both in the carbon black production industry and in some user industries suggested that there is *inadequate* evidence for the carcinogenicity in humans of carbon black. Several inhalation studies in female rats have shown increases in benign and malignant lung tumours. Carbon black extracts (solvent extracts) are also carcinogenic to the skin of mice. Although a large body of data on possible mechanisms of carcinogenicity in rats was considered by the Working Group, it was not possible to state with confidence that the mechanisms of carcinogenicity in rats do not operate in exposed humans. Carbon black was thus evaluated as possibly carcinogenic to humans (Group 2B).

Of the nitro compounds considered, 3,7- and 3,9-dinitrofluoranthenes, 2,4- and 2,6-dinitrotoluenes, 2-nitroanisole, nitrobenzene and tetranitromethane were evaluated as possibly carcinogenic to humans (Group 2B).

Chloronitrobenzenes, 3,5-dinitrotoluene, nitrotoluenes, 2,4,6-trinitrotoluene, musk xylene and musk ambrette could not be classified as to their carcinogenicity to humans (Group 3).

2.1.7 Quantitative estimation and prediction of cancer risks

(18–22 October 1993)

A small group of external advisers prepared background documents for a workshop on the scientific principles of quantitative estimation and prediction (QEP) of carcinogenic risks to humans, held in Lyon. The purpose of the workshop was to review critically the scientific principles of QEP and to advise IARC about its future role in this area.

The main recommendation of the workshop participants was that the primary function of the IARC Monographs programme should remain the identification of carcinogenic hazards to humans. They recommended that although the monographs should not include formal QEP, the presentation of quantitative data on exposure to carcinogens and on the effects of carcinogens should be enhanced. The participants identified a number of activities that IARC could conduct in areas of analysis, research, education and training in the area of QEP, including other IARC publications.

An extensive summary of the workshop conclusions is available as IARC Internal Report No. 94/004. The background papers are being revised and edited for publication in the IARC Scientific Publications series.

2.1.8 Ad-hoc Working Group to select priorities for evaluation in the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

(7–9 December 1993)

At approximately five-year intervals, IARC selects chemicals, groups of chemicals, mixtures, physical and biological agents and exposure circumstances for evaluation in the Monographs series on the basis of advice from an international group

of scientists. The fourth priorities working group discussed lists of 260 agents and exposures nominated by scientists and national institutes from several countries and assigned priorities for consideration or re-consideration within Monographs planned for the period 1995–2000. A total of 90 agents were given high priority. The final report was issued as IARC Internal Report No. 93/005.

2.1.9

Meeting on peroxisome proliferation and its role in carcinogenesis

(7–9 December 1994)

An ad-hoc meeting of experts in chemical carcinogenesis was convened in Lyon to discuss current knowledge on peroxisome proliferation and how data on peroxisome proliferatation can be used in making evaluations of carcinogenicity to humans. Many chemicals, including some hypolipidaemic drugs, pesticides, plasticizers, solvents and food flavours, have been shown to induce peroxisome proliferation in rodent liver.

The group considered that peroxisome proliferation in mouse and rat liver is mediated by activation of peroxisome proliferator-activated receptors, which are members of the steroid hormone receptor superfamily. Receptor activation may be a direct effect of the peroxisome proliferator or may be mediated through perturbation of lipid metabolism. Such receptors have also been identified in humans. There is a strong concordance between peroxisome proliferation and hepatocellular carcinogenesis in rats and mice. On the basis of a more limited database, a similar concordance is seen between hepatocellular proliferation induced by peroxisome proliferators and hepatocellular tumour induction. Proposed mechanisms of peroxisome proliferator-induced hepatocellular carcinogenesis include oxidative stress, increased hepatocellular proliferation and preferential growth of preneoplastic lesions.

Hepatocellular carcinogenic peroxisome proliferators are generally inactive in assays for genetic and related effects. Some such agents can cause morphological cell transformation and inhibit gap-junctional intercellular communication. These cellular effects appear to be independent of the process of peroxisome proliferation. Chemicals that induce peroxisome proliferation may have additional carcinogenic effects unrelated to that phenomenon.

Data on the effects in humans of peroxisome proliferators are derived from studies of subjects receiving hypolipidaemic drugs and of cultured human hepatocytes. The limited data *in vivo* suggest that therapeutic doses of hypolipidaemic agents produce little if any peroxisome proliferation in the human liver. Hypolipidaemic fibrates and other chemicals that induce peroxisome proliferation in rat and mouse hepatocytes when given at high concentrations do not do so in cultured human hepatocytes.

The Group's conclusion was that chemicals showing evidence of inducing peroxisome proliferation should be evaluated on a case-by-case basis. The evaluation of agents by independent expert groups is a matter of scientific judgement. When the data support the conclusion that a tumour response in mice or rats is secondary only to peroxisome proliferation, consideration could be given to modifying the overall evaluation, as described in the Preamble to the *IARC Monographs*, taking into account the following evidence: (*a*) information is available to exclude mechanisms of carcinogenesis other than those related to peroxisome proliferation; (*b*) peroxisome proliferation (increases in peroxisome volume density or fatty acid β-oxidation activity) and hepatocellular proliferation have been demonstrated under the conditions of the bioassay.

The authored background papers and the consensus report have been published in IARC Technical Report No. 24 [237].

2.2 *Occupational causes of cancer*

Occupational cancers have long been a focus of attention in research on etiology and mechanisms of cancer because individual exposures, and therefore risks, in the work environment tend to be higher than in the general environment. In addition, the exposed population can be relatively easily defined, and exposures can be estimated from measurements or known characteristics of the work environment.

Studies at IARC have adopted two main approaches: on the one hand, multicentric international studies have been conducted, mainly in industrialized countries, to investigate the effects of either low-level exposure to known carcinogens or suspected carcinogens with relatively weak potency; on the other hand, collaborative studies have been conducted in specific cases in developing countries, where high levels of exposure are often encountered, but conducting studies focused on occupational risks may be problematic.

Preparation of the chapter on cancer for the fourth edition of the *ILO Encyclopaedia of Occupational Health and Safety* has been coordinated at IARC. In particular, the chapter includes articles on the historical background [464] and on occupational carcinogens [70]. A comprehensive review of occupational risk factors for lung cancer [69] has also been published.

Studies of molecular aspects of occupational cancers are in progress, as described in Sections 3.3.6, 3.3.7 and 6.1.7 (vinyl chloride) and 3.6.5 (aromatic amines). The effects of ionizing radiation in workers in the nuclear industry have been examined in order to obtain precise risk estimates for chronic exposures to low doses of radiation (Section 2.5.1).

2.2.1 Occupational cancer in industrialized countries

2.2.1.1 International cohort study of workers exposed to phenoxyacid herbicides and contaminants

M. Kogevinas, P. Boffetta, R. Saracci and D. Colin; in collaboration with H. Becher, Heidelberg, Germany; T. Benn, Bootle, UK; P.A. Bertazzi, Milan, Italy; H.B. Bueno de Mesquita, Bilthoven, Netherlands; D. Coggon, Southampton, UK; M. Fingerhut, Cincinnati, USA; D. Flesch-Janys, Hamburg, Germany; L.M. Green, Toronto, Canada; T. Kauppinen, Helsinki, Finland; M. Littorin, Lund, Sweden; E. Lynge, Copenhagen, Denmark; J.D. Mathews, Casuarina, Australia; L. Needham, Atlanta, USA; M. Neuberger, Vienna, Austria; and N. Pearce, Wellington, New Zealand

Studies of cancer risk have revealed excesses of soft-tissue sarcoma and non-Hodgkin lymphoma in populations exposed to phenoxy herbicides, chlorinated phenols and dioxins during manufacture, spraying or accidents. Dioxins, present as contaminants in some types of phenoxy herbicides, have been suggested as a causal factor, although excess risks have also been associated with exposure to herbicides not believed to have been contaminated with dioxins. Chronic bioassays and mechanistic data have indicated that contaminants of the herbicides, and in particular 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), are extremely potent carcinogens. Other chemicals in the same occupational environment (herbicides, chlorophenols, dioxin congeners other than TCDD, polychlorinated dibenzofurans, solvents) have also been associated in epidemiological studies and/or chronic bioassays with adverse health effects, including cancer.

IARC maintains an international register of workers exposed to phenoxy herbicides, chlorophenols and dioxins ([268]; Kauppinen *et al.*, 1994, *Scand. J. Work Environ. Health*, **20**, 262–271). In a cohort mortality analysis, excess risk was found among exposed subjects for soft-tissue sarcoma (SMR = 196), while only a slightly elevated risk was observed for non-Hodgkin lymphoma (SMR = 129). Additional analyses have been conducted in women [285], as well as on national sub-cohorts [85]. A case–control studies on soft-tissue sarcoma and on non-Hodgkin lymphoma nested within the international cohort were conducted, in order to examine exposure to various chemicals in the work-place, applying an exposure model approach [284]. Eleven sarcoma and 32 lymphoma cases occurring within an international cohort were matched for age, sex and country of residence with 55 and 158 controls respectively. Exposures to 21 chemicals or mixtures were estimated by three industrial hygienists who were blind to the subject's case/control status. Excess risk of soft-tissue sarcoma was associated with exposure to any phenoxy herbicide (OR = 10.3, 95% CI 1.2–91) and to each of the three major classes of phenoxy herbicides (2,4-dichlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid and 2-methyl-4-chlorophenoxyacetic acid), to any polychlorinated dibenzodioxin or furan (OR = 5.6, 95% CI 1.1–28) and to TCDD (OR = 5.2, 95% CI 0.85–32). Sarcoma risk was not associated with exposure to raw materials or other process chemicals. In the non-Hodgkin lymphoma study, associations were generally weaker than those found in the study on sarcoma. The international cohort study currently includes 26 615 exposed workers from Australia, Austria, Canada, Denmark, Finland, Germany, Italy, Netherlands, New Zealand, Sweden and the United Kingdom. A second mortality and cancer incidence follow-up and a study to determine serum levels of dioxin and furans in a sample of workers [307] are in progress.

2.2.1.2 International cohort study of workers exposed to styrene

M. Kogevinas, P. Boffetta, G. Ferro and R. Saracci; in collaboration with A. Andersen and J.E. Bjerk, Oslo, Norway; M. Biocca and C. Galassi, Bologna, Italy; D. Coggon and B. Pannett, Southampton, UK; V. Gennaro and V. Ferraro, Genoa, Italy; H. Kolstad, Aarhus, Denmark; I. Lundberg and T. Bellander, Stockholm, Sweden; E. Lynge, A. Astrup-Jensen and N.O. Breum, Copenhagen, Denmark; T. Partanen and P. Pfaffli, Helsinki, Finland; and A. Spence, Bootle, UK

Increased risks for leukaemia and lymphoma have been suggested in studies of workers exposed to styrene in the rubber and plastics industry. An historical cohort study has been conducted in Denmark, Finland, Italy, Norway, Sweden and the United Kingdom involving 40 688 workers employed in the reinforced plastics industry, where high exposure to styrene occurs [282, 283]. Exposure to styrene was reconstructed through job histories, environmental and biological monitoring data [185] and production records of the plants in the study. Among exposed workers, no excess was observed for mortality from all neoplasms; mortality from lymphohaematopoietic neoplasms increased with time since first exposure and average exposure to styrene, but was not consistently associated with duration of exposure or with cumulative exposure (Figure 7). Additional detailed analyses have been conducted on mortality from selected groups of non-neoplastic diseases. In particular, mortality from diseases of the central nervous system increased with latency, duration of exposure and average level of exposure. The feasibility of a nested case–control study on lymphohaematopoietic neoplasms has been examined.

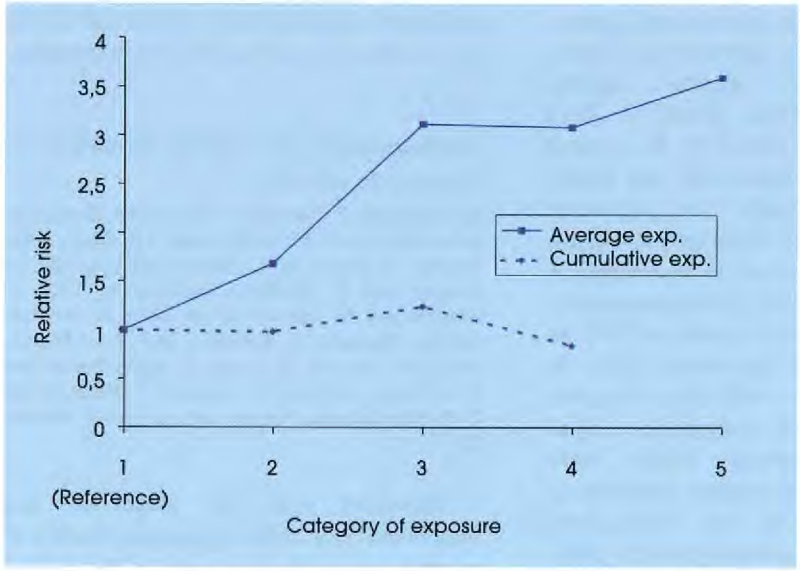


Figure 7. Relative risks of lymphatic and haematopoietic neoplasms by average exposure and cumulative exposure, among workers exposed to styrene

Categories of exposure: average exposure (ppm) <60 (ref.), 60–99, 100–119, 120–199, 200+; cumulative exposure (ppm-years) <75 (ref.), 75–199, 200–499, 500+

2.2.1.3

International cohort study of workers employed in the man-made vitreous fibre production industry

P. Boffetta, R. Saracci and G. Ferro; in collaboration with A. Andersen, Oslo, Norway; P.A. Bertazzi and D. Consonni, Milan, Italy; J. Chang-Claude, Heidelberg, Germany; J. Cherrie, Edinburgh, UK; R. Frentzel-Beyme, Bremen, Germany; J. Olsen and J. Hansen, Copenhagen, Denmark; N. Plato, Stockholm, Sweden; L. Teppo, Helsinki, Finland; P. Westerholm, Solna, Sweden; and P. Winter, Southampton, UK

A historical cohort study has been conducted since 1977 in 13 factories producing man-made vitreous fibres in seven European countries. A follow-up to 1991 shows an increased risk of lung cancer in the rock/slagwool component of the study, which was related to technological phase, time since first employment and duration of employment. No such increase was present in the other components of the study, glass wool and continuous filament production (Figure 8). An additional analysis based on a mathematical model of past fibre exposure in the rock/slagwool component (Krantz *et al.*, 1991, *Modelling of Past Exposure to MMMF in the European Rock/slagwool Industry*, Solna, Arbetsmiljöinstitutet) has shown a dose–response relationship between lung cancer mortality and estimated cumulative fibre exposure, which was no longer present when short-term workers were excluded and time since first exposure was accounted for. A case–control study of lung cancer has been planned in the rock/slagwool component, to disentangle the contributions of fibres, other occupational agents such as asbestos and extra-occupational factors in the lung cancer excess. A feasibility study has been conducted on 120 living workers, their next-of-kin and the next-of-kin of 149 deceased workers: this study has provided evidence that it is possible to identify and interview next-of-kin of deceased workers and obtain

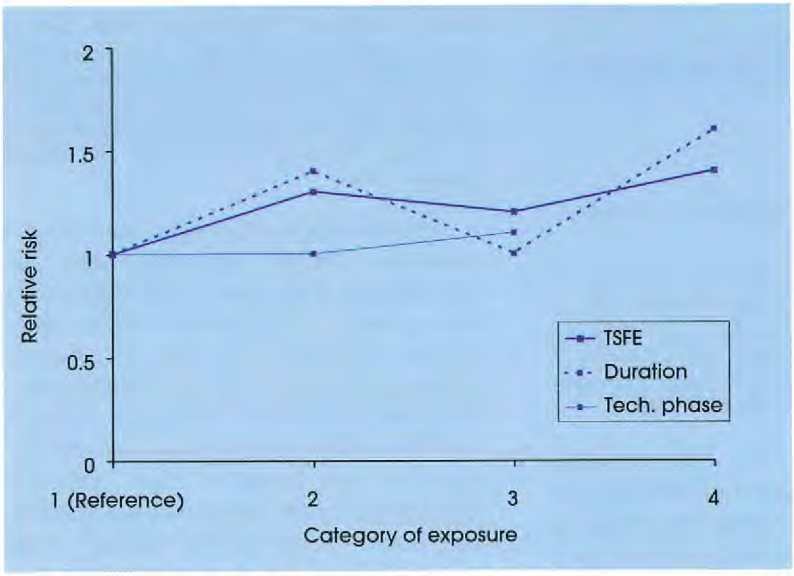


Figure 8. Relative risks of lung cancer by time since first employment (TSFE), duration of employment and technological phase, in rock/slagwool workers with more than one year of employment

Categories of exposure:
TSFE 0–9 (ref.), 10–19, 20–29, 30+ yrs;
Duration of exposure 1–4 (ref.), 5–9, 10–19, 20+ years;
Technological phase late (ref.), intermediate, early

valid information on tobacco smoking and occupational exposures of the workers.

2.2.1.4

International cohort study of workers employed in the pulp and paper industry

P. Boffetta, M. Kogevinas, R. Saracci, R. Winkelmann and G. Ferro; in collaboration with W. Ahrens, Bremen, Germany; A. Andersen, Oslo, Norway; P. Band and K. Teschke, Vancouver, Canada; W. Boal, Cincinnati, USA; C. Bruno, Rome, Italy; D. Coggon; Southampton, UK; L. Facchini, Pelotas, Brazil; M. Finkelstein, Toronto, Canada; D. Heederik, Wageningen, Netherlands; P.K. Henneberger, Syracuse, USA; M. Hours, Lyon, France; P. Jäppinen, Imatra, Finland; T. Kauppinen, Helsinki, Finland; D. Kielkowski, Johannesberg, South Africa; E. Lynge, Copenhagen, Denmark; H. Miyake, Sapporo, Japan; N. Pearce, Wellington, New Zealand; B. Persson, Linköping, Sweden; J. Siemiatycki, Montreal, Canada; C. Soskolne, Edmonton, Canada; J. Sunyer, Barcelona, Spain; I. Szadkowska-Stanczyk, Lodz, Poland; and P. Wild, Vandoeuvre-lès-Nancy, France

In view of a possible increased risk for cancer at certain sites (lung, gastrointestinal tract, lymphatic tissues) among workers in the pulp and paper industry—an activity employing hundreds of thousands of workers worldwide—a multicentric international cohort study is being developed. Personnel employed in plants producing pulp, paper and paper products and in mills involved in recycling are included. The cohort study has been completed in British Columbia (Canada), Finland, New Zealand, Norway, Poland, Spain and the USA; it will completed in the other participating countries or regions (Brazil, Denmark, France, Germany, Italy, Japan, Netherlands, Ontario, Quebec, South Africa, Sweden, United Kingdom) during 1995. The final cohort size is planned to be more than 100 000 workers. The results of the

combined study will be available in 1997. An industrial hygiene study is being conducted; the results will be available in 1996.

2.2.1.5 *International study of workers exposed to lead*

P. Boffetta, R. Saracci and M. Kogevinas; in collaboration with P.L. Cocco, Cagliari, Italy; J. Davies and G. Kazantzis, London, U K; D. Fanning, Manchester, UK; G. Nordberg, Umeå, Sweden; K. Steenland, Cincinnati, USA; N. Szeszenia-Dabrowska, Lodz, Poland; and O. Wong, Alameda, USA

A meta-analysis of epidemiological studies of workers exposed to inorganic lead compounds has been conducted [184]: an increased risk of lung and stomach cancer is suggested (Table 2), which may be explained to some extent, but probably not completely, by extra-occupational factors. In addition, a cohort study of lead smelters from Sardinia, Italy, has been completed. A combined re-analysis of existing cohort studies from Italy, Poland, Sweden, the UK and USA is planned.

2.2.1.6 *International study of workers employed in the wood and leather industries*

P. Boffetta, M. Kogevinas, D. Colin and R. Saracci; in collaboration with A. Blair, R. Hayes, L. Brinton and B. Miller, Bethesda, USA, U. Bolm-Audorf, Hamburg, Germany; S. Bonassi, Genoa, Italy; P. Comba, Rome, Italy; P. Demers, Vancouver, Canada; K. Fukuda, Kurume, Japan; L. Hardell, Orebro, Sweden; L. Hagmar, Lund, Sweden; A. Leclerc and D. Luce, Paris, France; C. Magnani, Turin, Italy; E. Merler and A. Seniori-Constantini, Florence, Italy; S. Preston-Martin, Los Angeles, USA; C. Robinson, R. Roscoe and F. Stern, Cincinnati, USA; S. Rodella, Verona, Italy; S. Stellman, New York, USA; T. Vaughan, Seattle, USA; P. Winter, Southampton, UK; and W. Zheng, Shanghai, China

Employment in the wood and leather industries entails exposures that are carcinogenic to humans. The main target sites in both cases are the nose and the nasal sinuses. However, the role of specific exposures such as wood dust, leather dust, formaldehyde, solvents and preservatives is not clear. Although information on specific exposures was present in many epidemiological studies, this information could not be fully used, because of the relatively small size of each individual study. The raw data of the cohort studies on workers employed in these industries and the case–control studies on nasal cancer have been obtained from the original investigators and transformed into a common format. The complete data-set has been analysed according to specific exposures.

The analysis of five cohorts of wood workers [133] has shown that the well known excess risk of sinonasal cancer among these workers was present only in European studies and suggested an increased risk of multiple myeloma. The analysis of twelve case–control studies of sinonasal cancer [134] (Table 3) has provided support for the hypothesis of heterogeneity of risk of sinonasal adeno-

Table 2. Results of meta-analysis of studies on lead-exposed workers

Occupational exposure to inorganic lead compounds		Stomach cancer	Lung cancer	Kidney cancer
Any exposure	RR (N)	1.33 (10)	1.24 (15)	1.19 (5)
	95% CI	1.18–1.49	1.16–1.33	0.96–1.48
Heavy exposure	RR (N)	1.50 (4)	1.44 (4)	1.26 (3)
	95% CI	1.23–1.83	1.29–1.62	0.70–2.26

CI, confidence interval; N, number of studies; RR, relative risk

Table 3. Results of combined analysis of 12 case–control studies of sinonasal cancer among men

Study location(s)	Number of subjects[a]	Odds ratios	
		AC	SCC
Shanghai, China	4/18/269	0.0	2.7
France	82/59/320	161	1.2
Hessen, Germany	3/13/33	64	2.1
SVV, Italy	13/25/184	12	1.0
Brescia, Italy	5/12/70	32	0.0
Biella, Italy	9/8/92	15	1.7
Vigevano, Italy	11/1/29	0.5	0.0
Netherlands	23/50/195	13	0.4
Sweden (Northern)	3/31/541	0.5	0.8
NC and VA, USA	13/53/181	0.9	0.7
Los Angeles, USA	2/40/108	0.0	0.2
Seattle, USA	1/19/327	0.0	1.8
Total, any exposure	169/329/2349	15	0.9
Total, high exposure	104/11/82	45	0.8

[a] Number of AC cases/number of SCC cases/controls
AC, adenocarcinoma; SCC, squamous cell carcinoma
SVV, Siena, Verona, Vicenza; NC, North Carolina; VA, Virginia

carcinoma in different countries, suggesting a higher risk for workers exposed to hardwood dust as compared to softwood dust. No clear evidence of an increased risk of sinonasal squamous cell carcinoma emerged. The analysis of cohorts of workers employed in the leather industry will be completed in 1995.

2.2.1.7

Cancer risks due to asphalt fumes

P. Boffetta, M. Castegnaro, C. Genevois, C.P. Wild, T. Partanen and R. Saracci; in collaboration with P. Bertazzi, Milan, Italy; P. Bonnet, M. Lafontaine and S. Binet, Vandoeuvre, France; H. Brandt, Amsterdam, Netherlands; M. de Méo, Marseille, France, R. Frentzel-Beyme, Bremen, Germany; D. Heedrick, Wageningen, Netherlands; M. Hours, Lyon, France; B. Jarvholm, Gothenburg, Sweden; T. Kauppinen, Helsinki, Finland; A.J. Kriech, Indianapolis, USA; S. Langard, Oslo, Norway; A. Morabia, Geneva, Switzerland; M. Neuberger, Vienna, Austria; B. Pannett, Southampton, UK; J. Sunyer, Barcelona, Spain; and O. Svane, Copenhagen , Denmark

The investigation of a possible cancer risk from exposure to asphalt fumes is particularly difficult because of the complex and variable nature of asphalt, the occurrence of co-exposures (motor engine exhaust, tobacco smoking) and the characteristics of the workforce (seasonal employment, instability, low skill). Epidemiological studies suggest an increased risk of cancer of the lung and other organs [455].

The feasibility of a historical cohort study and a case–control study nested in a cohort of European asphalt workers was assessed for the investigation of cancer risk possibly associated with bitumen fumes [463]. Such a study was judged feasible in seven European countries (Denmark, Finland, France, Germany, Netherlands, Norway, Sweden). The cohort would involve 54 000 asphalt workers and an average of 11 years of follow-up for cancer mortality, and a conventional cancer mortality study can be completed for the major cancer sites. The effective number of lung cancers is estimated at 150; that of matched controls in the nested study, 450.

Lifelong job and tobacco-smoking histories are proposed to be solicited by interviews of the cases and controls or their next of kin, combined with data abstracted from company records. Algorithms will be developed for the conversion of company and interview data into reconstructions of individual time-windowed intensities, periods, and integrated exposures to bitumen fumes and important covariates such as coal tar exposure and tobacco smoking. The power of the nested study to detect a 70% lung cancer excess associated with exposure to bitumen fumes is reasonable; for an 80% excess it is good; and for 100% or more, it is excellent.

In order to conduct epidemiological studies such as those mentioned above, it would be valuable to have biomarkers of exposure specific for bitumen fumes. A series of experimental studies were conducted to evaluate this possibility.

Fume production from two types of bitumen and from coal tar was performed using a laboratory rig. The system produces fumes representative of samples collected in the worksite in terms of exposure to particulates (benzene-soluble matter) and particle size distribution in the particulate phase, and polycyclic aromatic hydrocarbon (PAH) content. The particulate phase and the vapour phase were separately trapped. Fumes from the two bitumens were produced at 160°C and 200°C, and that from coal-tar at 110°C and 160°C. The fume condensates were analysed for 16 PAHs and for the content of UV-absorbing material at 254 nm.

Studies carried out using these condensates included *in vitro* testing of their ability to form DNA adducts; mutagenicity in a modified Ames mutation assay; and *in vivo* testing in rodents where the animals were exposed to an undiluted mixture of condensate by skin painting.

The bitumen fume condensates contained significantly lower levels of all the 4- to 6-ring and 3- to 7-ring PAHs and of UV-absorbing material than the coal tar condensate. While large amounts of unsubstituted PAHs are present in the coal tar condensate, these compounds are minor constituents of the bitumen fume condensates.

Two types of mutagens have been detected in coal tar and bitumen condensates. Frameshift mutagens were detected with strain TA 98; higher responses for this type of mutagen were also noted with strain YG 1041 in all samples. Base pair mutagens were detected by strain TA 100; lower responses were noted in all samples with strain YG 1042. The lack of mutagenic action of all samples without metabolic activation confirms the absence of nitro derivatives in bitumen.

The PAH content of fumes generated from bitumens did not correlate with the level of formation of DNA adducts *in vitro*, indicating that the PAH constituents of the bitumen condensate play a minor role in the production of the adducts detected. Other compounds, such as aza derivatives of PAH, may be implicated in the genotoxic effect of bitumen fume condensates.

In the skin painting study, groups of three rats were treated by direct application of the undiluted condensates. DNA adducts in lymphocytes, skin, lung, liver and kidney are being analysed by ^{32}P-postlabelling. The following conclusions could be drawn. Skin penetration was rapid, leading to systemic distribution of the product. All fume concentrates displayed genotoxicity; the adduct patterns of bitumen fume condensates are very different from those of coal tar concentrates. There is no relation between the content of 16 PAHs of the coal tar or bitumen fumes and the level of DNA adduct formation in skin, lung and lymphocytes; some adducts in lymphocytes may be usable as markers of skin contamination by coal tar and bitumen fumes.

A study on the DNA adduct formation following inhalation of bitumen fumes has

been undertaken in collaboration with the French Institut National de la Recherche et de la Sécurité (INRS) and the Heritage Research Group in the USA.

2.2.1.8

International cohort study of workers exposed to mercury

P. Boffetta and R. Saracci; in collaboration with M. Garcia-Gomez, Madrid, Spain; E. Merler, Florence, Italy; V. Pompe-Kirn, Ljubljana, Slovenia; G. Sallsten, Gothenburg, Sweden; and D.G. Zaridze, Moscow, Russia

An increase in lung cancer risks among workers exposed to mercury has been found in a number of epidemiological studies [64]. Among the industries entailing, in the present or the past, high levels of exposure to mercury are the mining or milling of the metal, thermometer production and felt-hat manufacture, but no large study on workers involved in these occupations has yet been conducted.

A historical cohort study has been started in the four European countries with large mercury mines (Italy, Russian Federation, Slovenia, Spain). Special care is being given to the reconstruction of industrial hygiene data (exposure levels to mercury and co-exposures such as silica and radon). A retrospective cohort study has been conducted among workers compensated for mercury intoxication in an area of central Italy with a large felt-hat manufacturing industry which showed an excess of stomach and lung cancer; while the former may be explained by local factors, the latter seems related to occupational exposures [344].

2.2.1.9

Estimate of the burden of occupational cancer in Europe

M. Kogevinas, P. Boffetta, R. Saracci and R. Winkelmann; in collaboration with A. Andersen, Oslo, Norway; W. Ahrens and K.H. Jockel, Hessen, Germany; L. Barlow, Stockholm, Sweden; F. Berrino, Milan, Italy; R. Cartwright, Leeds, UK; J. Chang-Claude, Heidelberg, Germany; S. Cordier and D. Luce, Paris, France; C.A. González and J. Sunyer, Barcelona, Spain; T. Kauppinen, Helsinki, Finland; E. Lynge and J. Olsen, Copenhagen, Denmark; E. Merler, Florence, Italy; F. Merletti and P. Vineis, Turin, Italy; T. Partanen and E. Pukkala, Helsinki, Finland; L. Simonato, Padua, Italy; and T. Tzonou, Athens, Greece

The prevalence and intensity of occupational carcinogenic exposures and the incidence of occupational cancer in European countries are being estimated in order to provide a basis for a comprehensive programme of prevention and control of occupational cancer in Europe [279]. Extensive epidemiological and industrial hygiene data are used to estimate the number of workers exposed to occupational carcinogens at levels above background and to identify the occupations and industries facing the greatest risk.

2.2.1.10

International study of cancer risk in biology research laboratory workers

A.J. Sasco, B. Rachet and I. Gendre; in collaboration with A. Ahlbom, Stockholm, Sweden; S. Belli, Rome, Italy; F. Berrino, Milan, Italy; S. Benhamou, Villejuif, France; G.J. Bourke, Dublin, Ireland; C. Chilvers, Nottingham, UK; F. Hatton, Le Vésinet, France; O.H. Iversen, Oslo, Norway; T. Kauppinen, Helsinki, Finland; R. Maximilien and M. Tirmarche, Paris, France; J.J. Moulin, Vandœuvre-lès-Nancy, France; C. Teissier, Strasbourg, France; F. van Leeuwen, Amsterdam, Netherlands; and D. Vecchio and R. Puntoni, Genoa, Italy

Following the occurrence of several cancer clusters in research institutions, and confronted with the lack of any large-scale assessment of cancer risk linked to biological hazards, IARC proposed a retrospective cohort study of all staff having been employed for at least one year and one day in public research institutions. Following a feasibility phase, the study was implemented in eight European countries (Finland, France, Ireland, Italy, Netherlands, Norway, Sweden and UK) [553]. So far,

66 958 subjects have been entered into the cohort, which is now almost complete. Mortality assessment has been carried out at most collaborating institutions and results for two subcohorts (one in Italy and the one in Ireland) have already been published. In the pooled analysis of all national data-sets, cancer risk will be assessed for specific scientific activities such as virology, molecular biology and biochemistry.

A meeting was held in May 1995 to assess exposures in the laboratory setting [568]. In particular, a specific study (Exposure to Viruses in the Laboratory (EVIL) Programme) is evaluating exposures to animal retroviruses as well as selected DNA viruses in various occupational research groups.

2.2.1.11

Other collaborative studies of occupational cancer

P. Boffetta, M. Kogevinas, T. Partanen, E. Weiderpass, N. Jourankova, R. Saracci, R. Winkelmann, G. Ferro and D. Colin; in collaboration with M. Goldberg, Montreal, Canada; B.K. Armstrong, Canberra, Australia; M. Bulbulyan, Moscow, Russia; V. Gennaro, Genoa, Italy; and S. Porru and F. Donato, Brescia, Italy

Several epidemiological studies have suggested possible associations of employment in textile manufacturing with oral cancer, intestinal cancer, nasal cancer, laryngeal cancer and bladder cancer. A lack of data on occupational exposure has been a major obstacle to evaluation of specific risks in this industry. The feasibility of a multicentric industrial hygiene investigation and of a multicentric cohort study in the textile-manufacturing industry in several countries, to evaluate both the overall risk and also to describe the effects of specific exposures, is being assessed.

A collaborative study of Russian fertilizer workers, with the Institute of Carcinogenesis in Moscow, suggested an increased risk of stomach cancer, possibly related to exposure to nitrogen oxides, and of lung cancer, probably due to exposure to arsenic. A collaborative study with the Institute of Cancer Research in Genoa, Italy, focused on asbestos exposure in oil refinery plants [193]. A collaborative study with the University of Brescia, Italy, consisted of a case–control study of bladder cancer, which suggested an association with exposures in the metal and the transport industries. An analysis based on the linkage between census and cancer registry data in Norway, Sweden, Finland and Denmark suggested an increased risk of ovarian cancer but not of non-Hodgkin lymphoma among female hairdressers [58].

2.2.2

Occupational and environmental cancer in developing countries

2.2.2.1

Review of occupational cancer in developing countries

P. Boffetta, M. Kogevinas, H. Vainio and R. Saracci; in collaboration with N. Pearce, Wellington, New Zealand; and E. Matos, Buenos Aires, Argentina

There have been few studies of exposure to occupational carcinogens in developing countries, and even fewer of the health consequences of such exposure. However, all industrial chemicals, occupations and industrial processes classified by the International Agency for Research on Cancer as Group 1 or Group 2A (carcinogenic or probably carcinogenic to humans) occur in developing countries [466, 647]. A systematic search of reports on past exposure to occupational carcinogens and on their health effects and a survey of current patterns of exposure have been conducted, leading to the IARC publication *Occupational Cancer in Developing Countries* [467].

2.2.2.2 *Case–control studies in Argentina and Uruguay*

M. Kogevinas and P. Boffetta; in collaboration with E. de Stefani, Montevideo, Uruguay; and E. Matos, Buenos Aires, Argentina

Uruguay and Argentina have among the highest death rates in the Americas for cancer of all sites and of the lung in particular. Two similar studies have been designed to identify associations between occupational exposures and risk for cancers of several sites in Uruguay, and for lung cancer in Argentina, and to examine the synergistic effect of selected occupational exposures and tobacco smoking. In both centres, asbestos is the exposure of main interest. Data collection will be completed in 1995 and analysis will be conducted in 1996.

2.2.2.3 *Multicentric case–control study in India*

P. Boffetta, M. Kogevinas and R. Sankaranarayanan; in collaboration with P. Chattopadhyay, Ahmedabad, India; V. Shanta, Madras, India; P.B. Desai, Bombay, India; and C. Varghese, Trivandrum, India

Although the industrial population in India is very large and many hazardous industries are present, virtually no information exists on occupational cancer risk factors. The presence of a network of well organized cancer registries is a favourable condition for conducting multicentric case–control studies.

A case–control study has been started in Bombay, Trivandrum and Madras, to investigate occupational and environmental factors for lung cancer and lymphatic and haematopoietic neoplasms. Data collection will be completed in 1996.

2.2.2.4 *Occupational cancer in Tianjin, China*

Q.-S. Wang, P. Boffetta, M. Kogevinas and D.M. Parkin

The results of a proportional mortality analysis for 32 cancer sites in relation to employment in several occupations and industries, based on the data from Tianjin Cancer Registry, have been published [671, 673].

2.3 *Diet, nutrition and cancer*

It is now clear that many dietary factors may have causative or protective roles in cancer etiology. Most studies have found that a diet rich in vegetables and fruit is associated with lower risk of developing cancers of the digestive and respiratory tract. Epidemiological and laboratory research is now attempting to identify specific foods or food constituents biologically responsible for these effects. High intake of meat and/or fat of animal origin seems to increase the risk of cancers of the colon and rectum, while for cancer of the breast, the data are more contradictory and inconsistent.

To investigate these issues, which may have important public health implications, the Unit of Nutrition and Cancer has developed a network of prospective cohort studies which will incorporate over 400 000 study subjects in ten countries.

In addition to the specifically diet-oriented epidemiological studies described in this section, diet and food constituents are factors considered in many other Agency projects, particularly those related to cancer of the digestive tract. Thus the effects of drinks such as alcoholic beverages and mate are being examined in relation to oesophageal cancer (Section 3.1), and various laboratory and epidemiological projects are

exploring the roles in gastric carcinogenesis of *N*-nitroso compounds formed endogenously from dietary components (Section 4.4) and of diet in general, including potentially protective vitamins (Sections 3.2 and 5.1.3). Heterocyclic amines formed in cooking and mycotoxins (aflatoxins, ochratoxins, etc.) that contaminate foodstuffs, especially in developing countries, are being studied as etiological factors for liver cancer (Sections 3.3.3–3.3.5) and urinary tract tumours (Sections 3.7.2 and 3.7.3).

2.3.1

European Prospective Investigation into Cancer and Nutrition (EPIC)

E. Riboli, R. Saracci, R. Kaaks, N. Slimani, C. Casagrande and B. Hémon; in collaboration with: *France*: F. Clavel, M. van Liere and C. Jadand, Villejuif; *Germany*: H. Boeing and A. Kroke, Potsdam; J. Wahrendorf and N. Becker, Heidelberg; *Greece*: A. Trichopoulou and K. Katsouyanni, Athens; *Italy*: F. Berrino and V. Krogh, Milan; P. Vineis and B. Terracini, Turin; D. Palli and E. Buiatti, Florence; G. Frasca, R. Tumino and L. Gafà, Ragusa; *Netherlands*: P. Peeters, Utrecht; H.B. Bueno de Mesquita, Bilthoven; *Spain*: C.A. González and A. Agudo, Mataró; J.R. Quíros and C. Lasheras, Oviedo; C. Martinez and J.G. Valls, Granada; M. Dorronsoro and P. Amiano, San Sebastian; C. Navarro and M.D. Chirlaque, Murcia; A. Barricarte and A. Barcos, Pamplona; *UK*: N.E. Day, S. Bingham, K.T.Khaw, S. Oakes and A. Welch, Cambridge; T.J.A. Key and G. Davey, Oxford

The EPIC project is a multi-centre prospective cohort study designed to investigate the relation between diet, nutritional status, various lifestyle and environmental factors and the incidence of different forms of cancer and other chronic diseases (e.g., cardiovascular diseases, stroke and diabetes). The study is designed to address the major issues regarding the role of diet in relation to the occurrence of specific cancers, namely:

(1) Search for the specific factors (nutritive and non-nutritive food components) involved in the biological processes by which diets rich in fruit and vegetables can reduce the risk of cancer of the digestive tract (oesophagus, stomach, colorectum), of the respiratory tract (larynx and lung), of the upper aerodigestive tract (oral cavity and pharynx) and of other anatomical sites.

(2) Identification of factors responsible for the increase in risk of cancers of the colorectum and breast seen in populations with a diet characterized by high consumption of animal fats, meat and meat products.

(3) Search for factors which could explain the wide geographical variations in cancers of the organs of the reproductive system, particularly cancers of the prostate, testis, ovary and endometrium, for which little is known about their relationship to environment and lifestyle.

(4) Investigation of the interaction of genetic predisposition and metabolic host factors with the environment and lifestyle in determining the risk of cancer.

A unique characteristic of the EPIC study is that detailed data on diet and lifestyle as well as biological samples (plasma, serum, lymphocytes and erythrocytes) are collected from all study subjects in an unprecedentedly large cohort of 400 000 healthy individuals.

Follow-up of the study subjects will be conducted through population-based cancer registries. Thanks to the privileged contacts that most registries have with anatomopathological departments, it is planned to collect and store tumour samples prospectively. This will permit studies of the genetic characteristics of DNA from stored lymphocytes, of exposure to environmental factors (from questionnaire data and from biomarkers measured in stored samples) and of genetic alterations in tumour samples.

Figure 9. Map showing centres collaborating in the European Prospective Investigation into Cancer and Nutrition (EPIC)

Table 4. Subject recruitment in the EPIC Study (May 1995)

Country	Starting date	Subjects included in the study with:		Expected final size of cohort	End of data collection
		Questionnaires	Blood collection		
Spain	Nov. 1992	35 000	33 000	40 000	Dec. 1995
Italy	Jan.-Sep. 1993	21 000	22 000	42 000	June 1997
UK	Jan. 1993	20 500	19 000	40 000	Dec. 1996
Netherlands	Jan.-June 1993	20 000	18 300	40 000	Dec. 1997
France	May 1992	77 000	1 600	80 000	Dec. 1996
Greece	Feb. 1994	5 500	5 900	30 000	Dec. 1997
Germany	Sep. 1994	7 000	6 700	50 000	Dec. 1998
Total 7 countries		186 000	106 500	322 000	
Sweden	Mid-1991	22 000	22 000	37 000	July 1996
Denmark	Mar. 1994	9 000	9 000	50 000	Dec. 1997
Total 9 countries:		217 000	137 500	409 000	

Data on usual current diet are collected by means of detailed dietary assessment methods developed and tested during methodological studies (see below). In addition, full information is obtained, by means of a standardized questionnaire, on physical activity, tobacco smoking, alcohol consumption, occupation and socio-economic status, reproductive history, contraception and hormone replacement therapy, previous illnesses and current drug use. These factors were selected because they may be related to diet and nutritional status or may interact with diet in multifactorial carcinogenic processes.

Anthropometric measurements (weight, height, waist and hip circumferences, sitting height) are taken using standard procedures. Blood samples are collected, separated into 28 small aliquots of serum, buffy coat and red blood cells, and stored in liquid nitrogen (–196 °C). Later, the samples from subjects who develop cancer (or other diseases of interest) and from appropriate control subjects who remain disease-free will be analysed. The range of laboratory analyses carried out will depend on the type of cancer, scientific advances in years to come, and the availability of new techniques for measuring biochemical and molecular markers.

The full project started in 1992 after completion of methodological and feasibility studies conducted between 1989 and 1992 in each of the collaborating centres.

The study originally included 17 regional centres in seven countries (France, Germany, Greece, Italy, Netherlands, Spain, UK). In 1995, the investigators in charge of two similar prospective studies in Sweden (Malmö) and Denmark (Copenhagen and Aarhus) decided to join the EPIC project. The enlargement of the study to these two Nordic countries will further enhance the scientific power of the project by increasing the overall size and diversity of the populations included. Table 4 summarizes the situation of subject recruitment in May 1995 and the expected final size of the cohort. Figure 9 illustrates the geographical coverage of the study.

A series of papers reporting the results of the pilot and methodological studies, including the validity of the dietary questionnaires designed for EPIC and the relationship between measured nutrient intakes and biomarkers, will be published in a supplement of the *International Journal of Epidemiology*, entirely devoted to EPIC.

2.3.2 Statistical methods for calibration and validation of dietary measurements

R. Kaaks, E. Riboli, J. Estève and M. Plummer; in collaboration with D. Clayton, Cambridge, UK; and W. van Staveren, Wageningen, Netherlands

Nutritional epidemiology is confronted with the difficulty that questionnaire measurements of individuals' habitual, long-term intake levels of foods and nutrients are generally subject to rather large errors. These errors reduce the probability that the study will identify a truly existing relationship between dietary intake levels and disease risk as a significant association (i.e., statistical power loss), and generally cause bias in estimates of relative risk or other measures indicating the strength of the association. The statistical power of a prospective cohort study on diet and risk of developing specific forms of chronic disease can be improved by maximizing the variation in true dietary level actually distinguished (or 'predicted') by dietary questionnaire measurements collected at baseline [253]. A first approach to achieve this is to conduct preliminary validity studies to select a questionnaire method that yields intake measurements as close as possible to the individuals' true, habitual intake levels. We have reviewed the statistical analysis of such preliminary studies in a general context of latent

variable models, and discussed basic requirements of their design, including the possibility of using biomarkers as additional measurements [250].

A second approach to maximize the variation in predicted dietary intake levels is to increase the heterogeneity of true dietary exposure levels by combining several prospective cohort studies in populations with different dietary intake patterns. This is the rationale of the EPIC project. The statistical analysis and evaluation of evidence from this type of multi-centre study raises specific methodological issues, that had to be taken into account during the design of the EPIC project. It was shown [252, 495] that information from a multi-centre cohort study on diet can be broken down into:

(*a*) estimated relations within separate study centres between measurements of dietary exposure level and disease outcome at the individual level; and

(*b*) an estimated between-centre, 'ecological' relation between mean exposure levels and average disease incidence rates.

Ideally, both types of comparison, within and between centres, lead to similar relative risk estimates, which may in this case be combined into an overall, more powerful summary value. Furthermore, we have shown that the within- and between-centre comparisons can be biased in different ways, and to different degrees, by errors in dietary questionnaire measurements obtained at baseline. We have described how such errors can be corrected in order to follow a 'calibration' approach, based on the collection of more standardized reference measurements (by means of a highly standardized 24-hour recall), in representative subsamples of each study centre [250, 495].

The calibration approach differs from more traditional validity studies whose aim is to estimate only the variation in true intake levels predicted by the dietary measurements obtained with a given dietary questionnaire, without the need to estimate the correlation between dietary questionnaire measurements and true intake levels. The reference measurements may therefore be based on only a single day's record of actual food consumption (in validity studies additional measurements are required), which is statistically more efficient [254] and which makes it easier to conduct the calibration on a truly representative sub-sample of cohort members. A crucial issue is the required size for calibration substudies, in order to provide accurate corrections of dietary questionnaire assessments; we have defined a rational approach, including a simple equation, to calculate these sample size requirements [253].

Future work will explore the application of the models described, as well as of more robust models that depend less on specific assumptions about distribution of true and measured intake levels, to the data collected in the calibration substudies that are currently in progress in the nine countries participating in EPIC.

2.3.3 Development of an internationally standardized method for 24-hour diet recall: EPIC-SOFT

N. Slimani, E. Riboli, C. Casagrande, B. Hémon, G. Deharveng, A.L. van Kappel, R. Arndt and J. Amoyel; in collaboration with A. Agudo and I. Ruano, Mataró, Spain; S. Bohlscheid-Thomas, Heidelberg, Germany; C. Boulous and A. Lagiou, Athens, Greece; V. Krogh and M. Bellegotti, Milan; M. van Liere and M. Niravong, Villejuif, France; M. Ocké and E. Goddijn, Bilthoven, Netherlands; S. Voss, Potsdam, Germany; and A. Welch and A. McTaggart, Cambridge, UK

In view of the multinational design of EPIC, it was decided to develop a new methodological approach to calibrate dietary measurements obtained in different

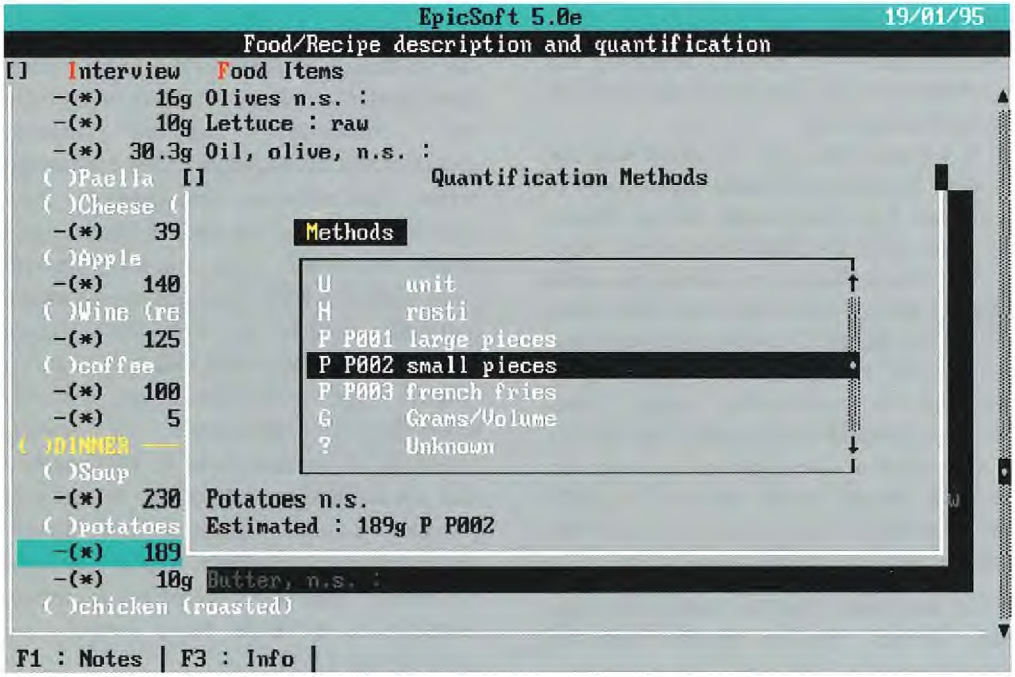


Figure 10. A typical screen of the English version of EPICSOFT, a program designed for conducting 24-hour recall interviews following strictly standardized criteria. Nine country- and language-specific versions of this program have been prepared.

populations. The statistical methods described in Section 2.3.2 required that diet be measured in a representative subsample of 10% of the EPIC cohort by means of a strictly standardized method independent of the dietary questionnaires used to measure usual diet in the entire cohort. To meet this requirement, 24-hour diet recall was considered the most appropriate method, as it generally provides high compliance and is suitable for standardization of the criteria for defining, describing and quantifying food consumption. However, no 24-hour diet recall methodology was available which had already been standardized for the European countries where the EPIC study was to be implemented.

In collaboration with researchers from all the EPIC centres, it was decided to structure the 24-hour diet recall interview with very strict guidelines on how to proceed, meal by meal, and, within meals, food by food, by defining sets of standard questions. For each type of food which may be reported by the subjects, a sequence of standard questions was defined regarding food identification, appearance, preparation, origin, cooking methods, addition of fat, and many other specific items of information.

The interview procedures were computerized, as the approach is so complex that it is difficult for the interviewer to keep in mind all the possible questions for any given food out of a list of several thousands which may be reported by the subject. A computer program was developed which guides the interviewer interactively (see Figure 10). Depending on the foods reported by the subjects, the software prompts the appropriate questions and possible answers

in a multiple-choice, sequential structure. Standardization between countries is achieved by applying the same procedures in the logical structure of the interview and also in the country-specific databases used by the software (e.g., a list of about 2000 main foods per country, food descriptions, standard recipes, quantification methods, probing questions).

Most of the country-specific versions are now ready. Field work has started in the EPIC centres in France, Netherlands, Spain and the UK, and is expected to start by the end of 1995 in Germany, Greece and Italy. In addition, Danish and Swedish versions are being prepared for use in the prospective studies on diet and cancer already in progress in Copenhagen, Aarhus and Malmö, where close collaboration with EPIC has been established.

An additional methodological component of the standardization of dietary data across countries is to ensure the comparability of the criteria for estimating nutrient intake from dietary questionnaires. Here, two major problems are, on the one hand, the lack of standardization of the structure and content of most current national food composition tables and, on the other, the limited data on chemical composition of foods available for nutritional epidemiology in Europe, particularly for foods consumed in Mediterranean countries.

In the particular case of EPIC, food composition tables are needed in order to estimate nutrient intake from the main dietary questionnaires on usual diet (including about 300–600 food items) as well as from the 24-hour diet recall used to calibrate dietary measurements which, in theory, can include several thousands of foods defined by the combination of food lists and food descriptors. During the pilot phase of EPIC, food composition databases which included the nutrient content of Italian, Spanish and French foods were compiled at IARC. Similar compilations were carried out by EPIC collaborators for the other countries involved. Subsequently, a more fundamental approach was adopted with the aim of developing a much larger, better standardized food composition database, for use in the analysis of the EPIC cohort data. An international working group has been set up which includes researchers from several institutes involved in nutrition and food chemistry in the nine European countries collaborating in EPIC.

2.3.4 Malmö Prospective Study on Diet and Cancer

E. Riboli, R. Saracci and B. Hémon; in collaboration with G. Berglund, L. Janzon, S. Elmstâhl and B. Gullberg, Malmö, Sweden

The Malmö prospective study was initiated in 1992 in close collaboration with IARC. The main aim is to investigate the role of diet, nutritional status and other lifestyle factors in the etiology of cancers of the breast, colorectum, stomach, prostate, lung and other less frequent cancer sites. Before the initiation of the study, two alternative dietary assessment methods designed for the Swedish population were tested for validity among volunteers and compared with a reference method involving 18 days of weighed food record covering a one-year period (3 days every 2 month, six times). The results indicated that a novel approach, i.e., a seven-day diary and a food frequency method, provided reliable measurements and good compliance [147, 148]. This method was adopted for the cohort study.

Data and blood samples have been collected from 22 000 subjects, and it is planned to continue enrolment of subjects up to the target of 35 000. In 1994 it was

decided to associate the Malmö project to EPIC. The protocol has been adapted to meet the requirements of between-country calibration of dietary measurements. A Swedish version of the PC software EPIC-SOFT for 24-hour diet recall is being prepared, and interviews of a random sample of 10% of the cohort subjects are to be started towards the end of 1995.

2.3.5
The New York University Women's Health Study

E. Riboli, R. Kaaks and C. Casagrande; in collaboration with P. Toniolo and R.E. Shore, New York, USA

The main goal of this prospective study, started in 1985, is to explore the role of hormonal and nutritional factors in the etiology of cancers of the breast, endometrium and ovary. The study includes 15 500 women living in the New York metropolitan area who were recruited during 1985–86 while attending mammographic screening for breast cancer at the Guttman Institute. Data on diet were collected by means of a self-administered food frequency questionnaire slightly modified from a design by the US National Cancer Institute. The reproducibility of food and nutrient intake estimated by this questionnaire was then tested under real field conditions by asking a subsample of the subjects to fill in the questionnaire on three occasions. Results indicated fairly good reproducibility in the short term (three months) and still a reasonable concordance of dietary measurements over a longer period (1–5 years). Blood samples were collected from half of the subjects in the cohort on the occasion of subsequent mammographic screening, and stored at –80 °C in 10 aliquots of 2 ml each of plasma and buffy coat.

Statistical analyses of the risk of developing breast cancer in relation to dietary habits conducted on the first 180 incident cases diagnosed between 1986 and 1990 indicated an association with consumption of meat. Breast cancer risk was linearly increased in relation to meat intake, and women with the highest quintile of intake (average of 79 g/day) had a two-fold increased risk compared to women with the lowest quintile (average of 4 g/day) [611].

The same cohort showed a strong increase in risk of breast cancer in relation to prediagnostic levels of albumin-bound and free estradiol (biologically active forms), while a reduction in risk was shown for women with a high proportion of estradiol bound to sex hormone-binding globulin (biologically inactive forms). Further analysis of the interaction between diet and hormonal factors is being conducted on more than 400 breast cancer cases diagnosed in the cohort up to 1994.

2.3.6
Multi-centre case-control study on diet and cancers of the hypopharynx and larynx

J. Estève, E. Riboli, A. Tuyns, A. Arslan; in collaboration with G. Péquignot, Paris, France; B. Terracini and F. Merletti, Turin, Italy; F. Berrino, P. Crosignani and F. Repetto, Milan, Italy; N. Ascunce and A. Del Moral, Pamplona, Spain; L. Zubiri, Zaragoza, Spain; L. Raymond, Geneva, Switzerland

In the early 1980s, IARC conducted a multi-centre case–control study on cancers of the hypopharynx and larynx in relation to tobacco, alcohol, occupational exposures and diet. The study included 1147 cases and 3057 population controls from Milan, Turin (Italy), Zaragoza, Pamplona (Spain), Geneva (Switzerland) and Caen (France).

A new statistical analysis of the dietary data shows that low consumption of fruit (particularly oranges), vegetables and vege-

table oil was associated with a significant increase in risk, while low consumption of butter was associated with reduced risk of laryngeal cancer. Low intake of vitamins C and E and of beta-carotene, and a low ratio of polyunsaturated to saturated fat (P/S ratio) were associated with increased risk. These results provide strong support for the hypothesis that high intake of fruit and vegetables reduces the risk of cancer of the upper aerodigestive tract [163, 512].

2.4 Tobacco and cancer

Tobacco is the product responsible for the most cancer cases (particularly cancer of the lung but also of the bladder, oral cavity, pharynx, larynx, oesophagus, pancreas, kidney and cervix) among all identified carcinogenic agents. As such, it is a subject for preventive action rather than research, but certain aspects of its use and effects still warrant study.

The extent to which lung cancer among non-smokers is attributable to passive smoking is also being studied (see Sections 3.7.2 and 3.7.4).

2.4.1
Smoking in France

A.J. Sasco; in collaboration with D. Grizeau, Vanves, France; G. Freyer and M. Jambon, Lyon, France; and E. Wynder, New York, USA

Tobacco use is regularly monitored at the national level and detailed investigations are being carried out among adolescents to evaluate risk factors for smoking and other substance abuse behaviour. Among adults, some encouraging trends [566] are being seen for men [558], but not yet for women [546, 552], and are more marked for the affluent sector of society [567]. However, there is no evidence of any impact on lung cancer mortality [544]. Among adolescents, tobacco use is still quite prevalent [548], with peer behaviour being one of the strongest determinants of substance abuse [549, 571]. The extension of health behaviour surveys to children aged 7–10 years is now being tested.

