Section of Nutrition and Metabolism (NME)

Section head
Dr Isabelle Romieu

The Section of Nutrition and Metabolism (NME) is composed of three groups. Research conducted in the Biomarkers Group (BMA) and the Dietary Exposure Assessment Group (DEX) complements the research in the Nutritional Epidemiology Group (NEP).

Diet, nutrition, metabolic/hormonal imbalances, excess energy consumption, obesity, and physical inactivity are thought to be important contributors to increasing cancer incidence worldwide. The mechanisms of action of these factors remain poorly understood, and little is known about the influence of exposure in utero and during early infancy on risk of cancer and other noncommunicable diseases (NCDs). These factors are particularly relevant given the dietary and lifestyle transitions taking place in many low- and middle-income countries (LMICs), leading to an increased burden of obesity and malnutrition.

Thus, the main objective of NME is to address these issues by evaluating the association of diet, nutrition, physical activity, energy imbalance, and related environmental factors with cancer risk and survival rates in high-income countries and LMICs using cohort and case–control designs or human intervention studies. NME plays a leading role in the coordination and maintenance of the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a large ongoing prospective cohort initiated by IARC, and is actively involved in the recently initiated Mexican teacher cohort (EsMaestras) study and in multicentre breast cancer studies in LMICs (in Latin America and Africa). NME participates in various consortia and large-scale projects and collaborates with international and national institutions, as well as several other IARC Groups/Sections.

New methodological approaches are being developed to improve the accuracy, understanding, and interpretation of dietary exposures in an international context (DEX), to measure the exposome using high-throughput analytical methods (BMA), and to study cellular, biochemical, and physiological changes considering genetic and epigenetic modulations (NEP). Ultimately, the translation of findings into public health recommendations and the development of appropriate cancer prevention and control strategies are of major importance to NME.

The more than 120 peer-reviewed articles published by NME, or accepted for publication, in 2012–2013 provide evidence of the Section's high productivity and many international collaborations.

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In cancer epidemiology, biomarkers are invaluable tools to improve the assessment of exposures to various environmental (diet, contaminants, pollutants) and endogenous factors (hormones, metabolic status) that may influence disease risk. However, most often only small sets of biomarkers are measured and this limited number cannot adequately describe the diversity of exposures contributing to cancer etiology. The goal of the Biomarkers Group (BMA) is to apply the most advanced analytical technologies to discover, validate, and implement biomarkers of environmental exposure and metabolism for cancer epidemiology. Emphasis is placed on the concept of the exposome, defined as the totality of environmental exposures faced by an individual during their lifetime, and on the use of powerful high-throughput metabolomic approaches to measure the exposome.

Metabolomics for measuring the exposome

During the past biennium, significant effort has been devoted to the development of the BMA laboratory and the establishment of methods for measuring the exposome, complementing the well-established laboratory activities on fatty acids (collaboration with NEP) and hormones. Two rooms were fully renovated in the BMA laboratory to accommodate two new mass spectrometers. Computing capacity was increased and software was installed to allow storage and treatment of the large data sets generated with these high-throughput instruments. A virtual machine on a large central facility set up by ITS has been dedicated to mass spectrometry data analysis. Two researchers and a data manager with skills in mass spectrometry, chemometrics, multivariate statistics, and bioinformatics were recruited, and BMA staff members have been trained to run analyses on the new mass spectrometers. Both untargeted methods to measure thousands of metabolites and specific methods targeted at specific classes of metabolites, such as polyphenols, have been developed. A robust, organized, and standardized workflow for metabolomic analyses and data processing incorporating a series of standard operating procedures has been set up.

Metabolic phenotypes and cancer

The exposome includes several thousand endogenous and exogenous metabolites that, together, define a metabolic phenotype characterizing a particular individual at a given time. This characterization should enable the identification of novel risk factors for cancers and the development of new hypotheses about the mechanisms of action involved. A customized and automated method using high-resolution mass spectrometry was developed that enables the detection of more than 2000 metabolites in plasma and the identification of up to 400 endogenous metabolites. Using this method, we will identify metabolic phenotypes associated with exposure to polluted air or contaminated water, as part of the EXPOsOMICS project (involving 12 partner institutions led by Imperial College London), in which BMA is responsible for metabolomic analyses. We will also use the method to detect metabolic phenotypes associated with cancer risk, in several nested case–control and case–control studies either under way or planned in EPIC and other cohorts on liver, colorectal, and breast cancer (collaboration with NEP).