2.4.2
Evaluation of the efficacy of various anti-smoking strategies

A.J. Sasco; in collaboration with J.C. Cêtre, C. Ducos-Mieral, J. Fabry and C. Gindre, Lyon, France; and P. Dalla-Vorgia, Athens, Greece

Evaluation of anti-smoking strategies is being carried out at the local, national and European levels. This comprises evaluation of activities for health promotion among children and adolescents, as well as activities more specifically targeted at decreasing exposure to tobacco smoke in the workplace [555] or inducing general practitioners to become more determined health advocates. At the national level, legislation is an integral part of any comprehensive anti-smoking programme [557] and may have a substantial impact. The 1992 study comparing all EC anti-smoking legislation is being updated.

2.4.3
Cohort study of tobacco use and mortality in Bombay, India

D.M. Parkin, A.J. Sasco and R. Sankaranarayanan; in collaboration with P.C. Gupta, Bombay, India; R. Peto, Oxford, UK; and A. Lopez, Geneva, Switzerland

Enrolment of a cohort of individuals resident in Bombay began in 1991. The objective was to recruit about 50 000

Table 5. Current use of smoking and oral tobacco in Bombay, India

	Women	Men	
Smokers	0.2%	13.7%	of which bidi 13%
Smokers + oral tobacco	0.2%	9.9%	and cigarettes 11%
Oral tobacco	57.1%	45.7%	

subjects of each sex, who would be followed up for cancer incidence (via the cancer registry) and mortality (via the municipal corporation). Subjects are administered a questionnaire concentrating upon habits of tobacco use, and measurements are taken of height, weight, blood pressure and peak expiratory flow.

Analysis of tobacco habits at the end of the recruitment phase showed rather lower prevalence of smoking than expected (Gupta, 1995, *Tobacco Control*, in press), contrasting with a high prevalence of smokeless tobacco use, in particular among women. For this reason, recruitment was continued in order to include an additional 100 000 males aged 45 or more.

Follow-up is to continue for many years, with relative risks being calculated for tobacco use with respect to different cancers, and causes of death.

2.4.4
Tobacco use in Africa

A.J. Sasco and D.M. Parkin

Although estimates have been produced on lung cancer incidence attributable to tobacco use worldwide [450], little is known for some parts of the developing world, in particular for Africa [554]. Tobacco use surveys using a standardized data collection form have been carried out in Egypt, Ghana, Kenya, Morocco, Nigeria, Tanzania, Uganda, Zambia and Zimbabwe. Plans have been made for an international case–control study of lung cancer.

Figure 11. Tobacco market in Harare, Zimbabwe

2.4.5
Biological relevance, chemical characterization and mechanism of action of substances in human urine strongly inhibiting bacterial mutagenicity of aromatic and heterocyclic amines

C. Malaveille, A. Hautefeuille, and B. Pignatelli; in collaboration with H. Bartsch, Heidelberg, Germany; G. Talaska, Cincinnati, USA; and P. Vineis, Turin, Italy

Tobacco smoking causes a major fraction of urinary bladder cancer in humans. Various studies implicate primary aromatic and possibly heterocyclic amines which are present in tobacco smoke as bladder carcinogens (Bartsch *et al.*, 1993, *Eur. J. Cancer*, **29A**, 1199–1207). Human urine contains substances that strongly inhibit the bacterial mutagenicity of some such amines (Malaveille *et al.*, 1992, *Carcinogenesis*, **13**, 2317–2320). The bacterial anti-mutagenicity of ten urine samples from smokers has been shown to be inversely related to the level of DNA adducts in exfoliated bladder cells (isolated from urine); these adducts are derived mostly from aromatic and heterocyclic amines present in tobacco smoke. This *in vitro* measurement thus appears to be a good predictor of the anti-genotoxicity and probably anti-carcinogenicity *in vivo*, at least within bladder mucosal cells, of urinary substances. The levels of unsaturated fatty acids, caffeine and paraxanthine, known inhibitors of heterocyclic amine mutagenicity, were far too low to account for the inhibitory effect of the urine extract on these mutagens. Experimental evidence strongly suggests that the anti-mutagens are dietary polyphenols.

It has been reported that the catechol moiety of particular flavonoids is responsible for their mutagenicity at concentrations much higher than those for anti-mutagenicity *in vitro* and that catechol-*O*-methyltransferase catalyses rapid *O*-methylation of catechol groups into non-mutagenic methoxyphenol derivatives. We have shown that *O*-methylation increased the anti-mutagenicity of quercetin, assayed as a model flavonoid.

HPLC fractions with the more lipophilic substances from two urinary extracts displayed the highest specific anti-mutagenic activity (expressed as % inhibition per μg phenolics). This is consistent with the fact that flavonoids may be converted into *O*-methylcatechol derivatives which are more liposoluble and anti-mutagenic than the parent compounds, as observed for quercetin.

2.4.6
N-Acetylation, glutathione conjugation polymorphisms and prevalence of pancreas cancer

C. Malaveille and A. Hautefeuille; in collaboration with H. Bartsch, Heidelberg, Germany; A. Lowenfels, New York, USA; and P. Boyle and P. Maisonneuve, Milan, Italy

Epidemiological studies have consistently demonstrated that cigarette smoking increases the risk of pancreatic cancer. In addition, frequent consumption of fried and grilled meat has been proposed as a risk factor. Heterocyclic amines are known to be abundant mutagens formed by heating of food, and are also present in tobacco smoke (Bartsch *et al.*, 1993, *Eur. J. Cancer*, **29A**, 1199–1207). 2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), one representative member of this class of carcinogens, forms DNA adducts in many rat tissues, the pancreas having the highest binding level. Experimental evidence indicates that polymorphic genes controlling the metabolism of carcinogens account for some of the variation in predisposition to certain tobacco-related cancers such as lung and bladder cancers. *N*- or *O*-acetylation of heterocyclic amines, by the polymorphic *N*-

acetyltransferase 1 and/or 2, may affect both their bioavailability and their activation in the pancreas, and an inability to detoxify electrophilic heterocyclic amine derivatives, by the polymorphic glutathione transferase M1, may maximize the carcinogenic effect of these substances. Logistics for collection of blood samples of pancreas cancer cases and controls have been established with nine American and European hospitals, in order to assess the role of acetylation and glutathione conjugation polymorphism, as revealed by genotyping assays, in the prevalence of this cancer. If shown, this would support a role for heterocyclic amines as a major class of etiological agents.

2.5 Radiation and cancer

Ionizing radiation is one of the best known, and most feared, causes of cancer. But despite the ease of making precise measurements of radiation dose, there remain uncertainties, in particular about the effects of prolonged low-level exposure to radiation, such as occurs in relation to natural and man-made sources of environmental radioactivity, as well as about the effects of different types of radiation and of factors that may modify the risk of radiation-induced cancers. Studies aimed at rectifying these deficiencies are being carried out focusing on cancer risk among workers in the nuclear industry and among persons exposed to radiation from the 1986 Chernobyl explosion.

2.5.1 Chronic low-dose exposures to ionizing radiation

2.5.1.1 Combined analyses of cancer mortality among nuclear industry workers

E. Cardis, B.K. Armstrong, J. Estève, I. Kato and C. Lavé; in collaboration with V. Beral and L. Carpenter, Oxford, UK; G. Cowper, Deep River, Canada; A. Douglas, London, UK; J. Fix and E. Gilbert, Richland, USA; S. Fry, Oak Ridge, USA; G. Howe, New York, USA; J. Kaldor, Sydney, Australia; I. Kato, New York, USA; L. Salmon, Harwell, UK; P.G. Smith, London, UK; G. L. Voelz and L. Wiggs, Los Alamos, USA

Results of the three-country study of cancer risk among nuclear industry workers have been published [98, 99, 236]. The study covered 95 673 workers (85.4% men) monitored for external exposure to ionizing radiation and employed for at least six months in the nuclear industry in the USA (Hanford, Oak Ridge and Rocky Flats), in the UK (Sellafield, Atomic Energy Authority; and Atomic Weapons Research Establishment) and in Canada (Atomic Energy of Canada). The analyses covered a total of 2 124 526 person years at risk and 15 825 deaths, 3976 of which were from cancer.

There was no evidence of an association between radiation dose and all-cause or all-cancer mortality. Mortality from leukaemia, excluding chronic lymphocytic leukaemia (CLL)—the cause of death most strongly and consistently related to radiation dose in studies of atomic bombing survivors and other populations exposed at high dose rates —was significantly associated with cumulative external radiation dose (one-sided p-value = 0.046; 119 deaths). Among 31 other specific types of cancer, a significant association was observed only for multiple myeloma (one-sided p-value = 0.037; 44 deaths) and this was attributable primarily to the previously reported associations between this disease and radiation dose in the Hanford (USA) and Sellafield (UK) c ohorts.

The excess relative risk estimates (ERR) for all cancers excluding leukaemia and for leukaemia excluding CLL, the two main groupings of causes of death for which risk estimates have been derived from studies of

atomic bomb survivors, were –0.07 per Sv (90% confidence interval (CI): –0.4, 0.3) and 2.18 per Sv (90% CI: 0.1, 5.7), respectively. These values correspond to a relative risk of 0.99 for all cancers excluding leukaemia and 1.22 for leukaemia excluding CLL for a cumulative protracted dose of 100 mSv compared to zero mSv. These estimates, which did not differ significantly across cohorts nor between men and women, are the most comprehensive and precise direct estimates obtained to date. Although lower than the linear estimates obtained from studies of atomic bomb survivors (Table 6), they are compatible with a range of possibilities, from a reduction of risk at low doses, to risks twice those on which current r adiation protection recommendations are based. Overall, the results of this study do not suggest that current radiation risk estimates for cancer at low levels of exposure are appreciably in e rror.

2.5.1.2

International collaborative study of cancer risk among radiation workers

E. Cardis, A. Mylvaganam and H. Renard; in collaboration with P. Ashmore, Ottawa, Canada; F. Berman, Paris, France; J. Bernar-Solano and A. Diez Sacristán, Madrid, Spain; A. Biau, Le Vésinet, France; M. Blettner, Heidelberg, Germany; L. Carpenter, Oxford, UK; P. Deboodt and H. Engels, Mol, Belgium; M. Eklöf, Osthammar, Sweden; E. Gilbert and J. Fix, Richland, USA; L.M. Green, Toronto, Canada; E. Gubéran, Geneva, Switzerland; G. Gulis, Trnava, Slovak Republic; C. Hacker, Menai, Australia; M. Hakama, Tampere, Finland; C. Hill, Villejuif, France; K. Holan, Bratislava, Slovak Republic; Y. Hosoda, Tokyo, Japan; G. Howe, New York, USA; J. Kaldor, Sydney, Australia; G. Kendall, L. Salmon and C. Muirhead, Harwell, UK; A. Kerekes and I. Turai, Budapest, Hungary; H. Malker, Sundsvall, Sweden; M. Moser, Bern, Switzerland; W. Murray and R. Rinsky, Cincinnati, USA; A. Auvinen and T. Rytomaa, Helsinki, Finland; G. Seitz, Cologne, Germany; and T. Yoshimura, Kitakyushu, Japan

The International Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry has been extended to three additional countries: Hungary, the

Table 6. Excess relative risk (ERR) estimates per Sv[a] (and 90% confidence intervals) from studies of nuclear workers, studies of atomic bombing survivors and other high-dose studies; men only

	All cancers excluding leukaemia		Leukaemia excluding CLL	
Population	ERR per Sv	90% CI	ERR per Sv	90% CI
Nuclear workers data [b]	–0.07	(–0.39, 0.30)	2.18	(0.13, 5.7)[c]
A-bomb [d], linear	0.18	(0.05, 0.34)	3.67	(2.0, 6.5)
A-bomb [d], L–Q[e]	–		1.42	(<0, 6.5)
UNSCEAR	0.24	–	3.7	–
	Multiplier [f]	90% CI	Multiplier	90% CI
BEIR V	–0.17	(–0.76, 0.57)	0.71	(–0.04, 2.0)
A-bomb, linear	–0.39	(–2.2, 1.7)	0.59	(0.04, 1.6)

[a] Estimates of organ dose and of 1 cm depth dose were used in analyses of atomic bombing survivors and nuclear industry workers, respectively.
[b] Adjusted for age, socioeconomic status, facility and calendar time.
[c] Simulated confidence interval.
[d] A-bomb: data for atomic bombing survivors, adjusted for age, city and calendar time.
[e] Based on the linear term of a linear-quadratic (L-Q) dose-response model in the atomic bombing survivors data
[f] ERR in nuclear workers expressed as a multiple of the high-dose ERR; for example, the leukaemia risk estimate is 0.71 times the BEIR V estimate with confidence interval ranging from –0.04 times to twice the BEIR V estimate

Slovak Republic and the USA. In the former two countries, a feasibility study has been completed and a detailed protocol is in preparation. Data collection is proceeding in the original 11 countries (Australia, Belgium, Canada, Finland, France, Germany, Japan, Spain, Sweden, Switzerland, UK) according to the detailed procedures document. Special care is being given to the construction of a socioeconomic status indicator to adjust for the possible confounding effects of lifestyle factors on the relationship between low-dose radiation and cancer risk. A study of comparability of coding of cause of death across countries and over time will be carried out using anonymized death certificates in most countries. Cross-sectional surveys of smoking habits are being planned in most of the participating countries.

A detailed protocol has been developed for the study of biases and random errors in the radiation dose estimates. The main aims are: (1) to identify workers with substantial doses from neutrons or from internal contamination with radionuclides for which dose estimates may be inaccurate; and (2) to quantify the systematic and random errors in dose estimates for workers whose dose is predominantly from higher-energy γ-rays.

2.5.2 Health consequences of the Chernobyl accident

2.5.2.1 Emergency accident workers

E. Cardis, D. Guo, A. Mylvaganam and H. Renard; in collaboration with A.E. Okeanov, G. Tolochko, A. Sobolev and M. Davidovich, Minsk, Belarus; V.K. Ivanov, A. Sevanka'ev, E. Rastopchin and A. Konogorov, Obninsk, Russia; H. Storm, Copenhagen, Denmark; C. Muirhead and D. Lloyd, Harwell, UK; A. Kellerer, Munich, Germany; M. Tirmarche, Fontenay-aux-Roses, France; A.T. Natarajan, Leiden, Netherlands

In order to evaluate the feasibility of long-term epidemiological studies of cancer risk among emergency accident workers, three pilot studies were set up in Belarus and the Russian Federation within the framework of an experimental collaboration project of the European Commission.

The first study, a test of follow-up mechanisms, was completed in the spring of 1994. A sample of 500 emergency accident workers having worked in the 30 km zone around the Chernobyl reactor between May 1986 and December 1987 was chosen at random from a computerized list of emergency accident workers in the Chernobyl Registry in each country. Vital status of these subjects, and date and cause of death for deceased individuals, was ascertained by consultation of various records. Follow-up was almost complete (99%) in both countries. In Belarus, 80% of the population could be followed using only two sources of information: the Chernobyl Registry and the Passport Department. As there are plans to centralize the Passport Department information at the republican level in Belarus, passive follow-up for vital status based on the Passport Department information appears to be feasible. In the Russian Federation, it was possible to follow up 85% of the population using three sources: the central and regional branches of the Chernobyl Registry and visits to local hospitals. A long-term retrospective study using this approach could be envisaged, but its success would depend on the continuation of the existing Chernobyl registration system.

The second study, a pilot case–control study of leukaemia among emergency accident workers registered in the Chernobyl Registries in Belarus and Russia, was completed in late 1994. Approaches for identifying cases and selecting controls have been evaluated; the questionnaire, which was adapted from the questionnaire of the Estonian study of emergency accident workers

(a joint Estonian/Finnish/US collaboration), has been tested. The case–control approach was successful in both countries and a detailed protocol for a case–control study of leukaemia and thyroid cancer in emergency accident workers is in preparation.

The third study was a validation and calibration study of biological dosimetric techniques. The aim was to assess the feasibility of constructing a gradient of individual radiation dose from analyses of stable chromosomal aberrations in blood cells collected several years after the accident. A stratified random sample of 60 emergency accident workers (20 each with total registered dose of 0–100 mSv, 100–200 mSv and greater than 200 mSv) having worked in the 30 km zone around the Chernobyl reactor between May 1986 and December 1987 and residing in the Obninsk area, was chosen from a computerized listing of emergency accident workers in the Chernobyl Registry in Russia. The subjects were interviewed concerning the type, date and location of their work in the 30 km zone, and asked to donate a blood sample. Blood cells were cultured in Obninsk and Didcot (UK), and fluorescent *in situ* hybridization (FISH) was carried out in parallel in partner laboratories in western Europe and the CIS. Preliminary results do not show a correlation between the number of aberrations scored and the dose registered in the Chernobyl Registry, or the history of work as a liquidator (dates, duration, place and type of work). In most cases, however, the number of cells scored for each subject was too low (mostly between 100 and 600) for results to be meaningful in the range of radiation doses received; the analyses are now being repeated using remaining cultured blood cells. The final results will be available in late 1995. Attempts are also being made to construct an index of exposure based on information on working conditions and radiation fields in the 30 km zone.

2.5.2.2 *Thyroid cancer in children*

E. Cardis, D. Guo and H. Renard; in collaboration with L.N. Astakhova, A. Stozharov, A. Arinchin, I. Khmara, E.A. Holodova, A.E. Okeanov, Y. Averkin and E. Demidchik, Minsk, Belarus; K. Baverstock, Rome, Italy; D. Williams, Cambridge, UK; A. Pinchera and F. Pacini, Pisa, Italy; T. Abelin, Berne, Switzerland; M. Schlumberger, Villejuif, France; S. Nagataki, Nagasaki, Japan

A small-scale survey of childhood papillary thyroid cancer cases was carried out in Belarus within the framework of the WHO International Thyroid Project, in order to obtain additional information on the reported increase in this disease in Belarus, Russia and Ukraine. A questionnaire was administered to the mothers of the first 50 children attending the Endocrinology Clinic of the Institute of Radiation Medicine for thyroid examination or for follow-up after thyroid surgery between 1 December 1993 and 15 March 1994. The questionnaire requested information about the mode of diagnosis of the thyroid cancer (through a screening programme vs. self-presentation because of illness), the location and behaviour of the child at and around the time of the Chernobyl accident and participation of the children's parents in the clean-up of the Chernobyl accident. The majority of the children were residents of the Gomel (60 %) and Brest (24 %) areas of Belarus; 64 % were girls. In 80% of the cases, the thyroid tumour was diagnosed as a result of screening (in the annual medical examination at school in 46% of cases or in a formal screening programme in 24%), but only in 17% by ultrasound.

The results of this study must be interpreted with caution, as no information is available on the variables of interest from

suitable controls. Overall, the behaviour of the cases in the days following the accident (consumption of milk, water, locally grown food, time spent out of doors, sleeping with open windows) would tend to have maximized the radiation dose to the thyroid from iodine isotopes. Estimates of the dose to the thyroid from iodine-131 (^{131}I) were available for only 24 of the 50 cases. The levels of dose were, however, relatively low: only 3 received doses above 1 Gy, although it is estimated that several hundred children in the region of Gomel may have received doses of more than 10 Gy to the thyroid. Two of the children in the study have a sibling who also had papillary thyroid cancer. Additional information suggests that at least one other sibling pair exists among the cases in Belarus. Even in the region of Gomel, where the contamination with iodine isotopes is likely to have been the greatest and where the prevalence of thyroid cancer in children has been estimated to be as high as 1 per 1000 in recent years, the probability of observing two or more siblings with thyroid cancer is extremely low.

As a result of this survey, a case–control study of factors modifying the risk of ^{131}I-induced thyroid cancer is being set up. The primary factors of interest are a possible genetic predisposition to radiation-induced thyroid cancer, iodine status (deficiency and supplementation) and short-lived isotopes of iodine. A parallel study of familial non-medullary thyroid cancers is being carried out in western Europe, in order to identify a possible gene predisposing to radiation-induced papillary thyroid cancer.

Several related projects are also being carried out within the WHO International Thyroid Project; in particular a registry of operated thyroid pathologies is being set up and a survey of current and past iodine deficiency is being carried out in Belarus.

2.5.2.3

European Childhood Leukaemia and Lymphoma Incidence Study (ECLIS)

D.M. Parkin, R.J. Black and E. Masuyer; in collaboration with E. Apjok and D. Schuler, Budapest, Hungary; L. Barlow, Stockholm, Sweden; B.G. Bennett, Vienna, Austria; J.L. Bernard, P.M. Carli, M.C. L'Huillier, F. Ménégoz, P. Schaffer and S. Schraub, France; A. Boukhny and V. Merabishvili, Moscow and St Petersburg, Russian Federation; D. Clayton, Cambridge, UK; J.W.W. Coebergh, Eindhoven, Netherlands; P. Crosignani, C. Magnani and B. Terracini, Turin, Italy; F. Enderlin, F. Levi, L. Raymond, G. Schüler and J. Torhorst, Geneva, Switzerland; H.P. Friedl, Vienna, Austria; E. Geryk, Brno, Czech Republic; E. Ivanov, Minsk, Belarus; P. Kaatsch and J. Michaelis, Mainz, Germany; E. Kramárová and I. Plesko, Bratislava, Slovakia; R. Kriauciunas, Vilnius, Lithuania; F. Langmark, Oslo, Norway; V. Pompe-Kirn, Ljubljana, Slovenia; E. Pukkala, Helsinki, Finland; M. Rahu, Tallin, Estonia; L. Sharp, Edinburgh, UK; J. Sinnaeve, Brussels, Belgium; A. Stengrevics, Riga, Latvia; C.A. Stiller, Oxford, UK; H.H. Storm, Copenhagen, Denmark; R. Tulbure, Bucharest, Romania; C.G. Tzvetansky, Sofia, Bulgaria; and W. Zatonski, Warsaw, Poland

This project was initiated in 1988 with the aim of evaluating the effects of radiation exposure due to the Chernobyl accident on risk of childhood leukaemia in Europe. On the basis of recommendations of an expert committee appointed by the European Commission, trends in childhood leukaemia incidence are being studied in relation to levels of contamination in 34 regions in 21 countries. Regional estimates of the total body radiation dose attributable to the accident have been provided by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Cancer registries throughout Europe have contributed data on incident cases of childhood leukaemia and lymphoma from 1980 up to, thus far, 1991.

Analysis of the first five years of follow-up of data after the accident in 1986 has been completed. A small increase in incidence was observed in Europe between 1980 and 1991, but there is no evidence that

the regional trends after the accident are related to levels of contamination. Furthermore, the birth cohort of children who received the highest doses *in utero*, for whom the leukaemogenic effect of radiation may be enhanced, do not appear to have experienced an increased risk of leukaemia.

Data collection for the study will continue until a further five years of follow-up data have been accumulated. Interim analyses will focus on trends in the incidence of the main leukaemia cell types and a more detailed assessment of trimester-specific risks for children exposed *in utero*.

The project is supported by the Nuclear Fission Safety programme of the European Commission.

2.6 *Role of viruses in the etiology of human cancer*

Viruses are being increasingly implicated in the etiology of cancer, and both epidemiological and molecular studies are yielding ever-improving understanding of the interactions of these organisms with other carcinogenic agents and of the mechanisms by which the effects observed seem to arise. The IARC programme dealing with Epstein–Barr virus has been terminated, but much work has continued on the effects of human papillomavirus as the principal causal agent of cervical cancer (Section 3.4), and of hepatitis viruses as contributory factors to hepatocellular carcinoma (Section 3.3). The latter is also the focus of the Gambia Hepatitis Intervention Study (Section 5.1.1).

2.6.1 Monitoring of trends in incidence of cancers related to infection with human immunodeficiency virus (HIV)

D.M. Parkin and J. Ziegler; in collaboration with V. Beral and R. Newton, Oxford, UK; and K. Soldan, Colindale, UK

Two of the African cancer registries (Kampala, Uganda and Harare, Zimbabwe) provide long enough time series to evaluate trends. Kaposi's sarcoma has increased enormously in incidence and in these countries is now predominantly of the 'epidemic' HIV-related clinical types, at ages closely paralleling prevalence of HIV infection. There is some suggestion in Harare that incidence of non-Hodgkin lymphoma may have increased (a longer observation period is needed), but no evidence of changing incidence or age distribution of cases of cervix cancer.

An analysis of Kaposi's sarcoma incidence in European cancer registries has been carried out for periods before and after the onset of the AIDS epidemic (as defined by notification rates). Preliminary results indicate that rates were highest in the early period in Italy and Israel, with moderate incidence rates in Finland and Iceland. The changes in rates after the onset of the AIDS epidemic appear to be unrelated to the incidence before it.

2.6.2 Case–control studies of Kaposi's sarcoma, non-Hodgkin lymphoma and carcinoma of the cervix in Africa in relation to infection with HIV

D.M. Parkin and J.L. Ziegler; in collaboration with V. Beral, R. Newton and R. Weiss, Oxford, UK; P.-J. Ngilimana and B. Sindikubwabo, Butare, Rwanda; H. Jaffe, Atlanta, USA; K. De Cock, London, UK; E. Kantangole-Mbidde, E. Katabira, S. Mbulateiye and H. Wabinga, Kampala, Uganda

The initial case–control study was started in Rwanda in October 1992. All

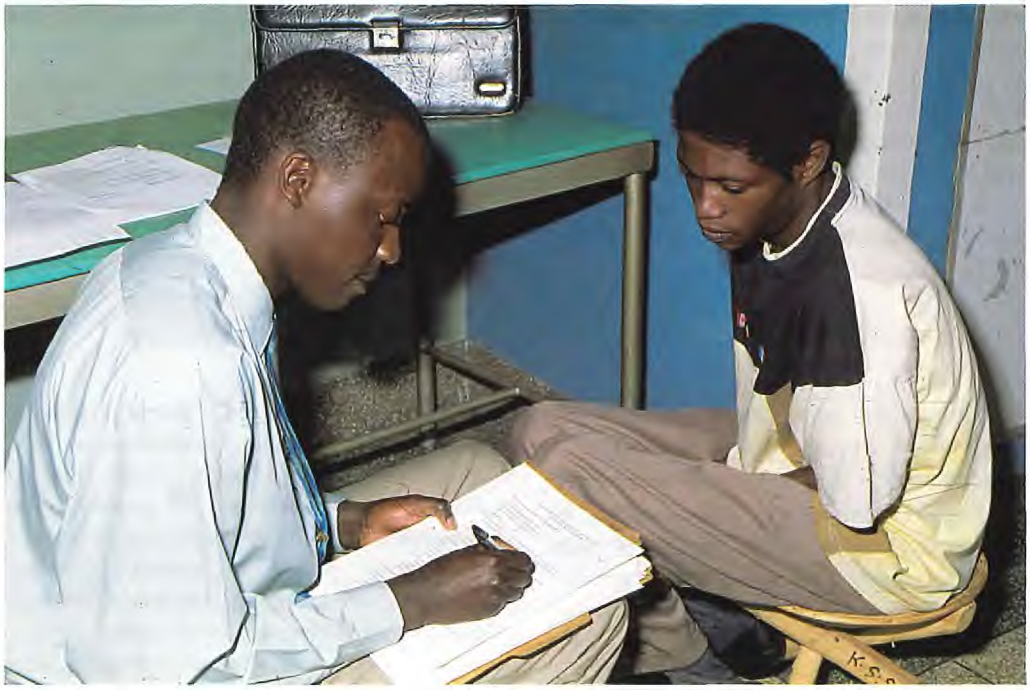


Figure 12. Interview of a Kaposi's sarcoma patient in Kampala, Uganda

cases of suspected cancer in Butare prefecture were interviewed, and samples of blood taken for antibody studies. The study proceeded slowly, and was terminated by the genocide which began in April 1994, by which time full information could be retrieved for only 245 cancer cases. The relative risk for different cancers associated with HIV infection was 35.0 for Kaposi's sarcoma (KS), 12.6 for non-Hodgkin lymphoma, and 8.4 for squamous cell tumours of conjunctiva; cervix cancer was not associated with HIV infection [418].

A larger-scale study began in Kampala, Uganda, in August 1994. The initial objective is to investigate KS, in particular to quantify the association with HIV infection, to identify any putative infectious agents and to investigate modes of transmission. Cases of KS attending hospitals in Kampala will be enrolled, as well as subjects with other cancers and HIV-positive subjects without evidence of KS from the same hospitals, from which control subjects can be selected.

A possible etiological agent (a herpes-like virus) has been identified in tissues from both AIDS-related and classical (endemic) KS subjects [114].

The possible modes of transmission investigated via questionnaire include interpersonal contact (crowding, housing conditions), faeco-oral spread (water supply, sanitation) and sexual contact (sexual history, serology). In addition, the hypothesis that exposure to volcanic soils with resulting local immunosuppression might be related to endemic KS [701] is being tested.

The component related to KS will terminate in early 1996, when it is expected that about 1000 KS cases (with 10–15% HIV-negative) will have been enrolled.

Enrolment of cases of other cancers will continue for probably a further year, to investigate associations of cancers such as lymphoma, cervix cancer, liver cancer, conjunctival and penile neoplasms with HIV and other viral infections.

In January 1995, a study of childhood KS was begun, following the observation that most such children were HIV-positive (about 75%), but that KS was not observed in their mothers. The study groups comprise mother–child pairs: (1) mothers of children with KS ('cases') (2) mothers of children with other cancers and (3) mothers of children who are HIV-positive, but without KS.

The study focuses not only upon the role of HIV infection in mother and child, but also on possible modes of transmission of the 'KS agent': through the same mechanisms as in adults, by transmission intrapartum, or via breast milk.

It is intended that at least 60 mother–child 'case' pairs should be enrolled in this study.

2.7 Second malignancies following cancer treatment

Although cancer is still often a fatal disease, for which the use of aggressive therapies is justified, better and earlier diagnosis combined with more effective forms of treatment have led to complete cure or at least much prolonged survival of many cancer cases. In these circumstances, it is essential to clearly understand the possible carcinogenic effects, as well as other toxicity, of the treatments available.

2.7.1 Prospective study on markers of DNA damage and risk of second malignancy in Hodgkin's disease patients

P. Boffetta, C.P. Wild, H. Yamasaki, R. Montesano, H. Nakazawa, J. Hall, R. Saracci and E. Weiderpass; in collaboration with H.O. Adami, Uppsala, Sweden; P. Boyle, Milan, Italy; A. Daudt, Porto Alegre, Brazil; M. Henry-Amar, Caen, France; K. Holli, Tampere, Finland; J. Iscovich, Jerusalem, Israel; S. Kvinnsland, Oslo, Norway; S.A. Kyrtopoulos, Athens, Greece; J.J. Lopez, Barcelona, Spain; D. Shuker, Leicester, UK; L. Simonato, Padua, Italy; H. Storm, Copenhagen, Denmark; A. Swerdlow, London, UK; L. Petruzelka, Prague, Czech Republic; F. Rilke, Milan, Italy; E. Robinson, Haifa, Israel; M. Tucker, Rockville, USA; and D.G. Zaridze, Moscow, Russia

Investigation of the risk of second malignancy among cancer patients treated with chemotherapy is important for two main reasons. First, epidemiological studies are useful in identifying effective regimens with minimal adverse effects. Second, they are useful in studying the mechanisms of carcinogenesis in persons at high risk of developing another cancer. Hodgkin's disease (HD) patients treated with drugs such as nitrogen mustard, vincristine, procarbazine and prednisone (MOPP) and adriamycin, bleomycin, vinblastine and dacarbazine (ABVD), which contain alkylating agents, are at substantial risk of second neoplasms, in particular leukaemia, non-Hodgkin lymphoma and lung cancer [60]. A collaborative group of hospitals treating HD patients has been established, and a central database is being established of all patients diagnosed with HD. The patients will be prospectively followed up for the occurrence of second malignancies. As each second malignancy arises, the therapy record for that case and several matched controls will be examined, to try to identify carcinogenic therapeutic modalities as rapidly as possible. In parallel, blood samples are taken from each patient, immediately after diagnosis, and then subsequent to therapy. The red and white blood cells and plasma are separately stored. For patients who develop an acute leukaemia or another malignancy following

therapy for HD and for matched controls who remain free of a second malignancy, the samples will be analysed for markers of DNA damage and repair, and comparison made between the second malignancy cases and controls. If markers of DNA damage are linked to risk of second cancer, the frequency and the level of such markers will be increased among cases as compared to controls. Similarly, blood samples will be analysed from a sample of patients not responding to therapy and a sample of respondents, to investigate whether markers of DNA damage predict response to therapy. A total of 200 patients has been enrolled in the study during 1994.

2.7.2
Pilot study on markers of DNA damage following chemotherapy for Hodgkin's disease

P. Boffetta, C.P. Wild, F. Bianchini, J. Hall, E. Weiderpass and A. Schouft; in collaboration with M. Henry-Amar, Caen, France; J. Kaldor, Sydney, Australia; S. Kyrtopoulos and G. Pangalis, Athens, Greece; A. Natarajan, Leiden, Netherlands; A.T. Van Oosterom, Edegem, Belgium; and P. Roy, Lyon, France

The study was intended to measure the level of markers of DNA damage and repair, as well as to test the feasibility of taking, preparing, storing and shipping blood samples. HD patients treated with MOPP/ABV within the framework of two EORTC clinical trials were enrolled from Brussels (Belgium), Villejuif and Lyon (France), Athens (Greece), Amsterdam and Rotterdam (Netherlands). Information on clinical characteristics of the disease and the outcome of the therapy has been collected for 25 patients out of 29 enrolled. Blood samples were collected before the first cycle, on day 7 of the first cycle and after completion of chemotherapy. A combined immunopurification/HPLC–electrochemical detection method [45] to measure 7-methylguanine (7-MeG) has been applied to peripheral blood cell DNA from HD patients. Of 19 patients treated with procarbazine and sampled immediately at the end of the first cycle of chemotherapy, all had detectable levels of 7-methylguanine (>1 pmol/μmol guanine) and there was an approximately 2.5-fold interindividual variation (range 8 to 20 pmol 7-MeG/ μmol guanine) in adduct levels. Only two patients had detectable levels before chemotherapy and these were only slightly above the detection limit. The promutagenic adduct, O^6-methylguanine (O^6-MeG) was detectable in all patients at levels from 0.17 to 0.35 pmol O^6-MeG/μmol guanine. No correlation was observed between the levels of two methyl–DNA adducts (O^6-MeG and N7-methylguanine) (see Figure 13); no difference in mean adduct levels was seen between patients experiencing treatment failure or death and other patients. Additional analyses are planned on enzymes which repair DNA methylation (O^6-alkylguanine-DNA alkyltransferase, 3-methyladenine DNA glycosylase) and on cytogenetic alterations.

2.7.3
Studies of DNA damage following chemotherapy for testicular cancer

P. Boffetta; in collaboration with D. Bron, Brussels, Belgium; A.M.J. Fichtinger-Schepman, Rijswijk, Netherlands; J. Kaldor, Sydney, Australia; A. Natarajan, Leiden, Netherlands; P. Roy, Lyon, France; and R. Somers, Amsterdam, Netherlands

The reaction between alkylating chemotherapeutic agents and cellular DNA is probably the main pathway to both their cytotoxic and their carcinogenic effects. A collaborative study has been set up to measure cisplatin–DNA adducts in testicular cancer patients, and to assess to what extent adduct levels can be used to predict the clinical outcome of chemotherapy.

The study is being performed in conjunction with a clinical trial of cisplatinum in testicular cancer conducted by

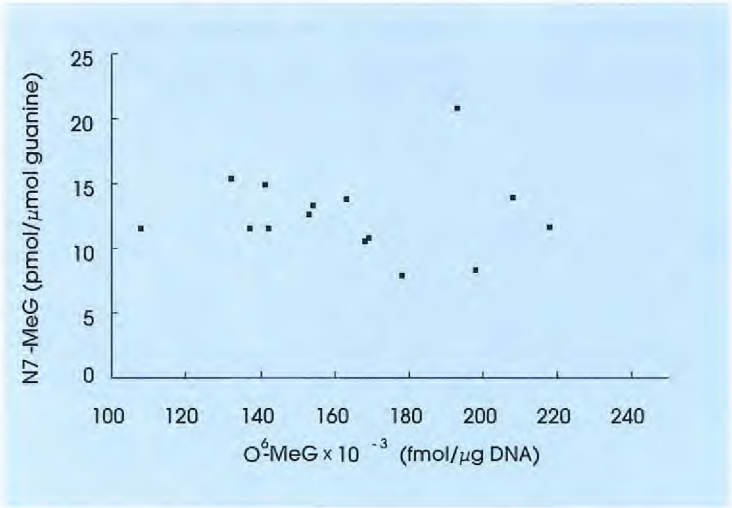


Figure 13. Levels of N7-methylguanine and O^6-methylguanine in 15 Hodgkin's disease patients after seven days' treatment with procarbazine (100 mg/m^2). r = 0.01; p = 0.96

the genitourinary groups of the European Organization for Research and Treatment of Cancer (EORTC) and the Medical Research Council of the UK. DNA adducts and haemoglobin have been measured in testicular cancer patients and will be analysed in relation to the response to chemotherapy. Preliminary analyses suggest strong correlations between cisplatin–DNA adducts and total platinum protein content, as well a correlation between DNA adduct levels before and after treatment.

2.7.4

Case–control study of selected second primary cancers following breast cancer and tamoxifen use

A.J. Sasco and I. Gendre; in collaboration with C. Bouchardy, Geneva, Switzerland; F. Berrino, Milan, Italy; J. Iscovitch, Jerusalem, Israel; and P. Schaffer, Strasbourg, France

Tamoxifen is a synthetic non-steroidal anti-estrogen of the triphenylethylene family which has been widely used for the treatment of breast cancer, and more recently has also been proposed for the prevention of the disease among high-risk women. However, the potential carcinogenicity of this product warrants further investigation before widespread preventive use [551]. In order to evaluate the risk of occurrence of selected second primary cancers following breast cancer, a series of international case–control studies have been set up. The initial study was restricted to endometrial cancer following breast cancer and was conducted in the Rhône and Côte d'Or regions of France. Women who have been treated for breast cancer with tamoxifen have an increased risk of developing endometrial cancer and the risk increases with duration of treatment. Elevated risk may persist after cessation of tamoxifen administration [572]. An international study is now in progress. Cases of selected second cancers [556], namely endometrial, liver and ovarian cancers [559] occurring among women who had previously developed breast cancer are being selected from

population-based cancer registries in France, Israel, Italy and Switzerland. They will be matched to controls who had breast cancer at the same time and age as the case and who are still at risk of disease. The role of tamoxifen and other treatment modalities in the occurrence of second cancers will be evaluated. It is envisaged that about 150 endometrial, 150 ovarian and 10 liver cancer cases will be recruited.

PART 3. CARCINOGENES IS BY ORGAN SITE

3.1 Cancer of the oesophagus

Oesophageal cancer is ninth in rank among the most common cancers worldwide, and the wide geographical variations in its incidence and the large sex difference suggest that many cases are preventable. The major established risk factors are tobacco smoking and alcohol drinking, and molecular studies on tumours clearly linked to these factors can provide important mechanistic information. Epidemiological work is continuing meanwhile to identify agents responsible for cancers that cannot be accounted for by those already known.

3.1.1
Case–control studies of oesophageal cancer in high-risk populations of Latin America

N. Muñoz and M. Benz; in collaboration with R. Castelletto and J. Iscovich, La Plata, Argentina; X. Castellsagué, Barcelona, Spain; E. de Stefani, Montevideo, Uruguay; P.A. Rolón, Asunción, Paraguay; and C. Victora, Pelotas, Brazil

Five case–control studies of the role of hot mate drinking in oesophageal cancer have been conducted in Argentina, Brazil, Paraguay and Uruguay (two studies). The results of the studies in Argentina, Brazil and Uruguay have been published and those from Paraguay are in press. In the study in Paraguay, specially designed to investigate the role of hot and cold mate drinking, the amount and duration of cold or hot mate drinking were not found to be associated with oesophageal cancer risk, but the temperature at which hot mate is drunk was significantly associated with risk, after adjustment for the strong effects of alcohol and tobacco consumption [511].

A pooled analysis of these studies, including 830 cases and 1779 controls, confirmed the central role of tobacco smoking and alcohol drinking in determining the risk of oesophageal cancer. In these South American populations, heavy smokers and alcohol drinkers have a risk 76 times higher than non-smokers and non-drinkers. However, the increase in risk with alcohol drinking among non-smokers was higher than the increase in risk with tobacco smoking among non-drinkers of alcohol. The effect of hot mate drinking was stronger among females and among non-drinkers of alcohol. Frequent consumption of fruits and vegetables was associated with a protective effect; high consumption of salt and barbecued meat was associated with increased risk.

3.1.2
Cellular and molecular alterations in oesophageal cancer

R. Montesano, P. Hainaut, C. Barnas and G. Martel-Planche; in collaboration with F. Berger, Lyon, France; M. Hollstein, Heidelberg, Germany; S.-H. Lu, Beijing, China; and A. Ruol and L. Simonato, Padua, Italy

Mutations in cancer genes are informative in tracing the molecular pathogenesis of neoplasia and also provide clues to the etiology of specific cancers. The *p53* gene is particularly important in both respects, since mutations in this gene are involved in the natural history of practically all major human cancer types, including cancer of the

oesophagus, where the frequency of *p53* point mutations is at least 45% [229]. The p53 protein plays an essential role in controlling the proliferation and survival of cells exposed to DNA-damaging agents, and loss of p53 function by mutation is thought to facilitate the propagation of potentially oncogenic DNA lesions.

Experimental studies have shown that carcinogens produce characteristic mutation patterns in a defined DNA sequence. In the *p53* gene, mutations can affect many different codons within the regions encoding the 150-residue DNA-binding domain of the protein. This area thus represents a broad target for mutational events in which specificities of exogenous or endogenous factors can be examined.

It is therefore envisaged that *p53* mutation profiles generated from sequence analysis of an epidemiologically-defined set of tumours will provide insights into the origins of genetic changes leading to neoplasia.

Samples of oesophageal lesions have been collected from different sources with well defined history of exposure to different risk factors. Mutations within the central portion of the *p53* gene (exons 4 and 9) are being determined by denaturing gradient gel electrophoresis (DGGE) and direct sequencing of PCR-amplified DNA regions. In parallel, immunohistochemical analysis of p53 protein is performed on paired tissues samples in order to correlate genetic alterations with protein expression. High expression of normal p53 in early lesions or in dysplastic tissues may reveal subsets of cells in which p53 expression is induced by carcinogen exposure. Such cells may be at high risk of becoming precursors of malignant lesions. Data from our laboratory and others clearly show an association between tobacco and alcohol and prevalence of p53 mutations in squamous cell carcinomas of the oesophagus (Figure 14).

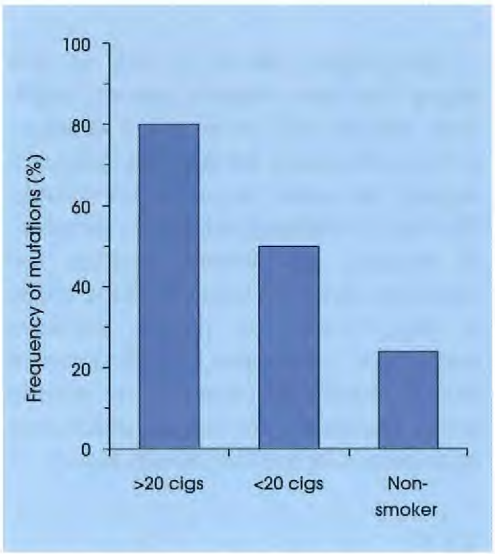


Figure 14. Prevalence of p53 mutations (%) in squamous cell carcinomas of the oesophagus in relation to subjects' smoking habits

Studies on oesophageal squamous cell carcinomas and on adenocarcinomas of the gastric cardia from Linxian (China) indicate that the pattern of p53 mutations in the latter type of cancer differs from those present in Barrett's adenocarcinomas or other types of gastric cancer [298].

The p53 protein contributes to complex pathways that control the G1–S checkpoint during cell-cycle progression. Considerable evidence indicates that alterations in genes other than *p53* are also important in the process of transformation in various human cancers. In oesophageal cancers, several other genes involved in the regulation of the G1–S transition are also altered with significant frequency, including *Rb1* (deletions), c-*myc* (amplifications) and *cyclin D1* (amplifications). Recently, a new cell-cycle-related gene, *p16/CDKN2*, has been identified on chromosome 9p21. The product of this gene plays an important role in the control of G1–S progression by

binding to and inhibiting cyclin-dependent kinases 2, 4 and 6, which phosphorylate and inactivate the RB-1 tumour-suppressor protein as cells progress into S-phase. Some mutations in *p16* have been found in oesophageal squamous cell carcinomas. Other important genes in the regulation of this checkpoint are *p21Waf-1* (which also encodes a cyclin-kinase inhibitor) and genes of the E2F family (which encode proteins released and activated after phosphorylation of RB-1). In addition to the analysis of primary tumour samples, we are studying alterations in these genes, their expression and the activity of their protein products in a panel of oesophageal cancer cell lines (Nishihira *et al.*, 1993, *J. Cancer Res. Clin. Oncol.*, **119**, 441–449). Such alterations are being analysed in relation to cell-cycle progression, capacity to undergo cell-cycle arrest induced by growth-inhibitory factors as well as by genotoxic chemicals, and survival after exposure to DNA-damaging agents. The effect of alkylating agents is of particular interest in this context due to the importance of these environmental carcinogens in oesophageal cancer. This study is expected to reveal any overlap between parallel molecular pathways controlling cell-cycle progression that are deregulated in oesophageal cancers.

3.1.3
The induction of cytochrome P450 2E1 by alcoholic drinks

C.P. Wild and M. Lechevrel

Tobacco and alcohol consumption confer a multiplicative increase in risk of cancer of the oesophagus, but the molecular basis of this interaction is unclear. One hypothesis is that alcoholic beverages containing different alcohol congeners could differentially induce expression of cytochrome P450 (CYP) 2E1. This was tested by administering equivalent amounts of ethanol in alcoholic drinks (farm Calvados, commercial Calvados, red wine, cider, whisky and beer) to rats in drinking water for three days. measure Cytochrome P450 levels in microsomes from oesophagus and liver were measured by Western blot and enzyme activities. Hepatic CYP 2E1 was induced in relation to the dose of ethanol (from 4% to 20%) and similar levels of induction were observed for all drinks compared to a control group exposed to an equivalent amount of ethanol. CYP 1A was also induced in the liver of rats exposed to ethanol but to a lesser extent than CYP 2E1. No increase in these isoenzymes was observed in oesophagus. These data show that induction of CYP 2E1 by acute alcohol treatment is predominantly determined by the ethanol content of the beverage.

3.1.4
Expression of cytochrome P450s and DNA adducts in human oesophagus

C.P. Wild, M. Lechevrel, A.-M. Camus, M. Lang and R. Montesano; in collaboration with A. Casson, Toronto, Canada; A.-M. Mandard, P. Gauduchon and G. Launoy, Caen, France; C.R. Wolf, Dundee, UK; and L. Simonato, Padua, Italy

Oesophageal tissue has been collected from oesophageal cancer patients in high-risk (Normandy, France and north-east Italy) and low-risk (Toronto, Canada) regions and for whom detailed information on exposure to alcohol and tobacco is available. Microsomes have been prepared from normal mucosa surrounding the excised tumour to allow examination of cytochrome P450 expression, while DNA has been extracted from the same tissue sample for analysis of methylation adducts. The effect of alcohol intake on expression of P450 in oesophageal mucosa will be examined, as well as the association between P450 expression and the level of DNA adducts. These data on the normal oesophageal mucosa will be related to information on mutations in specific genes being studied in the corresponding tumour tissue.

3.1.5
Co-carcinogenicity study of fumonisin B1 in relation to cancer of the oesophagus

C.P. Wild, M. Castegnaro, L. Garren, H. Ohgaki and D. Galendo; in collaboration with D. Miller, Ottawa, Canada

Fumonisins have been proposed as a possible risk factor for oesophageal cancer in parts of Africa and Asia. These mycotoxins can co-occur with *N*-nitrosamines. Therefore, we examined whether combined exposure of fumonisins with the known rat oesophageal carcinogen nitrosomethylbenzylamine (NMBA) would have a synergistic effect on oesophageal carcinogenicity, in groups of male BDIV rats. Initial results showed no increase in oesophageal papillomas or cell proliferation in the oesophagus of rats receiving both carcinogens compared to those receiving NMBA alone. No oesophageal papillomas were observed in rats receiving only fumonisin B1 or vehicle only. No abnormalities were found in the livers of any group. Levels of natural fumonisin contamination in the animal feed were low compared to the experimental doses. Urines and tissues of these animals are being examined for altered sphingolipid base composition (see Section 6.1.5).

3.2 Cancer of the stomach

The causes of stomach cancer, one of the commonest malignancies in the world despite decreasing incidence in recent decades, remain largely unknown. The evidence for an association with *Helicobacter pylori* infection has been evaluated in the IARC Monographs programme (Section 2.1.1.4). Case–control epidemiological studies to study further the association with *H. pylori* are described below. Endogenous formation of *N*-nitroso compounds is strongly suspected of playing role, and studies of various related aspects are described in Sections 4.4.2–4.4.5. Screening for stomach cancer (Section 5.3.2) and chemoprevention of precancerous gastric lesions (Section 5.1.3) are both being studied in Venezuela.

3.2.1
Case–control study of stomach cancer in Tachira, Venezuela

N. Muñoz, P. Pisani, M. Benz, H. Ohshima and M. Castegnaro; in collaboration with J.L. Fauchère, Poitiers, France; G. Lopez, W. Oliver, S. Peraza and J. Vivas, San Cristobal, Venezuela; and A. Merrill, Atlanta, USA

A case–control study to identify the main risk factors and to evaluate the efficacy of a screening programme for gastric cancer in Tachira State, Venezuela, is being implemented (see Section 5.3.2). All new and histologically confirmed cases of stomach cancer diagnosed at the Central Hospital in San Cristobal since January 1991 are being included, as well as two controls per case. Information on diet during the year before diagnosis is collected by personal interview with a dietary history questionnaire. Information on screening is retrieved from the records of the Cancer Control Centre. Serum samples to measure antibodies to *Helicobacter pylori* and selected micronutrients are being collected from cases and controls; biopsies of tumorous and non-tumorous gastric mucosa are being collected from the cases to look for genetic alterations.

A total of 208 cases and 360 controls have been interviewed and have provided histological specimens. No association with *H. pylori* was found in a preliminary analysis of the first 119 cases and their controls. However, the serological assay used to detect antibodies to *H. pylori* was shown to be inaccurate. Other serological assays using antigens derived from French

and Venezuelan *H. pylori* strains are being developed in collaboration with Professor Fauchère. Antibodies to *H. pylori* cytotoxin are being measured in sera from the first 100 cases and their controls using immunoblotting (see Section 4.5.1).

Preliminary analysis of the questionnaire data suggests an increased risk associated with high consumption of corn. To explore the possibility of an association with fumonisins (produced by *Fusarium moniliforme*, a common fungus on corn), exposure to these mycotoxins is being assessed in a subsample of cases and controls, using a recently developed biomarker, in collaboration with Dr Merrill and Dr Castegnaro (see Section 6.1.5.2).

Recruitment of cases and controls will continue until December 1995.

3.2.2 Case–control study of stomach cancer in Costa Rica

N. Muñoz; in collaboration with F. Mégraud, Bordeaux, France and R. Sierra, San José, Costa Rica

A pilot case–control study has been initiated to assess whether the *H. pylori* strains isolated from non-tumorous gastric mucosa of 50 patients with gastric cancer differ genetically and/or antigenically from those isolated from 50 patients with chronic gastritis. *H. pylori* strains isolated from these patients are being cultured. DNA is extracted from each strain and the *cagA* gene is detected by PCR using specific primers. *H. pylori* has been cultured from 11 out of 18 patients (5 cases and 6 controls); the presence of *cagA* was detected in 4 of the 5 cases and in all 6 control patients.

3.3 Cancer of the liver

Liver cancer is among the commonest cancers in many developing countries, apparently because of widespread infection with hepatitis viruses and liver flukes, and food contamination with mycotoxins. Studies are in progress to clarify the interaction between such agents at both the epidemiological and mechanistic levels. The Gambia Hepatitis Intervention study is designed to assess the effect of reducing hepatitis virus infection on the incidence of liver cancer (Section 5.1.1).

The liver is also a target organ for specific chemical agents used industrially or medicinally, due to its major role in detoxication of foreign substances in the body. Examples being studied are vinyl chloride, encountered in occupational settings (see below and Section 6.1.7), and tamoxifen, used to treat breast cancer (see Section 2.7.4). The cytochromes P450 are the main enzymes involved in activation processes in the liver, and molecular studies of their mode of action and polymorphisms, are reported in Section 4.1.

3.3.1 Cohort study of hepatocellular carcinoma in HBsAg carriers in Thailand

N. Muñoz, C. Wild and M. Benz; in collaboration with S. Puribañat and P. Srivatanakul, Bangkok, Thailand

The purpose of this project is to identify liver cancer cases developing within a cohort of 1972 male subjects over 30 years of age identified as carriers of the hepatitis B virus surface antigen (HBsAg) in Bangkok and to describe their exposure to selected risk factors for liver cancer. A set of controls matched to the cases by age and period of recruitment will be identified within the cohort. Active follow-up is being conducted at regular intervals for five years and blood and urine specimens are being

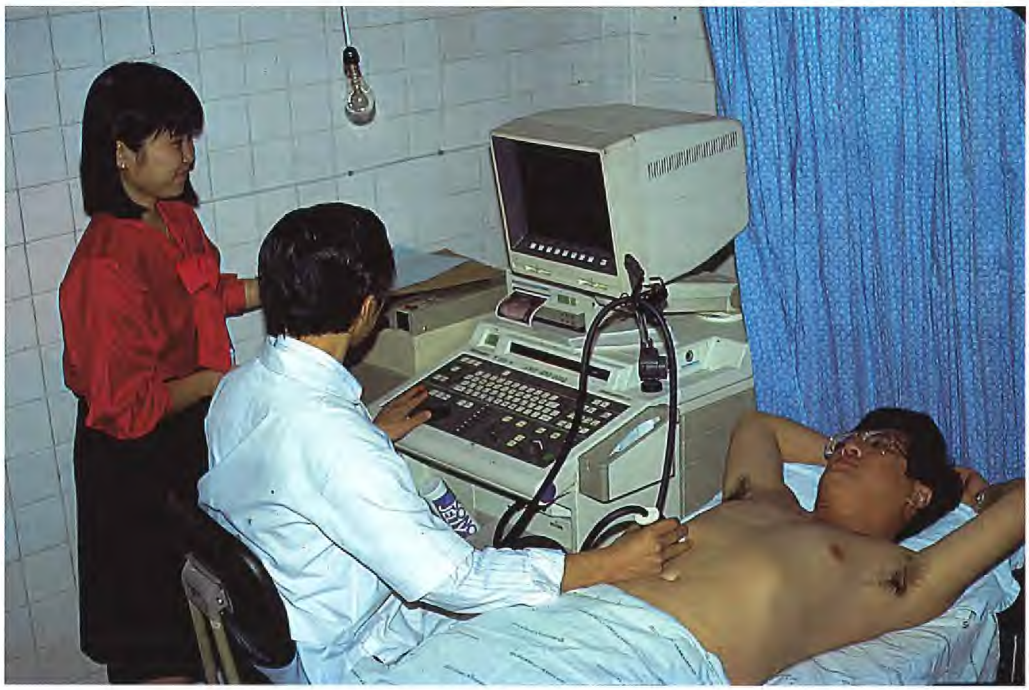


Figure 15. Ultrasound examination for early detection of liver cancer, in Thailand

collected and stored (Figure 15). Biological markers of exposure to aflatoxin and other environmental carcinogens will be measured in these specimens. Exposure to other risk factors such as tobacco smoking and alcohol is assessed through questionnaires. A nested case–control study will be performed with the cases of liver cancer diagnosed up to December 1995.

3.3.2

Epidemiology of cholangiocarcinoma in Thailand

P. Pisani and D.M. Parkin; in collaboration with V. Vatanasapt and S. Sriamporn, Khon Kaen, Thailand

A cohort study has been started in north-eastern Thailand to clarify the role of diet as a source of carcinogens (aflatoxin, nitrate and nitrosamines) and protective agents (some vitamins and anti-oxidants), and as a vehicle for *Opisthorchis viverrini* infection in the etiology of cholangiocarcinoma (CCA) and hepatocellular carcinoma (HCC), in a population at very high risk of CCA. Recruitment exploits a screening programme offered to the whole population of the region. Information on betel-nut chewing, usual dietary intake, tobacco and alcohol consumption, together with socio-demographic variables, is being collected through a personal interview. Blood and urine samples are stored for study of hepatitis B and C infection, intake of aflatoxins and antibodies to *O. viverrini*.

The recruitment of the cohort is approaching the target of 9000 individuals, approximately half men and half women. The number of subjects fully enrolled (blood, faeces and interview data collected) by June 1995 was 8500. A new dietary questionnaire has been designed, based on the results of a cross-sectional survey. Follow-up of the cohort, by linkage with the database of the cancer registry, is in progress.

3.3.3
Aflatoxin, HBV and HCV prevalence surveys in Guinea: a basis for pilot intervention studies

C.P. Wild, B. Chapot and B. Sylla; in collaboration with K. Sidebe, M. Diallo and A. Sylla, Kindia, Guinea

In an initial study in Kindia, Guinea, the prevalence of exposure to aflatoxin and infection with hepatitis B and C viruses was determined in 75 subjects. Over 90% were positive for aflatoxin–albumin adducts in sera and 15% were chronically infected with HBV. A total of eight subjects were positive for HCV antibodies [135]. The prevalence of exposure to HBV and aflatoxin is thus similar to that in other West African countries. Data from the population-based cancer registry in Conakry has shown that hepatocellular carcinoma is by far the most common cancer in men. A more comprehensive survey was therefore organized to better define the geographical variations in prevalence of the above risk factors. Sera were collected from 600 adults in villages in each of four regions of the country (Lower, Middle, Upper Guinea and Guinea Forestière). Overall, 14% of subjects were positive for HBsAg, with a relatively uniform percentage in the different regions of the country. The sera are now being analysed for aflatoxin–albumin adducts. The survey will be repeated to provide data on seasonal variations in aflatoxin exposure. This information should provide a basis for developing and targeting intervention measures to reduce aflatoxin exposure and HBV infection in Guinea.