Exogenous metabolites, part of the "food metabolome", resulting from the digestion of food-derived compounds, have also been analysed. They define a metabolic phenotype characteristic of the diet of an individual. The untargeted metabolomic workflow has been applied to urine samples from about 500 subjects from the cross-sectional study nested within EPIC. Highly detailed dietary data are available for these subjects, and this workflow enabled the identification of novel dietary biomarkers that can be used in future cancer epidemiological studies. Iterative regression and discriminant analyses led to the identification of a large number of signals characteristic of the 400 dietary variables (collaboration with DEX). The corresponding biomarkers are identified through the screening of customized databases developed by BMA during the biennium. These databases include FooDB, a database on all known food constituents (collaboration with the University of Alberta) (Wishart *et al.*, 2013), and Phenol-Explorer, a database on all known polyphenol metabolites (Rothwell *et al.*, 2012). In a first exploration of the data, approximately 100 polyphenol metabolites could be identified as putative novel biomarkers for some polyphenol-rich foods. This unique approach will be extended to the whole food metabolome, with special focus on dietary factors associated with cancer risk, such as coffee and dietary fibre. Various studies will be conducted to evaluate the reliability over time and validate the putative biomarkers.

BMA organized the 1st International Workshop on the Food Metabolome and Biomarkers for Dietary Exposure (Glasgow, 4–5 July 2013), which gathered 50 experts from Europe and North America. This workshop led to the definition of recommendations for future research in the field.

Hormones and cancer

Over the past biennium, BMA has focused on the study of associations of thyroid stimulating hormone (TSH), thyroglobulin, thyroid hormones, growth factors, estrogens, insulin-related markers, cytokines, and inflammatory factors with cancer risk in large-scale epidemiological studies. In collaboration with the Section of Infections, the Group has undertaken a case–control study nested within EPIC to characterize associations between thyroid hormones and differentiated thyroid cancer risk on samples from 300 women and 57 men. This study showed a strong direct association between increasing circulating levels of thyroglobulin and differentiated thyroid cancer risk, and an inverse association with increasing TSH concentrations.

In collaboration with NEP, a cross-sectional study of 798 premenopausal and 1360 postmenopausal women undertaken in EPIC showed that increased physical activity levels were associated with lower concentrations of circulating androgens and estrogens, independent of body size. Several cross-sectional studies have also been carried out in a subsample of the large Mexican EsMaestras cohort (led by Dr Isabelle Romieu, NEP) to study the association between anthropometry, mammographic density, and circulating hormones,

insulin-related markers, cytokines, and inflammatory factors in premenopausal and postmenopausal women in this understudied population. Major results showed an inverse association between growth factor concentrations and dense tissue, which was, however, driven by adiposity. Single-nucleotide polymorphisms (SNPs) in specific genes were associated with circulating levels of growth factors but not with mammographic density features. Preliminary analyses also showed that circulating growth factors significantly increased with increasing height and leg length, and strongly decreased with increasing body mass index (BMI), weight, waist and hip circumferences, waist-to-hip ratio, and waist-to-height ratio, while circulating C-reactive protein, leptin, the leptin-to-adiponectin ratio, and C-peptide concentrations strongly increased. These results suggest a strong relationship between endogenous hormones, inflam-matory factors, and body size in this population of premenopausal Mexican women.

BMA scientists are involved in several cancer-related EPIC working groups (breast, ovarian, and endometrial cancer), are coordinating the activities of the EPIC thyroid cancer working group (in collaboration with the Infections and Cancer Epidemiology Group), and are leading studies on obesity, thyroid hormones, reproductive factors, and differentiated thyroid cancer risk. BMA also participates in an international consortium led by the United States National Cancer Institute to study the associations between obesity, reproductive factors, and thyroid cancer risk in cohort studies worldwide. In addition, the Group is involved in setting up case–control studies on breast cancer risk in Latin America and South Africa (studies led by NEP).

Dietary polyphenols and cancer

Polyphenols constitute the most widely consumed class of dietary antioxidants. Their anti-carcinogenic effects have been well documented in many studies conducted in cell culture or experimental animals. Much less evidence exists on their anti-carcinogenic effects in humans as epidemiological data is still very limited. New tools are being developed in collaboration with DEX to assess exposure to the polyphenol metabolome and to identify those polyphenols most strongly associated with cancer risk. A food composition table for polyphenols is being developed based on food composition data from the Phenol-Explorer database. To increase the reliability of the polyphenol exposure measurements, 4600 values of retention factors, describing the amount of polyphenols retained after cooking and food processing, have been collected from the scientific literature and inserted into the Phenol-Explorer database (Rothwell *et al.*, 2013). This new food composition table will be used to assess associations with colorectal cancer in EPIC. In parallel, a highly sensitive and innovative method using differential stable isotope coding of the exposome is being developed to measure 40 different polyphenols by mass spectrometry in urine and blood. These biomarkers will be used in the first nested case–control studies on colorectal cancer in EPIC and to validate polyphenol intake measurements obtained with the new food composition table.

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The overall goal of the Dietary Exposure Assessment Group (DEX) is to improve the accuracy, understanding, and interpretation of dietary exposure (and changes in dietary exposure) in studies on diet and cancer and other intermediate diseases. The Group has a leading role in the development of standardized dietary assessment methodologies and in improving their integration into dietary monitoring and diet–disease analyses, particularly in international study settings.

International methodologies and web-based infrastructures to support large international nutritional studies

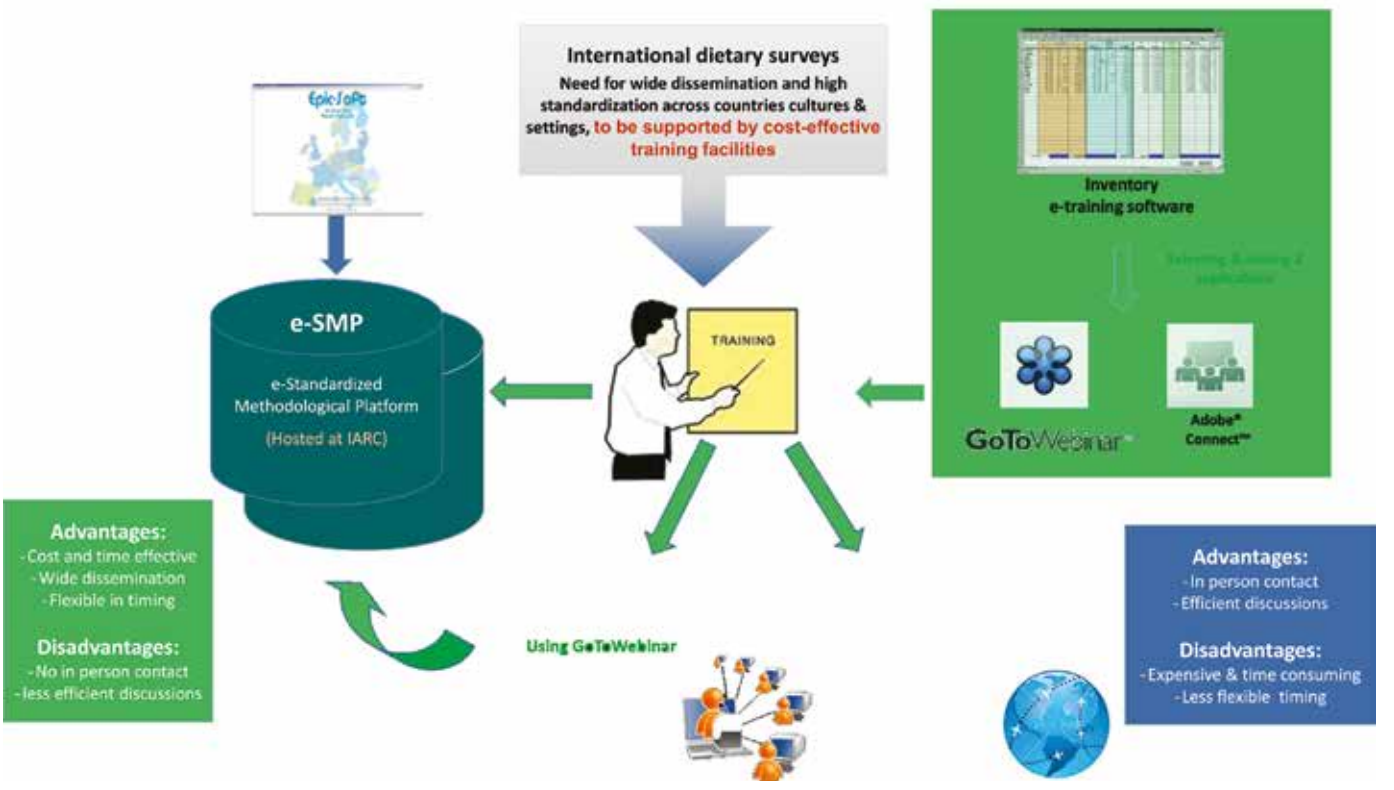
The standardized computerized 24-hour dietary recall method EPIC-Soft®-24-HDR, and its related tools, was initially developed by IARC within the framework of the EPIC study. Interest in its use has increased, particularly but not exclusively for international nutritional surveillance. Indeed, this international methodology was recommended by the European Food Safety Authority as the reference dietary methodology for pan-European dietary monitoring surveys (http://www.efsa.europa.eu/en/press/news/datex100212.htm). In view of the first pan-European dietary survey, EU Menu, various methodological and feasibility studies – such as EFCOVAL (http://www.efcoval.eu/), PANCAKE (http://www.efsa.europa.eu/fr/supporting/pub/339e.htm), and PILOT- and EMP-PANEU http://www.efsa.europa.eu) – were launched to adapt, test, and evaluate this methodology for nutritional surveillance and risk assessments.