3.3.4
Exposure to aflatoxin and its metabolism in relation to hepatitis infection

C.P. Wild, I. Chemin and B. Chapot; in collaboration with A.J. Hall, London, UK; T. London, Philadelphia, USA; and H. Whittle, Fajara, Gambia; supported by a grant from the US National Institute of Environmental Health Sciences, No. IP01ESO6052

Individual susceptibility to aflatoxin exposure may depend on expression of carcinogen-metabolizing enzymes; the expression of such enzymes could in turn be influenced by liver injury induced by hepatitis B virus (HBV) [681, 682, 684]. We therefore examined the relation between HBV infection, the activity of a major human liver cytochrome P450 (CYP3A4) and the level of aflatoxin–serum albumin adducts in a large study of chronic HBV carriers and non-carriers in the Gambia. The influence of glutathione *S*-transferase (GST) M1 genotype on aflatoxin–albumin adduct levels was also examined.

The populations of the rural villages of Keneba and Manduar were surveyed in 1974, 1980, 1984 and 1989 for markers of HBV infection and from these surveys a group of individuals were identified as being chronically infected with HBV. These individuals were resurveyed in 1992 to check HBV status. In addition, a comparison group was selected comprising individuals who had either never been positive for HB surface antigen (HBsAg) or had reverted to HBsAg-negative before 1992. Over 350 subjects were tested for aflatoxin–serum albumin adducts, GSTM1 genotype, markers of HBV infection, and serum transaminases. The same subjects were phenotyped for CYP3A4 activity by

Figure 16(a) Gambian children making groundnut (peanut) paste, a source of aflatoxin exposure; (b) groundnuts with fungal contamination of some individual nuts

examining urinary cortisol metabolites. Over 95% of the individuals in the study were positive for aflatoxin–albumin adducts, but there was no association between adduct level and either CYP3A4 phenotype or GSTM1 genotype. In addition, the CYP3A4 activity was not affected by HBV status or serum transaminase levels. The major determinants of aflatoxin–albumin adducts in this study were the season in which the individual was sampled and, to a lesser extent, the geographical location of the individual, those living in rural areas having higher adduct levels than those in periurban areas. These data do not support the hypothesis that GSTM1 genotype or CYP3A4 expression influences the level of aflatoxin binding to albumin.

In a study in Ghana [331], the GSTM1 null genotype was more common among individuals positive for aflatoxin–albumin adducts, but the level of aflatoxin exposure was markedly lower than in the Gambia. It is possible therefore that the impact of polymorphisms in aflatoxin-metabolizing enzymes depends on the level of exposure to the carcinogen. P450s other than CYP3A4, e.g., CYP1A2 and epoxide hydrolase, are involved in aflatoxin metabolism in humans and may be more important at environmental levels of aflatoxin exposure. CYP3A4 does not appear to be induced by chronic HBV infection. However, other P450s should be examined, in view of the specific induction of other isoenzymes, such as CYP2A6, in experimental models of liver injury (see below).

3.3.5

Experimental studies of aflatoxin metabolism and carcinogenicity

C.P.Wild, I. Chemin, P. Chomarat, B. Chapot, C. Kaplanski, M. Lang and R. Montesano; in collaboration with F. Chisari, La Jolla, CA, USA; and L. Cova and J.-L. Riviere, Lyon, France

The modulation of expression of enzymes involved in the metabolism of aflatoxins is being examined in a number of animal models, namely HBV transgenic mice, Peking duck and woodchuck. These models have differing properties which make their study complementary. A number of HBV transgenic mouse lineages are available, providing models in which the degree of liver injury is different depending on the level of expression and secretion of the hepatitis B surface antigen. Woodchucks and Peking ducks represent "natural" infections. The association between woodchuck hepatitis virus (WHV) and hepatocellular carcinoma is well established and follows a chronic infection associated with marked liver pathology. In contrast, infection of Peking ducks with duck HBV (DHBV) has not been associated with development of hepatocellular carcinoma (HCC), other than in Qidong, China, an area of high aflatoxin exposure, and is associated with only mild liver pathology.

3.3.5.1

Hepatitis B transgenic mice

Various strains of HBV transgenic mice exhibiting either chronic progressive liver injury due to accumulation of HBsAg in hepatocytes or an acute liver injury mediated by a cytotoxic T lymphocyte (CTL) response against hepatocytes containing HBV antigens have been examined for expression of a range of cytochrome P450s by immunohistochemistry, Northern blot, Western blot and enzyme activity. These studies show that some specific P450s are increased during liver injury in these models [272] (see also Section 4.1.3). The increase is related to the degree of liver injury associated with HBsAg accumulation in the chronic injury models, but is particularly strong in the acute liver injury model associated with the immune response to HBV antigens. In this model a marked increase in Cyp2a-5 and 1a was observed by immunohistochemistry (Figure 17) but no or little change in Cyp2b, 2c, 2e and 3a. There was a five-fold decrease in total microsomal P450 content three days after CTL injection, with the result that the relative proportion of Cyp2a-5 and 1a compared to other P450s is increased. Individual microsomal P450 enzyme contents measured by immunoblot, hepatic Cyp2a-5 mRNA levels measured by Northern blot analysis and *in vitro* metabolism studies using P450-specific substrates were consistent with the immunohistochemical data. The results suggest that liver cell injury induced by a process of acute fulminant-like hepatitis can lead to the induction of some carcinogen-metabolizing enzymes. The impact of this induction on susceptibility to aflatoxin and the mechanistic basis for the increase is being studied.

In addition, livers from HBV transgenic mice which developed chronic progressive liver injury and eventually HCC were examined for alterations in minisatellite sequences using multilocus probes. Although in human HCC a number of genetic alterations have been observed in oncogenes or tumour-suppressor genes, such changes have not been found in HCC of HBV transgenic mice. Therefore it was of interest to look more generally for genetic rearrangements during hepatocarcinogenesis in this model. No alterations in minisatellite fingerprints were observed in any of the HCC or nodular liver samples compared with normal liver or brain DNA from the same mouse, suggesting that minisatellite rearrangement is an infrequent event during the development of malignancy in these mice.

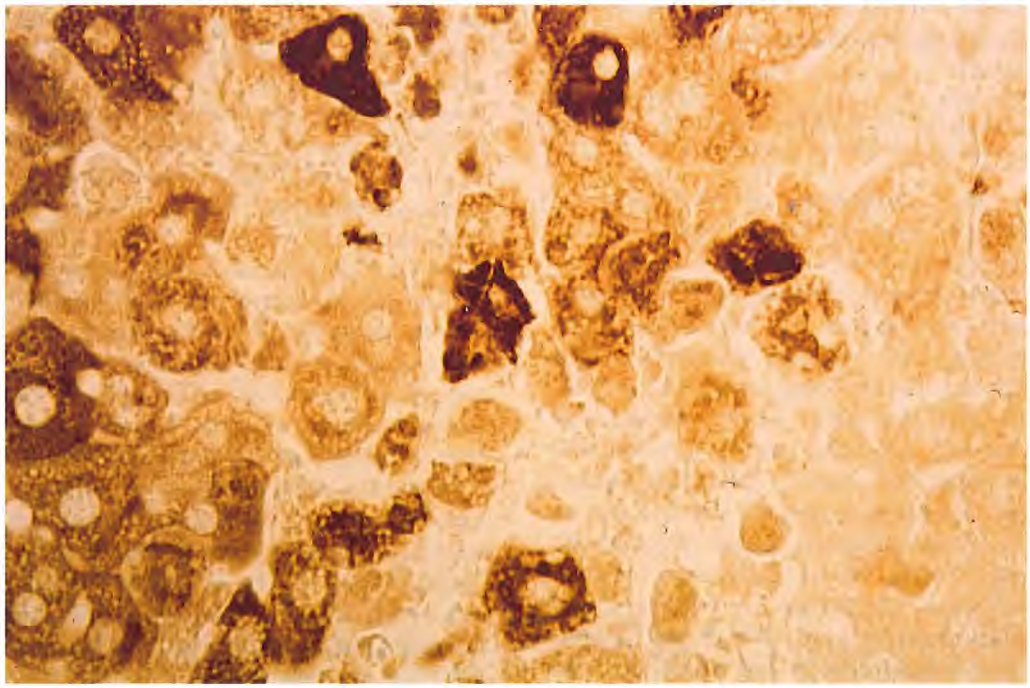


Figure 17. Immunochemical staining of cytochrome P450 2a-5 in liver of transgenic mice (HBV lineage 107.5) three days after injection of cytotoxic T lymphocytes (× 250)

3.3.5.2

Peking duck and woodchucks

Peking ducks inoculated with DHBV initially undergo a phase of viral replication (within one week after inoculation), followed by an asymptomatic, persistent viral infection which is associated with only mild liver pathology. In the current study, the ability of microsomal preparations from DHBV-positive or -negative ducks to metabolize aflatoxin B_1 and other P450 substrates was examined *in vitro*. No differences could be observed between infected animals and controls, either in the acute phase of infection (one week after inoculation) or in the chronic phase (10 weeks after inoculation).

A total of 11 HCC from Qidong, China, were examined for mutations in codon 249 of the p53 gene, but none was found. No mutation at this site was found in four HCC induced by aflatoxin B_1. In humans, the mutation and preferential binding of aflatoxin B_1 to codon 249 occurs at the third nucleotide guanine, while in duck the codon 249 lacks this G residue, which could explain the differences in mutation spectra between the two species [136, 137].

Thirteen woodchucks, caught in the wild, were studied for carcinogen metabolism with respect to WHV infection. Six were chronic carriers of the virus and seven had cleared the infection. The livers of these animals were examined by immunohistochemistry for expression of a range of P450s and GST enzymes. Preliminary results show a marked increase in staining with antibodies to CYP 1A and 2A in infected wood-

chucks and a three-fold higher capacity to activate aflatoxin B_1 *in vitro* in this group.

3.3.5.3

Comparative carcinogenicity

in collaboration with N. Ito and R. Hasegawa, Nagoya, Japan; and W. Anwar, Cairo, Egypt

Aflatoxin–serum albumin and aflatoxin–DNA adducts in the liver were measured in rats, hamsters, guinea-pigs and mice after multiple exposures to aflatoxin B_1. There was a relatively constant ratio between the two parameters across species, with adduct levels falling from rats > guinea pig > hamster > mouse. When data from exposed human populations were included in the analysis, the aflatoxin–albumin adduct levels formed for a given exposure were similar to those seen in the rat (which is sensitive to aflatoxin carcinogenesis) and two orders of magnitude higher than in the mouse (resistant to aflatoxin carcinogenesis).

Further experiments examined the relationship between aflatoxin–serum albumin adducts and genetic damage (micronuclei, chromosomal aberrations) in bone marrow in rats and mice. The level of chromosomal aberrations was about 10 times higher in rats than in mice. Both chromosomal aberrations and micronuclei were correlated with aflatoxin–albumin adducts at the individual level in rats [11].

3.3.6

p53 mutations at A:T base pairs in angiosarcomas of vinyl chloride-exposed factory workers

M. Hollstein, G. Martel-Planche and R. Montesano; in collaboration with C.C. Harris, Bethesda, USA; and M.-J. Marion, Lyon, France. Supported by a grant from the European Commission, No. EV5V-CT92-0199

Occupational exposure to vinyl chloride causes liver angiosarcomas and increases the risk of several other cancers. Loss of p53 function in osteosarcomas and fibrosarcomas can occur by two different mechanisms, *p53* mutation or amplification of the *MDM2* gene. We examined tumours from five vinyl chloride-exposed patients, four with liver angiosarcoma and one with hepatocellular carcinoma, for evidence of *MDM2* proto-oncogene amplification or *p53* mutation in exons 5–8. Amplification of *MDM2* was not found, but in two of the angiosarcomas an AT→TA missense mutation was detected. This type of mutation is expected from binding of vinyl chloride to DNA that results in an etheno-adenine adduct (see also Section 6.1.7) [228].

3.3.7

p53 gene mutations in liver cancers induced by vinyl chloride in rats

O. Froment, A. Barbin and R. Montesano; in collaboration with F. Belpoggi and C. Maltoni, Bologna, Italy

To elucidate molecular mechanisms of chemical carcinogenesis, we have investigated mutation spectra in the *p53* gene in liver tumours induced in Sprague–Dawley rats by vinyl chloride. Among 22 liver angiosarcomas and three hepatocellular carcinomas, point mutations in exons 5 to 8, including nine base-pair substitutions and one deletion, were found in 9 tumours. Most of these were observed at AT base pairs (3 AT→TA; 2 AT→GC and 1 AT→CG). In addition, three GC→AT transitions at non-CpG sites were found. In one vinyl chloride-induced hepatocellular carcinoma, an AT→TA transversion was observed in codon 283. This same tumour was previously shown to contain an H-*ras* gene activated at codon 61 by the same type of base-pair substitution [183].

These results are compatible with the known promutagenic properties of the three DNA etheno adducts formed by vinyl chloride and with their accumulation and persistence in liver DNA (see Section 6.1.7).

3.4 Cancer of the cervix

Epidemiological studies have shown that the association of human papillomavirus with cervical cancer is strong, independent of other risk factors and consistent in several countries. The evidence has been evaluated in the IARC Monographs programme (Section 2.1.1.8). A number of international collaborative efforts in this area have been conducted and/or co-ordinated by IARC, entailing linkage of the latest tools of molecular biology for detection of biological agents, especially human papillomaviruses, with the most advanced epidemiological methodology (Figure 18).

3.4.1 Case–control studies of cervical cancer in Spain and Colombia

N. Muñoz, M. Rosato and A. Arslan; in collaboration with P. Alonso de Ruiz, Mexico City, Mexico; N. Aristizabal and L. Tafur, Cali, Colombia; N. Ascunce and M. Santamaria, Pamplona, Spain; F.X. Bosch, X. Castellsagué, S. de Sanjosé and V. Moreno, Barcelona, Spain; M. Gili, Seville, Spain; L.C. Gonzalez, Salamanca, Spain; E. Guerrero, Madrid, Spain; J. Icenogle, Atlanta, USA; I. Izarzugaza, Vitoria-Gasteiz, Spain; I. Lind, Copenhagen, Denmark; C. Martos and P. Moreo, Zaragoza, Spain; C. Navarro and M.J. Tormo, Murcia, Spain; J. Orfila, Amiens, France; K.V. Shah, Baltimore, MD, USA; P. Viladiu, Gerona, Spain; V. Vonka, Prague, Czech Republic; and B. Wahren, Stockholm, Sweden

Four concurrent case–control studies of risk factors for cervical cancer were conducted in Colombia, a country at high risk for cervical cancer (age-adjusted incidence rate 48 per 100 000) and in Spain, a country at low risk (age-adjusted incidence rates between 5 and 8 per 100 000). Two of

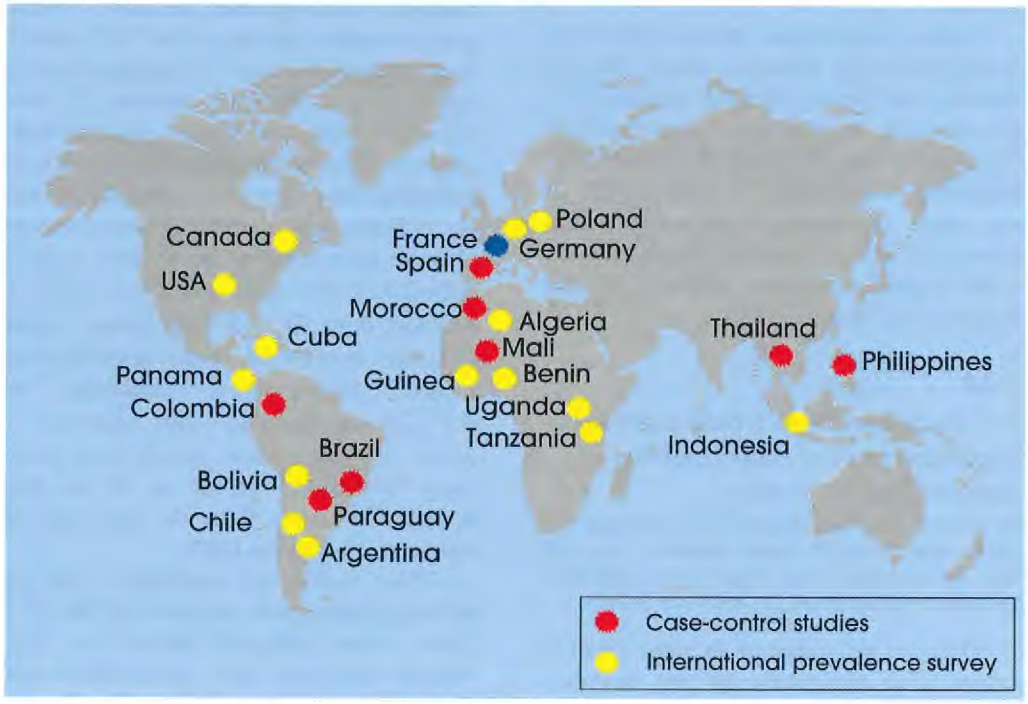


Figure 18. Locations of collaborative studies of human papillomavirus and cervical cancer

the studies included cases of invasive cervical cancer and two included cases of CIN III.

All incident cases of cervical neoplasia occurring in pre-defined populations were invited to participate before treatment. Controls for invasive cancers were selected from among the residents of the province or city. Controls for the cases of CIN III were recruited among women participating in screening programmes or providing a cytological specimen for any other reason. Husbands of cases and controls were also invited to participate. The total number of subjects interviewed was nearly 3000 (918 cases, 912 controls and 1073 husbands of cases and controls).

The results of these four studies clearly established the central role of HPV in the causation of both invasive cervical cancer and CIN III. In addition, they show that hormonal factors may interact with HPV to increase the risk of progression to cancer among women with persistent HPV infections, and that other presumptive risk factors, such as other sexually transmitted agents and tobacco, do not play important roles in cervical cancer development. These results have been published in 24 journal articles.

Further statistical analyses have also revealed that:

Male sexual behaviour and the resulting HPV DNA prevalence appear to be the main determinants of the eight-fold difference in risk of cervical cancer between Spain and Colombia, as can be seen from the data from control women and their husbands presented in Table 7 and Figure 19.

In Spain, an increased risk of cervical cancer was associated with the number of concurrent extramarital contacts with prostitutes, the presence of HPV DNA in exfoliated cells of the penis and antibodies to *Chlamydia trachomatis* in their husbands. In Colombia, low educational level and antibodies to *C. trachomatis* in their husbands were the only factors associated with an increased risk of cervical cancer in their wives.

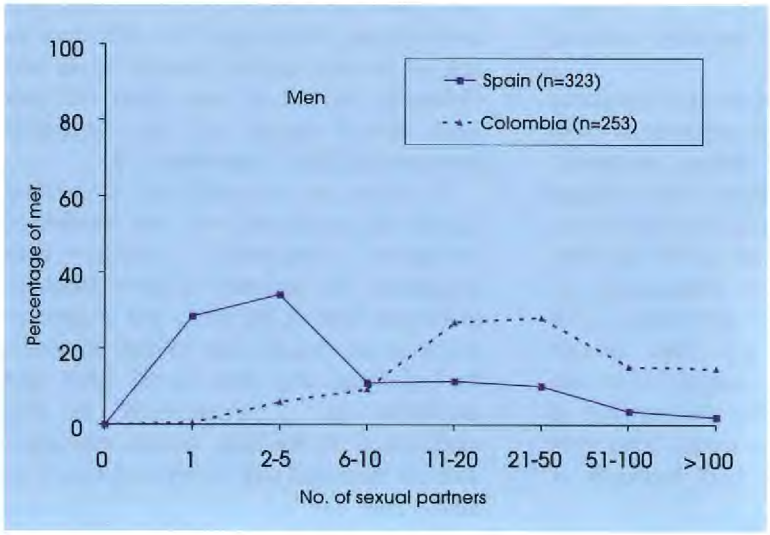
The higher risk of cervical cancer among women of low socioeconomic status may be explicable by a higher prevalence of HPV DNA, a lower use of Pap smears and a higher frequency of husbands' contacts with prostitutes.

CIN III and invasive cervical cancer have very similar profiles of risk factors and none of the risk factors showed consistent differences that would suggest a potential role in the progression from CIN III to invasive cancer [384].

An analysis of the inter-observer variation in histological diagnosis on about 2400 slides revealed excellent agreement (99%) between the original diagnoses and

Table 7. HPV DNA prevalence in women and their partners in Spain and Colombia

	Control women		Husbands of control women	
	Spain	Colombia	Spain	Colombia
Lifetime partners:				
mean/median	2/1	6/1	12/3	41/15
only one	85.8%	59.2%	28.1%	0.4%
HPV DNA prevalence	4.9%	12.9%	3.5%	18.9%



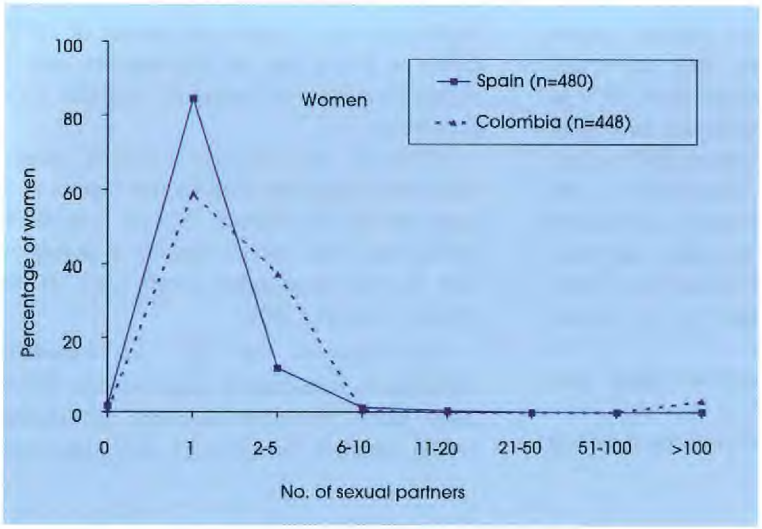


Figure 19. Distribution of numbers of sexual partners among control men and women in Spain and Colombia.

the final panel diagnoses for normal or inflammatory cytology and for invasive cancer. A lower level of agreement was observed for CIN III diagnosis (72%), but this had little impact on the risk estimates for the major risk factors for CIN III [266]

Clinical stage and treatment modality were the main determinants of survival, as indicated by active follow-up of 410 incident cases of invasive cervical cancer during an average of 4.9 years. The presence of HPV DNA was not a prognostic factor, although cases positive for HPV 18 appear

to have a poorer prognosis than HPV 16-positive cases, as well as cases with antibodies to three HPV 16 E7 peptides.

Antibodies to E2, E4, E6, E7, L1 and L2 proteins of HPV 16 were more frequent in women with cervical cancer than among controls women, but this difference was much smaller than that seen for HPV 16 DNA prevalence [217,399,601,666]. Antibodies to HPV 16 virus-like particles detected in a subsample of cases and controls were more frequent in CIN III cases (73% in Spain and 81% in Colombia) than among invasive cervical cancer cases (about 50% in both countries). Among population controls, its prevalence was 3% in Spain and 22% in Colombia, while for CIN III controls, the prevalence was 10% in Spain and 43% in Colombia [419].

The E6/E7 genes in HPV 16 DNA from three specimens showed sequence variation at various positions, with clustering in the amino-terminal half of the E6 protein. These natural variants of HPV 16 differ in immortalizing activity and ability to degrade p53 protein.

3.4.2 Multicentre case–control study of cancer of the cervix

N. Muñoz, J. Deacon, M. Rosato, D. Magnin and A. Arslan; in collaboration with F.X. Bosch, Barcelona, Spain; S. Bayo, Bamako, Mali; N. Chaouki, Rabat, Morocco; S. Chichareon, Hat Yai, Thailand; J. Eluf-Neto, São Paulo, Brazil; C. Ngelangel, Manila, Philippines; P.A. Rolón, Asunción, Paraguay; K.V. Shah, Baltimore, USA; and J. Walboomers and C. Meijer, Amsterdam, Netherlands

This multicentre study is designed to explore risk factors for cervical cancer in areas of the world where the incidence of

Figure 20. Preprocessing of cervical specimens for HPV DNA detection, in Manila, the Philippines

the disease is high and in which few studies have been completed. Particular attention is devoted to aspects of sexual behaviour and other risk factors for which epidemiological evidence is limited or contradictory. These include the role of the male as a vector of the relevant sexually transmitted agent(s), the implications of the practice of prostitution by women and the use of prostitutes by men, the use of oral contraceptives and the role of other sexually transmitted agents.

The results of the hospital-based case–control study carried out in Brazil confirm the central role of HPV and show an additional independent effect of hormonal factors (parity and oral contraceptives) among HPV DNA-positive women [149].

Antibodies to HPV 16 E6 and E7 proteins detected by radioimmunoprecipitation assay were more common in cases (54% for E6 and 30% for E7) than among controls (6% for E6 and 5% for E7). The most marked contrast between cases and controls was observed for sera with high antibody titres (41% in cases and 0.5% in controls). Reactivity to the E6 protein was higher in cases with stages II–IV (63%) than in cases with stage I (31%). These results confirm the association of HPV with cervical cancer previously established by HPV DNA assays and suggest that HPV serological assays may be useful in clinical management of HPV-associated cervical cancers [600].

A preliminary analysis of the HPV DNA prevalence among husbands of cases and controls (42% and 48% respectively) did not show an association with the risk of cervical cancer in their wives, as was observed in our studies in Colombia. A high background prevalence of HPV in the male population may preclude detection of any association.

Collection of data and specimens has been completed in Mali, Morocco, Paraguay, Philippines and Thailand, as have most of the PCR-based HPV assays (Figure 20). Preliminary results confirm the results of previous studies. The prevalence of HPV DNA in exfoliated cells among cases ranged from 83.3% in Paraguay to 86% in the Philippines, and in biopsy specimens reached 95.1% in Morocco. Among controls, HPV DNA prevalence ranged from 9.1% in the Philippines to 33.3% in Mali. However, as a high proportion of the specimens from Mali and Paraguay were β-globin-negative, these preliminary results should be interpreted with caution.

All specimens negative for β-globin amplification were further processed by extracting the DNA and re-running the PCR-based HPV assays, and those specimens positive for unidentified HPV types are being tested with additional type-specific probes. Statistical analysis of the individual studies will be completed in 1996. A pooled analysis including the 1398 cases, 1365 controls, 466 husbands of cases and 371 husbands of controls will subsequently be carried out.

3.4.3 International prevalence survey of human papillomavirus markers in cervical cancer tissue and sera

N. Muñoz and D. Magnin; in collaboration with E. Alihonou, Cotonou, Benin; S. Bayo, Bamako, Mali; F.X. Bosch and V. Moreno, Barcelona, Spain; H. Cherif Mokhtar, Sétif, Algeria; S. Chichareon, Hat-Yai, Thailand; A. Daudt, Porto Alegre, Brazil; E. de los Rios, Panama City, Panama; A. Jansen, M. Manos, R. Kurman and K.V. Shah, Baltimore, USA; P. Ghadirian, Montreal, Canada; J.N. Kitinya, Dar es Salaam, Tanzania; M. Koulibaly, Conakry, Guinea; C. Ngelangel, Manila, Philippines; J. Peto, London, U.K.; Ll. M. Puig Tintoré, Barcelona, Spain; J.L. Rios-Dalenz, La Paz, Bolivia; Sarjadi, Semarang, Indonesia; M. Schiffman, Bethesda, USA; A. Schneider, Jena, Germany; M. Sherman, Washington D.C., USA; L. Tafur, Cali, Colombia; A.R. Teyssie, Buenos Aires, Argentina; P.A. Rolón, Asunción, Paraguay; M. Torroella, Havana, Cuba; A. Vila Tapia, Concepción, Chile; H.R. Wabinga, Kampala, Uganda; and W. Zatonski, Warsaw, Poland

This project was designed to determine whether the association between HPV infection and cervical cancer is consistent

worldwide and to investigate geographical variation in HPV type-distribution. Over 1000 specimens from consecutive cases of invasive cervical cancer were collected and stored frozen in 22 countries. Histological slides from all cases were reviewed centrally to confirm the diagnosis and assess histological characteristics. PCR-based assays capable of detecting at least 25 different HPV types were used. A generalized linear Poisson model was fitted to the data on viral types and geographical region to assess geographical heterogeneity. HPV DNA was detected in 93% of the tumours, with no significant variation in HPV positivity between countries. HPV 16 was present in 50% of the specimens, HPV 18 in 14%, HPV 45 in 8% and HPV 31 in 5%. HPV 16 was the predominant type in all countries except Indonesia, where HPV 18 was more common. There was significant geographical variation in the prevalence of some less common virus types. A clustering of HPV 45 was apparent in western Africa, while HPVs 39 and 59 were largely confined to Latin America (Figure 21). In squamous cell tumours, HPV 16 predominated, but in adenocarcinomas and adenosquamous tumours HPV 18 was predominant. A new HPV type was also discovered [477]. Our results confirm the role of HPV, a sexually transmitted agent, as the central etiological factor for cervical cancer worldwide. They also suggest that most genital HPVs are associated with cancer, at least occasionally. The demonstration that over 20 different HPV types are associated with cervical cancer has important implications for prevention strategies including vaccine development [73].

Further virological and serological assays are in progress to characterize the HPV DNA-negative cases. An ecological analysis will also be carried out using the information on the main risk factors for cervical cancer that was collected by interview.

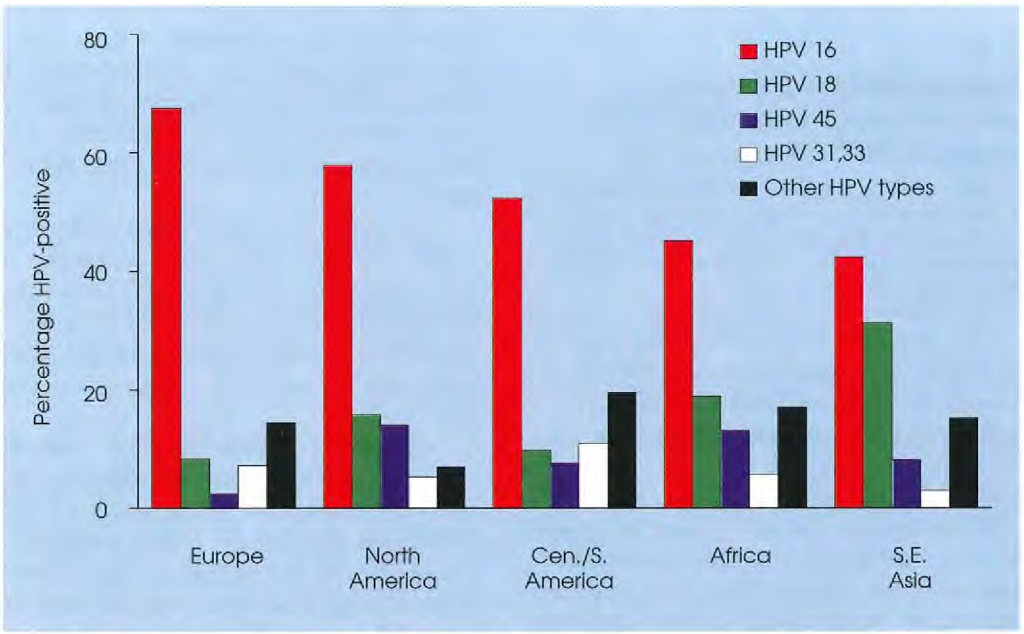


Figure 21. HPV type distribution by geographical region (percentages of subjects positive for HPV types 16, 18, 31 and 33, 45 or others)

3.4.4
Studies of high-risk groups for cervical cancer in Spain and Colombia

N. Muñoz; in collaboration with N. Aristizabal and L. Tafur, Cali, Colombia; F.X. Bosch and S. de Sanjosé, Barcelona, Spain; and V. Palacio and S. Vazquez, Oviedo, Spain

As a complement to the case–control studies, the prevalence of CIN lesions was compared in a group of prostitutes and non-prostitutes from Spain and Colombia. No significant difference was found in the prevalence of CIN between the two countries, either among prostitutes (2.5% in Spain and 1.8% in Colombia) or among non-prostitutes (1.2% in Spain and 1.1% in Colombia). These results could suggest that the eight-fold difference in risk of cervical cancer between the two countries is due to a higher prevalence in Colombia of factors acting in the progression from CIN to invasive cancer [129].

3.4.5
Comparison of two sampling methods from the normal cervix in assessing HPV DNA prevalence

N. Muñoz and D. Magnin; in collaboration with F.X. Bosch and Ll.M. Puig Tintoré, Barcelona, Spain; S. Chichareon, Hat-Yai, Thailand; C. Ngelangel, Manila, Philippines; and J. Walboomers, Amsterdam, Netherlands

To assess the importance of the type of specimen in measurement of HPV DNA prevalence in non-neoplastic uterine cervix, a validation study is being carried out in the Philippines, Spain and Thailand. Cervical scrapes and biopsies are being collected in 300 women with normal cytology in whom hysterectomy is performed for reasons other than cervical cancer. The field work is planned to be completed in 1995 and the HPV DNA assays in 1996.

3.4.6
Cohort study on HPV, hormonal contraception and cervical neoplasia

N. Muñoz; in collaboration with M. Ronderos, O. Orozco, Bogotá, Colombia; O. Meirik, Geneva, Switzerland; K. Shah, Baltimore, USA; and J. Walboomers, Amsterdam, Netherlands

A cohort study has been initiated in Bogotá, Colombia to study the natural history of HPV infection and in particular to identify the determinants of progression to persistent HPV infection and cervical neoplasia. Special attention is being paid to the role of hormonal contraception as a predictor of progression in women with HPV infection.

Between November 1993 and May 1995, a cohort of 2100 women 13–69 years of age was recruited from four health districts of Bogotá. At study entry, a detailed questionnaire was administered followed by a gynaecological examination and collection of exfoliated cervical cells for a Pap-smear and HPV DNA detection. Serum samples were also collected. These women will be followed up for a minimum of three years, with a brief questionnaire and collection of cervical cells every six months. A total of 758 women have so far undergone one follow-up examination and 123 two examinations.

A preliminary analysis based on the first 1118 women recruited revealed a prevalence of 5.7% of squamous intraepithelial lesions (SIL), 4.3% for low-grade SIL and 1.4% for high-grade SIL. The prevalence of hormonal contraceptive use was 14.3%.

A random sample of 200 cervical specimens were selected for detection of HPV DNA using the latest version of the PCR-based assay at Dr Shah's laboratory. The prevalence was 18.2% overall, and was twice as high in women under 24 years of age (27%) as in women over 35 years (14.5%) (Figure 22). An ELISA version of the PCR-based assay developed at Dr

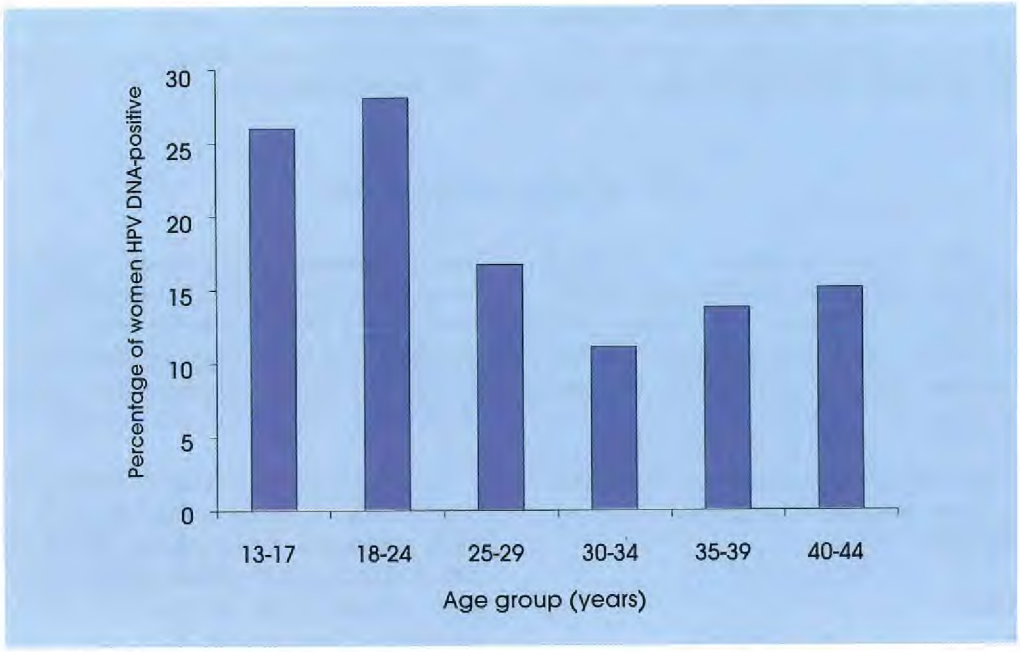


Figure 22. Prevalence of HPV DNA in cervical specimens from Bogotá, Colombia, by age

Walboomers' laboratory is being transferred to Bogotá for testing all the specimens derived from this study.

3.4.7 Prospective study of CIN lesions in Thailand

D.M. Parkin, P. Pisani and N. Muñoz; in collaboration with V. Vatanasapt and S. Sriamporn, Khon Kaen, Thailand

Unambiguous evidence for the hypothesis that some types of human papillomavirus (and possibly other sexually transmitted infective agents) are the major cause of cancer of the cervix can be provided only by prospective studies in which the presence of viral DNA in epithelial cells is assessed before the occurrence of the malignant transformation. Moreover, the role of the infection in the process of progression or regression from non-invasive types of neoplasia to invasive cancer can only be described by prospective observation.

A cohort study on the association between sexually transmitted infective agents and the incidence of CIN lesions and cervix cancer has been initiated, taking advantage of an on-going cohort study on liver cancer conducted in a region of north-eastern Thailand (see Section 3.3.2), where cervix cancer is the second most frequent cancer of females. Women enrolled provide interview data on their reproductive history and exposure to sources of exogenous hormones, and samples of blood and cervical exfoliated cells which are appropriately processed and stored in a biological bank at –20°C for future analysis. The cohort is

being followed up by the Khon Kaen cancer registry to identify incident cases of CIN I–III, carcinoma *in situ* and invasive cancer. The most accurate and sensitive techniques will be used to assess the presence of viral DNA in the stored cells.

3.5 Cancer of the brain

With the exception of inherited neoplastic syndromes involving the nervous system, the etiology of human brain tumours is still largely unknown. The only exposure unequivocally linked to brain tumours is therapeutic X-irradiation, particularly in children. Epidemiological studies are being complemented by research into the molecular characteristics of such tumours.

3.5.1 Brain tumours in children

J. Little and R. Saracci; in collaboration with P. Boyle, Milan, Italy; N.W. Choi, Winnipeg, Canada; S. Cordier, Paris, France; G. Filippini, Milan, Italy; R. Gurevicius, Vilnius, Lithuania; E.A. Holly, San Francisco, USA; M. McCredie, King's Cross, Australia; B. Modan, Tel Hashomer, Israel; B. Mueller, Seattle, USA; R. Peris-Bonet, Valencia, Spain; and S. Preston-Martin, Los Angeles, USA

Data collection has been completed in all of the centres. In centre-specific analyses for New South Wales, Australia (McCredie *et al.*, 1994, *Int. J. Cancer*, **56**, 6–10, 11–15) and Milan, Varese and Como, Italy (Filippini *et al.*, 1994, *Int. J. Cancer*, **57**, 769–774), a positive association with passive exposure of the mother to tobacco smoke during the index pregnancy was found. In the study in New South Wales, the risk of childhood brain tumours increased with increasing consumption of cured meats during pregnancy, which is consistent with some other reports. A centre-specific analysis for Ile de France (Cordier *et al.*, 1994, *Int. J. Cancer*, **59**, 776–782) showed a statistically significant positive association with exposure of the child to tobacco smoke during his/her lifetime. In addition, there were statistically significant positive associations with the child having lived on a farm, having lived in a house treated with pesticides, and having used anti-histamines. Intake of vitamin supplements during childhood was associated with a decrease in risk.

In a preliminary combined analysis of data from five of the ten centres, there was a weak association with a family history of cancer. This was not related specifically to brain tumours or to any reported genetic syndromes. There was no association with reported congenital anomalies in the index child.

3.5.2 Brain tumours in adults

J. Little and R. Saracci, in collaboration with A. Ahlbom, Stockholm, Sweden; M. Blettner, B. Schlehofer and J. Wahrendorf, Heidelberg, Germany; P. Boyle, Milan, Italy; N.W. Choi, Winnipeg, Canada; S. Cordier, Paris, France; R. Gurevicius, Vilnius, Lithuania; G. Howe, New York, USA; J. McNeil, Melbourne, Australia; F. Ménégoz, Meylan, France; B. Modan, Tel Hashomer, Israel; S. Preston-Martin, Los Angeles, USA; and P. Ryan, Adelaide, Australia

Data collection has been completed in all ten centres, and centre-specific and combined analyses are in progress. The analysis for Melbourne (Giles *et al.*, 1994, *Int. J. Cancer*, **59**, 357–362) adds only limited support to the *N*-nitroso compound hypothesis for the etiology of gliomas, while the analysis for Heidelberg (Steindorf *et al.*, 1994, *Int. J. Epidemiol.*, **23**, 451–457) suggests absence of an association between nitrate levels in drinking water and incidence of brain tumours.

In a preliminary combined analysis of data from seven centres, there was no evidence that glioma or meningioma occurring in adult life is associated with a family history of cancer or with a family history of epilepsy. Tuberous sclerosis and neurofibromatosis in either the index subject or his/her relatives was reported for less than 1% of cases.

3.5.3

Molecular mechanisms underlying the development of brain tumours

H. Ohgaki and P. Kleihues; in collaboration with R. Eibl, B Lüdeke and I. Peterson., Zürich, Switzerland; and L. Anker and M. Westphal, Hamburg, Germany

Our studies have the following objectives: (i) to investigate whether mutations in transformation-associated genes in human brain tumours are indicative of a causation by environmental carcinogens; (ii) to identify the sequence of genetic alterations associated with brain tumour evolution and progression; and (iii) to analyse the etiopathogenesis of inherited brain tumour syndromes, particularly those caused by *p53* germline mutations. In addition, transgenic brain transplants were used to study the effect of specific oncogenes on the developing nervous system [141].

Diffusely infiltrating low-grade astrocytomas (WHO Grade II) have an inherent tendency for progression to anaplastic astrocytoma (WHO Grade III) and glioblastoma (WHO Grade IV). This change is due to the sequential acquisition of genetic alterations, several of which have recently been identified. In low-grade astrocytomas, *p53* mutations with or without loss of heterozygosity on chromosome 17p are the principal detectable change [275,427]. These mutations persist during tumour progression and long-term culture of glioma cells *in vitro*. Anaplastic astrocytomas contain *p53* mutations at an overall incidence of 34% and, in addition, loss of heterozygosity on chromosome 19q and frequent homozygous deletion of the *p16* tumour-suppressor (MTS-1) gene. The most malignant astrocytic neoplasm, the glioblastoma, further shows loss of chromosome 10 and amplification of the epidermal growth factor receptor (EGF-R) gene at overall incidences of 66% and 34%, respectively. The type and distribution of *p53* mutations in astrocytic brain tumours are not suggestive of specific environmental agents operative in their etiology [275, 315, 427]. A new *p53* germline mutation (deletion of codon 236) was identified in a Swiss family, which was associated with four brain tumours in only two generations [318]. The role of the *Fas* gene in brain tumour progression has also been investigated (see Section 3.5.4).

We have modified the DNA sequence protocol (dideoxynucleotide method of Sanger) for PCR products by introducing a pre-incubation step with the first base to be incorporated in the extended primer sequences. This allows the reading of the entire sequence, including the bases closest to the primer [476].

3.5.4

Role of the *Fas* gene in brain tumorigenesis

O. Tachibana, H. Nakazawa, P. Kleihues and H. Ohgaki

Recent results from our own and other laboratories suggest a critical role of inhibited apoptosis (programmed cell death) in carcinogenesis. To determine whether such alterations in the *Fas* gene play a role in malignant progression of melanomas and glioblastomas, we have studied *Fas* expression in normal counterparts of these cells and analysed mutations of the cytoplasmic / signal transduction / death domain and transmembrane domain in the tumours.

A total of 34 astrocytic tumours (4 grade I, 9 grade II, 12 grade III and 9 grade IV) were examined for expression and mutation of the *Fas* gene, which is not expressed in normal brain cells. Many of these tumours expressed this gene, with a higher prevalence in higher grades of tumour (e.g., 11% in grade II, 50% in grade III and 100% in grade IV). Interestingly, one of grade III and two of grade IV samples expressed RNA coding for a soluble form of *Fas* lacking the transmembrane sequence. Further analysis confirmed that this was derived from alternative splicing of the *Fas* gene [603].

3.6 Cancer of the urinary tract

Urinary tract tumours comprise mainly those of the urinary bladder and kidneys. The common feature of these sites is their role in the elimination from the body of ingested foreign substances and their metabolites. As such, many of these tumours are associated with exposure to chemical carcinogens, including those in tobacco smoke. Bladder cancer is additionally associated with infection with *Schistosoma* parasites(see Section 2.1.2). Kidney cancers are relatively rare, but bladder cancer is the eighth commonest in men worldwide.

3.6.1

Case-control studies of bladder cancer in Egypt

P. Boffetta; in collaboration with W. Anwar and A. Samy Ibrahim, Cairo, Egypt; R. Bedwani and E. Rangatanam, Alexandria, Egypt; and C. La Vecchia, Milan, Italy

Bladder cancer incidence is very high in Egypt (17.5% of all cancers in the Delta area), mainly due to chronic infection with *Schistosoma haematobium* [33]. The areas of Alexandria and Cairo have many industries that may entail risks of bladder cancer, such as rubber, dye and textile manufacture. Therefore, the roles of occupational exposures, dietary factors, tobacco smoking, as well as genetic factors are being studied. A hospital-based case–control study has been started in Alexandria to involve approximately 400 male cases and an equal number of controls. A similar project is planned in Cairo. History of *Schistosoma* infection is checked via ELISA tests and egg search in urine. Blood, urine and bladder tissue samples are collected for glutathione *S*-transferase M1 genotyping and NAT2. Results of the study in Alexandria are expected in 1996.

3.6.2

Epidemiology of nephropathy and urinary tract tumours

M. Castegnaro and J. Estève; in collaboration with N.E Day and C. Gill, Cambridge, UK; and I.N. Chernozemsky and I. Nikolov, Sofia, Bulgaria

A first epidemiological study of Balkan endemic nephropathy (BEN) and urinary tract tumours was published in 1977 by Chernozemsky *et al.* New data on cancer incidence in the BEN villages were analysed for the period 1975–89 to assess in particular whether the cancer incidence rates remain as high as found in the original study, which was based on the period 1965–74. Special attention was given to sub-sites of the urinary system. A relative risk of about 30 for cancer of the renal pelvis and ureter was found in villages with high incidence of BEN compared with unaffected villages; women were more affected than men.

3.6.3
Mechanism of action of ochratoxin A

M. Castegnaro and H. Bartsch; in collaboration with I.N. Chernozemsky and I. Nikolov, Sofia, Bulgaria; A. Leszkowicz and Y. Grosse, Toulouse, France; and U. Mohr, J. Steinman and T. Tillmann, Hannover, Germany

A two-year bioassay showed that ochratoxin A induced kidney tumours in male DA and Lewis rats, and to a lesser extent in female Lewis rats, while no kidney tumours were found in female DA rats. This is consistent with the hypothesis that slow metabolizers of debrisoquine (female DA rats are slower metabolizers than Lewis) may be less susceptible to ochratoxin A carcinogenicity than fast metabolizers (Castegnaro *et al.*, 1989, *Xenobiotica*, **19**, 225–230). Administration of 2-mercaptoethane sulfonic acid sodium salt (Mesna) did not reduce the incidence of tumours in either strain. Analysis of DNA adducts in various organs from a selection of animals in each group seems to confirm the hypothesis that slow debrisoquine metabolizers are less susceptible to the genotoxic activity of ochratoxin A, more adducts being detected in the kidneys of male than female rats. The analysis of adducts in other organs (bladder, liver, testis, gonads) is in progress.

3.6.4
p53 gene mutations in kidney tumours

H. Ohgaki and P. Kleihues; in collaboration with I. Petersen, Zürich, Switzerland

Chronic abuse of the analgesic drug phenacetin is associated with an increased risk of development of transitional cell carcinomas of the urinary tract. It is unclear whether phenacetin acts through chronic tissue damage (phenacetin nephropathy) or via a genotoxic metabolite causing promutagenic DNA lesions. Among 15 urothelial carcinomas from 13 patients with evidence of phenacetin abuse, we found that 57% of the tumours contained *p53* mutations. These were neither specific mutations nor mutational hot-spots, suggesting that phenacetin may act through chronic tissue damage.

Urothelial carcinomas located in the renal pelvis and in the ureter of the same patient exhibited two different mutations, strongly suggesting that they developed independently. Another patient had tumours in the renal pelvis and bladder, both of which contained the same *p53* mutation, indicating intracavitary metastatic spread. This demonstrates that screening of *p53* mutations allows the determination of the clonal origin of tumours in patients with multiple primary and metastatic lesions. None of the tumours investigated contained mutations in codons 12, 13 or 61 of H-*ras* or K-*ras* protooncogenes [475].

3.6.5
Genetic alterations in bladder cancers attributable to exposure to aromatic amines

M. Hollstein, G. Martel-Planche and R. Montesano; in collaboration with J. Lewalter and M. Stephan-Odenthal, Leverkusen, Germany; and P. Vineis, Turin, Italy

The main objective of this study was to examine the prevalence and the patterns of *p53* mutation in samples of bladder cancers originating from industrial workers specifically exposed to aromatic amines and to distinguish possible differences from bladder cancers associated with tobacco smoke. A similar prevalence (~40%) and patterns of p53 mutations were found in the two groups of patients, and the p53 mutations were found predominantly in high-grade tumours, with none at CpG dinucleotides.

In accordance with previously published data, mutations in H-*ras* occur very rarely [155].

3.7 Cancer of the lung

Lung cancer is the most frequent cancer worldwide—some 900 000 new cases are estimated to have arisen in 1985. Around three quarters of these are due to tobacco smoking (most of the cases in men, and about half of those in women). Studies at IARC are oriented mainly towards identifying causes of lung cancer in non-smokers, but also to refining our understanding of the molecular and biological processes involved, including possible genetic susceptibility.

3.7.1

Case–control study of lung cancer in northern Thailand

D.M. Parkin, P. Boffetta and P. Pisani; in collaboration with P. Srivatanakul, Bangkok, Thailand; N. Martin, Chiang Mai, Thailand; and V. Saensingkaew, Bangkok, Thailand

The incidence of lung cancer in the northern part of Thailand is quite high, especially in females. The presence of numerous coal-fired electricity-generating plants in one northern province (Lampang) has led to local concern about a possible role of air pollution in this phenomenon.

Cancer registration in Lampang province confirmed the relatively high rates of lung cancer (age-standardized rate 41.8 per 10^5 in men; 20.1 per 10^5 in women), but geographical distribution of cases appears to be unrelated to the site of the plants. A case–control study comparing 200 cases of lung cancer with two groups of controls (200 hospital controls and 200 community controls, drawn at random from the population of the province) was started in 1993. Factors under investigation include place of residence, habits of tobacco use, exposure to domestic smoke, cooking practices. Place of residence will be taken as the variable of interest with respect to air pollution, drawing upon environmental measurements of arsenic and cadmium in different areas. Biological samples (blood, urine) from all subjects are being stored for analysis of heavy metals or metabolites and adducts of components of tobacco smoke. Data collection was completed during 1995.

3.7.2

Multicentric case-control study of lung cancer in non-smokers

R. Saracci, P. Boffetta, R. Winkelmann and G. Ferro; in collaboration with W. Ahrens, Bremen, Germany; S. Benhamou, Villejuif, France; S.C. Darby, Oxford, UK; F. Forastiere, Rome, Italy; C.A. González, Barcelona, Spain; J. Trédaniel, Paris, France; S.K. Jindal, Chandigarh, India; A. Mendes, Lisbon, Portugal; F. Merletti, Turin, Italy; G. Pershagen, Stockholm, Sweden; L. Simonato, Padua, Italy; H. Wichmann, Munich, Germany; and C. Winck, Porto, Portugal

Environmental tobacco smoke (ETS) is a likely cause of lung cancer [619], while evidence of an association with other adult neoplasms [617], childhood neoplasms [616] and non-neoplastic respiratory diseases [618] is inconclusive. However, the quantitative aspects of the association between ETS exposure and lung cancer risk are not yet well established, nor is the interaction between exposure to ETS and exposure to other carcinogens.

An international collaborative case–control study initiated in 1988 is investigating the relationship between exposure to ETS and to other environmental and occupational risk factors and the risk of lung cancer in subjects who have never smoked tobacco. A common questionnaire on exposure to ETS was adopted as well as a common basic protocol. Over 600 cases and 1200 controls have been enrolled in 12 centres in Europe and India. Information on exposure to occupational carcinogens, urban air pollution, background radiation and

dietary habits, as well as lifelong exposure to ETS, has been collected by personal interview of cases and controls. Self-reported (non-)smoking status is cross-checked by interview of spouses, and measurement of cotinine levels in urine, in a subsample of subjects. Data collection was completed in 1994, and the analysis is in progress.

3.7.3
Multicentric case–control study of lung cancer in smokers

R. Saracci, P. Boffetta and G. Ferro; in collaboration with W. Ahrens, Bremen, Germany; S. Benhamou, Villejuif, France; S.C. Darby, Oxford, UK; F. Forastiere, Rome, Italy; C.A. González, Barcelona, Spain; S.K. Jindal, Chandigarh, India; F. Merletti, Turin, Italy; G. Pershagen, Stockholm, Sweden; L. Simonato, Padua, Italy; and H. Wichmann, Munich, Germany

In parallel to the study on non-smokers described above, smoking cases of lung cancer and controls have been enrolled in a multicentric study in 10 centres in Europe and India. Standard information on tobacco smoking, exposure to occupational carcinogens, urban air pollution, dietary habits and family history of cancer has been collected from about 9000 cases and 10 000 controls. Data will be ready for a common analysis in 1995; this analysis will focus on the interaction between tobacco smoking and occupational and environmental exposures, and on the effect of very light smoking. It is planned in addition to analyse mutations in specific genes in lung tumour samples of selected subgroups of cases with high exposure to selected carcinogens.

3.7.4
Case–control study of environmental tobacco smoke and genetic succeptibility to lung cancer

P. Boffetta, M. Lang, M. Friesen, S. Atawodi, J. Hall and R. Saracci; in collaboration with W. Ahrens, Bremen, Germany; S. Benhamou, Villejuif, France; V. Constantinescu, Bucharest, Romania; F. Forastiere, Rome, Italy; A. Menezes, Pelotas, Brazil; F. Merletti, Turin, Italy; L. Simonato, Padua, Italy; L. Tammilehto and K. Husgafvel-Pursiainen, Helsinki, Finland; C. Winck, Porto, Portugal; and D.G. Zaridze, Moscow, Russia

Among lung cancer cases, non-smokers have been exposed on average to lower levels of carcinogens than smokers; genetic susceptibility may play a greater role in risk of lung cancer in the former group of cases.

In some of the centres participating in the case–control study on lung cancer and environmental tobacco smoke (ETS) and in additional centres, blood samples are being collected from non-smoking lung cancer cases, smoking lung cancer cases and non-smoking control subjects, in order to evaluate genetic polymorphism of some enzymes implicated in the metabolism of lung carcinogens and therefore in determining individual susceptibility to cancer, such as certain cytochromes P450 (CYP1A1 and 2D6) and glutathione *S*-transferase M1.

In addition, the levels of DNA repair enzymes (O^6-methylguanine-DNA methyltransferase and methylpurine- and formamidopyrimidine-DNA glycosylases) will be determined, and the formation of haemoglobin adducts with tobacco-specific nitrosamines will be measured. Finally, genetic alterations in the *p53* gene and K-*ras* mutations in lung neoplastic tissue will be determined. Enrolment of patients and collection of samples started in 1995; the study will be completed in 1997.

3.7.5
p53 gene mutations in lung tumours

H. Ohgaki and P. Kleihues; in collaboration with R. Reichel and I. Petersen, Zürich, Switzerland

In a total of 26 primary human lung tumours and 60 metastases derived from them, the *p53* tumour-suppressor gene was analysed for alterations. Mutational inactivation was identified in four out of five

squamous cell carcinomas, in three out of nine adenocarcinomas, and in two out of nine small-cell carcinomas, the overall incidence being 35%. Point mutations occurred at a similar incidence in exons 5 to 8, with a preference for G →T transversions. In seven out of nine cases (78%), mutations were identical in the primary tumour and all of its metastases, indicating that in lung tumours, *p53* mutations usually precede metastatic spread. In one case, a kidney metastasis exhibited the same mutation as the primary squamous cell carcinoma, whereas a liver metastasis showed no mutation, indicating heterogeneity of the primary lung neoplasm and selective metastasis of mutated and non-mutated tumour cells to kidney and liver, respectively. Only in one liver metastasis was a mutation identified which was not present in either the primary lung tumour or in a kidney metastasis, suggesting that *p53* mutations may occasionally occur after metastatic spread [504].

3.8 Cancer of the head and neck

Cancers of the head and neck are mainly those of various subsites of the mouth, and the pharynx. They are particularly common in the Indian subcontinent, due to the habit of tobacco chewing, but the incidence in other parts of the world is rising, probably because of increasing tobacco and alcohol consumption.

Preventive actions aimed at reducing the scale of oral cancer in India are being studied, from the points of view of both primary (chemoprevention; see Section 5.1.5) and secondary (screening; see Section 5.3.4) prevention.

3.8.1 Oral cancer in the Indian subcontinent

R. Sankaranarayanan, N. Muñoz and D.M. Parkin; in collaboration with P.C. Gupta, Bombay, India; and R. Maher and S.H. Zaidi, Karachi, Pakistan

A high incidence of oral cancer is observed in several regions of the Indian sub-continent. The causal association of tobacco chewing (either alone or in combination with other ingredients such as betel leaf, areca nut and slaked lime), tobacco smoking and alcohol with oral cancer in this region has been well established [208]. However, uncertainty exists regarding the role in oral carcinogenesis of areca nut chewing and betel quids without tobacco. Although the presence of human papillomavirus (HPV) DNA in biopsy specimens from squamous cell carcinomas has been reported in various case series, this association has not been tested in case–control studies. A case–control study involving 350 cases of oral cancer and 700 age- and sex-matched controls is being conducted in Karachi, Pakistan, to address the oral carcinogenic potential of chewing quids without tobacco, areca nut chewing and HPV. Recruitment of cases and controls will be completed in two years.

3.8.2 Case–control studies of oral cancer

P. Boffetta and R. Winkelmann; in collaboration with P. Boyle, Milan, Italy; L. Garfinkel, New York, USA; A. Mashberg, East Orange, USA; and F. Merletti, Turin, Italy

Alcohol drinking and tobacco smoking are established risk factors for oral cancer; however, their interaction has not been studied in detail; in particular, little is

known on the effect of smoking under extreme circumstances of drinking, such as in very heavy drinkers and abstainers; and few data have been reported on the effect of these exposures on oral cancer survival. A case–control study in a population of US veterans characterized by a very high consumption of alcoholic beverages showed an increase in cancer risk up to the level of 35 cigarettes per day and 21 whisky equivalents per day, and no further increase for higher levels of exposure to either factor, and no difference in risk according to type of alcoholic beverage drunk [325]. Analysis of survival of a population-based series of cases of oral cancer included in a previous case–control study from Turin, Italy, suggested no effect of alcohol drinking nor of tobacco smoking on survival.

3.8.3
p53 gene mutations in head and neck cancer

H. Ohgaki and P. Kleihues; in collaboration with M. Zariwala, R. Schäfer and S. Schmid, Zürich, Switzerland

Despite the steadily increasing number of patients suffering from squamous-cell carcinomas of the oropharyngeal region, little is known about the molecular steps involved in the induction of these neoplasms. We have investigated oropharyngeal cancers from 38 patients for mutations in the *p53* tumour-suppressor gene. The majority of patients (74%) had a history of tobacco and alcohol abuse. A total of 16 tumours (42%) contained point mutations which were scattered throughout exons 5 to 8. Most mutations (56%) were transitions, predominantly G→A. Among the transversions, G→T mutations prevailed; these have also been found in smoking-related lung cancers. In one patient, two primary carcinomas had different mutations, indicating that they had developed independently. Similar mutations were seen in a case with a *p53* mutation in the third of three primary tongue carcinomas which developed over a period of 23 years. One lymph-node metastasis had a 12-bp deletion which was not detected in any of the primary malignancies. The frequent occurrence of *p53* mutations in oropharyngeal carcinomas supports the view that they play a role in the initiation or progression of the malignant phenotype [699].

3.8.4
Mutations of the *p53* gene in oral cancer

M. Hollstein, G. Martel-Planche and R. Montesano; in collaboration with S. Thomas and I. Frazer, Brisbane, Australia; and D. Sidransky and J. Brennan, Baltimore, USA

We examined 20 oral squamous cell carcinomas from Baltimore, USA, and 30 from Papua New Guinea (PNG), for mutations in exons 5–9 of the *p53* gene. Mutations were found in three of the tumours from PNG (10%), and nine among those from Baltimore (45%). In agreement with the low number of PNG cancers with mutations, only 17% of the cases from PNG were positive for p53 by immunostaining. A polymerase chain reaction-based procedure was used to identify human papillomavirus (HPV) DNA in PNG cases, and viral sequences (HPV strains 11/16) were detected in two tumours. HPV-triggered degradation of the tumour-suppressor protein is thus unlikely to be a common pathway to *p53* dysfunction in tumours from PNG [607].

3.9 Skin cancer

The most frequent form of skin cancer is malignant melanoma. Although this is still relatively uncommon on a worldwide basis, its incidence has been rising sharply in many Caucasian populations, where it now features among the top ten malignancies. This has been ascribed to high-intensity recreational exposure to sunlight, especially the ultraviolet component, among people whose normal lifestyle entails little exposure.

3.9.1 Case–control study of plantar melanoma in Paraguay

D.M. Parkin and E. Kramárová; in collaboration with P.A. Rolon, Asunción, Paraguay

In Paraguay, a high proportion of malignant melanomas (61% in men and 34% in women) appear on the sole of the foot (Figure 23). No case of plantar melanoma has been seen in the capital city during 1987–92, and therefore the lifestyle of rural residents seems to be an important risk factor for plantar melanoma.

This study was set up to examine the relationship between melanoma of the sole and the principal risk factors suggested by previous studies. Information was collected about the socioeconomic status of the subjects, their personal habits (diet, smoking, alcohol drinking), reproductive factors in women, type of residence, shoe-wearing habits, incidence and nature of injuries of the feet, number of naevi and other spots on the skin of feet and legs, overall colour of the skin, hair and eyes and occurrence of cancer in the family. Sixty newly diagnosed cases and 256 controls, recruited during the period 1988–93 in 11 hospitals in Paraguay were included in the study. The controls were selected to match cases by sex and age.

Few factors were found to be related to the risk of plantar melanoma. Adjusted for sex, age and period of recruitment, a significant contribution to the risk was seen for junctional naevi (OR = 5.3; 95% CI 1.7–16.5) and for injuries (OR = 4.4; 95% CI 1.4–14.1). For shoe-wearing habits, no association was apparent. For patients used to walking barefoot during their entire life, the risk of plantar melanoma was nonsignificantly increased (OR = 2.1; 95% CI 0.8–5.6).

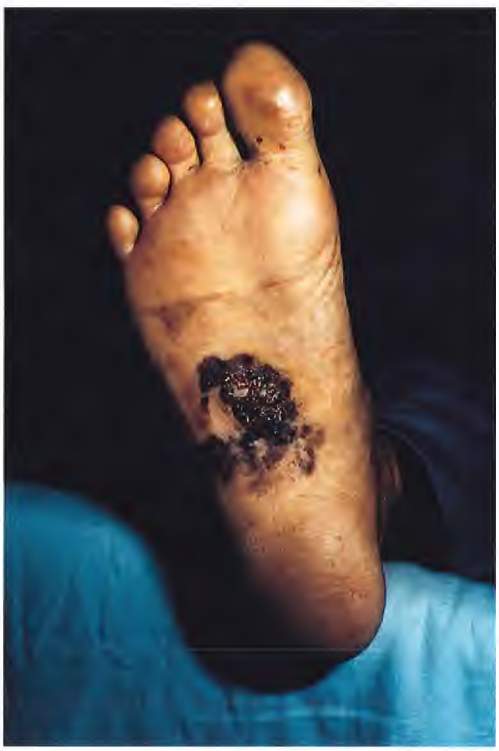


Figure 23. A malignant melanoma of the sole of the foot

3.9.2

Roles of the *Fas* gene and apoptosis in skin carcinogenesis

H. Nakazawa, M. Kallassy, N. Martel and H. Yamasaki; in collaboration with J. Lübbe, Zürich, Switzerland

Fas, a 45 kDa transmembrane protein, is related to a family of tumour necrosis factor receptors and is a major regulator of apoptosis in various cell types and tissues. Fas point mutations within the cytoplasmic/signal transduction (death) domain in Lpr (lymphoproliferation) mice prevent Fas-mediated apoptosis and cause a complicated immunological disorder (defects in both T and B cells). A deletion mutant of *Fas* (so-called 'soluble Fas') in systemic lupus erythrematosus prevents apoptosis.

We and other groups have suggested that *p53* gene alteration is one of the essential early steps in human non-melanocytic skin carcinogenesis. We have detected expression of the *Fas* gene in normal human melanocytes and identified the insertional frame-shift mutation in the signal transduction domain and observed deletion of the transmembrane domain of the *Fas* gene, the major regulator of apoptosis in melanocytes, in two out of four melanoma cell lines. This suggests a significant role of inhibition of *Fas*-mediated apoptosis in melanocyte transformation and malignant progression.

3.9.3

Regulation of telomerase activity in human cells and tumours

H. Nakazawa, N. Martel and H. Yamasaki; in collaboration with M. Oshimura, Yonago, Japan; J.C. Barrett, Research Triangle Park, USA; and K. Nakazawa, Lyon, France

Telomerase activity is present in embryo and germ cells but absent in somatic cells (Kim *et al.*, 1994, *Science,* **266**, 2011–2014). Activation of this enzyme is seen in most types of tumour and may constitute a prerequisite event for multistage carcinogenesis.

We are therefore studying the positive or negative regulation of telomerase activity by specific genes and chemical treatments. Telomerase was activated in all skin tumours tested (four squamous cell carcinomas and four basal cell carcinomas) from various sun-exposed or non-exposed body sites. In human primary keratinocytes, in which no telomerase activity could be detected, retrovirus-mediated infection with human papillomavirus type 16 E7 gene or E6+E7 genes reactivated the telomerase, but not E6 gene alone (Figure 24). In a human fibrosarcoma cell line, HT1080, the telomerase was totally or slightly suppressed by introduction of chromosome 1, 2 or 11 but not by chromosome 7 or 12, results which correlated well with the suppression of tumorigenicity of these cells following introduction of the same chromosomes. Telomerase activity in a transformed keratinocyte cell line was inhibited by treatment with the reverse transcriptase inhibitors, 3′-azido-2′,3′-deoxythymidine, 2′,3′-dideoxycytidine or ethidium bromide, but not by poly-ADP-ribose polymerase or topoisomerase I inhibitors. The telomerase in a non-tumorigenic, immortalized keratinocyte line was slightly inhibited by the anti-promoter retinoic acid, but was not affected by the tumour promoters 12-*O*-tetradecanoylphorbol 13-acetate and thapsigargin.

These results suggest that telomerase activity can be modulated by several factors involved in cellular immortalization and transformation, and that it plays an important role in tumorigenesis. This implies that the enzyme could be a target for new therapeutic methods.

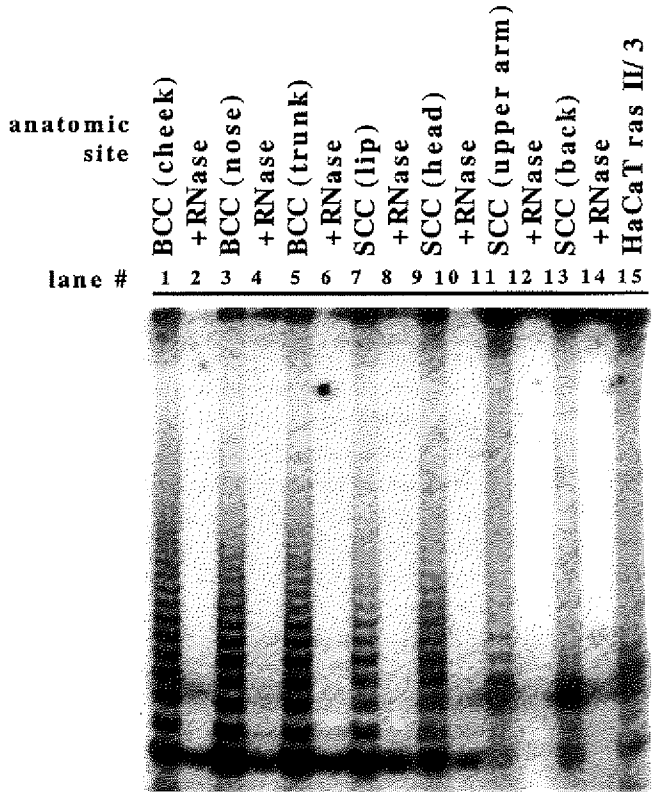


Figure 24. Detection of telomerase activity in human skin tumours (basal and squamous cell carcinomas) at various anatomical (sun-exposed and non-exposed) sites. Telomerase activity (odd-numbered lanes: 0.5 mg protein extract) in frozen tumour biopsies (lanes 1–4) was measured by the telomere repeat amplification protocol (TRAP: Kim et al., 1994, Science, 266, 2011–2014) with slight modifications. Some extracts (even-numbered lanes) were pre-treated with DNase-free RNase (Boehringer, Mannheim: 0.5 µg/extract) at 37°C for 10 min before the assay. Lane 15: transformed human keratinocytes HaCaT ras II/3 cells.

3.10 Soft-tissue tumours and lymphomas

3.10.1 Case–control study of soft-tissue sarcoma and non-Hodgkin lymphoma in relation to exposure to herbicides in Viet Nam

D.M. Parkin and M. Kogevinas; in collaboration with S. Cordier, Villejuif, France; Le Cao Dai and Le Bich Thuy, Hanoi, Vietnam; Nguyen Chan Hung and Cung Tuyet Anh, Ho Chi Minh City, Vietnam; M. Raphael, Paris, France; J.M. Rivera-Pomar, Vizcaya, Spain; and S. Stellman, New York, USA

During the second Indochina war, large quantities of herbicides contaminated with dioxins were sprayed onto the territory of what was, at the time, South Vietnam in order to defoliate forests and destroy crops.

Most of this spraying took place in 1965–71, but because of the relatively long biological half-life of dioxins, human exposure will have been more prolonged. The objective of this study is to identify any excess risk for two cancers: soft-tissue sarcoma and non-Hodgkin lymphoma. One hundred and fifty cases of each disease and two hospital controls per case are being interviewed, and samples of blood and adipose tissue stored. Estimation of exposures is initially based on detailed residential history in relation to the known location, type and quantity of herbicide sprayed by US forces. Direct measurement of dioxins in body tissues is expensive, but will be performed using the adipose tissue samples, should this become feasible. The study began in mid-1993, and by May 1995 some 400 subjects had been enrolled. The study is planned to continue until 1997.

4.1 The cytochrome P450 (CYP) enzyme system

CYP genes coding for cytochrome P450s are a superfamily of genes regulating the expression of enzymes that oxidize xenobiotics, including those that convert procarcinogens to their ultimate carcinogenic forms. The expression of *CYP* genes is regulated by environmental and genetic factors and most, if not all, have individual patterns of regulation. For each enzyme, either genetic polymorphism or wide interindividual variation in expression has been found, leading to great individual differences in capacity to generate carcinogenic metabolites. Our studies focus on enzymes of subfamilies 1A, 2A, 2E, and 3A, which appear to be essential in the metabolism of several important carcinogens.

Other studies relating to this topic are described in Sections 3.1.3, 3.1.4, 3.3.4 and 3.3.5.

4.1.1 Structure–activity relationships of carcinogen-metabolizing cytochromes P450

C.P. Wild and M. Lang; in collaboration with P. Pelkonen and R.O. Juvonen, Kuopio, Finland

Using recombinant yeasts constructed to express highly homologous mouse CYP2A enzymes, we have shown that CYP2A5 has a high affinity towards aflatoxin B_1 (AFB_1), while CYP2A4 and CYP7 α, although almost identical to CYP2A5, have much lower affinity and metabolic capacity. Genetically engineered point mutations in *Cyp2a-5* cCNA, changing only one amino acid at a time, drastically changed its catalytic properties towards AFB_1. The sensitivity of the recombinant yeast to AFB_1 and the binding of AFB_1 to the yeast DNA correlated well with the K_m of the expressed CYP isoform towards AFB_1, demonstrating a direct link between the affinity of the metabolizing enzyme to AFB_1 and the genotoxicity of AFB_1. It is concluded that CYP2A5 is the principal isoenzyme that metabolizes AFB_1 within the *Cyp2a* subfamily and that the recombinant yeasts provide a good test system to analyse the roles of individual CYP isoenzymes in AFB_1 toxicity [472].

Using nasal cavity microsomal preparations, we have also demonstrated that CYP2A5 is a good catalyst in the metabolism of *N*-nitrosodiethylamine (NDEA) and in particular the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) [42].

4.1.2 Tissue-specific expression

J.-C. Béréziat, F. Raffalli, O. Geneste and M. Lang

Hepatic expression of CYP2A4, CYP2A5 and CYP2A6 has been demonstrated before [93]. In addition, we have shown that expression of CYP2A enzymes is extremely high in the nasal epithelium. Consequently, these enzymes have a major role in the nasal metabolism of certain carcinogens. We have estimated that whereas in the liver, CYP2A enzymes may account for 20–60% of nitrosamine and aflatoxin B_1 metabolism, depending on the individual, their contribution to metabolism in the nasal epithelium may be up to 100% [42, 273]. In the lung, on the other hand, the

average expression of CYP2A enzymes seems to be low and therefore also their contribution to carcinogen metabolism is less significant than in the liver or the nasal epithelium. It is proposed that since CYP2A enzymes have such an essential role in carcinogen metabolism in the nasal epithelium, this tissue could serve as a good model for studying the role of the CYP2A enzymes in chemical carcinogenesis [42].

4.1.3
Expression of cytochrome P450s after liver injury

C.P. Wild, A.-M. Camus, O. Geneste, F. Raffalli, A. Ellul and M. Lang; in collaboration with F. Chisari, La Jolla, USA; G. Kirby, Montreal, Canada; and S. Satarug and M. Elkins, Khon Kaen, Thailand

It has been shown that liver injury, caused either by hepatotoxic chemicals [474], hepatitis B virus (HBV) [272] (see Section 3.3.5) or the liver fluke *Opisthorchis viverrini* (OV) [273], selectively increases the expression of CYP2A5 among several CYP enzymes. This increase seems to be local in the liver, being centrilobular in the case of toxic chemicals but restricted to areas of inflammation in the case of OV-infection. As a result of this selective increase, CYP2A5 may become one of the major CYP enzymes catalysing carcinogen metabolism in injured liver. Repair of DNA damage in hamsters and rats with liver injury has also been studied (see Section 4.2.2).

In a collaborative study with Khon Kaen University, Thailand, we have shown that hepatic CYP2A6 is possibly increased due to OV infection in humans. The increase is directly proportional to the severity of infection and interestingly a similar sex-dependent regulation to that seen in hamsters [273] can be detected in humans, leading to a greater increase in expression of CYP2A6 in males than in females [573]. This is in accordance with the association between OV infection and cholangiocarcinoma, and with its higher incidence among males than females.

4.1.4
Mechanism of expression

A.-M. Camus, A. Ellul, O. Geneste, F. Raffalli and M. Lang

The molecular mechanism of *Cyp2a-5* expression in relation to liver injury is largely unknown. In pyrazole-caused liver damage, we have found that mRNA stabilization rather than stimulated transcription may be important. Recently, we have found that a 44 kDa protein induced by pyrazole binds specifically to the 3 '-UTR of CYP2A5 mRNA, and may have a role in the specific regulation of *Cyp2a-5* expression.

4.1.5
Polymorphic regulation of CYP2A6

J.-C. Béréziat and M. Lang; in collaboration with S. Satarug and M. Elkins, Khon Kaen, Thailand

Using an *in vivo* test to measure human hepatic CYP2A6 activity (coumarin 7-hydroxylase: Venalot® assay), we have found that about 5–6% of individuals in Thailand have zero enzyme activity. This estimate is based on only 106 individuals and therefore further analysis is needed to establish the frequency more accurately. Preliminary studies suggest that the zero activity is due to polymorphism of the *CYP2A6* gene.

4.2 *Effects of DNA damage and repair on cell cycle control and carcinogenesis*

While the formation of DNA adducts is a critical step in the carcinogenic process, the occurrence of mutations is greatly dependent on the capacity of the cells to repair DNA damage. Thus the capacity of an individual (or cell) to carry out DNA repair processes could represent an important biomarker for cancer risk. Mammalian cells respond to DNA damage with a transient inhibition of DNA synthesis, an induction of the expression of several genes and a delay in cell cycle progression. At least two stages in the cell cycle can be modulated in response to damage, namely the G1/S and G2/M transitions. Such delays in the cell cycle could be considered as a surveillance mechanism allowing time for detection and repair of DNA damage before cellular replication or division; however, the molecular mechanisms that control such delays are still poorly understood. The *p53* gene product has been linked to the activation of G1/S inducible growth-arrest checkpoint in response to DNA damage. The level of wild-type p53 protein is dramatically increased in response to different DNA-damaging agents and found to be associated with the G1 cycle block. In cells lacking a functional p53, no such block is observed. The objective of the studies presented here is to assess the role in cancer induction and development of the repair of some forms of DNA damage induced by alkylating agents and reactive oxygen species and to investigate the role of different gene products in the signal transduction pathway resulting in cell-cycle arrest.

4.2.1 Control of expression of enzymes for DNA alkylation and oxidative damage repair during single and chronic exposures to carcinogens

J. Hall, H. Brésil, P. Pelkonen, S. Takahashi and R. Montesano; in collaboration with F. Bianchini and J. Cadet, Grenoble, France; A.A. van Zeeland, Leiden, Netherlands; and F. Donato, Brescia, Italy

Alterations in the repair processes for methylated and oxidative DNA adducts have been found in smokers compared to non-smokers, with mean levels of the methylpurine- and formamidopyrimidine-DNA glycosylases being higher in smokers than in non-smokers [215]. We are now examining the distribution and apparent induction of these enzymes, which are involved in alkylation and oxidative DNA damage repair, together with DNA adduct formation and urinary excretion in populations exposed to tobacco smoke. Single or chronic exposure to alkylating agents has been shown to result in species- and tissue-specific induction of certain DNA repair enzymes, such as the O^6-methylguanine-DNA methyltransferase (AGT), which specifically removes the promutagenic DNA adducts O^6-methylguanine and O^4-methylthymine from DNA (see IARC Biennial Report 1992/93). In particular, distinct differences between rat and hamster have been noted, with a rapid increase in AGT mRNA and protein levels in rat liver but not in hamster liver following treatment with alkylating agents. Preliminary experiments on the expression of the growth arrest and DNA-damage-inducible gene *GADD45*, which may be

involved in signalling replication arrest, have shown that this is also rapidly induced in rat liver following similar carcinogen exposures; its expression in hamster liver is being investigated. In order to extend our studies on alterations in mRNA expression for the AGT gene and to investigate these changes at the cellular level, *in situ* hybridization techniques have been established for AGT mRNA expression in rat tissue. A 356-base-pair rat AGT cDNA fragment, corresponding to nucleotides 269–625 of the rat cDNA, was cloned from rat liver RNA and used to prepare AGT riboprobes. In male outbred BDIV rats, constitutive AGT mRNA expression was found in the bile duct cells, vascular endothelial cells and mesenchymal cells but not in hepatocytes and Kupffer cells. Following exposure to nitrosodimethylamine, inducible AGT mRNA was rapidly expressed in hepatocytes, especially in the centrilobular hepatocytes, the cell type which showed the highest levels of O^6-methylguanine DNA adduct formation. These results clearly demonstrate that both the constitutive AGT mRNA expression patterns and its inducibility are different in different cell populations. The observation that the O^6-methylguanine persisted longest over the time-course of this study (96 h) in the centrilobular hepatocytes, the cell type where the highest inducible AGT mRNA was found, clearly demonstrates that the carcinogenic process must in addition be modulated by other factors such as cell proliferation and rates of protein synthesis.

4.2.2
DNA repair modulation by cellular injury

J. Hall, H. Ohshima and I. Brouet

The modulation of expression of the AGT repair protein by cellular injury resulting from inflammatory processes is being examined in experimental animal systems. No difference in hepatic AGT was noted in male or female hamster liver 12 weeks after infection with liver fluke (*Opisthorchis viverrini*), although this treatment produces alterations in other cellular defence systems such as cytochrome P450s (see Section 4.1.3). Preliminary experiments in rats treated intravenously with heat-killed *Propionibacterium acnes* followed by lipopolysaccharide (LPS) administration, which causes acute hepatic injury and induction of nitric oxide synthase (see Section 4.4.2), indicate a slight inhibition of AGT in treated animals (0.105 pmol/mg protein 8 hours after LPS administration, 0.132 pmol/mg protein in control liver). This result is in agreement with those of Laval and Wink (1994, *Carcinogenesis,* **15**, 443–447), who demonstrated, using a nitric oxide-generating system in cultured cells, the inhibition of AGT activity.

4.2.3
Regulation of the mammalian cellular response to DNA damage

M. Artuso, W. Jongmans, M. Vuillaume, H.Brésil and J. Hall; in collaboration with S. Jackson, Cambridge, UK

The ataxia telangiectasia (AT) gene product has been implicated in the signal transduction pathway that causes a delay in cell cycle progression following exposure to ionizing radiation, together with the product of the tumour-suppressor gene *p53* (Kastan *et al.*, 1992, *Cell,* **71**, 587–597). The time-course of p53 induction was examined in eight AT cell lines and found to be significantly delayed and reduced, with no dose–response in p53 induction compared to control cells following exposure to ionizing radiation (2 and 5 Gy). The increase of *WAF1/CIP1(p21)* and *GADD45* mRNA, two genes transcriptionally activated by p53, was also reduced in the AT cell lines after such treatments. In contrast, the

increase in p53 protein, *WAF1/CIP1(p21)* and *GADD45* mRNA expression following exposure to the alkylating agent methyl methanesulfonate (25 and 100 μg/ml) was similar in both cell types. No alterations in the expression of EBNA-5, an EBV-encoded nuclear antigen which has been shown to bind p53, and no mutations in the *p53* gene (exons 4 to 8) were found in the AT cell lines studied [17]. The AT gene product would thus appear to be involved upstream of *p53*, *GADD45* and *WAF1/CIP1 (p21)* in the signalling of the presence of damage specifically produced by ionizing radiation, with this defect in response contributing to the high cancer risk and radiosensitivity observed in this disorder. The exact nature of the signal remains unknown, but it appears reasonable to speculate that it includes some form of DNA strand-break formation, as has been postulated by Kastan and colleagues (Nelson & Kastan, 1994, *Mol. Cell Biol.*, **14**, 1815–1823; Zhan *et al.*, 1994, *Cancer Res.*, **54**, 2755–2760).

Recently important steps towards the molecular characterization of strand-break rejoining have been made with the elucidation of the genetic defects in several ionizing radiation-sensitive mutant cell lines belonging to different complementation groups. The proteins shown to be involved are ku70 and ku80, which bind specifically to DNA strand breaks, and DNA-PK, that recognizes the ku-DNA complex and upon binding becomes activated. Substrates of this p350 kinase include p53 and the transcription factor Sp1 (see Troelstra & Jaspers, 1994, *Current Biology*, **4**, 1149–1151). In order to examine the role of this DNA recognition pathway in the AT phenotype, the constitutive levels of the ku proteins have been examined in several AT and normal cell lines and appear to be similar. These studies are being extended to their measurement after treatment with DNA-damaging agents and the direct measurement of DNA-PK activity.

4.3 Genetic determinants of specific cancers

The main aim of the IARC programme on genetic susceptibility to cancer is to evaluate the role and the importance of inherited conditions predisposing to cancer through molecular, familial and population-genetic approaches. Another goal is to establish how molecular genetics can be used to better define the genetic make-up of individuals in epidemiological surveys. Research in this field is being developed through the creation of two new units: a Genetic Cancer Susceptibility Unit, headed by Professor G. Romeo since 1 April 1995, and a Genetic Cancer Epidemiology Unit.

Probably less than 5% of cancers occur in individuals who are strongly predisposed to a particular cancer type. If a genetic marker of risk is identified, these individuals (and their relatives) may benefit from screening and early diagnosis. Molecular investigations may allow the identification of the predisposing genes and elucidation of how they operate. Such information would be of general importance, since the more common non-familial forms of such a cancer may result from somatic mutation of the same gene.

The approach being used in order to study inherited predisposition to cancer is through linkage analysis in high-risk families. In linkage analysis, co-segregation of cancer susceptibility is sought with a specific allele of a polymorphic system

which has been mapped to a known chromosomal location.

During the last 10 years, the IARC laboratory has contributed to the identification of the genes predisposing to familial medullary thyroid cancer (in the framework of multiple endocrine neoplasia type 2 (MEN 2), to neurofibromatosis type 2 and to breast cancer. A major effort remains the identification of the X-linked lymphoproliferative syndrome (XLP) gene, now well localized.

4.3.1
X-linked lymphoproliferative syndrome (XLP)

B.S. Sylla, J. Lamartine, F. Heitzmann, S. Pauly, M.F. Lavoué, G. Lenoir and G. Romeo; in collaboration with A. Coffey, Cambridge, UK; D. Haber, Charleston, USA; G. Porta, Milan, Italy; J. Skare and J. Sullivan, Worcester, USA

X-linked lymphoproliferative disease (XLP) is a rare form of genetic immune deficiency characterized by a selective susceptibility to Epstein–Barr virus (EBV). Primary EBV infection of affected boys invariably results in severe or fatal infectious mononucleosis, acquired agammaglobulinaemia or B-cell lymphoma. Since XLP patients do not respond normally to EBV infection, the XLP gene appears to play an important role in the control of EBV infection by the immune system. XLP disease is a good model for examining the interaction between an environmental factor (EBV) and a genetic component (XLP gene) in the genesis of malignant lymphoma.

The XLP gene has been mapped to the X chromosome at the Xq25–q26 region. In order to isolate this gene, physical mapping of the region was undertaken. Screening of yeast artificial chromosome (YAC) libraries with probes closely linked to the XLP locus enabled us to estimate the physical distance of some markers in the region.

XLP patients harbouring interstitial deletions or chromosomal rearrangement are an important resource in identifying the XLP gene. One XLP patient has a large deletion in Xq25 including the marker DX100 (Skare *et al.*, 1993, *Genomics*, **16**, 254–255; [602]). The deletion amounts to about 2 megabase-pairs. cDNA clones obtained after screening of a human fetal cDNA library with cosmid clones deleted in this patient contained all repetitive sequences. cDNAs were also isolated after screening of placental and brain cDNA libraries, using CpG-containing cosmid clones mapped on Xq24-q26. Physical mapping of these clones indicated that they were outside the deletion and are therefore excluded as candidate genes for XLP; they were mapped at Xq12-q13 and 14q11-q12.

In order to define a minimal region containing the XLP gene, extensive screening was undertaken of available XLP patients with all the known markers deleted in the previous patient and with newly published probes mapped to the Xq24-q26 region. A second XLP patient with a relatively small deletion was identified. Screening of YAC libraries with probes deleted in this small interval has allowed isolation of several overlapping YACs covering the deletion. One YAC clone of about 1.6 megabase-pairs covering the entire deletion was subcloned into a mini-cosmid library. In addition we have screened a gridded X-chromosome cosmid and a P1 human genomic library and several clones have been identified. A contig map composed of cosmids and P1 clones covering the totality of the deletion has been recently established. Clones from this contig that should contain the XLP gene were used for exon trapping, cDNA selection, and cDNA library screening for gene identification. Genes isolated by these approaches will be tested for mutation in XLP patients.

4.3.2
Multiple endocrine neoplasia type 2

I. Schuffenecker, M.F. Lavoué and G. Lenoir; in collaboration with M. Billaud and M. Rossel, Lyon, France; the Groupement d'étude des tumeurs à calcitonine: Secretariat, E. Modigliani, Paris, France; and S. Narod, Montreal, Canada

MEN 2A is an autosomal dominant inherited cancer syndrome characterized by medullary carcinoma of the thyroid (MTC), phaeochromocytoma and hyperparathyroidism, accounting for at least 30% of medullary thyroid cancers. Almost all gene carriers will develop the disease (a very high penetrance of the gene), but their identification still relies on a screening test that detects an early stage of the malignancy. Through the Groupement d'étude des tumeurs à calcitonine in France and contacts with various European institutions, over 135 families have been identified, and blood has already been collected from most members.

Recent emphasis has been placed on the study of genetic heterogeneity of MEN 2 and on the development of a screening method using DNA markers. Most of the molecular analysis is now performed in the genetics laboratory of the Hôpital Edouard Herriot, Lyon and of the Lyon Medical School.

Hereditary MTC appears in three forms: (1) in association with phaeochromocytomas and parathyroid hyperplasia (MEN 2A); (2) with phaeochromocytomas, neuromas of the mucous membranes and a marfanoid appearance (MEN 2B); and (3) without phaeochromocytoma.

Following reports of germline mutations of the RET proto-oncogene as the molecular basis of inherited susceptibility to MTC, we have been actively analysing our panel of families. By sequencing exons 10 and 11 of the RET proto-oncogene in 68 unrelated familial cases of MEN 2A and familial MTC (without phaeochromocytoma), we identified germline mutations in 98% of the MEN 2A families and in 57% of the familial MTC cases. In 11 patients, we found a mutation in exon 10. In the remaining two cases, the mutation was located in exon 11.

All the genetic changes observed were missense mutations affecting one of three cysteine codons located in the extracellular domain of RET. The alterations identified in exon 11 invariably involved codon 634. Six different transitions or transversions were observed at this codon. The two most frequent were T to C and G to A transversions. The mutations identified in exon 10 affected codons 618 and 620. Segregation of mutant alleles with the disease was verified for a total of 40 families.

Despite sharing the same mutation at codon 634, 620 or 618, some families did not have the same haplotype in the *RET* region. Using four polymorphisms located either in the *RET* coding region or no further than 200 kb, we identified at least seven different haplotypes in the subgroup of families sharing the T to C transversion at codon 634. In the subgroup of families sharing the G to A transversion at codon 634, at least four different haplotypes were found [575].

When MEN 2B patients were analysed (the more severe form of MEN 2 associating MTC, phaeochromocytomas, schwannomas and a marfanoid appearance), a single point mutation at codon 918 leading to the replacement of a methionine by a threonine within the RET tyrosine kinase domain was identified, as in all other MEN 2B cases reported so far [525]. This mutation was identified in 19 out of our 20 unrelated MEN 2B families analysed. In these families we were able to demonstrate that, in five cases, the mutations arose *de novo*, and in one kindred it was coinherited with the disease. These results indicate that a unique mutation at codon 918 of the RET

gene is the most prevalent genetic defect causing MEN 2B, but also that rare MEN 2B cases are associated with different mutations yet to be defined.

A small proportion of familial MTC cases do not show germline mutations on RET exon 10 or 11. We demonstrated recently that in some families in which the risk of phaeochromocytoma is very low, a germline mutation can be present in exon 13 or 14 involving the tyrosine kinase domain of RET [72].

This project has now been phased out at IARC. The typing of families is continuing in a hospital-based setting and attempts to elucidate the biological basis of predisposition will be pursued mainly in national laboratories. The resources collected within the framework of these studies will be made available to investigators on request.

4.3.3
Neurofibromatosis type 2

G. Lenoir and C. Bonnardel; in collaboration with G. Fischer, Lyon; and G. Thomas, Paris, France

Following the identification of the neurofibromatosis type 2 (NF2) gene [526], the NF2 families we had collected have been analysed for germline mutation of the schwannoma gene. So far mutations have been identified in about 50% of the families, suggesting that either mutation in regulatory elements or deletions occur in a significant proportion of cases [355]. A search for genotype/phenotype correlations showed that, at least in these families, mild manifestations of the disease were associated with mutations which preserve the C-terminal end of the protein.

4.3.4
Linkage analysis in familial breast and ovary cancer

G. Lenoir, O. Serova, B.S. Sylla, M. Montagna, N. Puget, M.F. Lavoué and C. Bonnardel; in collaboration with J. Feunteun, Villejuif, France; H.T. Lynch, Omaha, USA; and S. Narod, Montreal, Canada

The objectives of this project are to locate breast cancer susceptibility genes, to participate in their identification and to evaluate the biological significance of the hereditary component in breast cancer. It is also intended to evaluate the feasibility of DNA screening in breast cancer families, once genetic markers become available.

Most cases of breast cancer appear to be sporadic. There are, however, some families in which there are several affected individuals, indicating either a chance clustering of sporadic cases or an inherited genetic effect. In other rarer families, there is a clear inherited susceptibility to breast cancer that can be traced through consecutive generations. In these families, breast cancer usually occurs at an early age (before menopause), is often bilateral, and is sometimes associated in the family with other cancer such as ovarian cancer. It has been evaluated that about 4% of breast cancer occurs in such high-risk families, and that cancer risk is transmitted as an autosomal dominant trait.

4.3.4.1
Linkage studies

In order to locate any breast cancer susceptibility locus by linkage analysis, we have examined a significant number of breast cancer families, originally identified by Professor H.T. Lynch at Creighton University, Omaha, NE, USA. More than 1350 blood samples from over 80 high-risk families were shipped to Lyon between 1989 and 1995.

Our linkage studies have enabled us to reduce the size of the BRCA1 locus. New recombinants have been identified, such as a key one placing the BRCA1 locus distal to the 17-hydroxysteroid dehydrogenase gene (EDH17B2), confirming the exclusion of this gene as BRCA1 [610].

4.3.4.2
Attempt to identify the breast and ovarian cancer susceptibility gene

The effort to generate a physical map of the region containing the breast and ovarian cancer susceptibility gene has led to the identification of a human homologue of a rat PRL-1 tyrosine phosphatase gene that shows enhanced expression during hepatic regeneration and in some tumour cell lines [380].

Analysis of an exceptional family in which epidermolytic palmoplantar keratoderma (EPPK) cosegregates with breast and ovarian cancer has raised the possibility that a single mutation might cause these conditions and offers a potential lead to the identification of a hereditary breast/ovarian cancer gene. Linkage analysis indicated that the EPPK locus lies on the long arm of chromosome 17 near the type 1 keratin gene cluster and the proposed breast cancer gene (BRCA1). The type 1 keratin 9 gene has been partially sequenced in four affected individuals. A single base mutation within the rod domain of the protein cosegregates with EPPK in all affected individuals tested. Although inheritance of this mutation is probably responsible for EPPK, it is unlikely to be the cause of breast and ovarian cancer [614].

Since the identification of the BRCA1 gene (Miki *et al.*, 1994, *Science*, **266**, 66–71), we have been able to demonstrate that this family also carries a BRCA1 mutation on the same chromosome 17 [577].

Another candidate gene was found to map near the BRCA1 locus: the plakoglobin gene. Through a collaboration with Dr R. Kemler (Freiburg, Germany), we have shown that although plakoglobin is not BRCA1, it might represent a putative tumour-suppressor gene for breast and ovarian cancer [1].

The risk of cancer in carriers of BRCA1 mutations was more precisely estimated with the Breast Cancer Linkage Consortium [174]. The resulting estimates of breast and ovarian cancer risks are useful for counselling BRCA1-mutation carriers. This study also shows that carriers are at increased risk of colon and prostate cancer, which may be of clinical significance in certain families if the risks are associated with specific mutations. In addition, this set of families was used to examine the variation in risk between and within families. There is significant evidence of heterogeneity of risk between families; a better fit to the data is obtained by assuming two BRCA1 alleles, one conferring a breast cancer risk of 62% and an ovarian cancer risk of 11% by age 60 years, the other conferring a breast cancer risk of 39% and an ovarian cancer risk of 41%, with the first allele representing 71% of all mutations (95% CI 55–87%). There is no evidence of clustering of breast and ovarian cancer cases within families [139].

Analysis of the histology of BRCA1-associated ovarian tumours has shown that BRCA1 mutations are unlikely to predispose to mucinous epithelial ovarian cancer. Our data imply that caution should be exercised when counselling family members of women with mucinous ovarian carcinomas about cancer risks, especially when BRCA1-linked markers are employed [416].

4.3.4.3
BRCA1 mutations

Through the analysis of 20 breast/-ovarian cancer families, the majority showing linkage to chromosome 17q21, we were able to identify mutations in 14 (70%) of them. In addition, two families showed a lack of transcription of the disease-associated allele in lymphoblastoid, suggesting an inferred regulatory mutation. As indicated in Table 8, 13 mutations appeared to be distinct, most of them leading to the production of a truncated BRCA1 protein [577]. One of the mutations (185 del AG) was found mainly in Ashkenazi Jewish families [609].

Table 8. BRCA1 mutations in the breast/ovary Creighton University families

Family number	Type[a]	Exon	Codon	Nucleot	Mutation[b] in the coding region	Partial loss of mutant transcript	Mutation reported previously
2979	FS	2	22	185	del AG →Ter 39	–	9 times
3079	FS	2	22	185	del AG →Ter 39	–	
2775	FS	2	23	188	del 11 →Ter 39	–	1 time
1252	MS	5	61	300	Cys →Gly (T–G)	–	2 times
2850	SP	5	–	–	Exon 5 missing in transcript	–	New
1086	FS2	11	266	916	del T T →Ter 285	–	New
EPPK	NS	11	526	1695	Gln →Ter (C–T)	+	New
2944	NS	11	908	2841	Glu →Ter (G–T)	–	New
3300	FS	11	1160	3598	del 11 →Ter 1166	–	New
2651	FS	11	1234	3819	del 5 →Ter 1242	+	New
2770	NS	16	1563	4808	Tyr →Ter (C–G)	+	New
1234	SP	intron 18	–	–	del A→delexon19→ Ter 1732	+	New
1973	FS	20	1756	5382	ins C →Ter 1829	–	7 times
1813	NS	24	1835	5622	Arg →Ter (C–T)	not done	New
2090	IR	–	–	–	–	+	1 time
3173	IR	–	–	–	–	+	

[a] FS: frameshift, MS: missense, NS: nonsense, SP: splice site, IR: inferred regulatory.
[b] Mutations are designated according to mutation presentation proposed by Shattuck-Eidens et al. (1995; J. Am. Med. Ass., 273, 535–541).

If the majority of hereditary breast/ovary cancer families in any ethnic subgroup can be attributed to a small number of mutations, our efforts to provide DNA-based predictive testing will be greatly enhanced.

Our group has participated in a consortium headed by M. Stratton and D. Easton (Sutton, UK), established in order to identify other breast cancer susceptibility loci. A genomic linkage study using 15 high-risk breast cancer families unlinked to BRCA1 on chromosome 17q21 localized a second breast cancer susceptibility locus (BRCA2) to a 6-centimorgan interval on chromosome 13q12–13. Preliminary evidence suggests that BRCA2 confers a high risk of breast cancer but, unlike BRCA1, does not confer a substantially elevated risk of ovarian cancer [686].

4.3.5
Mapping of gene(s) predisposing to papillary thyroid carcinoma

G. Romeo, B.S. Sylla, L. Yin, A. Bolino and M. Stark; in collaboration with M. Devoto, Genoa, Italy; M. Schlumberger, Villejuif, France; and the International Consortium for the Genetic Study of PTC

The aim of this project is the identification of gene(s) which may, alone or in cooperation with the RET protooncogene (see Section 4.3.2), initiate the tumour progression chain of events in the most common type of thyroid cancer, known as papillary thyroid carcinoma (PTC). PTC is essentially a sporadic tumour arising from one of the two cell lines that can give rise to thyroid carcinomas. One cell line, the C cells, leads to medullary thyroid carcinoma (MTC) (see Section 4.3.2). The second lineage, the folli-

cular cells, can lead to two types of differentiated tumours, the follicular carcinoma and the papillary thyroid carcinoma (PTC), which are regarded as distinct biological entities. A molecular feature observed in a variable percentage of PTC (from 11 to 33%) is a rearrangement of the RET proto-oncogene, whose tyrosine kinase domain becomes separated from its 5′ extracellular domain and translocated to an activated gene such as the regulatory subunit of the cAMP dependent protein kinase A, located on chromosome 17, or other genes (Bongarzone *et al.*, 1994, *Cancer Res.*, **54**, 2979–2985). This chimeric version of the RET proto-oncogene is the result of a somatic mutation that makes the gene constitutively active and therefore oncogenic. No RET translocation has been found in any other tumour, thyroid or non-thyroid. A similar translocation of the protein kinase part of the TRK proto-oncogene occurs in PTC. The causative role of RET mutations in tumour tissues from patients with PTC is suggested by the strong transforming capacity that chimeric RET/PTC cDNA constructs show in appropriate cell-culture systems (Pasini *et al.*, 1995, *Nature Genetics*, **10**, 35–40).

The best tool to test the possible involvement of RET in familial PTC is linkage analysis. Through collaboration with several clinicians, in particular Professor Martin Schlumberger (Villejuif, France), we have already established lymphoblastoid cell lines from 20 pedigrees in which recurrence of the tumour is compatible with autosomal dominant inheritance with incomplete penetrance. A computer simulation of a linkage study has been performed under the latter hypothesis using the information provided by affected individuals only. The results indicate an average lod-score of 4.01 for a marker with 70% heterozygosity at a recombination fraction of 0.01 from the putative disease locus. The probabilities of false positive results were calculated as the probability of a lod-score greater than 2 and 3 under the hypothesis of no linkage; they were found to be 0.4% and 0.0% respectively on a total of 500 replicates.

This linkage study could be complicated by genetic heterogeneity and/or the presence of a predisposing gene with incomplete penetrance, which might be frequent in the general population. For this reason we plan to collect a much larger sample of pedigrees with recurrence of PTC, by extending our collaboration to other clinicians through an International Consortium for the study of genetic predisposition to PTC. If RET is excluded by linkage studies as a candidate gene for familial PTC, additional genes will be taken into consideration using linkage analysis with DNA polymorphisms localized in the proximity of the same genes.

4.4 Endogenous formation of carcinogens

Chronic infection and inflammation have long been recognized as risk factors for a variety of human cancers. Active oxygen and nitrogen species, such as hydroxyl radical and nitric oxide (NO) radical, generated in inflamed tissues, can cause injury to target cells and also damage DNA, which could contribute to tumour development [28, 92, 428, 431]. Therefore, genetic polymorphism or alterations in genes encoding or regulating enzymes involved in free radical generation and defence against radicals may be associated with individual susceptibility to cancer development. We are studying the role of three key enzymes, i.e. NO synthase, superoxide dismutase and catalase in human carcinogenesis.

Endogenously formed *N*-nitroso compounds (NOC) may play a role in human carcinogenesis. A sensitive method to estimate total NOC in biological specimens has been applied to clinical studies.

4.4.1
Helicobacter pylori infection, oxidative stress and stomach cancer

B. Pignatelli, C. Malaveille, S. Calmels, M. Laval, N. Lyandrat, F. Smit, N. Muñoz and H.Ohshima; in collaboration with A.T.R. Axon, Leeds, UK; B. Bancel, L.M. Patricot, R. Lambert and B. Moulinier, Lyon, France; J. Cadet, M. Polverelli and M. Berger, Grenoble, France; P. Correa, New Orleans, USA; M. Crespi, Rome, Italy; E.M. Felley and A.L. Blum, Lausanne, Switzerland; and M. Hirai, Fukui, Japan

DNA and tissue injuries caused by excessive formation of reactive oxygen or nitrogen species at *Helicobacter pylori*-induced inflammation sites may contribute to gastric carcinogenesis, depending on the extent of host cellular antioxidant defence. We have investigated the relationship between the expression of key enzymes involved in the production of reactive species (i.e., inducible NO synthase (iNOS)) and defence against oxidative stress (i.e., catalase and superoxide dismutase (Mn-SOD)), gastric histopathology and intensity of *H. pylori* infection.

We have carried out immunohistochemical analyses of these enzymes in serial sections of paraffin-embedded gastric biopsies from 110 French patients with various gastric conditions and different types of

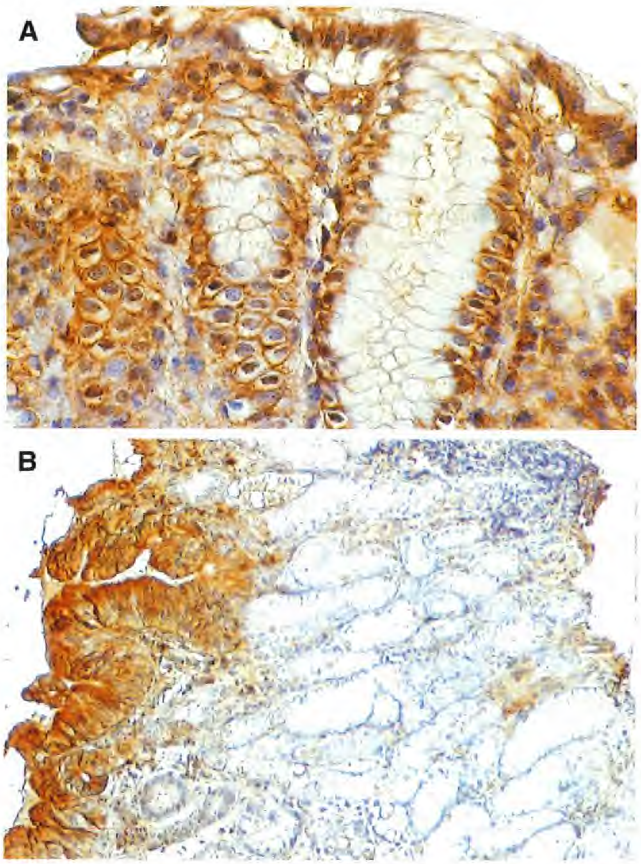


Figure 25. Typical immunohistochemical localization of iNOS in human gastric mucosa; (a) pit cells from gastritis patients, and (b) high-grade dysplasia tissue.

cancer. Figure 24 illustrates typical immunohistochemical localization of iNOS in gastric mucosa. The prevalence of *H. pylori* infection was low in normal mucosa, but as expected was higher in tissues from gastritis patients (Figure 25). iNOS immunoreactivity was observed in rare stromal mononuclear inflammatory cells in normal mucosa. The proportion of biopsies showing gastritis with iNOS present in numerous inflammatory cells was correlated with *H. pylori* infection; a similar relationship was observed for iNOS expression in pit cells. The proportion of biopsies showing gastritis and positive for catalase expression in pit cells was related to both the severity of the gastritis and *H. pylori* infection (Figure 26). The proportion of biopsies showing gastritis and positive immunoreactivity for both catalase and Mn-SOD in inflammatory cells was higher in cases with *H. pylori* infection. For all biopsies, Mn-SOD was never detected in pit cells. In carcinomatous cells, iNOS was present in 47% of tubular adenocarcinoma (n=30) but in none of the atypical undifferentiated and polymorphic adenocarcinoma (n=12). Antioxidant enzymes were usually absent in cancerous tissues [486, 489].

In order to investigate the interrelationship between production of reactive species, host anti-oxidant defence and the resulting oxidant injury, methods to measure DNA damage are being developed. These methods are being used to study the effectiveness of anti-oxidant treatments and *H. pylori* eradication in intervention studies of stomach cancer (see Section 5.1.3).

Vacuolating cytotoxin (Vac A) produced by *H. pylori* may play a role in the development of gastritis and stomach cancer. In order to examine whether subjects are infected with the cytotoxin-producing *H. pylori*, an immunoblotting method to detect circulating antibody against the cytotoxin is now being set up in this laboratory. Serum samples obtained from a case–control study of stomach cancer in Venezuela will be examined (see Section 3.2.1).

4.4.2
Role of nitric oxide synthase in carcinogenesis

H. Ohshima, B. Pignatelli, C. Malaveille, S. Calmels, I. Brouet, A Hautefeuille, M. Laval, N. Lyandrat, F. Smit, P. Hainaut, J. Hall and P. Kleihues; in collaboration with W. Anwar, Cairo, Egypt; B. Bancel and L.M. Patricot, Lyon, France; M. Fontecave, Grenoble, France; N.A. Habib, London, UK; J.F. Jeannin, Dijon, France; and M. Ozturk, Lyon, France

NO, produced by NO synthase, may play a role in carcinogenesis by various mechanisms (Figure 27), for example by exerting its cytotoxic and mutagenic effects, inducing apoptosis and modulating enzyme activities and gene expression. NO is also implicated in immunosuppression, tumour growth, invasion and metastasis. In collaboration with other laboratories, we are studying various aspects of the role of NO in carcinogenesis: DNA and protein damage (Section 6.1.2), apoptosis and *p53* gene expression, DNA repair (Section 4.2.2) and tumour-induced immunosuppression [295].

p53, a potent tumour suppressor, has been implicated in control of the cell cycle and apoptosis. We hypothesize that NO may modify the function of the p53 protein by changing its conformation or by increasing its degradation, as NO either inhibits or activates many enzymes (e.g., aconitase and soluble guanylate cyclase). Human hepatocellular carcinoma cell lines containing either wild-type or mutated p53 were treated with NO-releasing compounds and their p53 protein levels were analysed by immunoblotting. NO induced rapid translocation of p53 protein from the cytosol to nucleus. We are now testing whether NO can affect the functions of p53 protein.

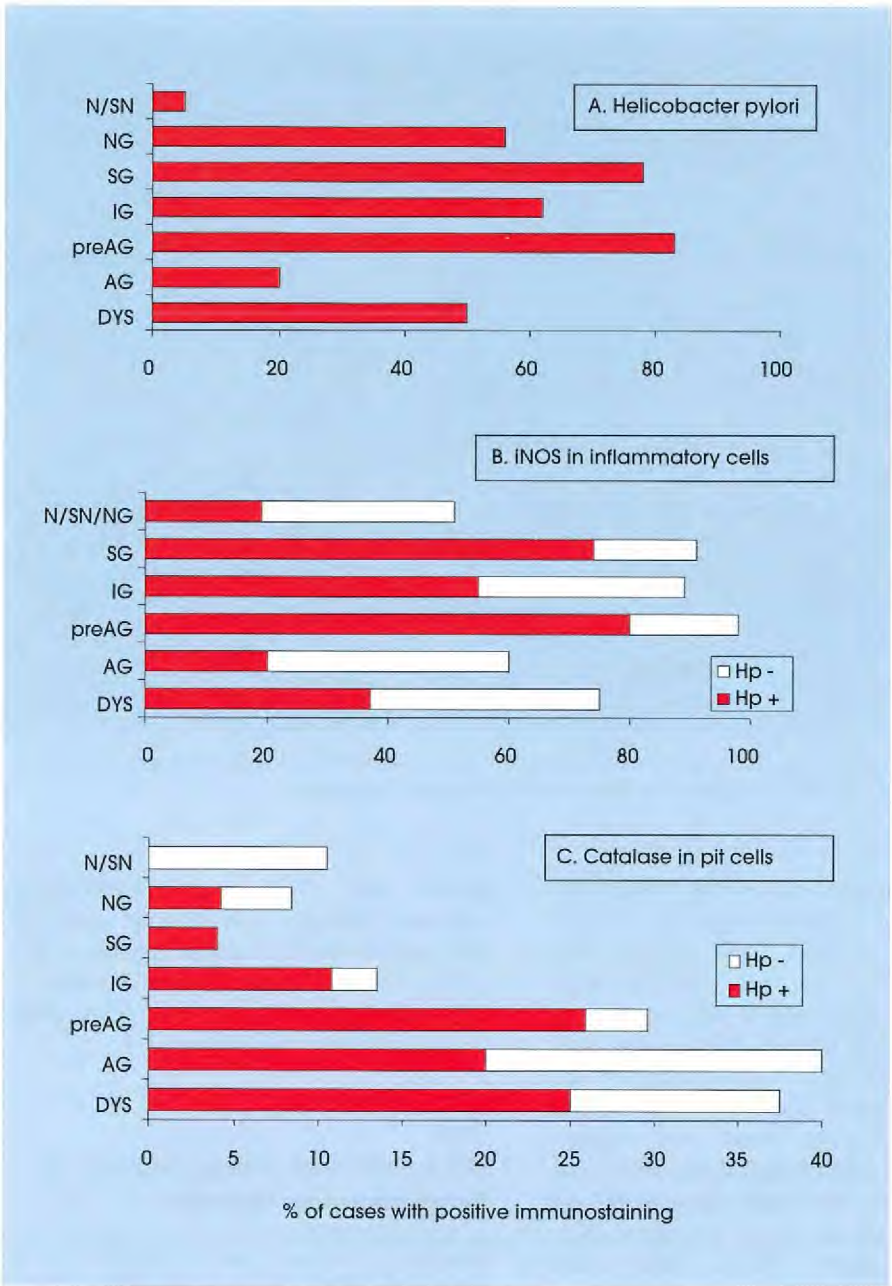


Figure 26. Percentage of subjects who were positive for H. pylori infection (A), iNOS expression in inflammatory cells (B) and catalase in the pit cells (C). A total of 152 tissue sections from 110 patients were examined from normal (N) and sub-normal (SN) subjects (n = 19), normal mucosa from patients with localized gastritis (NG) (n = 25), superficial gastritis (SG) (n = 23), interstitial gastritis (IG) (n = 37), pre-atrophic gastritis (pre AG) (n = 30), atrophic gastritis (AG) (n = 10) and dysplasia (DYS) (n = 8).

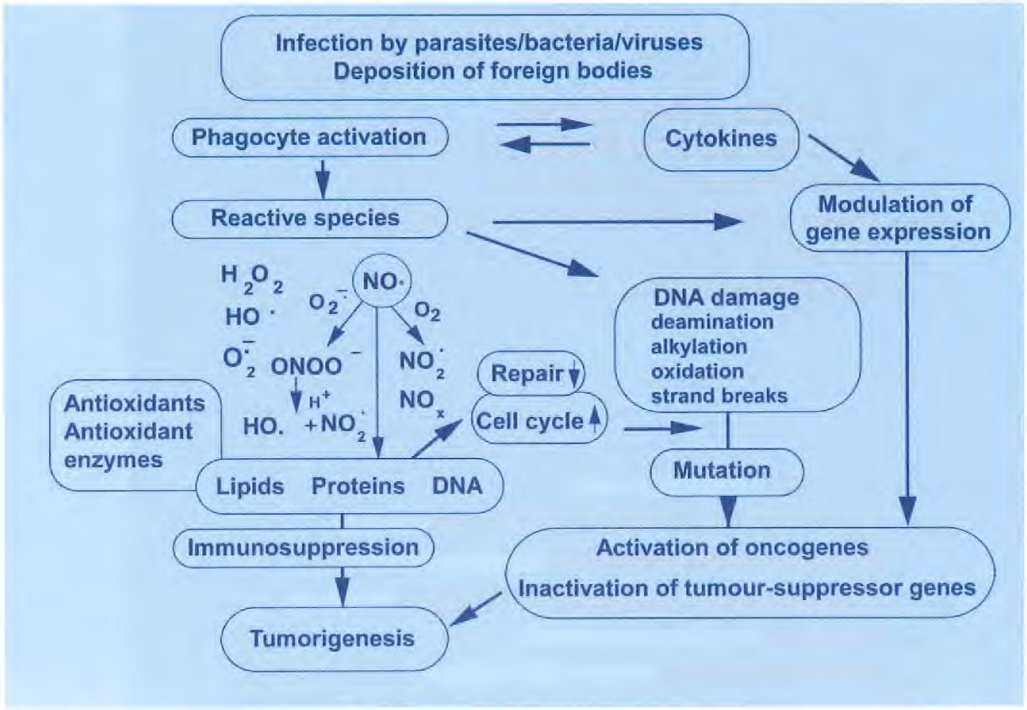


Figure 27. A hypothetical scheme for the role of NO and other reactive oxygen/nitrogen species in multistage carcinogenesis, triggered by chronic infection and inflammation

Human tissues are being studied for expression of various isoenzymes of NO synthase in normal, precancerous and tumour parts of specimens. Relationships between the expression of the enzyme and characteristics of tumours (histological type, invasion, metastasis) and prognosis are being investigated. The tissue sites include brain, liver, colon, breast and bladder. Results from pilot studies demonstrate that iNOS activity and immunoreactivity are elevated in human liver specimens from cirrhosis patients [432] and other precancerous tissues.

Experiments have been carried out to study the role of NO in animal carcinogenesis. In a rat urinary tract infection model and in hamsters infected with *Opisthorchis viverrini*, levels of nitrite, nitrate and NOC were significantly increased through activation of inducible NO synthase and bacterial production of NO [430]. Anti-oxidant enzymes and inducible NO synthase were also significantly expressed in infected tissues.

4.4.3
DNA and tissue damage induced by endogenous free radicals

H. Ohshima, J. Rubio, V. Yermilov, B. Pignatelli, C. Malaveille, I. Brouet and A. Hautefeuille; in collaboration with T. Suzuki and K. Makino, Kyoto, Japan; and H. Nukaya, Shizuoka, Japan

NO reacts rapidly with superoxide anion ($O_2^{\cdot -}$) to form the peroxynitrite anion ($ONOO^-$). Peroxynitrite (pK_a = 6.8) may itself be tissue-toxic and also decomposes

under physiological conditions to produce strong oxidants which initiate reactions characteristic of hydroxyl radical, nitronium ion and nitrogen dioxide. These radicals are implicated as compounds responsible for tissue damage induced in infected and inflamed tissues. We have studied the reaction of peroxynitrite with protein, DNA, nucleosides and DNA bases *in vitro*. Low concentrations of peroxynitrite induced strand breaks in double-strand supercoiled plasmid DNA (pBR322). We are now studying whether peroxynitrite can induce any sequence-specific damage in the same plasmid. The reaction of various deoxynucleosides with peroxynitrite resulted in formation of highly cytotoxic base-propenals (base–CH=CH–CHO), degradation products of DNA. Human glutathione transferase, especially Pi form (GST P1-1) was recently shown to catalyse the conjugation of glutathione with base-propenals (Berhane *et al.*, 1994, *Proc. Natl. Acad. Sci. USA*, **91**, 1480–1484). As GST P1-1 is expressed at high levels in many precancerous and cancerous tissues, base-propenals may be formed by oxidative DNA damage in these tissues. A new sensitive and specific method for analysis of base-propenals has been developed (see Section 6.1.2) and is now being used in studying further the reaction mechanisms as well as the occurrence, formation and metabolism of base-propenals in cells and animals.

Peroxynitrite also reacts with tyrosine residues in protein to form both nitrotyrosine and dityrosine. Anti-oxidants such as ascorbic acid and uric acid inhibit this reaction. These tyrosine modifications could be measured as markers of peroxynitrite-mediated tissue damage and oxidative stress in tissues. Short-term and long-term animal experiments are planned to study the effects of peroxynitrite on tumour induction and promotion.

4.4.4
Identification of 8-nitroguanine as a major reaction product of guanine with peroxynitrite

H. Ohshima, V. Yermilov, J. Rubio, B. Pignatelli, C. Malaveille, M.D. Friesen, I. Brouet and A. Hautefeuille; in collaboration with M. Becchi, Vernaison, France

Guanine was found to react with peroxynitrite at neutral pH to yield several compounds, two of which were yellow, a characteristic of nitro and nitroso compounds. On the basis of chromatographic and spectral evidence, we identified the major yellow compound (which accounts for about 80% of all the products formed) as 8-nitroguanine (Figure 28) [696]. Using a sensitive and specific method to analyse 8-nitroguanine in DNA developed in this laboratory (see Section 6.1.2), we found that 8-nitroguanine is also formed in DNA treated with peroxynitrite *in vitro*. Thus, 8-nitroguanine, a base modification induced uniquely by peroxynitrite, can be measured as a specific marker of DNA damage induced by NO and peroxynitrite in inflamed tissues. Studies are now in progress to elucidate the biological significance of 8-nitroguanine.

4.4.5
Inhibition of iNOS induction in activated macrophages by an anti-tumour promoter, curcumin

I. Brouet and H. Ohshima; in collaboration with H. Osswald, Heidelberg, Germany; and G. Winde, Münster, Germany

Cancer development and tumour promotion or progression could be prevented by reducing tissue damage induced by reactive oxygen/nitrogen species in inflamed tissues. We have studied the effect of various non-steroidal anti-inflammatory agents on the induction of NO synthase (iNOS) in macrophages activated by lipopolysaccharide and

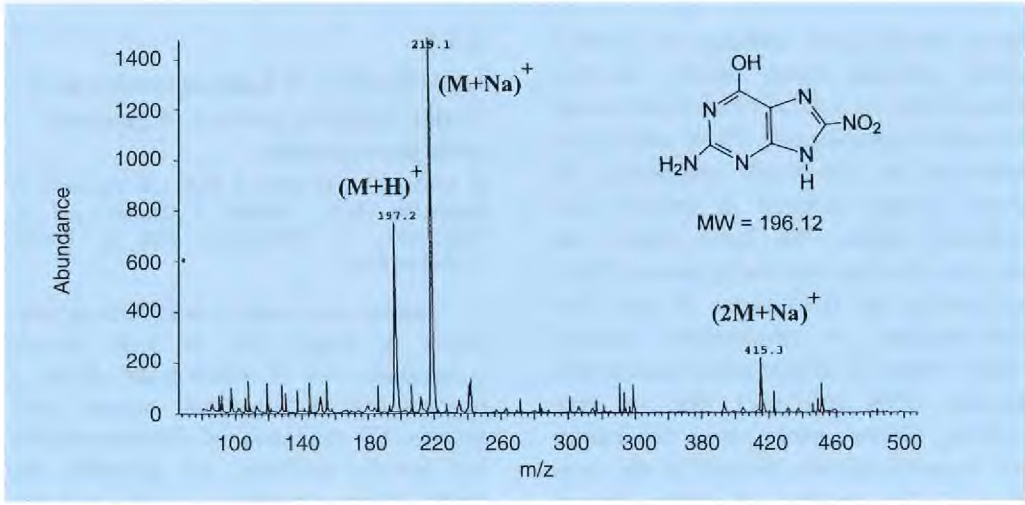


Figure 28. Electrospray-mass spectrometry analysis of 8-nitroguanine, a major compound formed by the reaction of peroxynitrite with guanine

interferon-γ. It was found that curcumin, a potent anti-tumour promoter in many organs, inhibits NO synthase induction at very low concentrations by inhibiting the transcription of the iNOS gene [84]. Thus, the anti-cancer properties of curcumin may be mediated, at least in part, by its inhibiting iNOS expression in inflamed tissues. A pilot study has been initiated to study the effects of non-steroidal anti-inflammatory agents on the expression of iNOS and anti-oxidant enzymes in colon biopsies from patients with large bowel inflammatory diseases.

4.4.6
Effect of treatment with omeprazole and cimetidine on bacterial overgrowth and gastric levels of nitrate, nitrite and *N*-nitroso compounds

B. Pignatelli; in collaboration with M. Fried, Zurich, Switzerland; and J. Thorens and A.L. Blum, Lausanne, Switzerland

Gastric and duodenal bacterial overgrowth frequently occurs as gastric acid secretion decreases. The colonization of the stomach by nitrate-reducing bacteria has been hypothesized to favour the endogenous formation of carcinogenic *N*-nitroso compounds (NOC). In a previous study [664], we found that in healthy volunteers, omeprazole treatment was associated with gastric bacterial proliferation but did not lead to consistent elevation of nitrite or total NOC concentrations. A similar study has been conducted in 47 patients with peptic disease who were randomly assigned to treatment with omeprazole or cimetidine. Gastric juice was obtained before and after the treatment course and nitrate, nitrite, NOC and pH were measured. The extent of gastric bacterial overgrowth was compared in patients as a function of the treatment received. The relationships between the degree of bacterial colonization and gastric levels of nitrate, nitrite and NOC compounds were investigated. Although elevation of gastric pH and bacterial overgrowth resulted from treatment with the two antacid drugs, and particularly with omeprazole, levels of nitrate, nitrite and NOC compounds were similar before and after treatment.

4.4.7
Increased excretion of *N*-nitroso compounds in patients with urinary diversion

B. Pignatelli, S. Calmels, G. Brun and A. Ellul; in collaboration with K. Steven, A.L. Poulsen and J. Carstensen, Herlev, Denmark

Patients with urinary diversion are at higher risk for cancer in the ureterocolic anastomosis after ureterosigmoidostomy, in reconstructed tissue after cystoplasties performed for contracted bladder or in colonic conduits. In these patients the presence of intestinal bacteria in the urine was frequently observed and associated with increased levels of nitrite and potentially carcinogenic *N*-nitroso compounds, as compared to control subjects. Detailed statistical analysis is being performed.

4.5 Role of cell–cell communication in carcinogenesis

Gap junctional intercellular communication (GJIC) is the only means by which multicellular organisms mediate the direct intercellular exchange of cellular signal factors from the interior of one cell to that of neighbouring cells. GJIC is considered to play a crucial role in the maintenance of homeostasis, and in turn, aberrant GJIC is likely to be involved in carcinogenesis; cancer cells do indeed behave as if they

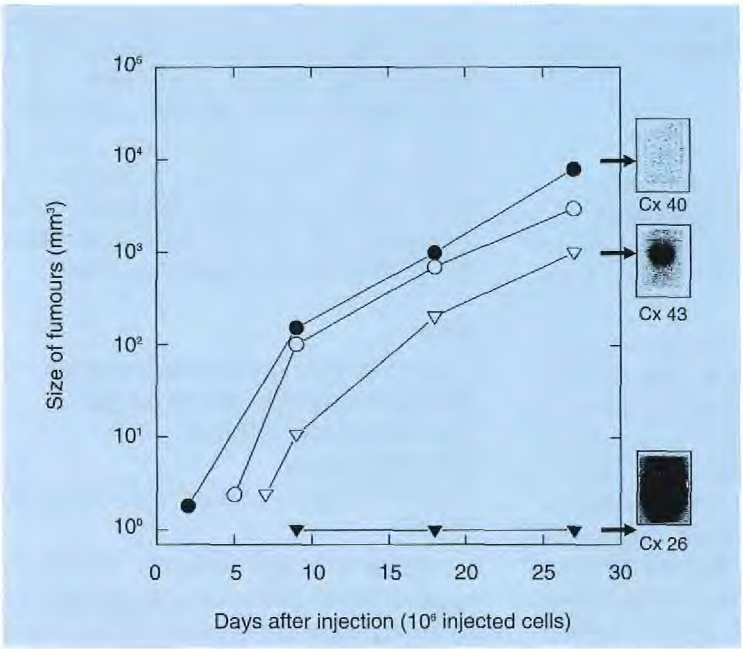


Figure 29. Differential tumour suppressor effects of various connexin species on HeLa cells. The tumorigenicity of HeLa cells transfected with the Cx26 gene, but not those with Cx40 or Cx43 genes, was suppressed. The tumour-suppressive effects were correlated with the level of connexin gene expression in cervical tissue, from which HeLa cells were originally isolated; Cx26 is the most abundantly expressed connexin gene in the cervix [347].

were dissociated from the homeostasis maintained by the organism.

Three main lines of evidence support the idea of involvement of aberrant GJIC in carcinogenesis: (1) the inhibitory effect of various tumour-promoting agents on GJIC, (2) the aberrant GJIC capacity observed in many rodent and human tumors, and (3) the restitution of growth control in GJIC-deficient tumorigenic cells by transfection of connexin genes (connexin is the structural protein of gap junctions).

Aberrant GJIC has long been considered to be a non-genotoxic event that is important for carcinogenesis, since many non-genotoxic tumor-promoting agents inhibit GJIC. More recently, it has become apparent that aberrant post-translational control of connexin proteins is a major mechanism of disruption of GJIC. However, it is also possible that connexin genes can be affected by genotoxic carcinogens, leading to aberrant GJIC.

4.5.1

Tumour suppression by connexin genes; connexin species specificity

M. Mesnil, C. Piccoli, V. Krutovskikh and H. Yamasaki; in collaboration with K. Willecke, Bonn, Germany

Results from our own and other laboratories suggest that connexin (gap junction protein) genes form a family of tumour-suppressor genes. In order to examine whether different connexin gene species exert different degrees of tumour-suppressive activity, we characterized the growth characteristics of a gap junction-deficient human cancer cell line, HeLa cells, before and after transfection with cDNA for three different connexins, connexins (Cx) 26, 40 and 43. All transfected cell lines (three clones transfected with the Cx26 gene, two clones with Cx40 and one with Cx43) showed establishment of GJIC. Two of the Cx26-transfected clones showed significantly slower growth compared with the parental HeLa cells. In soft agar, the three Cx26-transfected clones grew much less than the other transfectants or the parent HeLa cells. When injected into nude mice, the two Cx26 clones showing the highest amount of Cx26 transcript induced almost no tumours, whereas other transfectants, including the Cx26 clone with the lowest amount of Cx26 transcript, were tumorigenic. Among transfectants with various connexin genes, there was no clear inverse correlation between their GJIC and tumorigenicity. GJIC levels were significantly higher in tumours induced in nude mice by Cx26 transfectants [347]. These results suggest that all of the connexin genes examined could induce recovery of GJIC of HeLa cells, but only the Cx26 gene exerts strong negative growth control on HeLa cells; thus, this connexin gene may have different functions from other connexin genes. This conclusion is supported by a recent finding (Elfgang *et al.*, 1995, *J. Cell Biol.*, **129,** 805–817) that HeLa cells transfected with these genes show different permeability. It is interesting to note that the Cx26 gene is a major connexin gene expressed in the cervical tissue from which HeLa cells originate (Figure 29) [346].

4.5.2

Connexin gene mutations and their dominant negative effect on gap junctional intercellular communication

Y. Omori, M. Mesnil, A. Dancer, N. Mironov and H. Yamasaki

Mutation of the connexin 32 (Cx32) gene has been reported to be responsible for X-linked dominant Charcot–Marie–Tooth disease (CMTX) (Berghoffen *et al.*, 1993, *Science*, **262**, 2039–2042) (Figure 30). We have examined the ability of mutant Cx32 genes (i) to establish functional gap junctions among cells containing such mutations and (ii) to inactivate wild-type Cx32 by a dominant negative mechanism (Figure 31).

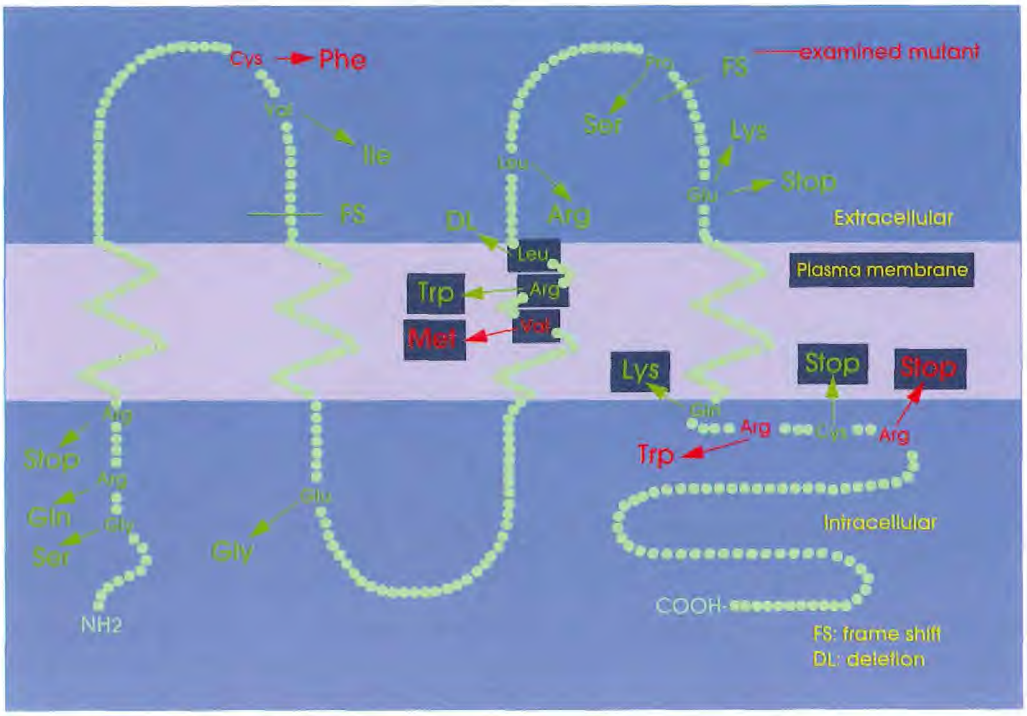


Figure 30. Cx32 gene mutations found in X-linked Charcot–Marie–Tooth patients and those selected for our study. Mutations designated in red were inserted into Cx32 cDNA by site-directed mutagenesis and their functions were examined.

Four mutated Cx32 genes found in CMTX patients were transfected into HeLa cells, which do not show detectable levels of any connexin. GJIC was restored in cells transfected with the wild-type Cx32 gene, but not in those transfected with genes carrying three different base substitutions, namely Cys 60 to Phe, Val 139 to Met and Arg 215 to Trp. Unexpectedly, however, cells transfected with a nonsense mutant at the 220th codon restored GJIC.

In order to examine the possible dominant negative effect of these mutations, we double-transfected these mutant constructs into the HeLa cells which had already been transfected with wild-type Cx32 gene. The three base substitution mutants reduced the level of GJIC restored by the wild-type gene, while vector-transfected cells maintained the same level of GJIC (Figure 32), suggesting that these three mutants can erase the wild-type's effect in a dominant negative manner.

The nonsense mutation at the 220th codon did not show such a dominant negative effect. In the double transfectants, both mutant and wild-type genes were expressed, and Western blot analysis suggested that Cx32 proteins were present. It is suggested that base substitution mutations can down-regulate wild-type Cx32, presumably through production of non-functional chimeric connexons composed of mutant and wild-type connexins. In view of the structural homology of other connexin species, our results suggest that such a dominant negative effect may be a general phenomenon and one-allele mutation of connexin genes may suffice to impair GJIC capacity.

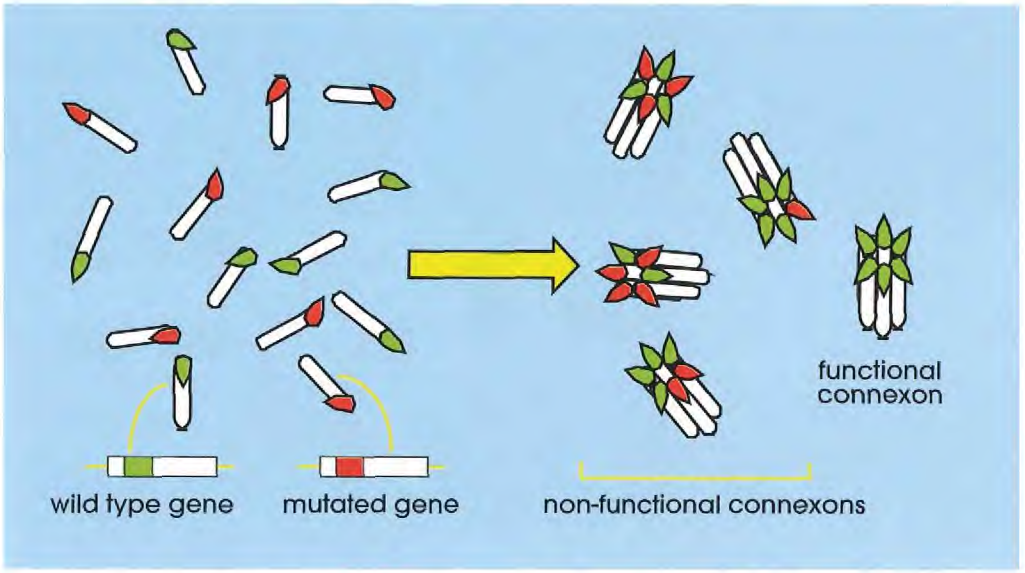


Figure 31. Schematic view of dominant-negative effect of mutant Cx32 on gap junctional intercellular communication

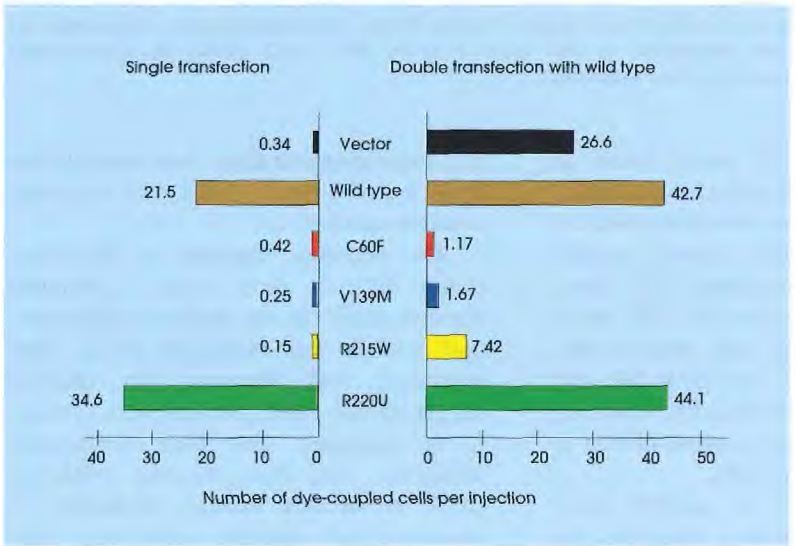


Figure 32. Capacity of connexin 32 mutants to restore GJIC in HeLa cells, and their dominant negative effect against wild-type connexin 32. Cloned transfectants were microinjected with Lucifer yellow and the extent of dye transfer was estimated. The left-hand side shows the GJIC capacity of each clone with the various mutants; the right-hand side shows the GJIC capacity of clones generated by secondary transfection of the same mutants into HeLa cells previously transfected with the wild-type connexin 32.

4.5.3
Mechanisms of aberrant regulation of gap junctional intercellular communication by tumour-promoting agents and in tumours

V. Krutovskikh, M. Mesnil, G. Mazzoleni, C. Piccoli, Y. Omori and H. Yamasaki; in collaboration with N.E. Fusenig, Heidelberg, Germany; E. Rivedal and T. Sanner, Oslo, Norway; H. Tsuda, Tokyo, Japan; and L. Wärngård, Stockholm, Sweden

In vitro studies have revealed that inhibition of GJIC by various agents is often associated with aberrant localization of connexin proteins, which are found in the cytoplasm instead of at cell–cell contact areas. We have shown that phosphorylation of connexin proteins may be involved in such an intracellular translocation process [345, 518].

We also showed that several liver tumour-promoting agents down-regulate GJIC *in vivo*, by molecular mechanisms similar to those observed *in vitro* [290]. Among Fischer 344 rats given repeated doses of four tumour-promoting agents (phenobarbital, polychlorinated biphenyls (PCB), dichlorodiphenyltrichloroethane (DDT) and clofibrate) dye-coupling in the liver was decreased. This decrease was associated with reduced numbers of gap junctions and aberrant localization of Cx32 proteins in hepatocytes, but only slight changes in the level of Cx32 proteins; Cx32 was often observed in the cytoplasm instead of at gap junctions in the plasma membrane. Although Cx26 proteins at gap junctions were usually decreased by tumour promoters in rat liver, local induction of Cx26 protein expression in centrolobular groups of hepatocytes was observed after PCB and DDT treatment. Expression of Cx43 was induced in hepatocytes after PCB, DDT and clofibrate exposure, but this protein was also localized intracytoplasmically, suggesting that it has no functional role [289].

All of the tumour-promoting agents tested also increased cell proliferation [289]. Similar inverse relationships between cell proliferation and GJIC were also observed after partial hepatectomy and during different stages of rat liver carcinogenesis [626, 692].

The changes in levels of expression of Cx32 and 26 proteins in rat liver after chemical treatments could indirectly reflect functional impairment of GJIC. Rat liver samples from two initiation–promotion hepatocarcinogenesis studies, in which 3,4,5,3′,4′-pentachlorobiphenyl (PCB 126) was used as tumour promoter, were analysed retrospectively by this approach. Decreased levels of these two connexins were observed in PCB 126-treated liver samples, but little change in mRNA levels. Even at doses of PCB 126 too low to promote the development of gamma-glutamyltransferase-positive foci, a clear reduction of Cx32-positive spots in plasma membrane of hepatocytes was seen [21].

Analysis of human primary liver tumours *in vivo* [288] as well as human tumour cell lines [173, 434] revealed much lower levels of GJIC than in their normal counterparts. Molecular studies indicated that aberrant expression of connexin genes and/or aberrant localization of connexin proteins may be responsible for their lower GJIC capacity.

4.5.4
Growth factor-mediated suppression of transformed cells by non-transformed counterparts—a novel mechanism of tumour suppression

P. Silingardi, J.-L. Klein, M. Mesnil and H. Yamasaki

Transforming growth factor β1 (TGF-β1) enhances the yield of transformed foci of BALB/c 3T3 cells, but continued presence of TGF-β1 after focus formation inhibits the growth of transformed foci. The

focus-forming ability of H-*ras*-, v-*src*- and PyMT-transformed cells growing on a monolayer of non-transformed cells was completely suppressed by TGF-β1, whereas growth of the transformed cells was little inhibited by TGF-β1 in the absence of their normal counterparts (Figure 5). The inhibition by TGF-β1 of focus formation among transformed BALB/c 3T3 cells on a normal cell monolayer remained when TGF-β1 was removed from the culture medium after two weeks. However, the transformed cells were not killed, since they grew in culture conditions under which only transformed cells are able to grow (soft agar). These results suggest that TGF-β1 suppresses growth of transformed cells in the presence of normal cells. Furthermore, when non-transformed cells were treated with TGF-β1 before co-culture with H-*ras*-transformed cells, formation of transformed foci was inhibited. When normal and transformed cells were cultured in the same dish but separated physically, focus formation was still inhibited. On the other hand, TGF-β1 enhanced the growth and changed the morphology of non-transformed cells only in the presence of transformed counterparts [582]. These results suggest a novel type of tumour suppression through cell–cell interaction via paracrine growth regulatory factors.

4.6 Mutator phenotype and carcinogenesis

Microsatellite changes observed in hereditary colorectal cancers as well as in sporadic forms of various human tumours are considered to represent genomic instability which contributes to the accumu lation of multiple genetic changes during multistage carcinogenesis (Aaltonen *et al.*, 1993, *Science*, **260**, 812–816). IARC laboratories are examining the role of exogenous carcinogens in such a mutator phenotype using (CA)n repeats as markers.

4.6.1 Microsatellite alterations in human and rat oesophageal tumours at selective loci

N. Mironov, A.-M. Aguelon, E. Hollams, J.-C. Lozano and H. Yamasaki

(CA)n simple repeats in DNA were examined at 17 loci in 18 human squamous cell carcinomas of the oesophagus and compared with those in normal oesophageal tissue from the same patients. Six loci were examined in 32 oesophageal papillomas induced in BDVI rats by *N*-nitrosomethylbenzylamine. Length-altered (CA)n repeats were found in two human tumours and four rat papillomas. Loss of heterozygosity was observed in three human tumours; two rat papillomas had lost microsatellite bands that are common in inbred BDVI rats (Table 9). Both (CA)n microsatellite length alteration and loss of heterozygosity were clustered at certain loci in the human tumour samples and in the chemically-induced rat oesophageal tumours [361]. Our findings indicate that genomic instability causing alteration of repeated sequences not only occurs in human tumours but may also be a consequence of chemical carcinogenesis in rodents. Recently, Canzian *et al.* (1994, *Cancer Res.*, **54**, 6315–6317) also reported that carcinogen-induced rat tumours show microsatellite changes.

Table 9. Microsatellite instability in oesophageal cancer

Samples	Length-altered (CA)n repeats		Loss of heterozygosity	
	Locus	Chromosome	Locus	Chromosome
Human oesophagus squamous cell carcinomas				
65	–	–	AFM267ve9	2p13
	–	–	SSM1 [a]	9q13.2-q13.3
	–	–	AFM234xa3	6p21.3
	–	–	Mfd84	12
	–	–	AFM283zb9	17q21-q22
	–	–	Mfd26	18q
67	Mfd26	18q	–	–
505	–	–	SSM [a]	9q13.2-q13.3
515	AFM267ve9	2p13	–	–
	Mfd84	12	–	–
	–	–	AFM234xa3	6p21.3
	–	–	Mfd32	18
Rat papillomas [b]				
79	TNF	20	–	–
94	TNF	20	–	–

[a] Samples 65 and 505 were homozygous at the SSM2 locus

[b] The samples listed are those with microsatellite lengths different from those found in inbred BDVI rats. Two samples (Nos. 9 and 60) had lost bands that were present in their normal counterparts and in all other tumour samples. Samples Nos. 43 and 89 were found to have germline mutations and not tumour alterations (from ref. [361])

4.6.2

Relationship between carcinogen-induced *ras* gene mutations and microsatellite changes in mouse

K. Sasaki, O. Bertrand, H. Nakazawa, D.J. Fitzgerald, N. Mironov and H. Yamasaki

In mouse skin, papillomas, carcinomas or fibrosarcomas can be induced by 7,12-dimethylbenz[*a*]anthracene (DMBA), depending on the mode of administration. Thus, upon DMBA painting (or transplacental exposure by intraperitoneal injection to pregnant mothers) followed by applications of 12-*O*-tetradecanoylphorbol 13-acetate (TPA) to the skin of CD1 mice, papillomas and carcinomas appeared, whereas fibrosarcomas were induced when DMBA was injected subcutaneously. The majority of the papillomas (17 out of 20) and carcinomas (9 out of 10) showed DMBA-specific mutations (A to T transversion at the 61st codon) in the H-*ras* gene. In contrast, many fibrosarcomas (5 out of 9) showed the same mutation only in the K-*ras* gene. When microsatellites were studied in these tumours at nine loci containing (CA)n repeats, no instability was detected.

In addition, among 14 BALB/c 3T3 cell lines transformed by various carcinogens (including three clones induced by DMBA which had the A→T mutation in the K-*ras* gene), no changes in (CA)n repeats were observed. These results suggest that DMBA-induced mouse tumours and transformed cells show cell-type specific *ras* gene mutations, that occur independently of microsatellite instability (Table 10). While murine cells are considered to be relatively susceptible to cancer induction partly due to genomic instability, our results indicate that

Table 10. Ras gene mutations and microsatellite instability in carcinogen-induced mouse skin tumours and transformed BALB/c 3T3 cells (from ref. [543])

Samples	Treatment [a]	No. of samples analysed	A to T mutation at 61st codon of		Microsatellite changes at nine loci [b]
			K-ras	H-ras	
Skin tumours					
Fibrosarcoma	DMBA (sc)	9	5/9	0/9	
Papilloma	DMBA + TPA (pt)	9	0/9	7/9	
	DMBA (tp) + TPA	11	0/11	10/11	None
Carcinoma	DMBA + TPA (pt)	2	0/2	1/2	
	DMBA (tp) + TPA	8	0/8	8/8	
Transformed BALB/c 3T3 cells					
	DMBA (10 nM)	3	3/3	0/3	
	MCA (3 nM)	3	0/3	0/3	
	MNNG (10 nM)	3	0/3	0/3	None
	MNU (10 nM)	2	0/2	0/2	
	UV (20 mJ)	3	0/3	0/3	

[a] sc, subcutaneous; pt, painting; tp, transplacental
[b] Loci studied are Il 2 (on chromosome 3), Orm-1 (on chromosome 4), D4Nds3 (on chromosome 4), Thy-1 (on chromosome 9), MUSANTP91A[b] (on chromosome 11), Igh (on chromosome 12), hr (on chromosome 14), Int1 (on chromosome 15) and li (on chromosome 18).
DMBA 7,12-dimethylbenz[a]anthracene; MCA 3-methylcholanthrene; MNNG N-methyl-N'-nitro-N-nitrosoguanidine; MNU N-methyl-N-nitrosourea; TPA 12-O-tetradecanoylphorbol 13-acetate

microsatellite instability is not induced in these cells by chemical carcinogens.

4.6.3 Identification of genes responsible for microsatellite DNA alterations in human oesophageal tumours

N. Mironov, A.-M. Aguelon and H. Yamasaki

Microsatellite instability is believed to be due to functional damage of genes, such as hMSH2, hMLH1, hPMS1 and hPMS2, that are involved in DNA mismatch repair. Alteration of the first of these seems to contribute to the majority of hereditary nonpolyposis colorectal cancer (HNPCC) cases. In order to examine whether a specific mutation of the hMSH2 gene is responsible for human oesophageal or stomach tumour genomic instability, we have sequenced the PCR product from amplified exons of this gene in six samples with (CA)n repeat alterations. After sequencing 8 out of 16 exons, we found two samples of stomach tumours with a mutated hMSH2 gene.

4.7 Role of p53 in carcinogenesis

Mutations in the *p53* gene are involved in the natural history of practically all major human cancer types. The p53 protein plays an essential role in controlling the proliferation and survival of cells exposed to DNA-damaging agents, and loss of p53 function by mutation is thought to facilitate the propagation of potentially oncogenic DNA lesions.

Studies of mutations in this gene are in progress at IARC in relation to cancers of the oesophagus (Section 3.1.2), liver (Section 3.3.6 and 3.3.7), lung (Section 3.7.5), brain (Section 3.5.3), kidney (Section 3.6.4) and head and neck cancers (Section 3.8.3 and 3.8.4).

4.7.1

Regulation of the p53 protein conformation and biochemical activity by redox factors and metal compounds

P. Hainaut, G. Verhaegh and G. Martel-Planche; in collaboration with K. Vähäkangas, Oulu, Finland; B. Jasani, Cardiff, UK; and M.J. Richard, Grenoble, France

The p53 protein is a transcription factor which regulates the expression of target genes by specifically binding to DNA through a highly flexible protein domain. Interaction with zinc is essential for maintaining the structural integrity of the form of the molecule associated with tumour-suppression (Hainaut & Milner, 1993, *Cancer Res.*, **53**, 1739–1742). Binding of zinc occurs through highly conserved residues (mainly cysteine) in a redox-dependent manner. Oxidation disrupts the wild-type p53 conformation and inhibits specific DNA-binding, whereas reduction favours folding of the protein into the structural form associated with tumour suppression (Hainaut & Milner, 1993, *Cancer Res.*, **53**, 4469–4473). The p53 protein may therefore be intrinsically capable of 'sensing' intracellular changes associated with exposure to many forms of genotoxic stress and this could be part of the mechanisms by which p53 is specifically induced by chemical and physical carcinogens (Hainaut, 1995, *Curr. Opin. Oncology*, **7**, 76–82).

We are investigating whether p53 conformation (determined by immunodetection with specific antibodies) and DNA-binding activity are also affected by redox conditions and by metals in intact cells. This includes (1) analysis of reactive oxygen species as 'second messengers' regulating p53 during the cell-cycle and in response to genotoxic chemicals; (2) effects of metal compounds, metal chelation and metal substitution on p53 protein activity in cells with defined genetic background, and (3) alterations in p53 redox- and metalloregulation as alternative mechanisms for p53 inactivation in cancer cells. A long-term aim is to determine whether metal and redox regulation can be used for pharmacological control of p53 activity, in particular in early cancer lesions that may express non-mutated p53 genes.

4.7.2

Database of *p53* gene somatic mutations in human tumours and cell lines

M. Hollstein, P. Hainaut and R. Montesano; in collaboration with C.C. Harris, Bethesda, USA; B. Smith-Sørensen, Oslo, Norway; and T. Soussi, Paris, France

A database has been established and maintained [229] in which over 2500 mutations in the *p53* gene of human tumours and tumour cell lines are compiled from a systematic search of reports published. Analysis of p53 mutations in human cancers can be used to make inferences about the important sources of DNA damage in humans and may provide information useful in the clinical setting. The compilation has been deposited with the EMBL Data Library and is available in electronic form free of charge.

PART 5. PREVENTION AND EARLY DETECTION OF CANCER

5.1 Studies of primary prevention of cancer

Primary prevention of cancer covers all interventions aimed at preventing initiation of carcinogenesis, by either removing exposure to a carcinogenic agent or inducing mechanisms to counteract the effect of such exposure, for example by vaccination or by administration of a protective chemical substance (chemoprevention). In general, prevention of exposure to a carcinogen will always be beneficial, but it is nevertheless valuable to conduct studies permitting the extent of the benefit to be evaluated. In contrast, the administration of a foreign substance, or of a natural substance in unnatural quantities, may well lead to undesirable side-effects that can negate any cancer-preventive benefit. It is therefore particularly important that such interventions are subjected to very careful scrutiny at all stages of their planning and implementation.

5.1.1 The Gambia Hepatitis Intervention Study

A.D. Jack, N. Maine, A. Cosimi, L. Insabato, M. Mendy, E. Bah, B.K. Armstrong, D.M Parkin and R. Montesano; in collaboration with M.O. George and F.S.J. Oldfield, Banjul, Gambia; B.M. Greenwood and H.C. Whittle, Fajara, Gambia; F. Aiuti, Rome, Italy; A. Cali, Naples, Italy; and A.J. Hall, London, UK

This long-term intervention study is aimed at evaluating the effectiveness of hepatitis B vaccination in prevention of persistent hepatitis B infection, chronic liver disease and primary hepatocellular carcinoma. A total of 124 577 children have been recruited into the study in two cohorts of vaccinated and unvaccinated groups. The effect of vaccination will be evaluated over the next 30 years.

The study is being conducted in collaboration with the Government of The Gambia and the UK Medical Research Council. Funding is from the Direzione Generale per la Cooperazione allo Sviluppo, Ministry of Foreign Affairs, Italy, the Swedish Medical Research Council and the Autonomous Region of Valle d'Aosta, Italy.

5.1.1.1 Monitoring the effect of HBV vaccination

A group of 1041 children (Group 1), who received hepatitis B vaccine in infancy, are being followed up to monitor the trend of antibody decay and the duration of protection against persistent infection. These children were selected from the first four centres to incorporate the vaccine into the Extended Programme of Immunization (EPI) schedule.

The seventh-year follow-up of these children was concluded in July 1994, with 68% of all recruited children traced and bled. While the majority of the children still showed protective levels of antibody, antibody decay continues to be evident (Table 11). However, 93% still remain free of infection at this age. The rate of chronic carriage remains very low; only four children tested positive for HBsAg. Two of these children have been persistently positive throughout the period of follow-up and have had a very poor response to the vaccine from the outset.

Of interest is the observation that the risk of core conversion among these vaccinated children reaches a peak at about three years of age and then decreases with increasing age. This is against the background of intense pressure of infection in the Gambia.

Table 11. Hepatitis B status of children in Group 1 at each of the first seven years of follow-up [a]

	HBsAb+ HBcAb−		HBsAb− HBcAb−		HBsAb+ HBcAb+		HBsAb− HBcAb+		Total
1st year	716	(94)*	11	(1)	33	(4)	4	(0.5)**	764
2nd year	664	(95)	27	(4)	8	(1)*	4	(0.6)**	703
3rd year	655	(93)	30	(4)	13	(2)*	6	(0.9)****	704
4th year	659	(91)	27	(4)	29	(4)**	4	(0.6)**	721
5th year	622	(84)	80	(11)	27	(4)	11	(1.5)****	740
7th year	479	(68)	178	(25)	28	(4)*	19	(2.7)***	704

[a] The number of asterisks indicates the number of children positive for HBsAg.

No follow-up for serology was scheduled for the eighth year. Instead, the children in this group were visited towards the end of 1994 to check on their state of health and to assist with treatment where necessary. Vaccine efficacy will be estimated again at age nine years.

5.1.1.2

Cancer registration

A population-based cancer registry was launched at the beginning of the study, with the primary aim of monitoring the occurrence of primary liver cancer in the Gambia, and to provide the basis for future evaluation of the effect of vaccination on the incidence of this tumour in the Gambian population. Since then its role has been expanded to include all the other types of cancer diagnosed within the health service.

Eight years of data on the incidence of different forms of malignancy are now available. Liver cancer continues to be the most commonly reported malignancy in males and is a close second to cervical cancer in females. Attempts continue to be made to strengthen the reporting system through regular visits to all units, the recruitment of additional staff for the registry, training of a Gambian pathologist and the provision of equipment for in-country histopathology. From October 1993 to date, there has been a rotation of three histopathologists to man the Histopathology Unit at the Royal Victoria Hospital, by arrangement with the University of Naples. An ultrasonographic service has been introduced at the Royal Victoria Hospital with both equipment and training provided through the project.

5.1.1.3

Ancillary studies

Interest in the occurrence of break-through infections with hepatitis B virus in the face of apparently protective levels of antibody has led to the investigation of possible viral variants. A novel hepatitis B variant virus has been isolated from two vaccinated children in the village of Manduar. A change from adenosine to guanosine at nucleotide 421 of the S gene has been demonstrated in these variants, resulting in substitution of glutamic acid for lysine in a part of the loop of the S antigen which is bound by HBS antibodies. This enables the variant to escape neutralization. The frequency of such variant viruses and their public health significance are yet to be determined.

The fieldwork for a study to evaluate environmental and genetic predispositions to HBe antigenaemia has been concluded. All serological assays on the 884 samples collected have also been performed. HLA typing, however, is yet to be conducted. In

Figure 33. Newborn babies are brought for vaccination

order to confirm the carrier status of 103 children who tested HBsAg-positive when first bled, a repeat blood sample was sought from each of these children, all of whom have again tested positive, confirming the high frequency of chronic carriage in families of HBe-positive mothers. The results of this study are undergoing detailed analysis.

The attempt to operate a jaundice surveillance system in order to monitor changes in the pattern and severity of hepatitis B infection in the face of a highly successful vaccination programme has been discontinued. This was recommended by the Steering Committee as a result of the limited success in achieving nation-wide coverage and the inability to validate most of the reports emanating from traditional healers on whom the success of the programme depended.

Mathematical models to predict post-vaccination antibody decline and the impact of vaccination on the dynamics of infection are being developed in collaboration with the University of Cambridge and Imperial College (London), respectively.

5.1.2

Chemoprevention studies—review of results

D.M. Parkin and N. Muñoz; in collaboration with V. Beral, Oxford, UK; E. Buiatti, Florence, Italy; A. Costa, Milan, Italy; J. Faivre, Dijon, France; M. Hakama, Tampere, Finland; and R. Kroes, Bilthoven, Netherlands

In recent years, many chemoprevention studies have been initiated to assess the

contribution of dietary constituents (including micronutrients and oligo-elements) and drugs to preventing the onset of cancer or its precursors, or in preventing progression of precancerous lesions. By the mid-1990s, several such studies had been completed and, in collaboration with the Europe Against Cancer Programme of the European Union and the UICC, a review of studies in progress and their results was completed.

Initially, an inventory of chemoprevention studies and their results was carried out by a consultant and published as an IARC Technical Report [86]. Building upon this, a workshop was held in January 1995, with invited speakers reviewing selected areas. The proceedings of this workshop, with conclusions and recommendations, are being prepared for publication.

5.1.3 Chemoprevention trial on precancerous lesions of the stomach in Venezuela

N. Muñoz, I. Kato and M. Benz; in collaboration with O. Andrade, E. Cano, D. Castro, G. Lopez, W. Oliver, V. Sanchez and J. Vivas, San Cristobal, Venezuela; E. Buiatti, Florence, Italy; K. Miki, Tokyo, Japan; H. Ramirez, Cali, Colombia; and J. Torrado, San Sebastian, Spain

An intervention study in Tachira state, Venezuela, is taking advantage of the infrastructure created for the screening programme for stomach cancer (see Section 5.3.2). The original aim of this double-blind randomized trial was to determine whether treatment for *Helicobacter pylori* infection followed by treatment with certain anti-oxidants (β-carotene, vitamins C and E) could interrupt the process of gastric carcinogenesis by blocking progression from chronic gastritis and intestinal metaplasia to dysplasia and cancer. The protocol requires recruitment of 2200 subjects 35–69 years of age. At recruitment a dietary questionnaire is completed, a gastroscopy performed taking five biopsies and blood and urine specimens are collected from each participant. These procedures will be repeated at the end of the treatment phase, three years later. Annual physical examination and collection of biological specimens will be performed on all participants and gastroscopy on a subsample (Figures 34 and 35).

Pilot studies showed a high prevalence (90%) of *H. pylori* resistant to metronidazole, and treatment with bismuth subcitrate and amoxycillin for two weeks eradicated *H. pylori* in only 6.5% as compared to 2.0% in those receiving a placebo. This contrasts with eradication rates of 36–60% in trials using the same treatment regimen in Europe and North America [87]. In a second eradication trial of *H. pylori* infection involving 80 subjects, subjects were randomly assigned to two treatment regimens: (A) colloidal bismuth subcitrate (DeNol), amoxicillin and metronidazole; (B) omeprazole and clarithromycin, for 14 days.

Two months after completion of the treatment, the eradication rate was 28% for treatment A and 19% for treatment B. The lower eradication rates in these trials as compared to those obtained in other populations (80–90%) might be due either to differences in *H. pylori* strains, including drug resistance, or to frequent re-infection. The anti-*H. pylori* treatment phase was therefore deleted and the main trial commenced in May 1992 randomizing the subjects to treatment with anti-oxidant vitamins (vitamins C, E and β-carotene) as three capsules a day each containing 250 mg of vitamin C, 200 mg of vitamin E and 6 mg of β-carotene, or with a placebo. Treatment is distributed every 1–2 months for three years.

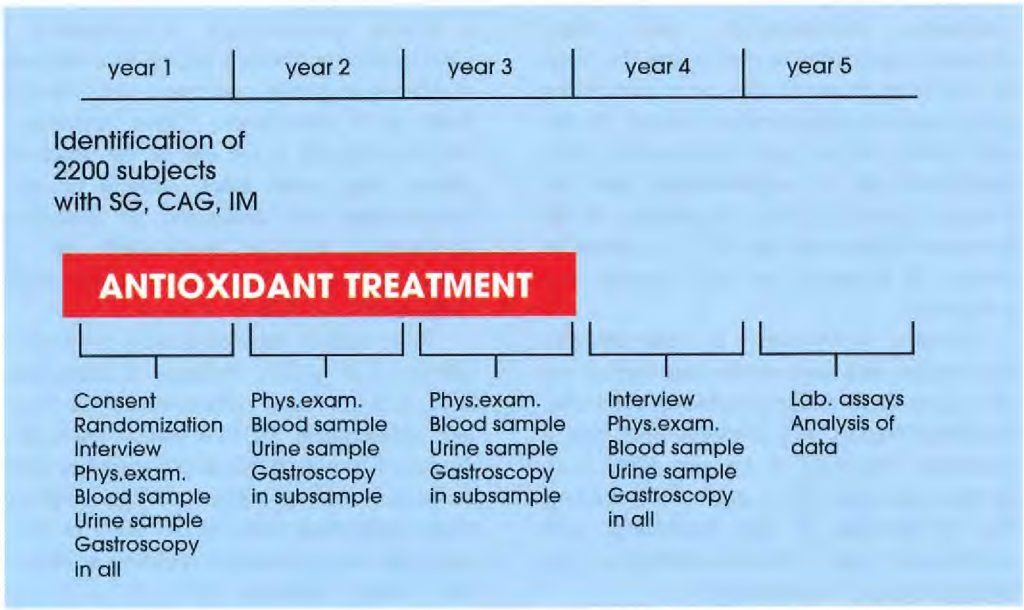


Figure 34. Protocol of chemoprevention intervention trial

Figure 35. Randomized distribution of treatment (vitamins or placebo) in chemoprevention intervention trial

Recruitment and randomization of 2200 subjects was completed in February 1995. Up to May 1995, 287 (13%) individuals have withdrawn from the trial.

Compliance with the treatment has been very good, with 87% of the subjects leaving less than 10% of the capsules. Twenty-four subjects have completed the three years of treatment and have undergone a final endoscopic examination. More than 1000 subjects have undergone a second endoscopic examination after one year of treatment, as have 90 patients with intestinal metaplasia type 3.

Preliminary results from specimens collected at base-line examination are summarized below:

Histopathological evaluation of the gastric biopsies of the first 1477 participants recruited into the trial revealed an overall prevalence of *H. pylori* infection and some type of chronic gastritis of 94%. Using a global diagnosis based on the most severe lesion among all biopsies, the following prevalences were recorded: superficial gastritis 4%, non-atrophic chronic gastritis 43%, atrophic gastritis 18%, intestinal metaplasia 28% and dysplasia 7%. The prevalence of the various lesions increased with age, but there was no clear difference by sex (Figure 36). *H. pylori* infection was positively associated with the degree of infiltration of polymorphonuclear leukocytes and lymphocytes and with that of active regeneration, and was inversely correlated with degree of atrophy, intestinal metaplasia and dysplasia.

The relationship of diet and other risk factors to the prevalence of more advanced precancerous lesions was investigated, by using subjects with superficial gastritis as controls. The prevalence of dysplasia was inversely associated with number of years of schooling and with fresh fruit consumption, and positively associated with tobacco use and with late use of refrigerator. Similar associations were observed for intestinal metaplasia, although they were weaker or not statistically significant.

Determinants of plasma pepsinogen (PG) levels were studied in the first 1365 participants of the trial. Levels of both PG-I and II increased progressively with the level of *H. pylori* infection in gastric biopsies, resulting in no clear trend in the I/II ratio. Instead, there was a progressive decrease in the I/II ratio with increasing degree of inflammatory infiltrate, atrophy, intestinal metaplasia and the stage of precancerous lesions. The mean I/II ratios for atrophic gastritis or more advanced lesions were less than 4.0. When subjects with a I/II ratio of 4 or higher were used as controls, severe reduction in the I/II ratio (<2.0) was inversely associated with tobacco consumption. A severe reduction of I/II ratio was also inversely associated with fresh fruit consumption [265].

Correlation analyses between baseline plasma levels of ascorbic acid (ASC), α-(ACAR) and β-carotenes (BCAR), cryptoxanthin (CRX), lycopene (LYC), and α- (ATOC) and γ-tocopherols (GTOC) and demographic and epidemiological variables among the first 1364 participants in the trial were performed. Males had lower levels of ASC, ACAR, BCAR and CRX and higher levels of ATOC than females. This finding was confirmed in non-smokers and in non-drinkers. Age was positively associated with levels of ASC, CRX, ACAR, BCAR and GTOC and inversely associated with ATOC. Male current tobacco users had lower plasma levels of ASC, ACAR, BCAR and CRX than non-users and regular alcohol drinkers had decreased plasma levels of BCAR compared with non-drinkers. Frequencies of consumption of fresh fruits, including juice, salad and plantains, were positively associated with plasma levels of several vitamins in both sexes.

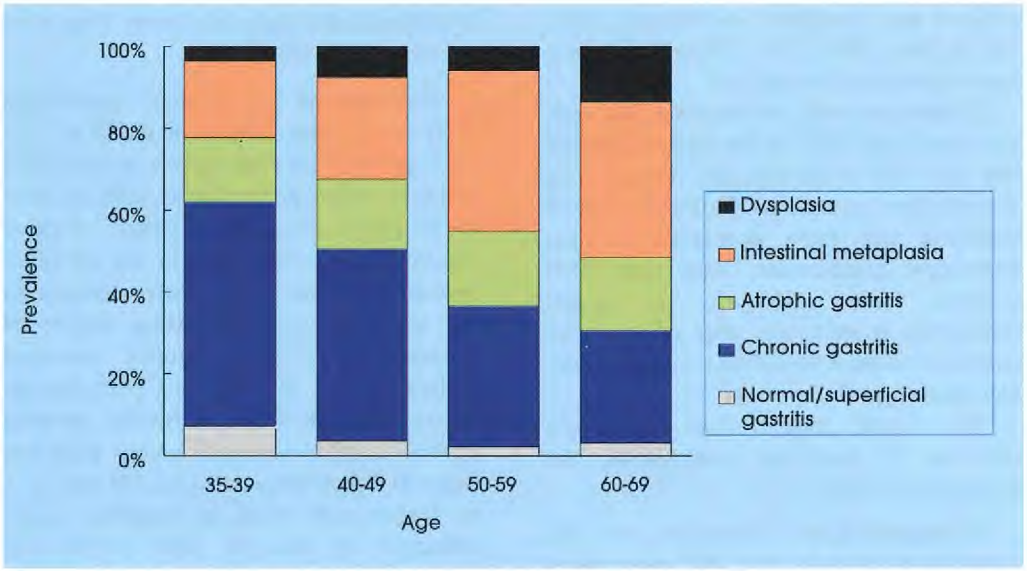


Figure 36. Global diagnoses of precancerous lesions of the stomach in Tachira, Venezuela (males)

5.1.4
HPV vaccines for cervical neoplasia

N. Muñoz; in collaboration with P. Coursaget, Tours, France and L. Crawford, Cambridge, UK

The potential use of HPV vaccines in prevention and treatment of cervical cancer was the theme of a workshop held in December 1994 (see Section 7.3.3). Results presented on the effectiveness of papillomavirus vaccines in preventing and treating tumours associated with these viruses in cattle, dogs and rabbits give strong encouragement to the development of equivalent vaccines against human papillomavirus. Two strategies were discussed in detail: therapeutic, to induce regression of precancerous and cancerous lesions associated with oncogenic HPV types, and prophylactic to prevent HPV infection and thus associated disease.

Small-scale phase I therapeutic trials have been initiated in the UK and Australia using vaccines against the transforming proteins of the virus (E6 and E7). In the UK, recombinant vaccinia vector expressing mutated E6 and E7 genes from both HPV 16 and 18 is being used. In Australia, bacterial fusion proteins for HPV 16 E7 with adjuvant is employed. A similar trial using peptides related to HPV 16 E7 will soon be started in the Netherlands.

Mass immunization with prophylactic HPV vaccines poses greater challenges but could have a greater long-term impact in reduction of cervical cancer than therapeutic vaccines.

There was consensus that the immunogens of choice are the virus-like particles (VLP) synthesized *in vitro*. These DNA-free particles appear to have the same conformation as authentic viral particles, as shown by their ability to induce neutralizing antibodies. The recent development of an animal xenograft model for HPV replication

has made possible the identification of neutralizing antibodies and antigens, the central part of the design and evaluation of HPV vaccines. Several companies are now proceeding to the development and production of VLPs of the standard required for human trials.

Both oncogenic and low-risk HPV types are of interest here. Evaluation of the vaccines against low-risk types should be easier and quicker than those against the oncogenic types. Emphasis was put in the discussion on the importance of the various endpoints to be used and on the necessity of developing adequate tests for cell mediated and humoral responses induced by vaccines. Endpoints for viral replication could be HPV DNA detection by PCR-based assays or by serological tests to be developed. Finally, the endpoints for disease development will be colposcopic, cytological and histological abnormalities of the uterine cervix.

The importance of careful design and ethical considerations was emphasized for large-scale trials having as an endpoint reduction in cervical cancer incidence, which will take many years to complete.

There was a strong optimism among the participants that advances at the preventive level will now follow the spectacular progress that has recently been achieved in understanding the molecular biology of HPV [394].

The implementation of phase I and II trials to validate safety and immunogenicity of HPV prophylactic vaccines is under consideration at IARC.

5.1.5
Chemoprevention of oral cancer

R. Sankaranarayanan; in collaboration with B. Mathew, N. Sreedevi Amma, M. Krishnan Nair and M. Sudhakaran, Trivandrum, India; P.P. Nair, Washington, USA; and R. Maher and S.H. Zaidi, Karachi, Pakistan

Short-term chemoprevention studies with vitamin A among pan tobacco chewers in Kerala, India, have demonstrated reversibility of oral precancerous lesions such as leukoplakia and erythroplakia. A randomized controlled intervention trial in Kerala, India, involving 600 subjects with high-risk oral precancerous lesions of nodular, ulcerated and dysplastic leukoplakias and erythroplakias has been designed to investigate whether long-term administration of vitamin A (200 000 IU per week orally for five years) can prevent oral cancer, without unacceptable toxic side-effects. The study has 80% power to detect a one third reduction, at 5% significance level, in the cumulative malignant transformation frequency in the intervention arm compared to the placebo arm, at eight years. A cumulative transformation frequency of 24% is expected in the control arm during this period. Recruitment of subjects to this study will be completed in one year.

A recently concluded study [326] has demonstrated the reversal of oral leukoplakias in subjects who were administered *Spirulina fusiformis,* a micronutrient-rich blue–green algae (1 g daily × 12 months), which is used as a food item. The preventive potential of *Spirulina* algae will be further evaluated in studies involving subjects with non-homogeneous leukoplakias and oral submucous fibrosis in India. Another study is being planned to be carried out in Karachi, Pakistan, to evaluate the preventive potential of a combination of vitamins A, B complex and E, minerals and iron in oral submucous fibrosis, a unique oral precancerous condition observed in the Indian sub-continent.

5.2 *Safe handling of carcinogens and destruction of carcinogenic wastes*

The aim of this programme is to ensure that safe techniques are available for handling and disposal of chemical carcinogens, particularly in clinical and research laboratories. An additional aspect is the dissemination of information about such methods through publications and courses.

5.2.1 Destruction of antineoplastic agents as hospital formulations

M. Castegnaro and J. Michelon; in collaboration with M. de Méo and M. Laget, Marseille, France; M.H. Sportouch, S. Hansel and J.C. Milhavet, Montpellier, France; E.B. Sansone and G. Lunn, Frederick, MD, USA; and J. Barek, Prague, Czech Republic

This work, co-ordinated by IARC, involves four collaborating laboratories (Frederick Cancer Research Facility, Frederick, MD, USA; Charles University, Prague, Czech Republic; St Charles Hospital, Montpellier and IARC, Lyon). Thirty-six drugs are being tested using three methods of degradation (sodium hypochlorite, hydrogen peroxide and Fenton reagent) on drug formulations as used in the treatment of patients in the St Charles Hospital, Montpellier, France and the National Cancer Institute, Bethesda, USA.

All the compounds so far tested are degraded with an efficiency of more than 99.9% by oxidation with 5% sodium hypochlorite or Fenton reagent. Degradation by 30% hydrogen peroxide was less successful; several of the compounds (dacarbazine, amsacrine, azathioprine, vindesine, vincristine, etoposide, teniposide, idarubicin, doxorubicin, daunorubicin) were not efficiently degraded. The residues from degradation of most drugs were non-mutagenic, with the exceptions of teniposide in glucose solution treated with sodium hypochlorite, etoposide and melphalan in saline solution and cyclophosphamide in glucose treated with Fenton reagent, and ifosfamide and cisplatin in glucose solution treated with hydrogen peroxide. For drugs which are not themselves mutagenic in the Ames assay, the drug and their residues after degradation will also be tested by the Comet Assay to test for induction of DNA damage.

5.2.2 Safe handling of genotoxic substances: training courses and dissemination of information

M. Davis and M. Castegnaro; in collaboration with M. Falcy, Paris, France; X. Rousselin, Avranche, France; and F. Valerio, Genoa, Italy

Two series of courses on safe handling of cytostatic drugs and genotoxic substances were held in Lyon in collaboration with the French National Institute of Research and Safety (INRS) as a follow-up to the courses held in 1990 and 1992 (see Sections 7.4.2 and 7.4.8).

A course organized in collaboration with the Istituto Nazionale per la Ricerca sul Cancro in Genoa on 4–5 November 1993 on safety measures in research laboratories was attended by over 50 participants.

A document dealing with good practices for handling genotoxic substances and methods of decontamination of chemical

carcinogens, prepared jointly with INRS, has been published in the INRS series 'La ligne sécurité' [111, 127, 483, 698]. Another is being prepared in collaboration with the Société Française de Toxicologie Génétique.

5.3 Studies of screening for cancer

Screening whole populations, or subgroups believed to be at elevated risk, for early signs of cancerous or precancerous lesions can greatly reduce the mortality from some cancers, by allowing treatment before a condition becomes incurable. However, the screening procedure may itself entail risks, and there is also the possibility that potentially harmful therapeutic procedures will be used to treat lesions that would never in fact have evolved into a cancer. Therefore it is essential that screening methods be thoroughly evaluated both before application to human populations and after introduction in order to ensure that the expected benefits are realized.

5.3.1 Screening for cancer of the breast in the Philippines

P. Pisani, D.M. Parkin and L. Gibson; in collaboration with D.B. Esteban, C.Z. Guzman, A.V. Laudico, C.A. Ngelangel, M.L. Munson and M.G. Reyes, Manila, Philippines

Screening for breast cancer by mammography, with or without physical examination of the breast, can reduce mortality from breast cancer in women over 50 years of age. However, since the procedure is expensive, such programmes are inappropriate for developing countries, even when breast cancer incidence is moderately elevated. The Manila area of the Philippines is one such area and offers a favourable setting for an experimental study because of an adequate health-care infrastructure and the presence of a population-based cancer registry serving a population with a moderately high risk of breast cancer (incidence in 1983–87 was 94/100 000 women aged 35–64 years). A protocol has been developed for a randomized controlled trial of screening for breast cancer by physical examination performed by trained paramedical personnel. This was modified following a pilot study of 14 000 women in the age-range 35–64 undertaken in 1991–93 to investigate aspects of the feasibility such as compliance and detection rate in the population.

A grant, which will cover the first five years of the randomized trial, through the US Army Medical Research Development Command, has enabled the implementation of the study.

The project will involve randomizing the 202 health centres into the intervention and control groups; establishing agreements with field operators to set up special clinics to receive the 'positive' women at physical examination and to complete the diagnostic process; establishing the procedure to recruit, identify and follow up the eligible women; acquiring the equipment; recruiting and training the examiners; and evaluating their performance.

The actual screening activity began in September 1995, in the two districts of Las Piñas and Mandaluyong.

5.3.2 Screening for cancer of the stomach

P. Pisani and D.M. Parkin; in collaboration with W.E. Oliver, San Cristobal, Venezuela; and R. Sierra, San José, Costa Rica

A review of the efficacy of screening for gastric cancer by photofluoroscopy suggests

a benefit associated with the examination [492]. However, the observational data (obtained mainly in Japan, where the technique was developed) are undermined by the well known potential for selection and length bias. Also, the technique is rather complex and its applicability in countries not as well equipped as Japan needs to be established. Therefore, the feasibility of conducting a randomized trial is been investigated.

A screening programme based on the Japanese technique has been active since the early 1980s in Tachira State, Venezuela. The low coverage of the eligible population makes this activity a diagnostic service rather than a proper screening intervention [491]. Recently, the Costa Rican Government has signed an agreement to establish a programme, including provision of equipment and training of medical personnel. These two instances provide opportunities to conduct an experimental study, the feasibility and power of which have been evaluated, allowing for various selection criteria at recruitment. Also, the pre-selection of high-risk groups by means of determination of serum pepsinogen levels was considered. Active collaboration is maintained with researchers in Costa Rica and Venezuela to harmonize the development (Costa Rica) or reorganization (Venezuela) of the screening activity with the planning of randomized trials.

5.3.3
Screening for cervical cancer in developing countries

D.M. Parkin, R. Sankaranarayanan and N. Muñoz; in collaboration with C. Ngelangel, Manila, Philippines; E. Lynge, Copenhagen, Denmark; N. Sreedevi Amma, M. Krishnan Nair, B. Shyamalakumary and R. Wesley, Trivandrum, India; and K. Jayant, Barsi, India

Organized Pap smear screening at regular intervals of 3–5 years and follow-up have substantially reduced the incidence of and mortality from cervical cancer in developed countries. Since this type of screening is not easy to introduce in developing countries due to manpower and financial constraints, several alternative low-technology screening procedures such as unaided visual inspection, aided visual inspection (gynoscopy, cervicoscopy) of the cervix and low-intensity cytology have been suggested for cervical cancer control in these countries.

Limited cytology-based screening programmes have been operating in certain urban populations. Information has been collected on the previous screening history of subjects who participated in a case–control study of etiological factors for cervical cancer in the Philippines. The risk of advanced disease in relation to the screening history and the magnitude of selection bias are being analysed.

Smaller studies have been conducted or are in progress in Barsi and Kerala, India, to study the relative performance of low-technology approaches to cervical cancer detection. Unaided visual inspection of the uterine cervix was validated against Pap smear in 3088 apparently healthy married women from a community near Trivandrum, in Kerala, India and in 2843 symptomatic women attending the opportunistic detection clinics in different regions of Kerala. Conditions of moderate dysplasias up to malignancy were considered as cytological abnormality, and visual examination abnormality (bleeds to touch, abnormal blood-stained discharge, and growth) was tested for sensitivity and specificity. The results are being analysed.

Another study that will involve around 10 000 married women has been initiated in Ernakulam, Kerala, India, to study the validity and relative performance of screening tests such as unaided visual inspection, cervicoscopy (visual inspection of the uterine cervix after 2–5% acetic acid intravital staining of the cervix to look for acetowhite areas) and Pap smear to detect

cervical precancerous lesions and cancer. Recruitment for this study will be completed in one year.

The effectiveness of health education and awareness in clinical 'down-staging' of cervical cancers is being evaluated in a non-randomized controlled design involving 236 villages (population 340 000) in rural Maharashtra, India.

A randomized intervention trial to evaluate cervicoscopy and the low-intensity cytology in terms of reduction in mortality from cervical cancer and cost-effectiveness has been designed. This will involve some 80 000 women aged 40–64 years in Trivandrum district, Kerala, India, randomized to the different study arms. Funding for this project is being sought.

5.3.4
Screening for oral cancer

R. Sankaranarayanan and D.M. Parkin; in collaboration with L. Fernandez Garrote, Havana, Cuba; P.C. Gupta, Bombay, India; and B. Mathew, N. Sreedevi Amma and M. Krishnan Nair, Trivandrum, India

An oral cancer screening programme, the 'Programa Nacional de Diagnostico Precoz del Cancer Bucal' (PDCB), has been in operation in Cuba since 1984. It requires all subjects aged 15 years and above to be subjected to an annual oral visual inspection by dental surgeons. The proportion of the target population covered by PDCB varied from 11.9% to 26.8%. A descriptive evaluation of PDCB indicated that there was no change in incidence of and mortality from oral cancer in Cuba over the last decade which could be ascribed to the PDCB [169]. Figure 37 shows the correlations between the percentage change in mortality from oral cancer in males and females aged 50 years and over, between 1984–86 and 1987–90, in fourteen provinces of Cuba, with the intensity of screening in the provinces, expressed as the average annual percentage of subjects (50 years and above) examined during 1987–90. There was no significant correlation between the average screening intensity and change in mortality.

A case–control study is in progress in Havana, Cuba, to address the risk of advanced oral cancer in relation to history of oral visual inspection offered by the PDCB programme. This study involves 200 cases of stage III and IV oral cancer and 800 age- and sex-matched apparently healthy controls. The association of HPV with oral cancer is also being investigated. Recruitment will be completed in two years.

The feasibility of mouth self-examination [328] and the routine utilization of health workers employed by the state health services [327] for oral cancer prevention in Kerala, India, were evaluated. A community-based randomized intervention trial has begun in Kerala, to evaluate oral visual inspection by trained health workers in terms of reduction in mortality and cost-effectiveness.

5.3.5
Screening for lung cancer

D.M. Parkin, P. Pisani and J. Reissigová; in collaboration with A. Kubik, Prague, Czech Republic; and U. Pastorino, London, UK

The relatively small randomized study on screening for lung cancer by the combination of chest radiography and sputum cytology examinations conducted in the Czech Republic (Kubik *et al.*, 1990, *Int. J. Cancer*, **45**, 26–33) was re-analysed with additional follow-up information on all subjects. The analysis, taking advantage of a maximum of 15 years of observation after entry into the study, confirmed that no reduction of mortality is associated with the screening intervention, in accordance with the results of the other four experimental studies published.

As low statistical power has been suggested as the cause of these negative

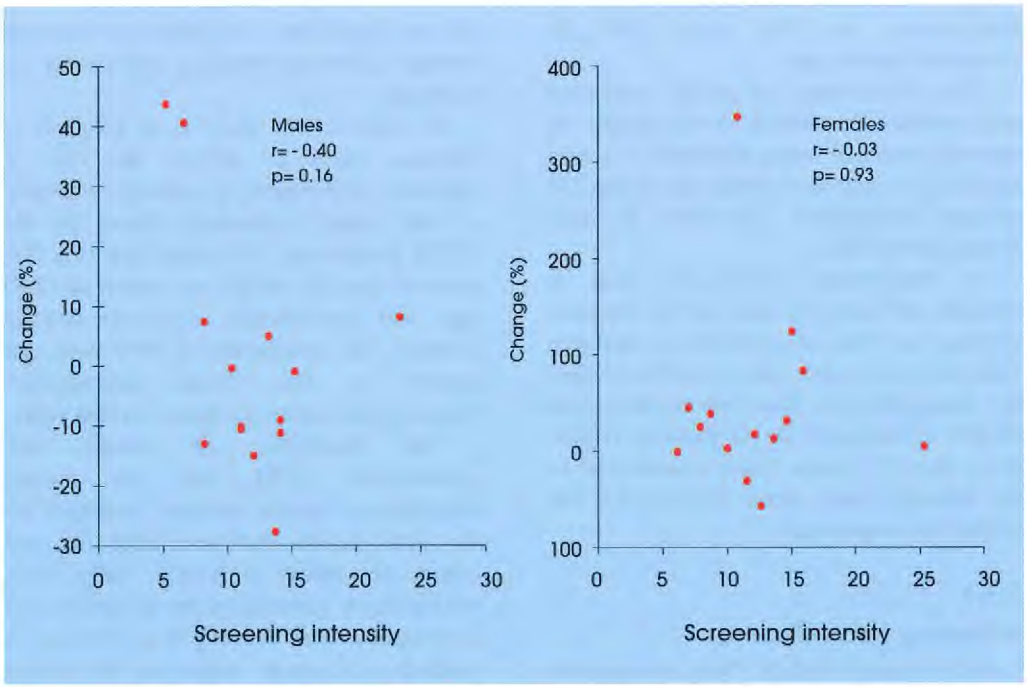


Figure 37. Changes in mortality from oral cancer in different provinces of Cuba, age 50 + years

results, we conducted a meta-analysis of the five randomized trials, and concluded that low power cannot explain the lack of any benefit, but over-diagnosis of cancers which would have not surfaced within the life-span of some individuals is a real concern [445, 446].

The experience so far accumulated indicates that, at this stage, priority should be given to research on new means of early diagnosis based on molecular and immunological characteristics of exfoliated cells, rather than to their morphological aspect, which may better predict the aggressiveness of the disease. Studies of the frequency, correlation and prognostic value of genetic abnormalities detectable in the bronchial mucosa, as the initial research phase towards the development of alternative means of screening for lung cancer are being planned in collaboration with Dr Pastorino (Royal Brompton Hospital, London).

5.3.6 Evaluation of screening for neuroblastoma

J. Estève; in collaboration with F. Berthold, Cologne, Germany; A.W. Craft, L. Parker and D. Worthington, Newcastle, UK; R. Errtmann, Hamburg, Germany; A. Jenkner, Rome, Italy; R. Kerbl and I. Starz, Graz, Austria; C. Lasset, P. Mathieu and T. Philip, Lyon, France; J. Mann, Birmingham, UK; R. Pettersen and I. Storm-Mathison, Oslo, Norway; and F. Schilling, Stuttgart, Germany

The efficacy of screening for neuroblastoma in children is still an open question. Following a consensus meeting held at IARC in April 1993 to determine the best strategy for evaluation, a report was

presented at the third international symposium on neuroblastoma screening in Kyoto, Japan [157] and a review published [162]. Following this work, the Study Group for the Evaluation of Neuroblastoma Screening in Europe decided to study the feasibility of screening at 12 months instead of six months. In the meantime, a detailed study of survival of children with neuroblastoma has been undertaken to provide better data for the evaluation of future screening trials.

6.1 Methods for measuring and monitoring exposure to particular carcinogens

Epidemiological studies have in the past often relied on very imprecise information about exposure to potentially carcinogenic agents, leading to misclassification and a consequent weakening of the resolving power of the study. An understanding of the molecular and cellular aspects of carcinogenesis now permits the development of biomarkers of exposure which improve the precision of exposure measurement. This improved precision is particularly critical where the relative risk associated with an exposure is small. Modern analytical techniques are being applied to this problem, for use both in IARC projects and more generally by cancer researchers worldwide.

6.1.1 Oxidative stress

6.1.1.1 Hydroxyl radical formation in the oral cavity of betel quid chewers

H. Ohshima and M. Friesen; in collaboration with U.J. Nair, J. Nair and H. Bartsch, Heidelberg, Germany

The habit of betel quid chewing is causally associated with an increased risk of oral cancer. To determine whether hydroxyl radical ($HO^{\cdot}$) is generated in the human oral cavity during chewing of betel quid, the formation of *o*- and *m*-tyrosine from L-phenylalanine was measured as a marker. Five volunteers chewed betel quid consisting of betel leaf, areca nut, catechu and slaked lime (without tobacco). Their saliva, collected after chewing betel quid, contained high concentrations of *p*-tyrosine, but no appreciable amount of *o*- or *m*-tyrosine. Saliva samples from the same subjects after chewing betel quid to which 20 mg phenylalanine had been added contained *o*- and *m*-tyrosine at concentrations above 1 μM. These levels were significantly higher ($p < 0.005$) than those of subjects who kept phenylalanine in the oral cavity without betel quid (see Figure 38). Our results clearly demonstrate that the $HO^{\cdot}$ radical is formed in the human oral cavity during betel quid chewing and is probably implicated in the genetic damage that has been observed in oral epithelial cells of chewers [402].

6.1.2 New methods to detect 8-nitroguanine and base-propenals in DNA

H. Ohshima, V. Yermilov, J. Rubio, B. Pignatelli, C. Malaveille, S. Calmels, I. Brouet and A. Hautefeuille; in collaboration with J. Nair, Heidelberg, Germany; and H. Nukaya, Shizuoka, Japan

We have found that peroxynitrite induces several new modifications in DNA, including formation of highly cytotoxic base-propenals (base–CH=CH–CHO) (see Section 4.4.3) and 8-nitroguanine (see Section 4.4.4). In order to study further the occurrence, formation and metabolism of these compounds *in vivo*, we have developed new sensitive and specific methods. Base-propenals were analysed by HPLC with fluorescence detection after post-column derivatization with thiobarbituric acid. 8-Nitroguanine was analysed by HPLC with electrochemical detection after

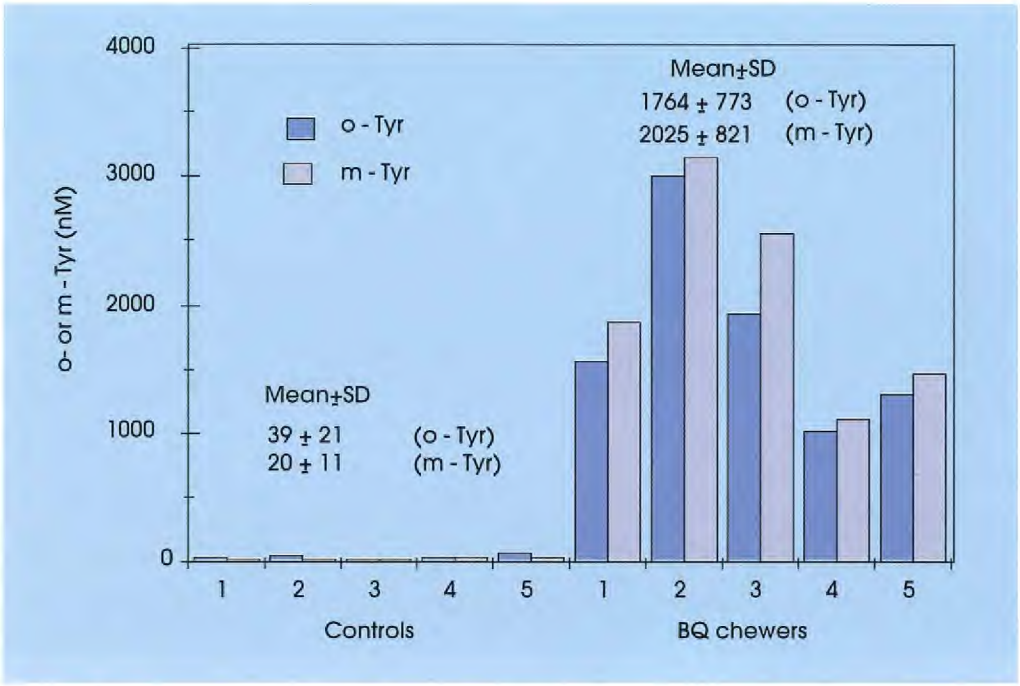


Figure 38. The levels of o- and m-tyrosine in saliva samples from subjects who kept powdered phenylalanine (20 mg) in the mouth without betel quid (controls) and from chewers who chewed betel quid containing 20 mg phenylalanine (BQ chewers)

reduction to 8-aminoguanine. The bases of acid-hydrolysed calf thymus DNA (1 mg/ml) treated with 1 mM peroxynitrite *in vitro* contained about 1 mmol of 8-nitroguanine/mol guanine, the minimum detection level being about 0.1 μmol/mol guanine. Analyses of base-propenals and 8-nitroguanine in cultured cells and animal tissues, in which NO synthase is strongly induced by cytokines and lipopolysaccharide, are in progress. Polyclonal antibodies against these modified bases are being raised. A ^{32}P-postlabelling method for 8-nitroguanine adducts is also being established. Methods for analysis of metabolites of 8-nitroguanine and base-propenals in urine are being established, for future application to epidemiological and clinical studies.

6.1.3
Monitoring human exposure to the food-borne carcinogen PhIP

M. Friesen, L. Garren and H. Bartsch; in collaboration with F.F. Kadlubar, Jefferson, USA; and H.A.J. Schut, Toledo, USA

The cooking of meat induces the formation of a family of structurally-related heterocyclic aromatic amines. One of these compounds, 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), has been shown to induce colon tumours in rats. A sensitive and specific method has been developed to measure levels of PhIP adducted to DNA in tissues. The method is based on a similar approach for DNA adducts of 4-aminobiphenyl [299] and involves alkaline hydrolysis of PhIP from DNA, followed by gas chromato-

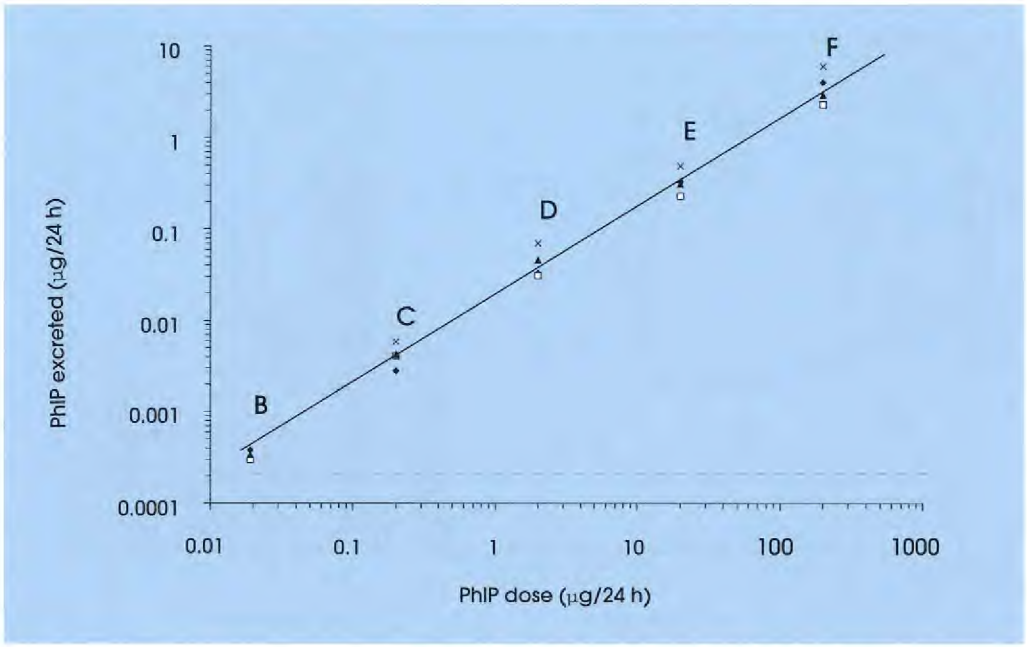


Figure 39. Urinary excretion of unmetabolized PhIP from five groups of rats (B–F) treated daily, by gavage, with PhIP at 1000 μg/kg (F), 100 μg/kg (E), 10 μg /kg (D), 1 μg/kg (C) and 0.1 μg/kg (B). Each point represents the mean ± standard deviation for a group of four animals following 2, 9, 16 or 23 days of treatment. The dashed line represents the lower limit of detection of the method, about 180 pg/day for a 0.1 ml sample of urine

graphy/electron capture mass spectrometry (GC/MS). The method can detect PhIP–DNA adducts at levels down to 0.03 fmol PhIP/μg DNA (1 PhIP adduct/10^8 normal nucleotides) for a 100 μg sample of DNA.

To validate the method, a series of 20 DNA samples from five tissues of rats treated with a single, oral dose of PhIP (50 mg/kg) were analysed both by alkaline hydrolysis–GC/MS and by ^{32}P-postlabelling. Results from the two methods were highly correlated (r = 0.91) [181]. Further comparison of the two methods with rats given doses of 1 and 0.1 mg/kg/day over 23 days again gave well correlated results (r = 0.77) and showed that PhIP–DNA adducts accumulate with repeated dosing in tissues like the liver, kidneys, heart and pancreas. A pilot survey of 24 human tissue DNA samples was carried out by alkaline hydrolysis–GC/MS and ^{32}P-postlabelling. Taken together, results from the two methods provided the first evidence for PhIP–DNA adducts in the human colon (2/6 samples) [181].

A sensitive GC/MS method to measure unmetabolized PhIP in the urine has also been developed which can measure recent exposure to PhIP in rats to less than 0.1 μg/kg/day, a level to which humans are commonly exposed. A linear dose–response relationship (Figure 39) was observed for the method over four orders of magnitude (1000 to 0.1 μg/kg/day) and PhIP was not detected in the urine of untreated rats. This method is now being validated for humans exposed to PhIP in the diet.

6.1.4
Postlabelling methodology study

M. Castegnaro; in collaboration with F.F. Kadlubar, Jefferson, USA; J.E. Lewtas, Research Triangle Park, USA; and D.H. Phillips, Sutton, UK

The US Environmental Protection Agency has organized, in collaboration with the National Cancer Institute and National Center for Toxicological Research, a biomonitoring working group in which IARC is participating. One of the major tasks of this group is to develop a bank of standard DNA adducts which can be used in collaborative studies and in interlaboratory comparison of biomonitoring methods.

A collaborative project has been set up to improve and standardize methodologies for postlabelling of bulky and small DNA adducts. A first meeting (Lyon, 20–21 October 1994) of 26 interested scientists from nine countries had the objectives of reviewing in detail the methodology used in each laboratory and standardizing the experimental protocols. Details of methods being used for the analysis of bulky DNA adducts were summarized and discussed during the meeting. With regard to the methods of analysis of small nucleotides, there was a very restricted choice and two methods were selected for analysis of (*a*) alkyl adducts, and (*b*) etheno adducts. These methods will be tested as published by the originators, after transcription in an ISO-like style. A number of initiatives and conclusions came from this meeting as follows:

Preparation of reference DNA adducts

Five DNA adduct standards are being prepared by modification of the same source of purified calf thymus DNA, and at a level of about one adduct per 10^6 normal nucleotides. These comprise benzo[*a*]pyrene diol epoxide, 4-aminobiphenyl, methylated, PhIP and etheno DNA adducts. Two locations for distribution of standards will be selected, one in the USA (to be determined) and one at IARC. Three DNA adduct standards have been received at IARC: benzo[*a*]pyrene diol epoxide, 4-aminobiphenyl and methylated. After this trial and checking for stability during storage, they will be made available, upon request, to other laboratories.

Method evaluation

The interlaboratory validation will proceed in two phases. In the first phase, the laboratories will examine the standard DNA samples, each laboratory knowing the approximate level of modification. In the second phase, participants will receive samples with unknown adduct levels and standards of known adduct level for calibration.

Other decisions were taken which concerned standardization of aspects of the protocols including: DNA quantitation and hydrolysis, methods for DNA storage, methods for adduct enrichment by butanol extraction and nuclease P_1 treatment, postlabelling, separation methods by TLC and how to quantitate results.

For other points concerning the protocol, particularly relating to storage of samples at different stages of the assay, consensus was not reached and a small pre-trial group of collaborators was created to work further on these points.

6.1.5
Analysis of fumonisins and of sphingolipids as potential biomarkers

C.P. Wild, M. Castegnaro and L. Garren; in collaboration with A. Daudt, Porto Alegre, Brazil

6.1.5.1
Analysis of fumonisins in foods

An evaluation of analytical methods for quantitative determination of fumonisins B1

and B2 in maize was organized (coordinated by the Community Bureau of Reference of the European Union). IARC laboratories evaluated the efficiency of two published methods (Shephard *et al.*, 1990, *J. Liq. Chromatog.*, **13**, 2077–2087; Ross *et al.*, 1991, *Mycopathologia*, **114**, 129–135). The results, together with the overall results of the study, indicate that the Shephard *et al.* method gives more reproducible results.

On the basis of results from a further collaborative test, the Shephard *et al.* method was recommended by the Association of Official Analytical Chemists for adoption as an official first action (Sydenham *et al.*, 1995, *J. Ass. Off. Anal. Chem.*, in press).

Food from families of oesophageal cancer cases and from control families in a high-incidence area of Brazil is being surveyed. Samples are being collected before and after cooking for analysis of fumonisins and their stability during cooking procedures. Urine and oesophageal cells are being sampled from control families and patients, for analysis of sphingolipids (sphinganine : sphingosine ratio) as a possible biomarker of fumonisin exposure (see below).

6.1.5.2 Analysis of sphingolipids

Fumonisins inhibit the acetylation of sphinganine, resulting in an accumulation of sphinganine and an altered sphinganine/sphingosine ratio. This alteration in sphingolipid biosynthesis can alter signal transduction, cell growth, differentiation and possibly neoplastic transformation. A method for determination of sphingolipids in urine and tissues was tested (Merrill *et al.*, 1988, *Anal. Biochem.*, **171**, 373–381). Recoveries of sphinganine, sphingosine and the C_{20} internal standard were relatively low, and there were some limitations in terms of clean-up of the samples. A new method was therefore developed, which is now undergoing validation.

6.1.6 p53 autoantibodies in lung cancer patients

C.P. Wild and B. Chapot; in collaboration with T. Soussi and R. Lubin, Paris, France; and H. Vainio, K. Husgafvel-Pursaianen, M. Ridanpää and S. Anttila, Helsinki, Finland

A study was performed to test whether serum antibodies to p53 protein constitute a good marker of p53 mutations in lung cancer patients. A total of 136 sera from patients with primary lung carcinoma were analysed by ELISA and 16 (12%) were positive for antibodies. For 92 of these patients, tumour tissue was available for mutation analysis. Among 47 tumours found to contain a mutation, seven (15.2%) were from patients with serum p53 antibodies. A further two patients had antibodies but no detectable mutation in exons 5 to 8 of the *p53* gene. Of 50 patients with other pulmonary diseases, none had p53 antibodies. Overall the high specificity of the association of p53 serum antibodies in human lung cancer is encouraging. However, the low sensitivity of the assay remains a limitation, at least for lung cancer [685].

Further validation of the p53 autoantibody approach was performed on sera from patients with cancer at a variety of sites as well as sera from blood donors. Using not only ELISA, but other complementary approaches, the specificity of the serum antibodies for p53 protein was demonstrated and the varying prevalence of antibodies in association with different cancer sites was demonstrated [312].

6.1.7
Biological monitoring of exposure to carcinogens that yield DNA etheno adducts

A. Barbin, J. Nair, F. El Ghissassi, Y. Guichard and G. Brun; in collaboration with M. Ahotupa, Turku, Finland; H. Bartsch, Heidelberg, Germany; M.-J. Marion, C. Trépo and J.-C. Contassot, Lyon, France; M. Nagao, Tokyo, Japan; and J. Swenberg, Chapel Hill, USA

6.1.7.1
An ultrasensitive method for analysis of DNA etheno adducts

The analysis of $1,N^6$-ethenoadenine (εA) and $3,N^4$-ethenocytosine (εC) residues in DNA by immunoaffinity purification and ^{32}P-postlabelling of the 3′-nucleotides [25, 401] was validated by comparison with an independent method based on HPLC pre-separation and radioimmunoassay of the etheno-deoxyribonucleosides. Duplicate analyses were performed on two DNA samples obtained from pre-weanling rats exposed to vinyl chloride or unexposed. The results were similar by the two methods.

6.1.7.2
Levels of DNA etheno adducts in unexposed animals and humans

Background levels of εA and εC were measured in DNA from various tissues of unexposed, adult Sprague–Dawley rats fed a standard pelleted chow. In the lungs, kidneys and circulating lymphocytes, molar ratios of εA/A and εC/C ranged from 2 to 6 $\times 10^{-8}$ and from 4 to 11 $\times 10^{-8}$, respectively. The liver had 40–100 times less εA and 70–180 times less εC than the other tissues examined. However, hepatic DNA samples from rats of different ages had widely varying molar ratios (between 5 $\times 10^{-10}$ and 5 $\times 10^{-7}$), with higher levels in pre-weanling and old rats, compared to young adults.

Background levels of etheno adducts also appeared to be affected by diet. Etheno adducts were analysed in DNA from seven-week-old male Sprague–Dawley rats fed either a standard pelleted or a powdered diet. Levels of DNA etheno adducts were higher in the animals fed the powdered diet: in liver, levels of both εA and εC were 20- to 30-fold higher; in lungs and kidneys, levels of εA were increased by a factor of 6 to 8, although levels of εC were similar to those in animals fed the pelleted diet.

εA and εC levels were also measured in liver DNA samples from unexposed mice and humans [25, 401].

6.1.7.3
Formation of DNA ethenobases by lipid peroxidation products

Lipid peroxidation (LPO) products can react *in vitro* with nucleosides or nucleotides to yield ethenobase adducts [143]. To examine whether stimulation of LPO *in vivo* could lead to formation of ethenobases in DNA, two animal models of LPO were investigated. In a first series of experiments, Sprague–Dawley rats were submitted to treatments known to stimulate LPO (dietary iron overload and administration of ethanol or carbon tetrachloride). Higher levels of etheno adducts in liver DNA were associated with stimulation of LPO *in vivo*. For example, a three-week treatment with iron fumarate and carbon tetrachloride doubled the levels of both ethenobases in liver DNA of rats fed a powdered diet.

Long–Evans rats with a cinnamon-like colour (LEC rats) have been established as a mutant inbred strain displaying hereditary hepatitis and hepatoma and copper accumulation. LEA rats are a sibling line of LEC rats with agouti coat colour, which do not suffer from liver disease. In hepatic DNA from LEC rats, etheno adducts accumulated

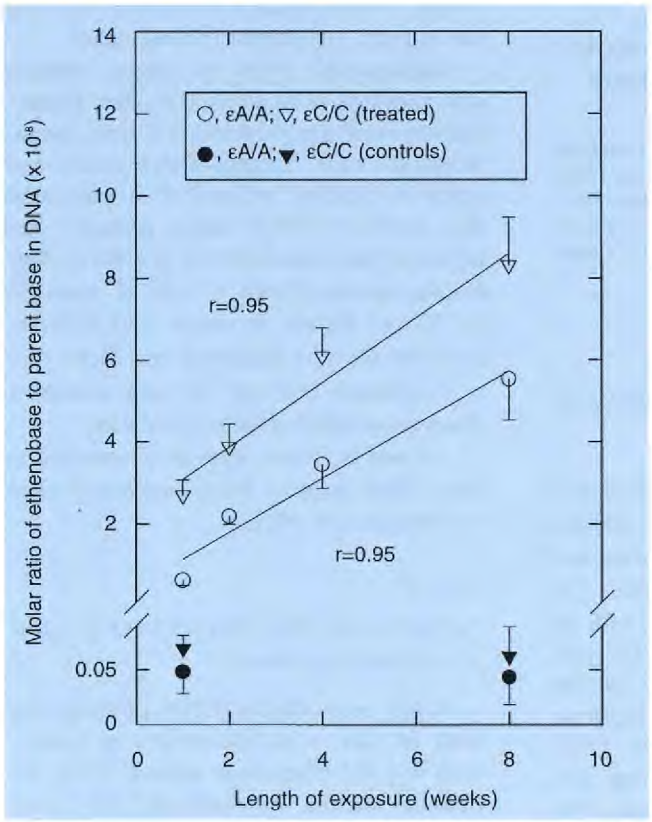


Figure 40. Accumulation of 1,N^6-ethenoadenine (εA) and 3,N^4-ethenocytosine (εC) in liver DNA from adult rats exposed to 500 ppm vinyl chloride (4 h/day, 5 days/week)

with age in parallel to both copper accumulation and progression of hepatic disease. No such accumulation was observed in LEA rats.

6.1.7.4

Formation and persistence of DNA etheno adducts in rats exposed to vinyl chloride

The formation and accumulation of ethenobases in DNA of various organs from adult male Sprague–Dawley rats exposed to vinyl chloride for up to eight weeks were measured. εA and εC were analysed by immunoaffinity purification and ^{32}P-post-labelling [401]. In addition, N^2,3-ethenoguanine (εG) was measured in hepatic DNA by electrophore labelling and gas chromatography/mass spectrometry. In the liver, the three ethenobases accumulated in DNA during exposure to vinyl chloride (Figure 40). In contrast, εC, but not εA, accumulated in lung and kidney DNA during exposure, suggesting an efficient repair of εA in these two organs. Accumulation of εC was 3- to 5-fold faster in lung than in liver or kidney. In liver, εG accumulated 24 times faster than εC. In mononuclear blood cells, no significant increase of ethenobase levels above control values was observed after two months of

exposure to vinyl chloride. The persistence of εA and εC in liver DNA after five days of exposure was investigated; levels of both adducts remained unchanged for at least two months.

In contrast to the young adult animals, pre-weanling rats exhibited much higher background levels of εA and εC in their hepatic DNA and no increase of these levels was observed following five days' vinyl chloride treatment.

It seems possible that vinyl chloride induces the formation of DNA ethenobases through both a direct pathway involving its metabolite chloroethylene oxide and an indirect pathway involving lipid peroxidation products. Endogenous lipid peroxidation could be enhanced following induction of cytochrome P450 2E1, the isoenzyme that activates vinyl chloride, and by 2-chloroacetaldehyde, the rearrangement product of chloroethylene oxide (Ekström & Ingerman-Sundberg, 1989, *Biochem. Pharmacol.*, **38**, 1313–1319; Sood & O'Brien, 1993, *Biochem. Pharmacol.*, **46**, 1621–1626). Thus, persistence of high levels of ethenobases in liver DNA following exposure to vinyl chloride could result from long-term stimulation of lipid peroxidation.

6.1.7.5 Markers of susceptibility in vinyl chloride-exposed workers

Vinyl chloride is detoxified mainly through the formation of glutathione conjugates, but the glutathione *S*-transferases involved in this process in humans have not been characterized. In this pilot study, we examined whether there is a relationship between polymorphism in the glutathione *S*-transferase M1 gene (GSTM1) and susceptibility to vinyl chloride-induced disease. The GSTM1 protein, a cytosolic enzyme involved in the detoxification of environmental carcinogens of several types, is absent in about half of the Caucasian population, due to a gene deletion. The homozygous GSTM1 null genotype has been associated, in certain cases, with an increased risk of cancer.

Workers occupationally exposed to high levels of vinyl chloride before 1974 were genotyped for GSTM1. The cohort included 57 individuals with signs of vinyl chloride disease and 8 with liver cancer. A prevalence of 61% for the null genotype was observed among the 100 workers without cancer, significantly higher than the prevalence previously reported for white populations (range, 42% to 53%). Five out of eight (62.5%) liver cancer patients were GSTM1-deficient.

The von Willebrand factor (vWF), a protein synthesized mainly by endothelial cells of the liver, was previously found to be slightly increased in the serum of vinyl chloride-exposed workers and highly increased in the serum of patients developing a hepatic angiosarcoma (Froment *et al.*, 1992, *Cancer Lett.*, **61**, 201–206). Among the 100 vinyl chloride-exposed workers without cancer, 32 exhibited normal levels of vWF in their serum (≤ 1 U/mL); in the remaining 68 individuals, serum levels were > 1 U/mL. The proportion of GSTM1-deficient individuals was 44% in the former group and 69% in the latter, suggesting an association between the GSTM1 genotype and stimulation of hepatic sinusoidal cells following exposure to vinyl chloride [145].

6.1.8 Detection of DNA methylation adducts following exposure to environmental methylating agents

C.P. Wild, F. Bianchini and A. Schouft; in collaboration with S. Kyrtopoulos, Athens, Greece;

A new technique using ^{32}P-postlabelling, chromatography and immuno-purification (Kang *et al.*, 1992, *Cancer Res.*, **52**, 5307–

5312) offers increased sensitivity for measurement of *O*-alkylated bases in comparison to other methods. This assay allows detection of 1 fmol O^6-methylguanine and O^4-methylthymidine, and is being applied to Lac Z transgenic mice treated with *N*-nitrosodimethylamine in order to correlate alkylation adducts with mutation spectra induced by this agent.

7-Methylguanine (7-MeG) levels in peripheral blood cells (PBC) and internal organs in rats exposed to various methylating agents (*N*-nitrosodimethylamine, 1,2-dimethylhydrazine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone and *N*-nitrosomethylbenzylamine) have been compared in order to validate the use of PBC as surrogate cells for internal organs in epidemiological studies. All of these methylating agents caused formation of 7-MeG in PBC, but the ratio of the 7-MeG level in the target organ to that in PBC varied by two orders of magnitude between carcinogens. However, the ratio between the adduct levels in PBC and in liver was the same for all the carcinogens [43]. These observations were the same for different routes of carcinogen administration [45]. The results imply that 7-MeG levels occurring in PBC following exposure to methylating agents could be predictive of those in the liver.

6.2 Methods for identification and characterization of carcinogens

Research on *in vitro* testing of substances for carcinogenic activity has led to a better understanding of the end-points measured, better validation of the capacity of these assays to detect carcinogens, and the introduction of new assays. However, there remain questions as to how well such tests reproduce the human situation *in vivo*, particularly with respect to substances that act through non-genotoxic mechanisms. Work in this area also can lead to the elucidation of fundamental mechanisms of environmental carcinogenesis.

6.2.1 Transformation of human mammary cells

K. Sasaki and H. Yamasaki; in collaboration with N. Odartchenko, Lausanne, Switzerland

In order to further explore cellular and molecular mechanisms of human carcinogenesis and to find new endpoints for carcinogen identification, IARC is coordinating the European Collaboration Project on human cell transformation. Other participants are: Dr N.E. Fusenig (Institute of Biochemistry of the German Cancer Research Centre, Heidelberg, Germany), Dr A. Haugen (National Institute of Occupational Health, Oslo), Dr R.F. Newbold (Brunel University, Uxbridge, Middlesex, UK) and Dr J.E.I.M. Simons (University of Leiden, Netherlands).

In the IARC laboratories, attempts are being made to analyse human mammary cell transformation processes in order to improve *in vitro* assays systems for carcinogen detection. We have employed a human epithelial cell transformation model, using ductal luminal cells desquamated in human milk during the first days of lactation, that were immortalized by microinjection of wild-type SV40 DNA. From this non-clonogenic cell line (HuMI),

further cell lines, clonogenic (HuMI-T) and tumorigenic (HuMI-TTu2) were isolated (Yilmaz *et al.*, 1993, *Br. J. Cancer*, **68**, 868–873). When these three cell lines were treated with a very low dose of 12-tetradecanoylphorbol 13-acetate (TPA) (1 ng/ml), the HuMI cells were unable to grow, while about 50% and 100% of HuMI-T and HuMI-TTu cells formed colonies, respectively. These results suggest that signal transduction pathways, e.g. involving protein kinase C, were changed during cell transformation and that acquisition of TPA-resistance may be an important feature of mammary cell transformation.

In order to see whether HuMI cells can be transformed into anchorage-independent cells by chemical carcinogens, they were treated with methyl methanesulfonate (50 µg/ml for 3 h) or 3-methylcholanthrene (MCA) (10 µg/ml for 72 h). After eight weeks of culture, none of the treated cells grew in soft agar. However, when HuMI cells were treated with MCA and then cultured with TPA (10 ng/ml), they grew in soft agar; cells treated with TPA alone did not grow in soft agar. These results indicate that HuMI cells can be transformed by MCA plus TPA, mimicking two-stage carcinogenesis.

In order to search for microsatellite changes, five cell lines from MCA- plus TPA-induced transformed cells were cloned. No change in (CA)n repeats at 14 loci was observed in HuMI, but the HuMI-TTu cell lines showed loss of heterozygosity at Mfd 44 locus of chromosome 13. In addition, all five MCA+TPA-transformed cell lines showed loss of heterozygosity at the Mfd3 locus of chromosome 1. Since the HuMI-T cell line did not show any change of microsatellite DNA, our results suggest that the loss of heterozygosity observed here is a late event in cell transformation.

6.2.2

Non-genotoxic mechanisms of carcinogenesis: mechanism-based detection methods

H. Yamasaki, V. Krutovskikh, M. Mesnil and H. Nakazawa; in collaboration with J. Ashby, Macclesfield, UK; M. Bignami, Rome, Italy; W. Jongen, Wageningen, Netherlands; K. Linnainmaa, Helsinki, Finland; R.F. Newbold; Uxbridge, UK; G. Nguyen-Ba, Villejuif, France; S. Parodi, Genoa, Italy; E. Rivedal, Oslo, Norway; D. Schiffmann, Rostock, Germany; J.W.I.M. Simons, Leiden, Netherlands; and P. Vasseur, Metz, France

While accumulation of genetic changes in a somatic cell is considered essential for the genesis of a cancer, it has become clear that not all carcinogens are genotoxic, suggesting that some carcinogens indirectly participate in the generation of genetic changes during carcinogenesis. A European Project funded by the European Commission was thus conceived to study mechanisms of non-genotoxic aspects of carcinogenesis, with IARC as coordinator, and the project was completed at the end of 1994.

The major results can be summarized as follows:

(1) Tests with Syrian hamster embryo (SHE) and BALB/c 3T3 transformation systems reflect both genotoxic and non-genotoxic carcinogenic events; they give positive results with not only genotoxic but also many, although not all, non-genotoxic carcinogens. This is supported by the finding that both genotoxic and non-genotoxic carcinogens can immortalize Syrian hamster dermal cells.

(2) Many non-genotoxic carcinogens, although not all, inhibit gap-junctional intercellular communication (GJIC) *in vitro* as well as *in vivo*. Mechanistic studies suggest that inhibition of GJIC plays an important role in carcinogenesis and that different mechanisms are involved in such inhibition by different agents. However, inhibition of GJIC is not a prerequisite for

the enhancement (or induction) of transformation of SHE or BALB/c 3T3 cells.

(3) Among compounds examined, there was good correlation between induction of micronuclei and cell transformation in SHE cells, but no such correlation between induction of cell transformation and ornithine decarboxylase activity.

(4) Two transgenic mouse mutation assays (lac I and lac Z) were established and validated. The genotoxin nitrosodimethylamine was shown to be mutagenic to the liver in both assays. *o*-Anisidine, a bladder-specific carcinogen that is inactive in standard rodent genetic toxicity assays was uniquely mutagenic to the bladder of the transgenic mice. The peroxisome proliferator methyl clofenipate was established as non-mutagenic to the liver of both transgenic mice, thus eliminating DNA damage as a cause of the liver tumours produced by this chemical and weakening the hypothesis that inhanced cell division leads to induction of mutation.

(5) With an *in vitro* DNA replication model, it was found that DNA damage induced by genotoxic agents can be responsible for inhibition of DNA replication, while certain non-genotoxic agents such as phorbol esters increase DNA replication.

(6) An attempt to establish a structure–activity relationship for subfamilies of non-genotoxic carcinogens, e.g. receptor-mediated carcinogens, has been initiated with some promising results.

From the above results and those of other studies, we conclude that (i) mechanism-based toxicology will provide the basis for future cancer hazard identification and risk assessment, (ii) no single test can reveal many classes of carcinogens, so that "studying" rather than "testing" agents may be a more appropriate approach, and (iii) further basic knowledge of cell biology, in particular of cell-cycle regulation, is essentail for elucidating environment–gene interactions related to carcinogenesis [690].

6.2.3
Prediction of carcinogenic potency of genotoxic chemicals

A. Barbin; in collaboration with H. Bartsch, Heidelberg, Germany; and E. Vogel, Leiden, Netherlands

With the aim of characterizing different classes of genotoxic carcinogens and establishing quantitative structure–activity relationships, the carcinogenic potency of various alkylating chemicals was compared with their DNA adduct patterns and acute toxicity in rodents, using data collated from the literature, and with their genotoxic activity profiles and mutation spectra in *Drosophila* (studies carried out by Dr E. Vogel).

For monofunctional alkylating agents, new linear relationships were established between: (i) their carcinogenic potency ($1/TD_{50}$ values) and their covalent binding index for *O*-alkylated bases in liver DNA; (ii) their acute toxicity ($1/LD_{50}$ values) and their covalent binding index for *N*7-alkylguanine in liver DNA; (iii) the ratio of their carcinogenic potency to acute toxicity in rodents (TD_{50}/LD_{50}) and the Swain–Scott constant *s* of their ultimate electrophilic species; and (iv) their TD_{50} value in rodents and hypermutability effect in *Drosophila* under excision repair-deficient conditions.

The carcinogenic potency of cross-linking agents was quantitatively correlated with their acute toxicity in rodents, and their clastogenic and mutagenic effectiveness in *Drosophila*.

Compounds yielding DNA etheno adducts (e.g., vinyl halides, urethane) were characterized as a new class of carcinogens. These chemicals show a relative clastogenic efficiency (ratio of chromosome aberrations to forward mutations) similar to that of

cross-linking agents. However, in contrast to cross-linking agents, they show a hypermutability effect when the nucleotide excision repair pathway is not functioning. Thus, they form a group of genotoxic agents which, on the basis of their activity profiles, are clearly separable from both monofunctional and cross-linking alkylating agents.

PART 7. IARC PUBLICATIONS, EDUCATION AND TRAINING

7.1 Publications

The aim of the IARC publications programme is to ensure rapid and comprehensive dissemination of information from Agency projects to other cancer researchers and public health decision-makers worldwide.

Improvements in computer technology have permitted simplification and acceleration of the processes of document transfer from authors to the Publications Service, editing and page layout, and transfer to printers.

Another recent development is the establishment of in-house facilities for promotion, distribution and sales of publications, to complement the activities of Oxford University Press and the World Health Organization Distribution and Sales Service, with the aim of improving the visibility and availability of the Agency's publications.

7.1.1 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

This programme is described in detail in Section 2.1.1. New volumes published during the period under review are the following:

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 57, *Occupational Exposures of Hairdressers and Barbers and Personal Use of Hair Colourants; Some Hair Dyes, Cosmetic Colourants, Industrial Dyestuffs and Aromatic Amines*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans . Volume 58, *Beryllium, Cadmium, Mercury and Exposures in the Glass Manufacturing Industry*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 59, *Hepatitis Viruses*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 60, *Some Industrial Chemicals*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 61, *Schistosomes, Liver Flukes and* Helicobacter pylori

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 62, *Wood Dust and Formaldehyde*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 63, *Dry Cleaning, Some Chlorinated Solvents and other Industrial Chemicals*

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 64, *Human Papillomaviruses*

7.1.2 IARC Scientific Publications

J. Cheney, S. Jones, E. El Akroud, M. Mainaud, A. Romanoff and J. Thévenoux

The Advisory Committee, under the chairmanship of Dr D.M. Parkin, continues to review all proposals for new publications, with particular emphasis on the procedures in place for each volume to ensure high scientific quality. An important new textbook is the latest in the series on Statistical Methods in Cancer Research, dealing with methods for descriptive epidemiology, and a major compilation of data on time trends in cancer incidence and mortality has been completed. Publication of Part I of the important new series on nomenclature and description of tumours in laboratory animals, the International Classification of Rodent Tumours, is almost complete. Produced in collaboration with the Fraunhofer Institut für Aerosolforschung in Hannover, Germany, and supported by

the International Life Sciences Institute, Washington, DC, the fascicles dealing with rat tumours are all published or in press, and the set covering mouse tumours is in preparation with the additional assistance of the Society of Toxicological Pathology.

New publications that have appeared during the period under review are the following:

Pathology of Tumours in Laboratory Animals. Vol. 2, *Tumours of the Mouse* (IARC Scientific Publications No. 111)

Time Trends in Cancer Incidence and Mortality (IARC Scientific Publications No. 121)

International Classification of Rodent Tumours. Part I. *The Rat* (IARC Scientific Publications No. 122) (fascicles 4–7)

Postlabelling Methods for the Detection of DNA Damage (IARC Scientific Publications No. 124)

DNA Adducts: Identification and Biological Significance (IARC Scientific Publications No. 125)

Butadiene and Styrene: Assessment of Health Hazards (IARC Scientific Publications No. 127)

Statistical Methods in Cancer Research. Vol. IV. *Descriptive Epidemiology* (IARC Scientific Publications No. 128)

Occupational Cancer in Developing Countries (IARC Scientific Publications No. 129)

Directory of On-going Research in Cancer Epidemiology 1994 (IARC Scientific Publications No. 130)

Survival of Cancer Patients in Europe: The EUROCARE Study (IARC Scientific Publications No. 132)

7.1.3 IARC Technical and Internal Reports

The IARC Technical Reports are specialized publications with a limited market. IARC Internal Reports are documents prepared within the framework of specific projects for use in-house and by collaborators in the project. The following reports were published during the period under review:

Manual for Cancer Registry Personnel , edited by D. Esteban, S. Whelan, A. Laudico and D.M. Parkin (IARC Technical Reports No. 10)

Cancer in the African Population of Bulawayo, Zimbabwe, 1963–1977: Incidence, Time Trends and Risk Factors (IARC Technical Reports No. 15)

Cancer in Thailand 1988–1991 (IARC Technical Reports No. 16)

Intervention Trials for Cancer Prevention: Results and New Research Programmes (IARC Technical Reports No. 18)

Comparability and Quality Control in Cancer Registration (IARC Technical Reports No. 19)

Epidémiologie du cancer dans les pays de langue latine (IARC Technical Reports No. 20)

ICD Conversion Programs for Cancer (IARC Technical Reports No. 21)

Cancer Incidence by Occupation and Industry in Tianjin, China, 1981–1987 (IARC Technical Reports No. 22)

An Evaluation Programme for Cancer Preventive Agents, by B.W. Stewart (IARC Technical Reports No. 23)

Peroxisome Proliferation and its Role in Carcinogenesis (IARC Technical Reports No. 24)

Combined Analyses of Cancer Mortality among Nuclear Industry Workers in Canada, the United Kingdom and the United States of America (IARC Technical Reports No. 25)

International Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry. III – Procedures Document . By E. Cardis and I. Kato (IARC Internal Reports No. 93/003)

Chemicals, Groups of Chemicals, Complex Mixtures, Physical and Biological Agents and Exposure Circumstances to be Evaluated in Future IARC Monographs. Report of an ad-hoc Working Group, Lyon, 7–9 December 1993 (IARC Internal Reports No. 93/005)

IARC Historical Multicentric Cohort Study of Workers Exposed to Styrene. Report of the Epidemiological Study and the Industrial

Hygiene Investigation. By M. Kogevinas, G. Ferro, R. Saracci, A. Andersen, T. Bellander, M. Biocca, J.E. Bjerk, N.O. Breum, D. Coggon, V. Fontana, S. Ferro, C. Galassi, V. Gennaro, S. Hutchings, A.A. Jensen; H. Kolstad, I. Lundberg, E. Lynge, B. Pannett, T. Partanen and P. Pfaffli (IARC Internal Reports No. 94/002)

Multiple Primaries (IARC Internal Report No. 94/003)

The Role of IARC in Quantitative Estimation and Prediction of Human Risks of Cancer (IARC Internal Reports No. 94/004)

Feasibility phase of a study on cancer risk among workers in the European asphalt industry. Epidemiology. Final report. T. Partanen, P. Heikkilä and P. Boffetta (IARC Internal Reports No. 94/005)

International Thyroid Project – Additional Documentation of Thyroid Cancer Cases (Belarus). Report. By L.N. Astakhova, E. Cardis, L.V. Shafarenko, L.N. Gorobets, S.A. Nalivko, K.F. Baverstock, A.E. Okeanov and C. Lavé (IARC Internal Reports No. 95/001)

7.1.4

Directory of On-Going Research in Cancer Epidemiology

E. Démaret, R. Sankaranarayanan and Z. Schneider; in collaboration with H.J. Baur and J. Wahrendorf, Heidelberg, Germany

The Directory is a compilation of descriptions of current research in cancer epidemiology, published in collaboration with the German Cancer Research Centre in Heidelberg. The Directory was published annually until 1992, when the cycle became biennial. Data for the 1994 volume were collected and prepared in 1993 and the Directory published in February 1994, as IARC Scientific Publications No. 130. It contains information on 1246 projects carried out by 876 investigators in 80 countries. Eight indexes (investigator, keyword, cancer site, study type, chemical, occupation, country and cancer registry) facilitate access to the information. Each entry gives the full address, telephone and fax number of the principal investigator. An address list of population-based cancer registries is also included. The main feature of the 1994 Directory is the increasing interest in genetic epidemiology, intervention and biomarkers. The number of studies on the role of viruses in cancer etiology has also increased, as well as those on the role of *Helicobacter pylori* in stomach cancer. Radiation, whether background, diagnostic or electromagnetic, is also an area of considerable interest.

The mailing cycle for the 1996 Directory started in January 1995 and the material received has largely been edited. In this edition, survival studies will be included.

Electronic searching of the Directory indexes with a system provided on diskette was not found to be much used, so this feature was not repeated for the 1994 edition. The entire directory content is now available in electronic form on a CD-ROM, together with other Agency publications (see Section 7.1.6).

7.1.5

Directory of Agents Being Tested for Carcinogenicity

M.J. Ghess, J. Wilbourn and H. Vainio

The *Directory of Agents Being Tested for Carcinogenicity* (formerly Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity) was initiated in 1973 in collaboration with the US National Cancer Institute. The Directory of Agents No. 16, published in 1994, gives information on 580 chemicals or agents being tested in 75 institutes in 23 countries; a total of 243 published reports on 208 chemicals or agents are listed. Each entry gives the name, Chemical Abstracts Registry Number and synonyms for the chemical, use category, purity, species, strain, sex and number of animals, route of administration

and dose levels, duration, starting date, stage of experiments and principal investigator.

Analysis of the data reported in Directories Nos 14, 15 and 16 shows that the number of carcinogenicity studies being undertaken in each two-year period appears to be diminishing.

7.1.6 Electronic publication

J. Cheney, E. Démaret, M.J. Ghess, H. Vainio, J. Wilbourn and G. Zizka

A range of information resources produced by IARC is now available electronically on a CD-ROM (compact disc, read-only memory). This IARCancer Disc contains the full text of the IARC Monographs (Volumes 1–55), the Directory of On-Going Research in Cancer Epidemiology (1994), the Directory of Agents Being Tested for Carcinogenicity, No. 15, the IARC/EPA Genetic Activity Profile Database and Cancer Incidence and Mortality Data for 1978–87. A structured database containing subsets of information from the IARC Monographs is also included to allow more rapid and efficient searching than can be achieved by free-text searching alone. Standardized index terms for chemical class, use, species, target organs, tumour types, mutagenicity and reproductive effects are given. The CD-ROM is published by SilverPlatter Information, Inc., and a discount subscription price is available for purchasers in developing countries. The data are being updated for the second annual release of the CD-ROM, which will cover IARC Monographs Volumes 1–62 and the latest volumes of the directories.

7.2 Organization of scientific meetings

7.2.1 Conference on Interactions of Cancer Susceptibility Genes and Environmental Carcinogens

9–13 November 1993, Lyon, France

Recent advances in molecular biology have created new opportunities to identify and control the causes of human cancers. To summarize current knowledge and explore future research opportunities, an interdisciplinary conference was held under the joint sponsorship of the International Agency for Research on Cancer and the American Association for Cancer Research, and supported by grants from the European Commission, the Ligue Nationale Française contre le Cancer, and the National Institute of Environmental Health Sciences (USA). An international panel of experts presented papers covering the following topics: human cancer epidemiology; biomarkers of individual susceptibility; mechanisms of transgenerational carcinogenesis; experimental models of genetic susceptibility; genetic instability; and DNA damage and repair. A total of 78 posters were also presented, with the participation of many young investigators [297].

7.2.2 International conference on retrospective assessment of occupational exposures in epidemiology

13–15 April 1994, Lyon, France

Retrospective exposure assessment in epidemiology has experienced interesting advances during the last decade. New approaches have been proposed and applied, particularly in the assessment of occupational exposures, as a result of collaboration

between epidemiologists and industrial hygienists. A second international conference, organized by IARC in collaboration with the US National Institute for Occupational Safety and Health and the US National Cancer Institute, and with support from the European Commission, Directorate General XII, was attended by over 200 participants. Four invited lectures and 30 proffered papers addressed issues related to community- as well as industry-based studies, the use of biomarkers of exposure, the choice and validation of measures of exposure, and theoretical aspects of exposure assessment. A total of 71 posters were also presented. The proceedings of the conference are being published in the journal *Occupational Hygiene*.

7.2.3

HPV vaccines in prevention and treatment of cervical cancer

12–14 December 1994, Annecy, France

The potential use of HPV vaccines in prevention and treatment of cervical cancer was the theme of a workshop organized in collaboration with the Fondation Marcel Mérieux at Veyrier du Lac, near Annecy, on 12–14 December 1994 (see Section 5.1.4). This international workshop, attended by 40 scientists from nine countries, was a follow-up to the two previous ones on the epidemiology of cervical cancer and HPV organized by the IARC.

7.2.4

Receptor-mediated mechanisms in carcinogenesis

14–16 November 1994, Lyon, France

During the last few years, improvements in understanding the cellular and molecular mechanisms of carcinogenesis have revealed that carcinogens may act by different mechanisms. One important finding is that covalent interaction of the chemical with DNA is not required in order to induce cancer. In some instances, specific receptors have been identified with which non-genotoxic carcinogens may interact either directly or indirectly. This workshop brought together some 120 international experts to discuss and share recent developments in the field. The European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), the International Committee for Protection against Environmental Mutagens and Carcinogens (ICPEMC) and the International Programme for Chemical Safety (IPCS) were co-organizers of the meeting with IARC.

7.2.5

Conference on Principles of Chemoprevention

6–10 November 1995, Lyon, France

This international conference was attended by many of the leading researchers in the field of chemoprevention. The first part focused on data from studies in humans and in experimental models aimed at identifying chemopreventive agents and the ways in which they might act. Ongoing, large-scale trials of cancer prevention, aimed at the general population, were reviewed, and aspects of the design, conduct and interpretation of studies of cancer prevention in humans were addressed by several speakers. The final days of the conference were devoted to the drafting of guidelines for the evaluation of putative cancer preventive strategies and agents. One concern expressed was how the information should be presented so as to avoid misinterpretation. It is of crucial importance that both beneficial and adverse effects are noted, together with the doses at which they are likely to occur.

7.3 *Cancer research fellowships programme*

7.3.1 IARC research training fellowships

R. Montesano, E. El Akroud and V. Hubert

The aim of this programme is to provide young scientists with training in aspects of cancer research ranging from biostatistics and epidemiology to mechanisms of chemical and viral carcinogenesis. The majority (60%) of the 437 fellowships awarded since 1966 have come from western Europe, Japan, North America, Israel, Australia and New Zealand. while 17% came from eastern Europe and 23% from other countries of Africa, Asia and South America (see below). Host laboratories have been mainly located in western Europe (50%) and North America (47%). The programme is one of the few to provide training in epidemiology, and the 94 fellowships awarded in this discipline have contributed substantially to the development of the subject in a number of countries.

Region of origin	No.	
North America	36	8%
Western Europe	132	34%
Eastern Europe & ex-USSR	80	17%
Israel	24	5.5%
Japan	42	9.5%
Australia & New Zealand	14	3%
Asia	53	12.5%
Others (Africa, S. America)	56	11.5%
Total	437	100%

The Fellowships Selection Committee met twice in Lyon over the period to review applications; the members of the Committee were:

Dr D. Bootsma (1995) (Chairman, 1995)
Department of Cell Biology and Genetics,
Erasmus University,
Rotterdam, Netherlands

Dr A. Brøgger (1994)
Department of Genetics
Institute for Cancer Research,
The Norwegian Radium Hospital
Oslo, Norway

Dr E. Buiatti (1994, 1995)
Epidemiology Unit,
Tuscany Cancer Registry,
Florence, Italy

Dr J. Cairns (1994, 1995) (Chairman, 1994)
Clinical Trial Service Unit,
Radcliffe Infirmary,
Oxford, UK

Dr H. Esumi (1995)
National Cancer Center Research Institute,
East, Chiba, Japan

Dr M. Hollstein (1994, 1995)
German Cancer Research Centre,
Heidelberg, Germany

Dr J.G. McVie (1995) (UICC Representative)
Scientific Department,
Cancer Research Campaign,
London, UK

Dr B. Mansourian (1994, 1995)
Office of Research Promotion and Development,
World Health Organization,
Geneva, Switzerland

Dr N. Odartchenko (1994) (UICC Representative)
Swiss Institute for Experimental Cancer Research,
Epalinges/Lausanne, Switzerland

Dr J. Samarut (1994, 1995)
Laboratory of Molecular and Cellular Biology,
Ecole Normale Supérieure,
Lyon, France

Dr S. Watanabe (1994)
Division of Epidemiology,
National Cancer Center Research Institute,
Tokyo, Japan

Dr D.G. Zaridze (1994, 1995)
Institute of Carcinogenesis,
Cancer Research Center,
Moscow, Russian Federation

The Agency representatives were Dr R. Montesano and Dr E. Riboli (1994–95).

In 1994, among a total of 123 candidates, 63 were declared eligible and 14 fellowships finally awarded; in 1995, among a total of 119 candidates, 54 were declared eligible and 13 fellowships finally awarded. In 1994, one fellowship was tenable at the IARC and in 1995 two. The distribution of fellowships awarded by discipline is given in Table 12; the list of fellows in Table 13.

The Italian Association for Cancer Research generously provided US$100 000 in 1994–95 to support the Fellowships Programme.

7.3.2 Visiting Scientist awards

In 1994, this Award was given to Dr C. Naus (Department of Anatomy, University of Western Ontario, London, Ontario, Canada), who spent one year in the Unit of Multistage Carcinogenesis and in 1995 to Dr W.C.A. Gelderblom (Programme on Mycotoxins and Experimental Carcinogenesis, Tygerberg, South Africa), who will spend one year in the Unit of Environmental Carcinogenesis.

Table 12. Distribution of research training fellowships awarded by discipline

Scientific discipline	No. of fellowships		
	1994	1995	1966–95
Epidemiology and biostatistics	4	1	95
Chemical carcinogenesis	0	1	31
Viral carcinogenesis	3	2	23
Cell biology, cell differentiation and cell genetics	6	4	64
Biochemistry and molecular biology	0	5	70
Others	1	0	154
Total	14	13	437

Table 13. Fellowships awarded in 1994 and 1995

Name	Institute of origin	Host institute
1994		
ALVARO, V.	Centre CNRS INSERM de Pharmacologie-Endocrinologie Montpellier, France	Columbia-Presbyterian Cancer Center College of Physicians & Surgeons of Columbia University New York, NY, USA
BOSE, B.	Biophysics Division Saha Institute of Nuclear Physics Calcutta, India	Swiss Institute of Experimental Cancer Research Epalinges/Lausanne, Switzerland
DE-MEDINA, T	Dept of Molecular Genetics and Virology Weizmann Institute of Science Rehovot, Israel	Dept of Pathology Harvard Medical School Boston, MA, USA

Name	Institute of origin	Host institute
GREBE, S.K.G.	Dept of Medicine Wellington School of Medicine Wellington, New Zealand	Endocrine Research Unit Depts of Medicine and Biochemistry/Molecular Biology Mayo Clinic Rochester, MN, USA
HABUCHI, T.	Dept of Pathology Faculty of Medicine Kyoto University Kyoto, Japan	Molecular Genetics Laboratory Marie Curie Research Institute Oxted, Surrey, UK
ISMAILI, J.	Laboratoire de Physiologie Animale Université Libre de Bruxelles Rhode-St-Genèse, Belgium	Lymphocyte Differentiation Unit Walter & Eliza Hall Institute of Medical Research Royal Melbourne Hospital Victoria, Australia
KANNAN, W.	Division of Cancer Research Regional Cancer Centre Trivandrum, India	Dept of Pathology Hiroshima University School of Medicine Hiroshima, Japan
KRISHNAN, E.	Regional Cancer Centre Medical College Campus Trivandrum, India	Institute of Public Health University of Cambridge Cambridge, UK
LUKANOVA, A.J.	National Center of Hygiene, Medical Ecology & Nutrition Sofia, Bulgaria	Epidemiology Program Division of Epidemiology & Biostatistics New York University School of Medicine New York, NY, USA
PETRENKO, Z.N.	Ukrainian Research Institute of Oncology & Radiology Kiev, Ukraine	Dept of Pathology Institute for Cancer Research Oslo, Norway
REISSIGOVA, J.	Institute of Chest Diseases Prague, Czech Republic	Unit of Descriptive Epidemiology IARC Lyon, France
STEWART, A.C.M.	Dept of Medical Genetics University of Uppsala Uppsala, Sweden	New Mexico Tumor Registry University of New Mexico School of Medicine Albuquerque, NM, USA
TUMINO, R.	Servizio di Anatomia Patologica, U.S.L. Ragusa Cancer Registry Ospedale G.B. Odierna Ragusa, Italy	Dept of Epidemiology London School of Hygiene & Tropical Medicine London, UK
ZHANG, X.	Guangdong Medical College Guangdong, PR China	Dept of Tumor Biology Karolinska Institute Stockholm, Sweden
1995		
CHEMIN, I.	IARC Unit of Environmental Carcinogenesis Lyon, France	Abt. Innere Medizin II (Gastroenterology, Hepatology) Klinikum der Albert-Ludwigs Univ. Freiburg Freiburg, Germany

Name	Institute of origin	Host institute
FURUKAWA, Y.	Dept of Biochemistry Cancer Institute Tokyo, Japan	IARC Unit of Mechanisms of Carcinogenesis Lyon, France
GUILLEMOT, J.-C.	Beth Israel Hospital Harvard Medical School Boston, MA, USA	Centre d'Immunologie INSERM/CNRS Marseille, France
HOFLACK, J.C.	Laboratoire de Toxicologie Centre des Sciences de l'Environnement Metz, France	Unité Santé et Environnement Centre de Recherche du CHU-Laval Ste Foy, PQ, Canada
INOUE, M.	Division of Epidemiology Aichi Cancer Center Research Institute Nagoya, Japan	Dept of Epidemiology Harvard School of Public Health Boston, MA, USA
JENA, G.	Laboratory of Genetic Toxicology Dept of Zoology Utkal University Orissa, India	Division of Environmental Sciences Columbia University New York, NY, USA
KAVALLARIS, M.	Children's Leukaemia and Cancer Research Centre, Prince of Wales Children's Hospital, Sydney, Australia	Department of Molecular Pharmacology Albert Einstein College of Medicine Yeshiva University New York, USA
LELIEVRE, S.A.J.	Unité de Biochimie Enzymologie CNRS URA 147 Physicochimie et Pharmacologie des Macromolécules Biologiques Institut Gustave Roussy Villejuif, France	Cell & Molecular Biology Laboratory Life Sciences Division Lawrence Berkeley Laboratory, Berkeley, CA, USA
MENGISTU, Y.	Dept of Microbiology and Parasitology Faculty of Medicine Addis Ababa University Addis Ababa, Ethiopia	Dept of Molecular Biology Paterson Institute for Cancer Research University of Manchester Manchester, UK
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7.4 *Training courses*

B.K. Armstrong, H. Vainio, N. Muñoz, M. Davis and C. Déchaux

Since 1974, about four courses per year have been held either at the Agency or elsewhere around the world; it is now planned to reduce the number to 2–3 per year, giving priority to the courses in developing countries or countries in transition. Most of these will be basic courses on cancer epidemiology. Consideration will also be given to organization of one-week practical workshops on specific topics, such as cancer registration or occupational cancer. Most of the advanced courses will be held in Lyon and will deal with specialized subjects such as genetic epidemiology, nutrition and cancer; for these courses a fee is being charged. Furthermore, IARC Technical Transfer Awards have been instituted to provide particularly promising course participants with the opportunity to receive further practical training in the Agency in epidemiology or laboratory research for a period of 2–3 months. The first Technical Transfer Award was offered to a biostatistician from the Cancer Research Centre in Lima, Peru, who attended the course on advanced methods in occupational cancer epidemiology at IARC.

It has been decided that IARC should produce a textbook entitled *Introduction to Cancer Epidemiology* within the framework of this programme, to be used in the Agency's courses. To this end, an expert from the London School of Hygiene and Tropical Medicine has been commissioned to prepare the manuscript in consultation with IARC epidemiologists.

Eight courses and one workshop were held during the period under review.

7.4.1

Detection of health hazards in humans exposed to mutagens and carcinogens, 15–26 November 1993, Bangkok, Thailand

This course was the fifth of its kind. The Chulabhorn Research Institute hosted the course and provided excellent facilities. The course was organized in collaboration with the United Nations Environment Programme (UNEP), the International Programme on Chemical Safety (IPCS), the International Labour Office and FINNIDA. Drs H. Vainio and C.P. Wild from IARC coordinated the scientific programme. There were 36 participants, from Egypt, Hong Kong, India, Indonesia, Kuwait, Malaysia, Myanmar, People's Republic of China, Philippines, Singapore, Tanzania and Thailand.

7.4.2

Safe handling of cytostatic drugs for health workers and **Safe handling of genotoxic substances in laboratory work**

30 November–1 December and 2–3 December 1993, Lyon, France

These courses were organized, as on previous occasions, in collaboration with the French Institut National de la Recherche et de la Sécurité (INRS). The first course was for advanced training for nurses and public health workers and was followed by practical training sessions at the Hôpital Edouard Herriot (Lyon). The second was more specifically for safety engineers and occupational health officers. The programme coordinators were Dr M.

Figure 41. Participants at the introductory course on cancer epidemiology, in Fajara, The Gambia

Castegnaro from IARC and Dr X. Rousselin from INRS. Approximately 60 participants attended the two courses.

7.4.3 Scientific communication

13–26 December 1993, Lyon, France

This course was designed for IARC scientific staff, with the aim of assisting them in presenting their findings clearly, concisely and convincingly. It concentrated on the structure of a scientific paper.

7.4.4 Introductory course on epidemiology

31 May–10 June 1994, Fajara, Gambia

The course was open to medical doctors, as well as to other health-related professionals with an interest in initiating or pursuing work in cancer epidemiology. The emphasis was on methods of cancer epidemiology and the epidemiological characteristics of cancer in Africa, including measurement of cancer occurrence, determination of cancer causes and evaluation of

the effectiveness of preventive measures. The programme coordinator was Dr A.J. Hall, from the London School of Hygiene and Tropical Medicine. The course was attended by 27 students originating from 11 sub-Saharan African countries (Cameroon, Congo, Gambia, Ghana, Guinea Conakry, Ivory Coast, Mozambique, Nigeria, Sierra Leone, Uganda, Zimbabwe).

7.4.5

European Educational Programme in Epidemiology—7th residential summer course

27 June–15 July 1994, Florence, Italy

For this year's session, there were 60 participants from 23 countries. Dr R. Saracci from IARC was the Course Director.

7.4.6

Workshop on occupational cancer in Brazil

22–26 August 1994, Pelotas, Brazil

As indicated in its title, this workshop was focused on occupational health to provide specific scientific tools for cancer research and public health workers. Out of the 32 participants, two thirds were epidemiologists and the remainder occupational health professionals. Dr P. Boffetta from IARC was the programme director.

7.4.7

Cancer epidemiology (in French)

5–16 December 1994, Lyon, France

This intermediate course on cancer epidemiology, the fourth in the series in collaboration with the French Institut National de la Santé et de la Recherche Médicale (INSERM), intended for clinicians and statisticians already involved in cancer epidemiology studies, was attended by 48 participants from 12 countries (Algeria, Belgium, Burkina Faso, Cameroon, Congo, France, Italy, Mali, Portugal, Senegal, Switzerland, Tunisia). Dr Jacques Estève (IARC) and Dr Denis Hémon (INSERM) jointly shared the scientific course direction. IARC provided financial support to five participants from developing countries.

7.4.8

Safe handling of cytostatic drugs for health workers and Safe handling of genotoxic substances in laboratory work

9–10 and 11–12 January 1995, Lyon, France

These sessions, organized in collaboration with the French Institut National of de la Recherche et de la Sécurité (INRS), were as successful as the previous ones (see above). A total of 75 nurses and public health workers attended. Dr M. Castegnaro (IARC) and Dr X. Rousselin (occupational physician, Centre Hospitalier Général, Avranches-Granville, France) were in charge of the scientific programme.

7.4.9

Advanced methods in occupational cancer epidemiology

3–7 April 1995, Lyon, France

This course, under the scientific direction of Dr P. Boffetta (IARC) and Dr N. Pearce (Wellington Medical School, New Zealand), presented and discussed recent developments in the design and analysis of studies on occupational epidemiology, with special emphasis on cancer. Forty-two participants came from 23 countries (Australia, Brazil, Canada, Denmark, Finland, France, Germany, Indonesia, Israel, Italy, Netherlands, Norway, Peru, Philippines, Poland, Singapore, Slovenia, Spain, Sri Lanka, Switzerland, United Kingdom, Uruguay, Yugoslavia).

PART 8. SCIENTIFIC S UPPORT ACTIVITIES

8.1 Computing support service

M. Smans, B. Charnay, P. Damiecki, X. Nguyen-Dinh, H. Renard and B. Kajo

The local area network (LAN) has experienced rapid growth during the last biennium, to reach more than 120 PCs, 15 Macintoshes, 15 VAX servers and stations and several other servers (CD-ROM, Print, Communications, etc.). Increasingly, applications run on the desktop, with the assistance of one or more specialized servers.

One example is word processing. Previously dependent on a Microvax, with more than 50 regular users, this now uses a networked PC-based system, allowing production of better quality documents as well as easier document exchange inside and outside the Agency.

A fax-server now allows users to send and receive faxes direct from their PCs, at the same time reducing paper circulation. The accounting system, which was handled on a specialized, single-user machine, has been temporarily moved to a small IBM AS400 server that finance office staff access through their PCs; this will ultimately be replaced by a true 'client-server' system being developed at WHO headquarters.

Scientific applications still rely heavily on the central computing equipment, in particular, for the use of epidemiology databases and statistical software. In this area also, nevertheless, there has been a tendency to move towards 'decentralized' computing, and the implementation of new computing strategies is being studied.

The Agency's communications with the outside world have again been improved: while e-mail, file transfer and remote log-in have been available to Agency staff for some years, we have become an Internet domain (iarc.fr) with an improved connection to the campus of the Institut National des Sciences Appliquées (IN2P3). The agency launched its Web server at the end of April 1995 (http://www.iarc.fr/).

In order to bring about these many changes and enhancements, the computing services group has had to spend a great deal of time setting up equipment and assisting users. The growing experience among all staff and the use of standard tools on the desktop will allow more time to be concentrated on the development of the LAN and the services it can provide to its users.

8.2 Library and information services

H. Miido, M. Coudert and L. Ossetian

The IARC library is responsible for ordering, processing and maintaining books, journals, in-house databases and interlibrary loans, as well as for searching external databases and providing general reference support.

Books are purchased from publishers or agents with the help of an internally

developed database which allows the reformatting and transmission of files through electronic mail, ftp and fax. The archival collection is periodically evaluated, to ensure that the subjects of the current scientific programmes are adequately represented. Cataloguing and indexing (and subsequent retrieval using the Online Public Access Catalogue or OPAC) are performed using the Soutron Library System.

Journals are ordered through a subscription service. The subscription list is periodically reviewed for its relevance to the scientific programmes of IARC. Cataloguing and indexing (and subsequent retrieval through the OPAC) are performed using the Soutron Library system.

In-house databases developed and maintained by the library using the Unesco ISIS software (with support from the Computer Services Group) include the book purchasing system, interlibrary loan system, and a Current Contents on Diskette reprint ordering system. These systems are maintained on the VAX. Databases maintained on the networked Reference Manager System include all publications of IARC staff and a collection of reprints maintained by IARC scientific staff.

The library maintains Medline/Cancerlit on CD-ROM (available from 1966 to the present) and up to twelve weekly issues of *Current Contents on Diskette* , searchable on any PC or Macintosh using the WinSpirs/MacSpirs software and the Current Contents program.

General reference services provided by library staff include the installation and instruction on use of the systems mentioned above, identification of new information systems of interest or use to IARC staff, and dissemination of unique systems and procedures developed for library applications through presentations at conferences or publications [358, 359].

8.3 Banks of biological specimens

Various banks of biological samples are available at IARC as a result of past or ongoing collaborative studies. Such samples are made accessible to scientists not involved in the original studies, under appropriate conditions. These banks include over 70 000 sera mainly from a study of the role of Epstein–Barr virus in the etiology of Burkitt's lymphoma and nasopharyngeal carcinoma, and 124 Burkitt's lymphoma cell lines from this and other studies. Further studies have been performed on the importance of 6q deletions in Burkitt's lymphoma cell lines [115], following the initial collaboration with Dr R. Dalla-Favera, and deletions and rearrangements of CDKN2 were analysed in Dr Dyer's group [599].

The Ewing sarcoma cell lines established at IARC were used to better define the molecular rearrangement involving chromosomes 11 and 22 [706]. It was shown that the subgroup of small-round-cell tumours identified as belonging to the Ewing family of tumours can be defined according to a specific molecular genetic lesion that is detectable by a rapid, reliable and efficient method. This approach can be applied to small specimens obtained by fine-needle biopsies [131].

A very large collection of blood samples is being made in the context of the European Prospective Investigation into Cancer and Nutrition (Section 2.3.1). Some four million 'straws' containing aliquots of plasma, serum, buffy coat and red blood cells will be shipped to Lyon from seven countries by the end of 1996, and are being stored in liquid nitrogen. Blood samples collected as part of the Gambia Hepatitis Intervention Study

(Section 5.1.1) to assess the efficiency of the vaccination are also used in ancillary studies of other related scientific questions.

The ethical issues related to the use of biological specimens are examined on a study-by-study basis by a Biological Specimen Committee that interacts closely with the Agency's Ethical Review Committee.

8.4 Common laboratory services

These services include animal breeding and maintenance of the animal house, the histology laboratory and the glass-washing service. The Agency's animal house performs carcinogenicity experiments, and maintains some strains of rats and normal and transgenic mice. Facilities for the maintenance of nude mice are also available. The histology laboratory processes all the histological material from experimental animals in the Agency as well as biopsy material sent by Agency researchers doing field work abroad. The glass-washing facility is a unified service for the experimental work carried out in chemistry, biochemistry and cell culture.

Annex 1

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28–29 April 1994

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Annex 2

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Professor of Viral Oncology
Director of Research
Institute of Cancer Research
Royal Cancer Hospital
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Governing Council
Dr Berit Mørland
Director, Strategic Planning
Research Council of Norway
P.O. Box 2700
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WHO, Geneva
Dr N.P. Napalkov
Assistant Director-General

UICC
Dr N. Odartchenko
I.S.R.E.C.
CH-1006 Epalinges/Lausanne
Switzerland

* Unable to attend

Annex 3

PERSONNEL AT IARC
1 July 1993–31 December 1995

Office of the Director

Director, IARC	Dr L. TOMATIS (until 31.12.93) Dr P. KLEIHUES (from 1.1.94)
Deputy Director	Dr B.K. ARMSTRONG (until 31.12.93)
Special Adviser on Biostatistics	Dr J. ESTEVE
Senior Editor	Dr J. CHENEY (half-time)
Visiting Scientists	Dr I. RAJOWER (from 22.5.95) Dr B. STEWART (1.9.94–30.11.94) Dr F. SÖYLEMEZOGLU (3.1.95–30.3.95)
Administrative Assistant	Mrs E. RIVIERE
Secretary	Miss Y. GRANJARD
Assistant (Documents)	Mrs M.-H. CHARRIER

Unit of Analytical Epidemiology (dissolved December 1994)

Chief	Dr R. SARACCI (until 31.12.94)
Scientist	Dr J. LITTLE (until 30.9.94)
Visiting Scientists	Dr S. CORDIER (1.9.93–31.7.94) Dr P. DEMERS (until 30.11.93) Dr F. FAGGIANO (1.3.94– 31.5.94 Dr HUA FU (17.11.93–16.11.94) Dr N JOURENKOVA (8.11.93–28.2.94 and 15.7.94–15.8.94) Dr T. PARTANEN (until 30.11.93) Dr N. PEARCE (until 30.11.93) Dr J. TREDANIEL (until 31.10 93)
Students	Ms F. AMOUSSOU-ADEBLE (7.4.94–8.7.94) Ms K. BLACHNIK (15.2.94–15.8.94) Ms E. WELP (1.12 93–31.5.94)
Secretaries	Mrs A. HANSS-COUSSEAU (until 31.7.94) Miss A. SHANNON (until 31.12.94)

Unit of Environmental Cancer Epidemiology (established January 1995)

Chief	Dr P. BOFFETTA
Scientists	Dr E. KOGEVINAS (unti l 17.4.95) Dr E. MERLER (from 1.9.95) Dr T. PARTANEN (1.9.94–22.10.95)
Visiting Scientists	Dr N JOURENKOVA (from 21.11.94) Dr M. KRAUSS (from 1.7.95) Dr D. SALI (1.3.95–30.6.95 and 1.9.95–30.9.95) Dr E. WEIDERPASS (7.11.94–31.8.95) Dr V. WUNSCH FILHO (from 15.3.94)
Assistants (statistics)	Mr D. COLIN (from 8.7.93) Mr G. FERRO Miss R. WINKELMANN
Students	Ms V. GABORIEAU (from 1.4.95) Ms Y. TAUSCHER (29.11.94–30.9.95)
Secretaries	Ms M. GEESINK Mrs S. STALLARD (until 30.9.95)

Unit of Nutrition and Cancer (established January 1995)

Chief	Dr E. RIBOLI
Scientist	Dr R. KAAKS
Technical Officers	Ms U.R. CHARRONDIÈRE (7.3.95–31.12.95) Mrs G. DEHARVENG (18.7.94–13.11.95) Mrs N. SLIMANI (from 1.1.94) Mrs A.L. VAN KAPPEL-DUFOUR (until 22.12.95)
Laboratory Technician	Miss B. VOZAR (until 31.12.95)
Assistants (Statistics)	Miss C. CASAGRANDE (from 1.1.94) Mr B. HEMON Mr M. MIGINIAC (1.3.95–22.12.95)
Students	Ms C. GROS, Special Training Award (until 30.4.94) Ms K. PETRI (from 1.10.95)
Clerk	Miss J. AMOYEL (until 28.2.95)
Secretary	Mrs S. SOMERVILLE

Unit of Field and Intervention Studies

Chief	Dr N. MUÑOZ

Scientist	Dr F.X. BOSCH (until 1.9.93) Mr M. PLUMMER (from 14.5.95)
Visiting Scientists	Dr J. DEACON (16.7.93–17.6.94) Dr S. DE SANJOSÉ (until 31.10.93) Dr S. FRANCESCHI (from 5.6.95–10.12.95) Dr V. MORENO (until 27.7.94) Dr A.P. VIZCAINO
Technical Officer	Dr I. KATO (until 27.3.95)
Assistants (Statistics)	Mrs A. ARSLAN Miss M. BENZ Mrs C. LAVÉ Miss D. MAGNIN Mr M. ROSATO (until 30.9.94)
Assistant (Courses)	Mrs M. DAVIS
Student	Ms M.-L. BLANC (1.2.94–3 5..94)
Secretary	Mrs H. LORENZEN

Unit of Descriptive Epidemiology

Chief	Dr D.M. PARKIN
Scientists	Mr R.J. BLACK (from 14.2.94) Ms L. GIBSON (Manila) (from 7.7.95) Ms A. KRICKER (until 17.12.93) Dr P. PISANI Dr R. SANKARANARAYANAN Dr J. ZIEGLER(Uganda) (from 5.4.94)
Visiting Scientists	Miss S. LEIJABOK, Special Training Award (until 11.10.93) Ms M.T. VALDIVIESO GONZALEZ, Special Training Award Dr P.C. GUPTA, IARC Visiting Scientist Award (9.9.93–8.9.94) Ms M.A. SUSARA, Special Training Award (17.9.93–16.9.94) Dr E. KRÁMAROVÁ, Special Training Award (from 16.5.94) Ms I. HAEVE, Special Training Award (from 12.9.94) Mrs B. SINDKUBWABO, Special Training Award (3.10.94–31.12.95) Ms V. MAGNE, Special Training Award (2.11.94–1.5.95) Dr J. REISSIGOVA, Research Training Fellowship (27.12.94–26.12.95) Mrs C. SAUVAGE, Interne en Santé Publique (3.1.95–2.5.95) Dr H. TULINIUS (27.9.93–27.12.93)
Technical Officer	Miss S. WHELAN
Assistants (Statistics)	Mr A. COOKE (from 3.4.95) Mr J. FERLAY Mr E. MASUYER Mr S. OLIVIER (until 29.12.94)

Technical Assistant	Mrs E. DEMARET
Computer Assistant	Mr P. SARTRE (1.4.95–4.10.95)
Secretary	Miss O. BOUVY
Clerks	Mrs E. BAYLE Mrs F. PETIT (half-time)

Unit of Environmental Carcinogens and Host Factors (dissolved January 1994)

Chief	Dr H. BARTSCH (until 30.9.93)
Scientists	Dr S. CALMELS-ROUFFET (until 31.12.93) Dr A. LOKTIONOV (until 30.7.93) Dr I. O'NEILL (until 31.12.93) Dr D.E.G. SHUKER (unt il 1.10.93)
Visiting Scientists	Dr K. ALEXANDROV (until 31.1.94) Dr M. KONSTANDI, Fellowship, University of Ioannina, Greece (until 15.9.93) Dr M. ROJAS-M1ORENO (until 31.1.94) Dr S. SATARUG, Australian National Health and Medical Research Council Fellowship (until 30.9.93) Dr H. SCHUT, NCI Fogerty Fellowship (until 31.8.93)
Laboratory Technician	Mr P. THUILLIER (until 31.12.93)
Students	Mr K.S. AMANING, Special Training Award (1.8.93–21.12.93) Miss B. DONVITO, Special Training Award (until 4.10.93) Miss P. PELKONEN, Fellowship from Ministère des Affaires Etrangères, Paris (20.9.93–19.11.93) Miss C. SUNYACH, Special Training Award (until 31.8.93)

Unit of Endogenous Cancer Risk Factors (established January 1995)

Chief	Dr H. OHSHIMA
Scientists	Dr C. MALAVEILLE Dr B. PIGNATELLI Dr S. CALMELS-ROUFFET (1.1.94–27.10.95)
Visiting Scientists	Dr J. RUBIO LIGHTBOURN, Scholarship from the Universidad Nacional Autonoma de Mexico (10.8.94–9.8.95) Dr Q. SHAO, Chinese Government fellowship (from 3.11.95) Dr V. YERMILOV, ESF Fellowship and Special Training Award (from 14.3.94)
Laboratory Research Assistant	Mrs I. BROUET
Laboratory Technician	Mrs A. HAUTEFEUILLE

Student	Miss F. SMIT, European and Dutch Fellowship (29.8.94–20.6.95)
Secretary	Mrs P. COLLARD

Unit of Environmental Carcinogenesis (established January 1995)

Chief	Dr C.P. WILD
Scientists	Dr A. BARBIN Dr M. CASTEGNARO Dr M. FRIESEN
Visiting Scientists	Dr S. ATAWODI, Special Training Award (from 10.1.95) Dr F. BIANCHINI, European Environmental Research Organisation Fellowship and Special Training Award (until 31.8.94) Dr I. CHEMIN, Special Training Award (until 31.8.95) Dr P. CHOMARAT, Fellowship from La Ligue Nationale Contre le Cancer (from 10.4.95) Dr D. EATON (21.8.95–30.11.95) Dr Y. FEN, Research Training Fellowship and Special Training Award (until 30.6.95) Dr O. FROMENT, Special Training Award (2.11.93–15.9.95) Dr P. JACKSON (from 1.10.95) Dr J. NAIR (until 22.4.94) Mr A. SYLLA, Special Training Award (from 9 June 1995)
Laboratory Research Assistants	Mrs L. GARREN Mrs G. BRUN
Laboratory Technicians	Miss B. CHAPOT Miss F. EL GHISSASSI (until 23.6.95) Mrs J. MICHELON Mr A. SCHOUFT
Students	Miss C. GENEVOIS, Special Training Award (from 2.11.93) Mr Y. GUICHARD, Special Training Award (until 30.9.94) Miss C. KAPLANSKI, Fellowship from the Fondation pour la Recherche Médicale (from 6.12.93) Miss M. LECHEVREL, Fellowship from Ministère de la Recherche et de la Technologie (until 30.9.95)
Secretaries	Mrs Z. SCHNEIDER (half-time) Mrs M. WRISEZ

Unit of Mechanisms of Carcinogenesis

Chief	Dr R. MONTESANO
Scientists	Dr J.R.P. CABRAL (until 31.12.93) Dr P. HAINAUT (from 28.2.95) Dr J. HALL Dr M. HOLLSTEIN (until 31.1.94)

Visiting Scientists	Dr M. ARTUSO, Special Training Award (until 31.12.94) Dr C. BARNAS, Special Training Award (from 21.4.95) Dr A. ESTEVE, Fellowship from the Commission of the European Communities (until 3.3.95) Dr W. JONGMANS, Special Training Award (from 1.6.95) Dr H. KANG, Research Training Fellowship (until 28.10.93) Dr Y.-Y. LIANG, Research Training Fellowship (until 21.1.94) Dr P. PELKONEN, Special Training Award (from 1.4.95) Dr M.F. RAJEWSKY, American Cancer Society International Fellowship (28.9.93–27.6.94) Dr T. SCHRAGER, UICC Yamagiwa-Yoshida Fellowship (30.8.93–22.11.93) Dr S. TAKAHASHI, Research Training Fellowship (10.1.94–31.12.94) Dr G. VERHAEGH, Special Training Award (from 6.6.95)
Laboratory Research Assistants and Technicians	Miss H. BRESIL (also Laboratory Safety Co-ordinator) Mrs A. ELLUL (until 30.9.94) Miss S. LAEJABOK, *with* Unit of Environmental Carcinogenesis, Special Training Award (from 3.4.95) Mrs G. MARTEL-PLANCHE Mr A. SOUABNI, Special Training Award (from 1.8.95) Mrs M. VUILLAUME
Students	Mr M. GARABET, Special Training Award (3.10.94–30.9.95) Miss E. KELLER, Special Training Award (27.3.95–28.4.95 and 1.7.95–31.8.95) Mr G. RODRIGO, Special Training Award (29.5.95–31.8.95) Ms T. SØRLIE, Special Training Award (until 29.7.94) Dr P. TANIERE (part-time), DEA student (from 9.10.95)
Secretaries	Mrs A.-M. MAILLOL Mrs E. EL AKROUD (Research Fellowships Programme) Mrs V. HUBERT (Research Fellowships Programme) (3.5.95–27.10.95)

Programme of Molecular Toxicology	*(from* 1.1.*95)*
Head	Dr M. LANG
Laboratory Research Assistant	Mrs A.-M. CAMUS-RANDON
Students	Mr O. GENESTE (Special Training Award) (until 31.1.95) Miss A. PEKKARINEN, Grant from the Association Franco-Finlandaise pour la Recherche Scientifique et Technique (1.6.95–31.8.95) Miss F. RAFALLI, Fellowship from Ligue nationale contre le cancer Mrs A. TILLOY-ELLUL, Special Training Award (from 2.11.94)

Gambia Hepatitis Intervention Study

Project Leader	Dr A. JACK
Project Co-ordinator	DrR. MONTESANO
Scientists	Dr A. COSIMI (16.12.94–15.6.95) Dr L. INSABATO (6.10.93–31.3.94) Dr M. KRSTULJA (3.6.94–25.11.94) Mr N. MAINE Dr S. VIVIANI (from 1.9.95)
Secretary	Miss B. GEOFFRE (half-time)

Unit of Genetic Cancer Susceptibility (established April 1995)

Chief	Dr G. ROMEO (from 1.4.95)
Scientist	Dr B. SYLLA
Technical Assistant	Miss C. BONNARDEL
Laboratory Research Assistant	Mrs M. F. LAVOUE
Laboratory Technician	Mrs S. PAULY
Secretary	Mrs A. TROCHARD

Unit of Molecular Pathology (established February 1995)

Chief	Dr H. OHGAKI (from 1.2.95)
Visiting Scientists	Dr W. BIERNAT, Special Training Award (from 3.12.95) Dr K. SATO, Fellowship from Japanese Ministry of Education (from 23.8.94) Dr O. TACHIBANA, Fellowship from Japanese Ministry of Education (from 12.12.94) Dr K. WATANABE, Special Training Award (14.4.95–31.12.95)
Laboratory Research Assistant	Mr J.C. BEREZIAT
Secretary	Mrs E. PEREZ (half-time)

Animal House

Laboratory Research Assistant	Mrs D. GALENDO
Laboratory Technicians	Mrs M.-P. CROS Mr J. GARCIA
Laboratory Aides	Mr J. CARDIA-LIMA Mr R. DRAY
Equipment Operator	Mr F. FARIA (until 31.12.94)

Histopathology Laboratory

Laboratory Research Assistant	Miss M. LAVAL
Laboratory Technician	Mrs N. LYANDRAT

Unit of Multistage Carcinogenesis

Chief	Dr H. YAMASAKI
Scientists	Dr V. KRUTOVSKIKH Dr N. MIRONOV Dr H. NAKAZAWA Dr M. MESNIL
Visiting Scientists	Dr A. DANCER, Special Training Award and fellowship from Ligue Nationale Française contre le Cancer (from 1.11.94) Dr G. MAZZOLENI, Fellowship from the Italian Government (until 31.3.94) Dr C. NAUS, IARC Visiting Scientist Award (from 21.2.95) Dr Y. OMORI, Research Training Fellowship and Special Training Award (from 1.9.94) Dr A. OUHTIT, Special Training Award (from 28.3.95) Dr T. SAITO, Sapporo Medical College fellowship (from 1.11.95) Dr K. SASAKI, Special Training Award (19.11.93–30.11.95) Dr P. SILINGARDI, Fellowship from the Italian Government (until 31.12.93) Dr Z. WEIBIN, Research Training Fellowship (from 1 December 1995)
Laboratory Research Assistants	Mrs A.-M. AGUELON-PEGOURIES Miss N. MARTEL Mrs C. PICCOLI
Laboratory Technician	Miss M.P. PAPERIN (24.12.93–3.2.95)
Students	Mr. O. BERTRAND, Fellowship from the 'Association pour la Recherche sur le Cancer' (until 31.12.93) Miss E. HOLLAMS, Special Training Award (25.1.94–31.1.95) Mr L. JANSEN, European Science Foundation Fellowship (28.2.95–31.5.95) Miss M. KALLASSY, Fellowship from Claude-Bernard University (1.12.94–30.11.95) Mr. J.-C. LOZANO, Special Training Award (until 31.3.94)
Secretaries	Mrs C. FUCHEZ (until 31.12.94) Mrs C. DECHAUX

Common glasswashing service

Laboratory Aides	Mrs M. ESSERTEL Ms N. FARINA Miss M. MARANHAO Mrs S. VEYRE

Unit of Carcinogen Identification and Evaluation

Chief	Dr H. VAINIO (until 31.8.95)
Scientists	Dr D. McGREGOR Dr H. MØLLER (until 31.8.95) Mrs I. PETERSCHMITT (half-time) (until 31.10.94) Mr J. WILBOURN (acting chief from 1.9.95)
Visiting Scientist	Dr A. HALLIKAINEN (15.9.95–15.12.95) Dr P. WEBB (9.10.94– 20.7.95)
Technical Officer	Mrs C. PARTENSKY
Technical Assistants	Mrs M.-J. GHESS (until 30.6.95) Mrs A. MENEGHEL Mrs D. MIETTON Mrs J. MITCHELL
Student	Miss I. ERAGNE (17.1.94–15.5.94)
Secretary	Ms S. REYNAUD
Clerks	Mrs M. LEZERE Miss S. RUIZ

Programme of Radiation and Cancer (established January 1995)

Head	Dr E. CARDIS
Visiting Scientist	Dr D. GUO (from 1.10.95) Dr A. MYLVAGANAM (16.5.94–31.8.95)
Assistant (statistics)	Miss H. RENARD
Students	Dr M. HOURS Dr D. SOLE (1.10.95–31.12.95)
Secretary	Mrs B. ANDRIEUX (half-time) Mrs O. DRUTEL (half-time) (from 1.7.95)

Programme of Epidemiology for Cancer Prevention (established January 1995)

Head	Dr A.J. SASCO (joint appointment with INSERM)
Students	Dr R. AH-SONG, Special Training Award (1.9.93–30.6.95) Ms E. AMOROS, Special Training Award (1.5.94–31.8.94)

	Mr O. CHATARD, Special Training Award (1.5.93–30.6.95) Mr P. CHATARD, Special Training Award (until 31.7.93) Dr D. DEJOUR, Special Training Award (1.8.94–18.11.94) Mr P. DE MONCUIT, Special Training Award (13.6.94–15.9.94) Mr F.-R. DE SALVE-VILLEDIEU, Special Training Award (1.12.93–26.10.94) Ms H. GARCIA-GIANNOLI, Special Training Award (18.5.93–6.6.94) Ms I. GENDRE, Special Training Award (from 1.5.94) Dr G. GILBERT, Special Training Award (1.10.93–30.4.94) Ms P. NEDDAM, Interne en médecine du travail (1.2.93–30.9.94) Mr B. RACHET, Special Training Award (from 14.11.94) Mr E. SAAD, Interne en santé publique (1.11.94–31.10.95) Dr F. TORRESANI, Interne en médecine du travail (6.7.94–15.10.94)
Clerk	Mrs V. BENHAÏM-LUZON (16.5.94–29.12.95)
Secretary	Miss S. HAVER

Programme of Viral and Hereditary Factors in Carcinogenesis

Head	Dr G.M. LENOIR (joint appointment with the University of Lyon)
Visiting Scientists	Dr M. BILLAUD, Fondation pour la Recherche Médicale fellowship and CNRS post (until 1.6.95) Dr L. DENG, Research Training Fellowship and Ligue Nationale contre le Cancer fellowship (until 4.2.95) Dr M. MONTAGNA, Associazione Italiana per la Ricerca sul Cancro fellowship and Special Training Award (17.1.94–26.5.95) Dr M. ROSSEL, Ligue Nationale contre le Cancer fellowship and Special Training Award (5.7.93–1.6.95) Dr O. SEROVA, Research Training Fellowship and Fondation Mérieux fellowship Dr P. STOLBA (until 17.8.93)
Laboratory Technician	Mrs L. FOURNIER (31.10.94–30.11.94)
Students	Mr R. BACHELIER, Special Training Award (5.9.94–1.6.95) Ms S. CHAPPUIS, MRT fellowship (until 1.6.95) Ms M.C. CROZE, (1.8.94–31.8.94) Dr V. DUBOIS (from 8.5.95) Mr F. HEITZMANN, Ligue Nationale contre le Cancer, Comité départemental de l'Yonne fellowship and Special Training Award (from 13.10.93) Mr J. LAMARTINE Dr A. PASINI, Associazione Italiana per la ricerca sul cancro fellowship, Special Training Award and COTRAO fellowship (1.9.93–1.6.95) Ms N. PUGET, Special Training Award (from 5.9.94) Mr A. SOUABNI, Special Training Award (2.4.94–31.10.94)

Computing Service Group

Head/Computer Systems Manager	Mr M. SMANS
Computer Analyst/System Manager	Mr P. DAMIECKI
Scientific Software Manager	Ms B. CHARNAY (until 31.7.95)
Programme Analyst	Mr X. NGUYEN-DINH (until 30.11.93)
Computer Operator	Mrs B. KAJO (half-time)

Editorial and Publications Services

Head	Dr S. JONES (from 1.6.95)
Consultants	Mr G.E.A. ZIZKA (until 30.11.93) Miss K. LAMAN (18.7.94–12.9.94 Mr P. SARTRE (4.1.95–30.3.95)
Assistant (IARC Press)	Miss S. COTTERELL
Laboratory Technician (Photography)	Mr G. MOLLON
Clerks	Mr J. DECHAUX (until 31.10.94) Mrs M. MAINAUD Mrs A. ROMANOFF (until 29.12.94) Mrs J. THÉVENOUX

Library

Librarian	Miss H. MIIDO
Technical Assistant (Search Analyst)	Mrs M. COUDERT
Assistant (Library)	Mrs L. OSSETIAN

Division of Administration and Finance

Director	Mr H.R. CROCKETT (until 31.8.93) Mr M.P. JOHNSON
Administrative Assistant	Mrs J. MARTINEZ (until 30.6.95) Mrs D. MARCOU
Translation	
Translator	Dr N. GAUDIN
Secretary	Mrs A.-C. MORET
Personnel	
Personnel Officer	Mrs A. ESCOFFIER
Clerk	Mrs C. MOGENET
Social Adviser	Mrs M.A. VIOT-COSTER

Budget and Finance	
Finance Officer	Mr S. SAPRA (until 8.9.95)
	Mr A. MITRA (21.8.95–20.12.95)
Administrative Assistants	Mr C. AUGROS
	Mrs W. FEVRE-HLAHOLUK
	Mrs A. GESER (until 31.10.94)
Assistant (Accounting)	Mrs M. HERIN
Assistant (Payments)	Mrs F. ROMAGNAN
Secretary	Mrs A. RIVOIRE
Clerk (Cashier)	Mr D. HORNEZ
Clerk (Accounts)	Mrs D. LOMBARDO
Clerks (Finance)	Mrs F. FLORENTIN (half-time)
	Mrs A. SEGURET (half-time)
Administrative Services	
Administrative Services Officer	Mr G. GUILLERMINET
Administrative Assistant	Mrs R. SEXTIER
Clerk	Mrs M. LEPETIT
Switchboard Operator	Mrs R. KIBRISLIYAN
Driver	Mr J.-F. DURAND-GRATIAN
Ushers (Messenger)	Mr D. LAGARDE (until 31.10.94)
	Mr M. JAVIN
Maintenance Technicians	Mr M. BARBIEUX
	Mr M. BAZIN
	Mr J.-P. BONNEFOND
	Mr G. THOLLY
Assistant (Registry)	Mrs M. GREENLAND
Clerk (Registry)	Mrs L. VIGIER
Assistant (Supplies)	Mrs J. POPOFF
Clerks (Supplies)	Mrs M. FILIPPI
	Mrs L. GRAVIER (half-time) (until 31.12.94)
	Mr M. PRAT
Equipment Operator (Reproduction)	Mr D. GRAIZELY
Documents and Stenographic Pool (dissolved December 1994)	
Clerk-stenographer	Miss G. RAWLING (until 15.11.94)

Annex 4

SHORT-TERM VISITING SCIENTISTS AND TRAINEES

Visitors

Dr M. Alam, Unit of Descriptive Epidemiology, WHO Fellowship (21–26 March 1994)
Dr M. Almonte-Pacheco, Unit of Field and Intervention Studies (2 April–30 June 1995)
Mrs L. Banda, Unit of Descriptive Epidemiology (30 September–26 October 1993)
Mr K.S. Bandama, Unit of Descriptive Epidemiology, ICRETT Fellowship (6 September–6 October 1994)
Mr L. Barraud, Unit of Mechanisms of Carcinogenesis, Special Training Award (1 June–31 August 1994)
Dr M.T. Bassett, Unit of Descriptive Epidemiology (22 August–2 September 1995)
Dr V. Bigirimana, Unit of Descriptive Epidemiology, ICRETT Fellowship (11 April–7 May 1994)
Dr F.X. Bosch, Unit of Field and Intervention Studies (13–21 September 1994)
Mr D. Boturyn, Unit of Environmental Carcinogenesis (15–19 May 1995
Dr M.L. Bouhidel, Unit of Descriptive Epidemiology (22–29 December 1994)
Mr F. Bray, Unit of Descriptive Epidemiology, Special Training Award (23 September–8 December 1995)
Dr E. Buiatti, Unit of Field and Intervention Studies (17–30 November 1994 and 20–27 January 1995)
Dr J.-G. Chen, Unit of Descriptive Epidemiology, ICRETT Fellowship (29 September–29 October 1995)
Dr P. Cocco, Unit of Analytical Epidemiology (18–27 July 1994)
Dr M. Davidovich, Programme of Radiation and Cancer (23 March–4 April 1995)
Dr G.F. De Girolamo, Unit of Environmental Cancer Epidemiology (1 March–30 April 1995)
Ms S. Deimat, Programme of Epidemiology for Cancer Prevention (13 April–21 June 1995)
Dr G.F. De Girolamo, Unit of Environmental Cancer Epidemiology (1 March–30 April 1995)
Dr M. D'Errico, Unit of Mechanisms of Carcinogenesis (21 June–2 July 1993)
Dr A. Derventzi, Unit of Mechanisms of Carcinogenesis, Fellowship from the Association for International Cancer Research (4–15 July 1994)
Dr E. de Stefani, Unit of Descriptive Epidemiology (16–30 September 1993) and Unit of Environmental Cancer Epidemiology (28 March–8 April 1995)
Dr G. Enow-Orock, Unit of Descriptive Epidemiology, ICRETT Fellowship (22–29 December 1994)
Dr M. Far, Unit of Descriptive Epidemiology, WHO Fellowship (6–10 September 1993)
Dr Z. Fedorenko, Programme of Radiation and Cancer (9–20 May 1994)
Dr C. Fernando, Unit of Environmental Carcinogenesis (7–18 February 1994)
Ms L.Gibson, Unit of Descriptive Epidemiology (29 May–2 June 95)
Dr M.E. Gonsebatt, Unit of Environmental Carcinogens and Host Factors (4–13 November 1993)
Ms K. Gornoi, Unit of Descriptive Epidemiology (24 September–1 October 1995)
Ms M. Graupera, Unit of Descriptive Epidemiology, UICC Fellowship (15 November–15 December 1994)
Dr M. Hamdi-Cherif, Unit of Descriptive Epidemiology (18–22 July 1994)
Dr J. Hansen, Unit of Analytical Epidemiology (15 August–14 October 1994)
Dr M. Hergenhahn, Unit of Environmental Carcinogens and Host Factors (17–22 January 1994)
Dr J. Iscovich, Unit of Descriptive Epidemiology (23 January–13 February, 28 August–23 September 1994 and 26 September–18 October 1995)
Dr E. Ivanov, Unit of Descriptive Epidemiology (16–26 August 1995)
Dr V. Ivanov, Programme of Radiation and Cancer (9–20 May 1994)
Dr I.S. Kabba, Unit of Descriptive Epidemiology (10–30 April 1994)
Dr A. Kane, Unit of Carcinogen Identification and Evaluation and Unit of Environmental Cancer Epidemiology (3–21 January and 7 March–5 April 1995)
Mr S. Kané, Unit of Descriptive Epidemiology, ICRETT Fellowship (4 September –2 October 1995)

Dr M.-A. Kedda, Unit of Environmental Carcinogenesis (3–22 June 1995)
Professor A. Klein, Programme on Viral and Hereditary Factors in Carcinogenesis, Unit of Mechanisms of Carcinogenesis (25 July–24 September 1994)
Dr A. Konogorov, Programme of Radiation and Cancer (23 March–4 April 1995)
Dr E. Kure, Unit of Mechanisms of Carcinogenesis, European Science Foundation Fellowship (15 November–13 December 1993)
Ms B.A. Lashley, ICRETT Fellowship (16 September–1 October 1995)
Professor J. Little, Unit of Environmental Cancer Epidemiology (20–24 February 1995)
Dr J.L. Lliberia Blasco, Unit of Endogenous Cancer Risk Factors (4 July–4 August 1994)
Dr R. Maher, Unit of Descriptive Epidemiology (10–16 March 1995)
Dr A. Mathew, Unit of Descriptive Epidemiology (13–18 May 1994)
Dr E. Merler, Unit of Environmental Cancer Epidemiology (3–7 July 1995)
Dr F. Merletti, Unit of Analytical Epidemiology and Unit of Environmental Cancer Epidemiology (several short-term visits)
Dr V. Moreno, Unit of Field and Intervention Studies (16–23 August 1994)
Ms L. Murgue, Programme of Epidemiology for Cancer Prevention (27 March–14 April 1995)
Dr B. Nahavandian, Unit of Descriptive Epidemiology, WHO Fellowship (9–13 May 1994)
Miss S. Nambooze, Unit of Descriptive Epidemiology (21 March–8 April 1994)
Dr A. Nandakumar, Unit of Descriptive Epidemiology (29 August–11 September 1993)
Dr N. Nemoto, Unit of Multistage Carcinogenesis, ICRETT Fellowship (29 October–25 November 1993)
Dr H. Nukaya, Unit of Endogenous Cancer Risk Factors (10 July–11 September 1995)
Dr F. E. Nze-Nguema, Unit of Descriptive Epidemiology, ICRETT Fellowship (29 March–27 April 1995)
Mrs S. Obrecht-Pflumio, Unit of Environmental Carcinogenesis (11–26 July and 16–27 August 1994)
Ms M. Ocké, Programme of Nutrition and Cancer, Unit of Analytical Epidemiology (28 November–23 December 1994)
Dr A Okeanov, Programme of Radiation and Cancer (9–20 May 1994)
Ms S. Osendarp, Programme of Nutrition and Cancer, Unit of Analytical Epidemiology (16–23 April 1994)
Dr D. Palli, Unit of Descriptive Epidemiology (12–16 June 1995)
Professor O. Pelkonen, Unit of Mechanisms of Carcinogenesis, Fellowship from the European Programme for Collaboration on Science and Technology (21 November–9 December 1994)
Ms F. Peyrot, Programme of Epidemiology for Cancer Prevention (3–28 January 1994)
Dr Pham Hoang Anh, Unit of Descriptive Epidemiology (31 October–18 November 1994)
Dr S. Piperakis, Unit of Mechanisms of Carcinogenesis, Fellowship from the Association for International Cancer Research (4–15 July 1994)
Dr A. Prisyazhnyuk, Programme of Radiation and Cancer (9–20 May 1994)
Dr K. Pritchard, Unit of Carcinogen Identification and Evaluation (4 May–31 July 1995)
Dr P.R. Prussia, Unit of Descriptive Epidemiology, ICRETT Fellowship (3–14 October 1994)
Dr Quoc Nguyen Manh, Unit of Descriptive Epidemiology (11–23 July 1994)
Dr E. Rastoptchine, Programme of Radiation and Cancer (9–20 May 1994)
Dr R. Ratanavikrant, Unit of Field and Intervention Studies and Unit of Descriptive Epidemiology (1–30 August 1993 and 25 May–18 June 1994)
Dr L. Reyes, Unit of Descriptive Epidemiology (29 October–17 November 1995)
Dr M. Ronderos, Unit of Field and Intervention Studies (1–11 September 1993 and 7–17 December 1994)
Dr M.A. Rossing, Unit of Descriptive Epidemiology (15–19 November 1993)
Dr E. Sala, Unit of Descriptive Epidemiology (5–11 June 1994)
Dr R. Saracci, Unit of Environmental Cancer Epidemiology (several short-term visits)
Dr P. Schmezer, Unit of Environmental Carcinogens and Host Factors (24–28 November 1993)
Dr L. Simonato, Unit of Analytical Epidemiology and Unit of Environmental Cancer Epidemiology (several short-term visits)

Mrs B. Sindikubwabo, Unit of Descriptive Epidemiology, UICC Fellowship (23 September–3 October 1993)
Mr W. Sobala, Unit of Environmental Cancer Epidemiology (10–14 April 1995)
Dr A. Sobolev, Programme of Radiation and Cancer (9–20 May 1994)
Mr D. Sossai, Unit of Environmental Carcinogenesis (14–25 March and 5 April–20 May 1994)
Dr S. Sriamporn, Unit of Descriptive Epidemiology (8 April–8 May 1994 and 11–22 October 1995)
Dr P. Srivatanakul, Unit of Descriptive Epidemiology, Unit of Analytical Epidemiology and Unit of Carcinogen Identification and Evaluation (25 May–18 June 1994)
Mr R. Swaminathan, Unit of Descriptive Epidemiology, ICRETT Fellowship (30 May–30 June 1995)
Dr A.G. Tardon, Unit of Environmental Cancer Epidemiology (22 May–15 July 1995)
Dr K. Tehrani, Unit of Descriptive Epidemiology, WHO Fellowship (6–10 September 1993)
Dr G. Tolochko, Programme of Radiation and Cancer (23 March–4 April 1995)
Dr S.S. Torbaghan, Unit of Descriptive Epidemiology, WHO Fellowship (15–19 May 1995)
Dr D. Torchard, Programme on Viral and Hereditary Factors in Carcinogenesis, Unit of Mechanisms of Carcinogenesis (28 February–3 March 1994)
Dr V.S. Turusov, Programme of Nutrition and Cancer, Unit of Analytical Epidemiology (4–10 December1994) and Unit of Environmental Carcinogenesis (12 November–10 December 1995)
Dr M. Ueda, Unit of Multistage Carcinogenesis (1 November–28 December 1995)
Dr C. Varghese, Unit of Descriptive Epidemiology (26–30 July 1993)
Dr A. Vincent, Programme on Viral and Hereditary Factors in Carcinogenesis, Unit of Mechanisms of Carcinogenesis (22 May–31 July 1995)
Ms E. Welp, Unit of Environmental Cancer Epidemiology (1 June –31 July 1995)
Dr Yong Bing Xiang, Unit of Descriptive Epidemiology, ICRETT Fellowship (19 September–18 October 1995)

Trainees

Miss G. Barbeaux, Unit of Multistage Carcinogenesis (29 May–15 July 1995)
Ms E. Borrel, Programme of Epidemiology for Cancer Prevention (12 June–7 September 1995)
Miss N. Bouheddou, Unit of Mechanisms of Carcinogenesis (7–11 March 1994)
MissM. Bouteiller, Unit of Multistage Carcinogenesis (1 July–31 August 1993)
Ms K. Brömen, Unit of Environmental Cancer Epidemiology (29 June–4 August 1995)
Mr J. Chandezon, Programme of Epidemiology for Cancer Prevention (27 July–30 September 1994)
Miss E. Charlot, Unit of Environmental Carcinogenesis (20–24 February 1995)
Mr P. Chatard, Programme of Nutrition and Cancer, Unit of Analytical Epidemiology, Special Training Award (1–31 August 1993)
Ms A. Chaussy, Unit of Environmental Cancer Epidemiology (31 July–29 September 1995)
Miss N. Chossat, Unit of Environmental Carcinogens and Host Factors (2 November–30 December 1993)
Ms C. Cour, Programme on Viral and Hereditary Factors in Carcinogenesis, Unit of Mechanisms of Carcinogenesis (24 April–1 June 1995)
Miss C. Cousson, Unit of Mechanisms of Carcinogenesis (5 April–6 May 1994)
Miss C. Debacker, Unit of Environmental Carcinogenesis (9 January–3 February 1995)
Mr L. Descroix, Programme of Nutrition and Cancer, Unit of Analytical Epidemiology (24 May–31 July 1994)
Ms D. Dubois, Programme of Epidemiology for Cancer Prevention (29 May–23 June 1995)
Miss V. Fataccioli, Unit of Endogenous Cancer Risk Factors (24 January–14 February 1995)
Miss P. Gaildrat, Unit of Multistage Carcinogenesis (18 April–13 May 1994)
Miss I. Gaucher, Unit of Environmental Carcinogenesis (6 June–28 August 1995)
Ms N. Gillet, Unit of Analytical Epidemiology (14 March–28 April 1994)
Ms I. Glinka, Programme of Epidemiology for Cancer Prevention (2–20 November 1993)
Mr R. Guérin, Unit of Mechanisms of Carcinogenesis (6–10 December 1993)
Ms C. Jégou, Programme of Epidemiology for Cancer Prevention (14 April–18 June 1994)
Ms A. Koeniger, Unit of Field and Intervention Studies (1 June–31 July 1994)

Miss M. Koppe, Unit of Mechanisms of Carcinogenesis (22 June–2 July 1993)
Miss M. Lechevrel, Unit of Environmental Carcinogenesis (6–17 November 1995)
Ms M.G. Luciani, Unit of Mechanisms of Carcinogenesis (1–31 August 1995)
Ms M. Marsot, Programme of Epidemiology for Cancer Prevention (22 May–10 June 1995)
Mr A. Popoff, Unit of Environmental Carcinogenesis (24–28 April 1995)
Ms W. Porini, Programme of Epidemiology for Cancer Prevention (6 March–31 March 1995)
Ms D. Prevot, Programme on Viral and Hereditary Factors in Carcinogenesis, Unit of Mechanisms of Carcinogenesis (1 July–31 August 1994)
Ms G. Racine, Unit of Environmental Cancer Epidemiology (from 15 November 1995)
Ms P. Raynaud, Programme of Epidemiology for Cancer Prevention (24 April–12 May 1995)
Ms N. Reybaud, Programme of Epidemiology for Cancer Prevention (2–27 January 1995)
Ms S. Rivoire, Unit of Endogenous Cancer Risk Factors (13–30 November 1995)
Miss N. Ronzon, Unit of Endogenous Cancer Risk Factors (16 January–17 February 1995 and 1 September–5 October 1995))
Mr S. Salanon, Programme of Epidemiology for Cancer Prevention (7 November–2 December 1994)
Ms M. Sinerchia, Unit of Environmental Cancer Epidemiology (2–27 October 1995)
Ms I. Sipos, Programme on Viral and Hereditary Factors in Carcinogenesis, Unit of Mechanisms of Carcinogenesis (27 March–29 April 1995)
Ms K. Soldan, Unit of Descriptive Epidemiology, Special Training Award (26 September–30 November 1994)
Mr A. Souabni, Unit of Mechanisms of Carcinogenesis (7 June–7 July 1993)
Ms N. Sri-Akajunt, Unit of Analytical Epidemiology (25 July–2 August 1994)
Mr P.-C. Vaintrub, Programme of Epidemiology for Cancer Prevention (30 May–24 June 1994)

Annex 5

RESEARCH AGREEMENTS BETWEEN IARC AND VARIOUS INSTITUTIONS
1 July 1993–31 December 1995

Cancer registries

DEB/73/16	International Association of Cancer Registries (Provision of a secretariat and other supporting services)
DEP/87/01	Hanoi Cancer Institute, Hanoi, Viet Nam (Cancer Registry of Hanoi)
DEP/87/02	National Institute of Public Health, Bamako, Mali (Cancer Registry of Mali)
DEP/89/10	Department of Pathology, National University of Trujillo, Trujillo, Peru (Cancer Registry of Trujillo)
DEP/89/11	Department of Epidemiology and Preventive Medicine, University Hospital, Sétif, Algeria (Cancer Registry of Sétif)
DEP/91/02	South Pacific Commission, Noumea, New Caledonia (Cancer registration in the Pacific area)
DEP/91/04	National Centre of Anatomo-Pathology, Faculty of Medicine, University of Conakry, Conakry, Guinea (Cancer Registry of Conakry)
DEP/91/05	Department of Pathology, Makerere University Medical School, Kampala, Uganda (Kampala Cancer Registry)
DEP/92/01	Oncology Center of Ho Chi Minh City, Republic of Vietnam (Population-based cancer registry for the city of Ho Chi Minh)
DEP/92/02	Argentinian Association on Education and Prevention of Cancer, Bahia Blanca, Argentina (Cancer registry of Southern Buenos Aires Province)
DEP/92/05	National University of Rwanda, Butaré, Rwanda (Cancer Registry of Butaré)
DEP/92/08	Zimbabwe Cancer Registry, Harare, Zimbabwe (Zimbabwe Cancer Registry)
DEP/92/10	Faculty of Medical Sciences, University of Niamey, Niamey, Niger (Cancer Registry of Niger)
DEP/92/15	National Cancer Institute, Bangkok, Thailand (IARC support for a monograph on "Cancer in Thailand" and a workshop on "The Cancer Control Program: Putting Science into Practice")
DEP/92/16	Barshi Rural Cancer Registry, Ashwini Rural Cancer Research and Relief Society, Barshi, India (Barshi Rural Cancer Registry)
DEP/93/01	National Cancer Registry of Uruguay, National Institute of Oncology, Montevideo, Uruguay (National Cancer Registry of Uruguay)
DEP/93/03	Zimbabwe Cancer Registry, Harare, Zimbabwe (Cancer Registry of Zimbabwe)
DEP/93/04	National University of Rwanda, Butaré. Rwanda (Cancer Registry of Butaré Prefecture)

DEP/93/05	Queen Elizabeth Hospital, Blantyre, Malawi (Cancer Registry of Blantyre)
DEP/93/08	Comprehensive Cancer Centre North, Groningen, Netherlands (European Network of Cancer Registries: Mini-fellowships programme)
DEP/93/09	Danish Cancer Society, Copenhagen, Denmark (European Network of Cancer Registries: Course in Cancer Registration)
DEP/93/12	Regional Cancer Centre, Trivandrum, India (Establishment of a surveillance system to monitor cancer incidence and mortality in Trivandrum, Kazhakuttam and Chirayinkil development blocks in Kerala, India)
DEP/94/11	National Committee for the Fight Against Cancer in Cameroon, Yaoundé, Cameroon (Establishment of a population-based cancer registry in Yaoundé)
DEP/94/12	Makerere University Medical School, Kampala, Uganda (Kampala Cancer Registry)
DEP/94/14	Escuela Andaluza de Salud Publica, Granada, Spain (European Network of Cancer Registries: Course in cancer registration)
DEP/95/01	Centre Hospitalier Universitaire de Treichville, Abidjan, Côte d'Ivoire (Etablissement d'un registre du cancer du sein de la population d'Abidjan)
DEP/95/06	Christian Fellowship Community Health Centre, Ambilikkai, Tamil Nadu, India (Computerisation of the population-based cancer registry in Ambilikkai for monitoring of cancer control)
DEP/95/07	Gujarat Cancer and Research Institute, Gujarat, India (Computerisation of the population-based cancer registry for Ahmedabad, for improvement of registry operations)

Incidence studies

DEP/92/03	Lithuanian Oncological Centre, Vilnius, Lithuania (European childhood leukaemia/lymphoma incidence study (ECLIS))
DEP/92/04	Estonian Cancer Registry, Institute of Experimental & Clinical Medicine, Tallinn, Estonia (European childhood leukaemia/lymphoma incidence study (ECLIS))
DEP/92/12	Institute of Hematology, Minsk, Belarus (European childhood leukaemia/lymphoma incidence study (ECLIS))
DEP/92/13	Petrov Research Institute of Oncology, St Petersburg, Russian Federation (European childhood leukaemia/lymphoma incidence study (ECLIS))
DEP/92/14	Research Institute of Pediatric Hematology, Moscow, Russian Federation (European childhood leukaemia/lymphoma incidence study (ECLIS))
AEP/93/01	Israel Center for Registration of Cancer and Allied Diseases, Jerusalem, Israel (Cancer risk in a cohort of immigrants from the former Soviet Union to Israel)
DEP/94/01	Latvian Cancer Registry, Riga, Latvia (European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))
DEP/94/06	Institute of Hygiene and Public Health, Bucharest, Romania
DEP/95/11	(European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))
DEP/94/07	Cancer Research Institute, Bratislava, Slovakia
DEP/95/12	(European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))
DEP/94/08	Institute of Hematology, Minsk, Belarus
DEP/95/15	(European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))
DEP/94/09	Department of Epidemiology and Cancer Control, National Oncological
DEP/95/13	Centre, Sofia, Bulgaria (European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))
DEP/95/14	Research Institute for Pediatric Hematology, Moscow, Russian Federation (European Childhood Leukaemia/Lymphoma Incidence study (ECLIS))

Studies of cancer survival

DEP/93/11	National Institute of Oncology and Radiobiology, Havana, Cuba (Estimation of population-based survival rates for various cancers in Cuba)
DEP/94/02	Cancer Institute, Madras, India (Estimation of population-based survival rates for various cancers in Madras)
DEP/94/03	Indian Cancer Society, Bombay, India (Estimation of population-based survival rates for various cancers in Bombay)
DEP/94/05	Regional Cancer Centre, Trivandrum, India (Estimation of survival from major cancers in Kerala)
DEP/95/10	Cancer Unit, Faculty of Medicine, Khon Kaen University, Thailand (Evaluation of follow-up methods in the estimation of survival from cancer in Khon Kaen Province)

Second cancers and DNA damage following chemotherapy

BRI/89/07	TNO Medical Biological Laboratory, Rijswijk, The Netherlands (Study of the relationship between cis-platinum adduct levels and therapeutic efficacy in testicular cancer patients)
BRI/89/09	Biological Research Center, National Hellenic Research Foundation, Athens, Greece (Detection of methylation adducts in Hodgkin's disease patients)
BRI/89/10	Department of Radiation Genetics and Chemical Mutagenesis, Sylvius Laboratories, State University of Leiden, Leiden, The Netherlands (Measurements of micronuclei in lymphocytes as an indication of DNA damage following chemotherapy in Hodgkin's disease patients)
BRI/89/11	Institut Gustave Roussy, Villejuif, France (Pilot study for the detection of methylation adducts in lymphoma patients)
BRI/91/02	Lymphoma Clinic, Universi ty of Athens School of Medicine, Athens, Greece (Pilot study for the detection of methylation adducts, oncogene mutation, micronuclei and DNA repair in Hodgkin's disease patients treated with MOPP/ABV chemotherapy)
AEP/94/08	MRC Toxicology Unit, University of Leicester, United Kingdom (Development of an assay for detecting DNA formed by nitrogen mustard drugs used in Hodgkin's disease chemotherapy)

Studies on breast cancer

DEB/86/10	Naylor Dana Institute for Disease Prevention, American Health Foundation , Valhalla, NY, USA (Breast cancer and hormonal profile in Chinese and Chinese-American women)
DEB/86/14	Naylor Dana Institute for Disease Prevention, American Health Foundation, Valhalla, NY, USA (Biochemical analyses for studies of (a) urinary levels of oestrogens and progesterone in relation to passive smoking in nonsmoking women, and (b) breast cancer and hormonal profile in males)
DEP/92/07	Rizal Cancer Registry, Rizal Medical Centre, Manila, Philippines (Feasibility of screening for breast cancer i n the population of Metropolitan Manila)
DEP/95/02	Department of Health, Manila, Philippines (Randomized controlled trial of breast cancer screening by physical examination in Manila)

DEP/95/03	Rizal Cancer Registry, Rizal Medical Center, Manila, Philippines (Enhanced surveillance of breast cancer incidence and mortality in the population of 12 municipalities of the greater Manila area)
ECP/95/01	Geneva Cancer Registry, Geneva, Switzerland (Etude du risque de deuxièmes cancers spécifiques après cancer du sein)
ECP/95/02	Association pour le développement et l'épidémiologie de santé publique, Strasbourg, France (Etude du risque de deuxièmes cancers spécifiques après cancer du sein)

Studies on cervical cancer

DEB/85/17	Foundation for Higher Education, Cali, Colombia (Case-control study on risk factors for cervical cancer)
FIS/90/10	Clinical Epidemiology Unit, College of Medicine, University of the Philippines Manila, Philippines (Multicentric case-control study on cervical cancer)
FIS/92/01	Department of Immunology and Infectious Diseases, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Maryland, USA (International biological study on cervical cancer: polymerase chain reaction (PCR) testing of specimens with histology confirming the presence of malignancy)
FIS/92/02	Department of Experimental Virology, Institute of Hematology and Blood Transfusion, Prague, Czech Republic (Role of HPV in the development of cervical cancer)
FIS/93/01	Department of Pathology, Free University Hospital, Amsterdam, The Netherlands (Multicentric case control study on cervical cancer)
FIS/93/03	Laboratory of Microbiology and Immunology, Institute of Virology, Tours, France (Role of HPV DNA in the development of cervical cancer)
DEP/95/05	Regional Cancer Centre, Trivandrum, Kerala, India (Evaluation of unaided visual inspection, cervicoscopy and pap smear in screening for cervical cancer)
FIS/95/01	Division de Epidemiologia, Instituto Nacional de Cancerologia, Bogotá, Colombia (Cohort study on human papillomavirus and cervical cancer)
FIS/95/02	Department of Immunology and Infectious Diseases, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, MD, USA (Cohort study on human papillomavirus and cervical cancer)

Studies on liver cancer

DDI/92/01	Medical Research Council, London, UK (Gambia Hepatitis Intervention Study)
FIS/87/01	National Cancer Institute, Bangkok, Thailand (Cohort study of HBsAg carriers in Bangkok)
DEP/92/09	Cancer Unit, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand (Prospective study on the etiology of liver cancer in Northeastern Thailand)
DEP/93/07	The Cancer Unit, Faculty of Medicine, Khon Kaen University, Thailand (Association between *O. viverrini* and coumarin 7-hydroxylation in humans)
MCA/93/01	Research Division, National Cancer Institute, Bangkok, Thailand (Investigation of expression of hepatic carcinogen-metabolising enzymes in the Thai population)

MCA/93/05 Institut de Recherches et de Biologie Appliquée de Guinée (IRBAG), Kindia, République de Guinée
(Enquête sur l'exposition aux facteurs de risque de carcinome hépatocellulaire en Guinée (Afrique occidentale))

MCA/95/01 Laboratoire de Biologie Moléculaire, INSERM U370, Paris, France
(Etude des échantillons pour la détection du virus de l'hépatite C par des tests sérologiques (ELISA et RIBA) et moléculaires (PCR))

Studies on nutrition and on cancer of the gastrointestinal tract

DEB/84/01 Singapore Cancer Registry, Department of Pathology, University of Singapore, Singapore
(Development of methodology for the conduct of diet-directed case-control studies in Singapore)

AEP/88/02 Department of Epidemiology and Statistics, Hospital San Jaume i Santa Magdalena, Mataro, Spain
(Case-control study on stomach cancer and diet)

FIS/90/12 Cancer Control Center, San Cristobal, Venezuela
(Etiology and prevention of stomach cancer in Venezuela)

AEP/93/02 Institute of Epidemiological and Clinical Research, Mataró, Spain
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/03 Department of Health, Planning and Order, Government of Navarra, Pamplona, Spain
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/04 Health Administration of Guipuzcoa San Sebastian, Spain
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/05 Andalusian School of Public Health, Granada, Spain
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/06 Department of Epidemiology, Health Council, Murcia, Spain
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/07 Department of Health Planning, Regional Administration of Public Health, Oviedo, Spain
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/08 Medical Research Council Biostatistics Unit, University of Cambridge, UK
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/09 Imperial Cancer Research Fund, Cancer Epidemiology Unit, Radcliffe Infirmary, Oxford, United Kingdom
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/10 German Research Cancer Centre, Division of Epidemiology, Heidelberg, Germany
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/11 Department of Nutrition and Biochemistry, Athens School of Public Health, Athens, Greece
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/12 Department of Epidemiology, University of Utrecht, The Netherlands
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/13 Department of Epidemiology, National Institute of Public Health and Environmental Protection (RIVM), Bilthoven, The Netherlands
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/14 Cancer Epidemiology Research Unit (U.351), National Institute for Health and Medical Research (INSERM), Institut Gustave Roussy, Villejuif, France
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/15 Department of Epidemiology, National Institute for Research and Treatment of Cancer, Milan, Italy
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/16 Ragusa Cancer Registry, Italian League Against Cancer, Ragusa, Sicily, Italy
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/17 Department of Biomedical Sciences and Human Oncology, University of Turin, Turin, Italy
(European prospective investigation into cancer and nutrition (EPIC))

AEP/93/20 Unit of Epidemiology, Centre for Preventive Oncology (CSPO), Florence , Italy
(European prospective investigation into cancer and nutrition (EPIC))

FIS/93/02 Institute of Health Investigations, San José, Costa Rica
(Aetiology and prevention of stomach cancer in Costa Rica)

NTR/95/01 Malmö Diet and Cancer Study, Malmö, Sweden
(European Prospective Investigation into Nutrition and Cancer (EPIC))

FIS/93/04 The First Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Japan
(Serum pepsinogen levels and precancerous lesions of the stomach)

FIS/93/05 Department of Gastroenterology, Free University Hospital, Amsterdam, The Netherlands
(Case-control study on stomach cancer in Venezuela: role of *H. pylori* and pepsinogens)

Studies of brain tumours

AEP/93/22 Lithuanian Cancer Registry, Vilnius, Lithuania
Brain tumours in children in Lithuania

Studies of oral cancer

DEP/93/10 National Institute of Oncology and Radiobiology, Havana, Cuba
(Case-control evaluation of oral visual inspection in the control of oral cancer in Cuba

DEP/95/04 Jinnah Postgraduate Medi cal Centre, Karachi, Pakistan
(Case-control study to evaluate the role of chewing areca nut/betel quid without tobacco and human papilloma virus (HPV) in the causation of oral cancer in Karachi, Pakistan

Studies on occupational caneer

DIR/87/02 Department of Biomedical Science and Human Oncology, University of Turin, Italy
(Study on early lesions produced by low environmental exposures [passive smoking and pollution] and by low levels of occupational exposures)

AEP/90/04 National Institute of Public Heal th and Environmental Protection, Bilthoven, The Netherlands
(IARC international register of workers exposed to phenoxy acid herbicides and their contaminants)

AEP/90/07 National Centre for Scientific Research (CNRS). Paris, France
(International study of cancer risk in biology research laboratory workers in Europe)

AEP/90/10 United Kingdom Co-ordinating Committee on Cancer Research, London, UK
(International study of cancer risk in biology research laboratory workers in Europe)

AEP/90/12	Institute of Pathology, University of Oslo, Oslo, Norway (International study of cancer risk in biology research laboratory workers in Europe)
AEP/90/13	Department of Epidemiology, Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden (International study of cancer risk in biology research laboratory workers in Europe)
AEP/90/14	TEAGASC, Agriculture and Food Development Authority, Dublin, Ireland (International study of cancer risk in biology research laboratory workers in Europe)
AEP/90/16	National Institute of Health and Medical Research (INSERM), Villejuif, France (International study of cancer risk in biology research laboratory workers in Europe)
AEP/91/01	Atomic Energy Agency, Paris, France (International study of cancer risk in biology research laboratory workers in Europe)
AEP/91/02	Institute of Occupational Health, Helsinki, Finland (International study of cancer risk in biology research laboratory workers in Europe)
AEP/91/03	National Institute of Health and Medical Research, Le Vesinet, France (International study of cancer risk in biology research laboratory workers in Europe)
AEP/92/01	Danish Cancer Registry, Danish Cancer Society, Copenhagen, Denmark (IARC International Register of Workers exposed to Phenoxy Acid Herbicides and their Contaminants)
AEP/92/06	National Institute of Oncology, Montevideo. Uruguay (Case-control study to evaluate the importance of exposures in the occupational environment for the occurrence of cancer in Uruguay)
AEP/92/07	Department of Social Medicine, Faculty of Medicine, Federal University of Pelotas, Pelotas, Brazil (International cancer study among pulp and paper industry workers)
AEP/92/09	Department of Epidemiology, National Institute for Research and Treatment of Cancer, Milan, Italy (International study of cancer risk in biology research laboratory workers)
AEP/92/13	Municipal Institute of Medical Research, Barcelona, Spain (International cancer study among pulp and paper industry workers)
AEP/92/14	Institute of Occupational Medicine, WHO Collaborating Centre for Occupational Health, Lodz, Poland (International cancer study among pulp and paper industry workers)
AEP/93/18	Institute of Occupational Health, Helsinki, Finland (International cancer study among pulp and paper industry workers)
AEP/93/19	Department of Occupational Medicine, Sahlgren Hospital, University of Gothenburg, Sweden (Multicentric study on European mercury workers)
AEP/93/21	Wellington School of Medicine, University of Otago, New Zealand (IARC International register of persons exposed to phenoxy acid herbicides and their contaminants)
AEP/93/23	Institute of Environmental and Occupational Medicine, University of Aberdeen, United Kingdom (Man-made mineral fibres case-referent pilot study: Occupational hygiene assessment)
AEP/93/24	Institute of Oncology 'Angel H. Roffo', Buenos Aires, Argentina (Case-control study to evaluate the importance of exposures in the occupational environment for the occurrence of lung cancer in Argentina)
AEP/93/25	Institute of Oncology, Hospital Duran i Reynals, Barcelona, Spain (Socio-economic factors and cancer: Meeting 25–26 May 1994, Barcelona)
AEP/93/29	Institute of Carcinogenesis, Moscow, Russian Federation (European study of workers exposed to mercury)
AEP/93/30	Epidemiology Unit, Department of National Health and Population Development, Johannesburg, South Africa (Cancer among pulp and paper industry workers in Swaziland)

AEP/93/31	Hospital Cancer Registry, Regional Cancer Centre, Trivandrum, India (Case-control study on the associations between occupational exposure and neoplasms of the lung and the lymphatic and hematopoietic system)
AEP/93/33	Hospital Cancer Registry, Tata Memorial Hospital, Bombay, India (Case-control study on the associations between occupational exposure and neoplasms of the lung and the lymphatic and hematopoietic system)
AEP/93/34	Department of Epidemiology, Harvard School of Public Health, Boston, Mass. USA (Autopsy study in relation to air pollution and other environmental factors)
AEP/94/01	Frédéric Joliot-Curie National Research Institute for Radiobiolgy and Radiohygiene, Budapest, Hungary (International Collaborative Study on Cancer Risk among Nuclear Industry Workers)
AEP/94/02	Institute of Hygiene and Epidemiology, Trnava, Slovak Republic (International Collaborative Study on Cancer Risk among Nuclear Industry Workers)
AEP/94/03	Institute of Oncology, Ljubljana, Slovenia (Occupational Cancer among European Workers (EUROC))
AEP/94/04	Institute of Occupational Medicine, Lodz, Poland (Occupational Cancer among European Workers (EUROC))
AEP/94/05	Masaryk Memorial Cancer Institute, Brno, Czech Republic (Occupational Cancer among European Workers (EUROC))
AEP/94/07	Department of Epidemiology, Institut Municipal d'Investigacio Medica, Barcelona, Spain (Cohort study of workers in a pulp and paper mill and feasibility phase of a cohort study among textile workers)
AEP/94/09	Cancer Institute, Adyar, Madras, India (Case-control study on the associations between occupational exposure and neoplasms of the lung and the lymphatic and hematopoietic system)
AEP/94/10	Postgraduate Institute of Medical Education and Research, Department of Pulmonary Medicine, Changdigarh, India (International collaborative study on lung cancer)
AEP/94/11	Occupational Hygiene Programme, University of British Columbia, Vancouver, Canada (Re-analysis of cohort and case-control studies on cancer risk among workers in the wood and leather industries)
DEP/94/13	National Cancer Institute, Bangkok, Thailand (Case-control study of lung cancer in relation to environmental exposures in Lampang Province)
ECE/95/01	Epidemiology Institute, GSF Forschungszentrum fur Umwelt und Gesundheit, Oberschleissheim, Germany (Environmental exposures and lung cancer in non-smokers)
ECE/95/02	Bremen Institute for Prevention Research and Social Medicine, Bremen, Germany (Environmental exposures and lung cancer in non smokers)
ECE/95/03	Cancer Epidemiology Unit, University of Turin, Italy (Environmental exposures and lung cancer in non-smokers)
ECE/95/04	Venetian Tumour Registry, Padua, Italy (Environmental exposures and lung cancer in non smokers)
ECE/95/05	Associazione Ricerca Epidemiologica, Rome, Italy (Environmental exposures and lung cancer in non-smokers)
ECE/95/06	Department of Medical Statistics, Institut Gustave Roussy, Villejuif, France (Environmental exposures and lung cancer in non-smokers)
ECE/95/07	Department of Epidemiology and Public Health, Institut Municipal d'Investigacio Medica, Barcelona, Spain (Estimation of the burden of occupational cancer in Europe)

ECE/95/08 Institute of Occupational Health, Helsinki, Finland
(Environmental exposures and lung cancer in non-smokers)

ECE/95/09 Equipe de Santé Publique, Hôpital Maisonneuve-Rosemont, Montreal, Canada
(Feasibility study of cancer risk among textile workers)

ECE/95/10 Cancer Registry of Norway, Oslo, Norway
(Estimation of the burden of occupational cancer in Europe)

Studies on the effects of active and passive smoking

DEP/89/12 Tata Institute of Fundamental Research, Bombay, India
(Prospective study on tobacco-related cancers and other diseases in the city of Bombay)

AEP/93/26 Cancer Registry of the Venetian Region, Padova, Italy
(Case control study on passive smoking and lung cancer)

AEP/93/27 Hospital Centre, Pneumology Department, Vila Nova de Gaia, Portugal
(International collaborative study on lung cancer in non-smokers)

Studies on chemical carcinogenesis

DEC/81/35 National Institute of Hygiene, Budapest, Hungary
(Long-term carcinogenicity testing of environmental chemicals)

DEC/84/01 Research Department, National Board of Occupational Safety and Health, Solna, Sweden
(Long-term carcinogenicity testing of environmental chemicals)

DEC/86/07 Laboratory of Carcinogenic Substances, Oncological Research Centre, Moscow, Russian Federation
(Role of prezygotic events in increasing cancer risk in subsequent generations)

ECH/87/06 Laboratory of Microbiology, Faculty of Pharmacy, Marseille, France
(Studies of methods for degradation of chemical carcinogens)

CIE/92/01 Lithuanian Oncological Centre, Vilnius, Lithuania
(Carcinogenicity testing of sulfuric acid mists in rats)

ECH/92/04 Cancer Research Centre, Moscow, Russian Federation
(Effect of treatment with β-carotene, vitamins C and E and/or *anti-Helicobacter pylori* drugs on chronic gastritis)

MSC/92/01 Agrotechnological Research Institute, Wageningen, The Netherlands
(The role of biotransformation of chemicals in nongenotoxic carcinogenesis)

MSC/92/02 Brunel University, Human Cancer Genetics Unit, Uxbridge, UK
(Induction of the infinite self-renewal (ISR) phenotype as an objective test endpoint for the detection of nongenotoxic carcinogens)

MSC/92/03 Institut du Cancer et Immunogénétique, Laboratoire de Pharmacologie cellulaire et moléculaire, Villejuif, France
(The relationship between ornithine decarboxylase (ODC) activity and carcinogenic process)

MSC/92/04 Imperial Chemical Industries, Central Toxicology Laboratory, Macclesfield, UK
(Study on the mechanisms by which nongenotoxic chemicals produce cancer in the rodent liver)

MSC/92/05 Institute for Cancer Research, Laboratory for Environmental and Occupational Cancer, Oslo, Norway
(The importance of gap junctional intercellular communication and growth factors in nongenotoxic mechanisms of carcinogenesis)

MSC/92/06	Institute of Toxicology, University of Würzburg, Würzburg, Germany (The mechanisms of cell transformation using the SHE cell system as a model)
MSC/92/07	National Institute of Cancer Research, Laboratory of Chemical Carcinogenesis, Genoa, Italy (The mechanistic role of changes in pattern and morphological organization of proteins of the nuclear matrix and other physicochemical parameters related to chromatin conformation)
MSC/92/08	Istituto Superiore di Sanità, Laboratorio di Tossicologia Applicata, Rome, Italy (The possible effects of nongenotoxic carcinogens on cellular DNA replication)
ECH/93/01	Institut National de la Santé et de la Recherche Médicale (INSERM), Unité 271, Lyon, France (Marqueurs biologiques de l'exposition au chlorure de vinyle (CV) et mécanismes de la cancérogenèse induite par le CV)
EVC/94/02	Institute of Cancer Research, Haddow Laboratories, Belmont, Sutton, UK (Interlaboratory standadization and validation of DNA adduct postlabelling methods for human biomarker studies)
EVC/95/01	Plant Research Centre, Agriculture & Agri-Food Canada, Ottawa, Canada (Carcinogenic action of fumonisins)
MCA/93/02	Institut de Biologie Moléculaire et Cellulaire, CNRS, Strasbourg, France (Tetracycline forward mutation spectra (*E. coli*) by environmental relevant mutagens, N-substituted aryl compounds)
MCA/93/03	Sylvius Laboratory, Leiden University, Leiden, The Netherlands (Genetic action spectra in Drosophila *in vivo*)
MCA/93/04	Istituto Superiore di Sanità, Roma, Italy (Specificity of mutations induced by chemical carcinogens in the p53 gene of epithelial cell cultures from rat intestine)
MCA/94/01	Institute of Molecular and Cell Biology, Tartu University, Tartu, Estonia (Functional characterization of p53 oncoproteins expressed in naturally occurring tumours)
MCA/94/03	Sylvius Laboratory, Leiden University, Leiden, The Netherlands (Apurinic sites and oxidative adducts in DNA)
MCA/94/04	Laboratory of Nucleic Acid Lesions, Centre of Nuclear Studies, Grenoble, France (Urinary DNA adducts)
MCA/94/05	Faculty of Medicine, Brescia University, Brescia, Italy (The statistical descriptive analysis of host factors and biomonitoring endpoints)
MCA/94/06	Institute for Cancer Research, Norwegian Radium Hospital, Oslo, Norway (Genetic alterations in bladder cancer)
MPA/95/01	Biologisches Zentrallabor, University of Zürich, Switzerland (The establishement of transgenic mice as models for human astrocytic brain tumours)
MSC/93/01	The University of Western Australia, Nedlands, Australia (UV and skin cancer)
MSC/93/02	The Flinders University of South Australia, Bedford Park, Australia (The tumour promoting and progressing activity of Microcystis in mouse skin after initiation with UV-light)
MSC/93/03	Cancer Research Center of Hawaii, Honolulu, Hawaii, USA (p53 mutations in normal skin as predictors of melanoma risk and as markers of biologically effective sun exposure)
MSC/94/01	Human Cancer Genetics Unit, Brunel University, Uxbridge, UK (Key genetic and epigenetic events generating the rate-limiting cell immortalization event in human and rodent cell transformation)
MSC/94/02	Division of Differentiation and Carcinogenesis, DKFZ, Heidelberg, Germany (The role of epithelial mesenchymal interaction on genetic stability, and on transformation markers of keratinocytes in different stages of transformation)

MSC/94/03 Department of Radiation Genetics and Chemical Mutagenesis, University of Leiden, The Netherlands
(The development of an assay system for transformation of epithelial cells, on the comparison of immoralization of human and rodent skin keratinocytes and on the induction of genetic instability by carcinogens)

MSC/94/04 Department of Toxicology, National Institute of Occupational Health, Oslo, Norway
(The role of p53 gene in immortalization and transformation process of human epithelial cells)

Studies of soft-tissue sarcomas and non-Hodgkin lymphomas

DEP/92/06 Oncology Center of Ho Chi Minh, Republic of Vietnam
(Pilot study to investigate the feasibility of case-control studies of soft tissue sarcoma and non-Hodgkin's lymphoma in the south of Vietnam)

DEP/93/02 Oncology Center of Ho Chi Minh, Republic of Vietnam
(Case-control studies of soft tissue sarcoma and non-Hodgkin's lymphoma in the south of Vietnam)

DEP/93/06 The 10-80 Committee, Hanoi, Viet Nam
(Case-control studies on soft tissue sarcoma and non-Hodgkin's lymphoma in Viet Nam: Estimation of exposure index)

Annex 6

MEETINGS AND WORKSHOPS ORGANIZED BY IARC

European cancer leagues meeting (Cancer Research Campaign)	Lyon, 1 July 1993
Editorial board meeting for the Directory of On-going Research in Cancer Epidemiology 1994	Lyon, 30–31 August 1993
Meeting of the working group on standardization of 24-hour diet recall methods in the EPIC project	Lyon, 1–3 September 1993
Annual Meeting of the International Association of Cancer Registries	Bratislava, Slovak Republic, 13–15 September 1993
European Network of Cancer Registries Meeting	Bratislava, Slovak Republic, 16 September 1993
ECLIS Meeting	Bratislava, Slovak Republic, 17 September 1993
Multiple endocrine neoplasia type I working group	Lyon, 24 September 1993
Sixth Steering Committee meeting of the European Network of Cancer Registries	Lyon, 13–14 October 1993
Workshop on the quantitative estimation and prediction of cancer risks	Lyon, 18–22 October 1993
Meeting of the coordinating committee of the EPIC project	Lyon, 4–5 November 1993
Joint AACR/IARC International Conference on Interactions of Cancer Susceptibility Genes and Environmental Carcinogens	Lyon, 9–13 November 1993
International course on the detection of health hazards in human populations exposed to mutagens and carcinogens	Bangkok, Thailand, 15–26 November 1993
Course on safe handling of cytostatic drugs	Lyon, 30 November–1 December 1993
Course on safe handling of genotoxic substances in research laboratories	Lyon, 2–3 December 1993
Meeting to review priorities for future IARC Monographs	Lyon, 7–9 December 1993
Meeting of European investigators on cancer risk among service station attendants and related occupations	Lyon, 10 December 1993
Workshop on scientific communication	Lyon, 13–16 December 1993
Meeting of the Liaison Committee for the Asphalt Study	Lyon, 13 December 1993
Ad hoc working party meeting on refractory ceramic fibres	Lyon, 14 December1993
Working group meeting on tamoxifen for prevention controversy	Lyon, 14 December 1993
Meeting of the collaborators of the multi-centre study on cervical cancer	Lyon, 16–17 December 1993
Planning meeting for IARC Scientific Publication on human cancer risks due to low-level ionizing radiation	Lyon, 10–11 January 1994
First meeting of the IARC study group on markers of DNA damage—risk of second malignancy among Hodgkin's disease patients	Lyon, 31 January –2 February 1994
IARC Scientific Council	Lyon, 7–10 February 1994
Working group of the investigators for the rockwool component of the study on man-made mineral fibres	Copenhagen, Denmark 14 February 1994

8th Steering Committee meeting for the Gambia Hepatitis Intervention Study	Fajara, The Gambia, 23–24 February 1994
IARC Monographs Working Group on Some Industrial Chemicals (Volume 60)	Lyon, 15–22 February 1994
Meeting of the coordinating committee of the EPIC project	Brussels, Belgium 21–23 February 1994
7th Steering Committee meeting of the European Network of Cancer Registries	Lyon, 21–22 March 1994
Meeting of the working group on the IARC historical cohort study on workers in the European MMMF industry	Lyon, 23–24 March 1994
Course for EUROCIM users	Lyon, 23–25 March 1994
Advisory meeting on sources of information on epidemiology of childhood cancer	Lyon, 5–6 April 1994
Meeting of the 'Groupe de Travail des Biothèques de l'Agence Française de Sang'	Lyon, 12 April 1994
International conference on retrospective assessment of occupational exposures in epidemiology	Lyon, 13–15 April 1994
IARC Fellowships Selection Committee	Lyon, 14–15 April 1994
Review of WHO programmes associated with radiation effects	Lyon, 15 April 1994
Group meeting of collaborating laboratories in EEC Environment Grant entitled "Environmental carcinogens and mutation spectra in p53 tumour suppressor gene and other critical genes"	Lyon, 22 April 1994
Meeting to prepare the minutes of the Liaison Committee for the Feasibility Study of cancer risk in European Asphalt Workers	Lyon, 21 April 1994
IARC Governing Council	Lyon, 28–29 April 1994
Course on cancer epidemiology	Banjul, The Gambia, 31 May–10 June 1994
Steering Committee, EC/UICC meeting on chemoprevention	Brussels, 1–3 June 1994
Meeting to discuss IARC Scientific Publication on 'Human Cancer Risks due to Low-level Ionizing Radiation'	Lyon, 2–3 June 1994
Epidemiology and Dosimetry Subcommittee meetings for the international collaborative study on cancer risk among nuclear industry workers	Lyon, 6–7 June 1994
IARC Monographs Working Group on Schistosomes, LiverFlukes and *Helicobacter pylori* (Volume 61)	Lyon, 7–14 June 1994
Meeting of the prospective study on biological markers of risk of second malignancy following chemotherapy in Hodgkin's disease patients—finalization of protocol	Paris, 16–17 June 1994
Meeting of the subgroups on exposure indicators of the IARC multicentric case-control study on lung cancer among non-smokers	Lyon, 20–22 June 1994
European Educational Programme in Epidemiology—annual residential summer course	Florence, Italy, 27 June–15 July 1994
Meeting of the working group on standardization of 24-hour diet recall methods in the EPIC project	Lyon, 28–30 June 1994

Meeting of the coordinating committee of the EPIC project	Lyon, 6–8 July 1994
Course on cancer epidemiology with emphasis on occupational cancer	Pelotas, Brazil, 22 August–2 September
European Commission Project Meeting on "Human Cell Transformation"	Lyon, 16 September 1994
The molecular epidemiology of cancer	Aghia Pelaghia, Crete, Greece, 17–22 September 1994
8th ENCR Steering Committee Meeting	Lyon, 10–11 October 1994
IARC Monographs Working Group on Wood Dust and Formaldehyde (Volume 62)	Lyon, 11–18 October 1994
International meeting on methods of determination of DNA adducts by ^{32}P-postlabelling	Lyon, 20–21 October 1994
Study of cancer survival in developing countries meeting	Bangalore, India, 25 October 1994
Annual Meeting of the International Association of Cancer Registries	Bangalore, India, 25–28 October 1994
Group meeting of collaborating laboratories in EEC Grant "Environmental exposures: modulation of host factors and biomonitoring end-points"	Lyon, 2 November 1994
International Workshop on Receptor-Mediated Mechanisms in Carcinogenesis	Lyon,14–16 November 1994
Workshop on 'Putting Science into Practice: The Cancer Control Programme'	Bangkok, Thailand, 15 November 1994
International collaborative study on cancer risk among nuclear industry workers: study group meeting	Lyon, 30 November–2 December 1994
Course on cancer epidemiology (in French)	Lyon, 5–16 December 1994
Ad-hoc Working Group on peroxisome proliferation	Lyon, 7–9 December 1994
HPV vaccines and their potential use in the prevention and treatment of cervical neoplasia	Veyrier du Lac, France, 12–14 December 1994
Meeting of the Commission "Prévention des cancers par l'alimentation" of the Centre National de Coordination des Etudes et Recherches sur la Nutrition et l'Alimentation (CNERNA-CNRS)	Lyon, 4–5 January 1995
Course on safe handling of genotoxic substances in research laboratories,	Lyon, 9–10 January 1995
Meeting on proposed study of Kaposi's sarcoma in the Mediterranean region	Lyon, 11 January 1995
Course on safe handling of cytostatic drugs	Lyon, 11–12 January 1995
UICC, IARC and EU Workshop on Chemoprevention	Lyon, 18–19 January 1995
Course on Cancer Registration (ENCR)	Granada, Spain, 23–27 January 1995
European Commission Project Meeting on "UV and Cancer"	Lyon, 24–25 January 1995
Meeting on the possible founding of a thyroid cancer registry in the Rhône–Alpes region	Lyon, 27 January 1995

IARC Scientific Council	Lyon, 31 January–1 February 1995
IARC Monographs Working Group on Dry cleaning, Some Chlorinated Solvents and Other Industrial Chemicals (Volume 63)	Lyon, 7–14 February 1995
Meeting of the coordinating committee of the EPIC project	Lyon, 1–3 March 1995
9th ENCR Network Steering Committee Meeting	Lyon, 21–22 March 1995
EUROCIM Course	Lyon, 23–25 March 1995
Course on advanced methods in occupational cancer epidemiology	Lyon, 3–7 April 1995
Meeting of the collaborators of the study on cervical cancer in Spain and Colombia	Barcelona, Spain, 10–11 April 1995
MMVF meeting	Lyon, 18 April 1995
IARC Governing Council	27–28 April 1995
Working group meeting of the Eurodeucatam project	Lyon, 10–13 May 1995
IARC Fellowships Selection Committee	Lyon, 11–12 May 1995
Working group meeting of the EVIL project	Lyon, 29 May 1995
Working group meeting on exposure assessment for the international study of cancer risk in biology research laboratory workers	Lyon, 30 May 1995
Pharmacogenetics meeting	Besançon, France, 10–12 May 1995
IARC Monographs Working Group on Human Papilloma Viruses (Volume 64)	Lyon, 6–13 June 1995
Editorial meeting 'Chemoprevention and Cancer'	Lyon, 16 June 1995
Training course for dieticians working on the EPIC project in the UK	Cambridge, UK, 20–22 June 1995
Editorial meeting for 'Cancer Incidence in Five Continents' Vol. VII	Lyon, 26–28 June 1995
Editorial meeting for 'International Incidence of Childhood Cancer, Vol. 2	Lyon, 6–7 July 1995
10th ENCR Network Steering Committee Meeting	Lyon, 2–3 October 1995
International course on cancer registration	Rio de Janeiro, Brazil, 25–28 October 1995
International Association of Cancer Registries Annual Meeting	Rio de Janeiro, Brazil, 30 October–1 November 1995
Conference on principles of chemoprevention	Lyon, 6–10 November 1995
Open day on p53	Lyon, 21 November 1995
International meeting on methods of determination of DNA adducts by ^{32}P-postlabelling	Lyon, 8–9 December 1995
ENCR Workshop on computerized data collection for cancer registries	Venice, Italy, 18–19 December 1995

Annex 7

SEMINARS PRESENTED AT IARC
1 July 1993–31 December 1995

The following visitors to IARC presented one or more seminars:

Dr C. Barnas, Research Institute of Molecular Pathology, Vienna, Austria
Molecular genetic analysis of the neuroblastoma cons ensus deletion region

Dr J. Baudier, INSERM U 244, CEA/CEN-G, Grenoble, FrancE
Interactions between protein kinase C and calcium-binding S100 protein with p53

Professor J.S. Beckman, University of Alabama at Birmingham, Birmingham, USA
Peroxynitrite, superoxide dismutase and nitrotyrosine: their relationship to motor neuron disease

Dr P. Berthon, Urology Service, Hôpital Saint-Louis, Paris, France
The genetics of prostate cancer

Dr M. Böhm, Urologische Klinik und Poliklinik, Medizinische Einrichtungen der Universität, Essen, Germany
Detection of homozygous deletions and loss of heterozygosity in human cancer by PCR

Professor A.-L. Børresen, Department of Genetics, Institute for Cancer Research, Norwegian Radium Hospital, Institute for Cancer Research, Oslo, Norway
CDGE (constant denaturing gel electrophoresis) as a rapid screening technique for mutation detection in tumours. Specific application on p53 and ESR

Dr N. Breslow, University of Washington, School of Public Health and Community Medicine, Department of Biostatistics, Seattle, Washington, USA
Epidemiology of Wilm's tumours

Dr P. Brookes, Laboratory of Mutagenesis, Institut Jacques Monod, CNRS – Université Paris 7, Paris, France
Enzymology of DNA mismatch repair

Professor R. Burton, University of Newcastle, Newcastle, NSW, Australia.
Why is the incidence of melanoma increasing?

Dr C. Conti, M.D. Anderson Cancer Center, Smithville, TX, USA
Role of cyclins in mouse skin chemical carcinogenesis

Dr M.G. Deo, Cancer Research Institute, Bombay, India
Molecular biology of tobacco related oral cancer

Dr G. de Thé, Institut Pasteur, Paris, France
Epidemiologie moleculaire des rétrovirus oncogènes

Dr T. Douki, Laboratoire des lésions des acides nucléiques, DRFMC/SESAM CENG, Grenoble, France
Oxidative DNA damage: base lesions in isolated DNA and model compounds

Dr K. Enomoto, Akita University, Japan
Identification of a novel tight junction protein, 7H6, and the significance of 7H6 expression in normal and cancer cells

Dr J.K. Field, The University of Liverpool, Molecular Genetics and Oncology Group, Clinical Dental Sciences, Liverpool, UK
The identification of genetic *loci* involved in aerodigestive track cancers

Dr M.E. Finbow, Beatson Institute for Cancer Research, Glasgow, UK
Ductin, a multipurpose ion channel and oncoprotein target

Professor M. Fontecave, Université Joseph Fourier, Grenoble
Nitric oxide: mechanisms of enzyme regulation

Dr S. Fujita, Department of Pathology, Kyoto Prefectural University of Medicine, Kyoto, Japan
The natural history of gastro-intestinal tumours

Dr A.P. Grollman, State University of New York at Stony Brook, New York, USA
8-Oxoguanine: mutagenesis and repair

Dr L. Grossman, Department of Biochemistry, The Johns Hopkins University, School of Hygiene and Public Health, Baltimore, MD, USA
DNA repair capacity as a biomarker for basal cell carcinoma in populations, adenoma carcinoma in families and in aging of human cells

Professor B. Halliwell, King's College, University of London, London, UK
Free radicals, DNA danmage an d human disease

Dr O. Hino, Cancer Institute, Tokyo
Molecular genetics of the Eker rat model of dominantly-inherited cancer

Dr U. Hubscher, Institute for Veterinary Biochemistry, Zurich, Switzerland
Enzymes and proteins with dual roles in DNA replication and DNA repair

Dr A. Ichihara, Tokushima Bunri University, Japan
Structure and function of proteasomes

Dr V. Jérôme, Unité de Recherches sur les Communications Hormonales, Institut National de la Santé et de la Recherche Médicale, Bicêtre, France
The regulation of hsp90 alpha protein by growth factors and during cell cycle

Dr J.-L. Klein, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA
Swainsonine overcomes the haematopoietic toxicity of chemotherapeutic drugs commonly used in cancer and AIDS therapy

Dr Y. Konishi, Nara Medical University, Nara, Japan
Endogenous liver carcinogenesis by choline-deficient amino acid defined diet in rats

Dr T. Kuroki, Department of Cancer Cell Research, Institute of Medical Science, Tokyo, Japan
A signal transduction pathway mediating squamous differentiation

Dr O. Laerum, Department of Pathology,Gade Institute, Bergen, Norway
Biological features of brain tumour invasion *in vivo* and *in vitro*

Dr M. Leng, Centre de Biophysique Moléculaire, Orléans, France
Transplatin has no antitumour activity: Why?

Dr S. Manié, Division of Hematological Malignancies,Dana Farber Cancer Institute, Boston, MA, USA
Signal transduction by integrin β-1 in human lymphocytes

Professor W.F.O. Marasas, Programme on Mycotoxins & Experimental Carcinogenesis, Medical Research Council, Tygerberg, South Africa
Fumonisins and their role in human disease

Dr T. Masui, Kyoto University, Japan
Study of growth arrest mechanisms of normal human epithelium: changes in EGF receptor cascade and isolation of epithelial topo-inhibition inducible (eti)genes

Dr M. Masutani, National Cancer Center Research Institute, Tokyo, Japan
Involvement of poly(ADP-ribose) polymerase in cell-cycle arrest following γ-irradiation

Dr J. McGregor, Institute of Dermatology, St John's Skin Center, St Thomas' Hospital, London
Human papillomavirus and p53 in transplant-associated skin cancer

Dr L.E. Moore-Robert, University of California, Berkeley School of Public Health, Department of Biomedical and Environmental Health Sciences, Berkeley, California, USA
Epidemiological and biomarker studies assessing potential risks of arsenic-induced bladder cancer

Dr C. Naus, University of Western Ontario, London, Canada
Intercellular communication in growth control and differentiation

Dr M. Ozturk, Centre Léon Bérard, Lyon, France
p53 and DNA damage

Dr J.C. Pelling, Department of Pathology and Laboratory Medicine, University of Kansas Medical Center, Kansas City, Kansas, USA
Response of keratinocytes to UV-B irradiation

Dr R. Peto, Oxford University, UK
Avoidance of premature death

Dr D. Pompon, Centre National de la Recherche Scientifique, Gif-sur-Yvette, France
Simulation of benzo[*a*]pyrene metabolism in recombinant yeast

Professor M.F. Rajewsky, Institut für Zellbiologie (Tumorforschung) and Dr T. Otto, Klinik und Poliklinik für Urologie, Universitätsklinikum Essen, Essen, Germany
Presentation of the tumor bank of the West German Cancer Center Essen with special emphasis on bladder cancer

Professor D. Roop, Baylor College of Medicine, Houston, TX, USA
Transgenic mice models for human skin carcinogenesis and for gene therapy

Dr W. Rushlow, University of Western Ontario, London, Canada
Differential display applied to neuroscience research

Dr J. Samarut, Ecole Normale Supérieure, Lyon, France
Oncogene transformation by nuclear hormone receptors of the v-erb A oncogene family

Dr C. Sappey, Laboratory of Biochemistry, CHU Grenoble, France
Role of anti-oxidant defences in the activation of human immunodeficiency virus type 1.

Dr J.R.Schlehofer, Centre National de la Recherche Scientifique, Lille, France)
The role of adeno-associated parvoviruses in human pathology and in tumour suppression

Dr B.W. Stewart, Children's Leukaemia & Cancer Research Centre, University of New South Wales, Randwick, Australia
Apoptosis as a consequence of genomic damage: determination of causes and effects

Dr P. Swann, Department of Biochemistry, University College London, London, UK
Using chemically-synthesised DNA to clarify the biological role of specific carcinogen-induced DNA modification

Dr J.-P. Thiery, CNRS, Ecole Normale Supérieure, Paris
Multifunctional growth factors in tumour progression

Dr A. Tritscher, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA
Mechanistic aspects of TCDD-induced tumor promotion in rat liver and implications for risk assessment

Dr A. Umar, Laboratory of Molecular Genetics E3-01, National Institutes of Health, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA
The relationship between genomic instability in cancer cells and the biochemistry of mismatch repair

Dr K. Vähäkangas, Department of Pharmacology and Toxicology, University of Oulu, Oulu, Finland
Molecular epidemiological and mechanistic approaches to carcinogenesis by polycyclic aromatic hydrocarbons

Dr W. Weinberg, National Cancer Institute, Bethesda, MD, USA
p53-mediated activity in epidermal differentiation and carcinogenesis

Dr E. Wynder, American Health Foundation, New York, USA
Tobacco and health: opportunities and limitations, and

Nutrition and cancer: opportunities and limitations

Professor H. Zarbl, Massachusetts Institute of Technology, Division of Toxicology, and Center for Environmental Health Sciences, Whitaker College of Health Sciences and Technology, Cambridge, MA, USA
NMU-induced rat mammary carcinomas arise from cells with pre-existing Ha-*ras* gene mutations: evidence for a new mechanism of chemical carcinogenesis

Annex 8

PUBLICATIONS BY IARC STAFF

1. Aberle, H., Bierkamp, C., Torchard, D., Serova, O., Wagner, T., Natt, E., Wirsching, J., Heidkamper, C., Montagna, M., Lynch, H.T., Lenoir, G.M., Scherer, G., Feunteun, J. & Kemler, R. (1995) The human plakoglobin gene localizes on chromosome 17q21 and is subjected to loss of heterozygosity in breast and ovarian cancers. *Proc. Natl Acad. Sci. USA,* **92,** 6384–6388
2. Adachi, H., Iida, S., Oguchi, S., Ohshima, H., Suzuki, H., Nagasaki, K., Kawasaki, H., Sugimura, T. & Esumi, H. (1993) Molecular cloning of a cDNA encoding an inducible calmodulin-dependent nitric-oxide synthase from rat liver and its expression in COS 1 cells. *Eur. J. Biochem.,* **217,** 37–43
3. Aguilar, C.C., Sun, H.T., Hollstein, M. & Cerutti, P. (1994) Geographic variation of p53 mutational profile in preneoplastic human liver. *Science,* **264,** 1317–1319
4. Albrecht, S., von Deimling, A., Pietsch, T., Giangaspero, F., Brandner, S., Kleihues, P. & Wiestler, O.D. (1994) Microsatellite analysis of loss of heterozygosity on chromosomes 9q, 11p and 17p in medulloblastomas. *Neuropathol. Appl. Neurobiol.,* **20,** 74–81
5. Andrion, A. & Boffetta, P. (1994) Diagnostic criteria and terminology in urinary cytology [letter]. *Cytopathology,* **5,** 62–63
6. Anh, P.T., Parkin, D.M., Hanh, N.T. & Duc, N.B. (1993) Cancer in the population of Hanoi, Vietnam, 1988–1990. *Br. J. Cancer,* **68,** 1236–1242
7. Anttila, S., Hirvonen, A., Husgafvel-Pursiainen, K., Karjalainen, A., Nurminen, T. & Vainio, H. (1994) Combined effect of CYP1A1 inducibility and GSTM1 polymorphism on histological type of lung cancer. *Carcinogenesis,* **15,** 1133–1135
8. Anttila, S., Hirvonen, A., Vainio, H., Husgafvel-Pursiainen, K., Hayes, J.D. & Ketterer, B. (1993) Immunohistochemical localization of glutathione S-transferases in human lung. *Cancer Res.,* **53,** 5643–5648
9. Anttila, S., Karjalainen, A., Taikina-aho, O., Kyyronen, P. & Vainio, H. (1993) Lung cancer in the lower lobe is associated with pulmonary asbestos fiber count and fiber size. *Environ. Health Perspect.,* **101,** 166–170
10. Anttila, S., Luostarinen, L., Hirvonen, A., Elovaara, E., Karjalainen, A., Nurminen, T., Hayes, J.D., Vainio, H. & Ketterer, B. (1995) Pulmonary expression of glutathione S-transferase M3 in lung cancer patients: association with GSTM1 polymorphism, smoking and asbestos exposure. *Cancer Res.* (in press)
11. Anwar, W.A., Khalil, M.M. & Wild, C.P. (1994) Micronuclei, chromosomal aberrations and aflatoxin–albumin adducts in experimental animals after exposure to aflatoxin B_1. *Mutat. Res.,* **322,** 61–67
12. Anwar, W.A. & Wild, C.P. (1994) The Pan African Environmental Mutagen Society, report on inaugural meeting: "Mycotoxins as mutagens and carcinogens: possibilities for disease prevention", Cairo, Egypt, 23–26 January 1993. *Mutat. Res.,* **312,** 61–63
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