Through these different projects, new software (EPIC-Soft Data Entry application®) designed for use in data entry of food consumption data among children (PANCAKE project) was successfully developed and field-tested. In addition, five new versions of EPIC-Soft®-24-HDR were developed, for Bulgaria, Finland, Hungary, Poland, and Portugal, and field-tested for use in adolescents, adults, and the elderly in four of the five countries (PANEU projects). Also, the newly developed web-based Interview Manager application for handling and management of collected interview data was field-tested.

Guidelines and e-training documents for the use of e-SMP are also under development. The EPIC-Soft®-24-HDR train-the-trainers course has been successfully implemented and evaluated as a conventional and e-learning course in the framework of the EMP-PANEU project (Huybrechts *et al.*, 2012). This e-training component was developed in collaboration with other IARC Groups/Sections (ETR, ASO, and ITS) to allow wider dissemination of the methods in a cost- and time- efficient way, which is particularly important for LMICs (Figure 1).

To disseminate these international tools and ensure their long-term maintenance and standardization, a comprehensive web-based infrastructure is needed to support nutritional studies, particularly in LMICs. Therefore, a web-based platform, the dietary e-Standardized Methodologies Platform (e-SMP), was designed to support the development and maintenance of EPIC-Soft®-24-HDR and other dietary tools. Although the development of e-SMP is ongoing and it is currently being tested in the pan-European dietary monitoring surveys, its implementation in other settings (e.g. cohorts and clinical trials) and regions worldwide has been initiated through different DEX initiatives and projects.

Figure 1. Development and evaluation of the e-training train-the-trainers course.



Implementation of the DEX methodologies and infrastructure worldwide

Building on successful experiences in Europe where various countries – the Netherlands, Germany, Belgium, France, Switzerland, and Austria (under negotiation) – have already endorsed the DEX methodologies for their national monitoring surveys, DEX has initiated projects to expand the implementation to other regions worldwide, including Latin America, Asia, and Africa. The ultimate purpose is to better measure, monitor, and understand the nutritional transition observed in these regions and determine whether there is an association with cancer and other NCDs. DEX is following a stepwise approach, with several parallel projects – LaDieta (in Brazil and Mexico), a project in Asia (Republic of Korea), and AS-PADAM (in *n* = 22 African countries) – aimed at adapting, testing in real study conditions, and validating EPIC-Soft®-24-HDR and its web-supported infrastructure (e-SMP) for these regions. The planned next steps will be the expansion/adaptation of this software to other countries in these regions and its implementation, preferably in international nutritional surveillance settings and research studies. For Africa (AS-PADAM), the project started with an inventory on the availability, quality, and challenges of dietary and physical activity assessment methods available or currently being used in different African regions. This is a prerequisite to exploring the methodological infrastructure needed to improve nutritional research and monitoring in the continent within international frameworks.

Evaluation of dietary measurement errors in multicentre studies

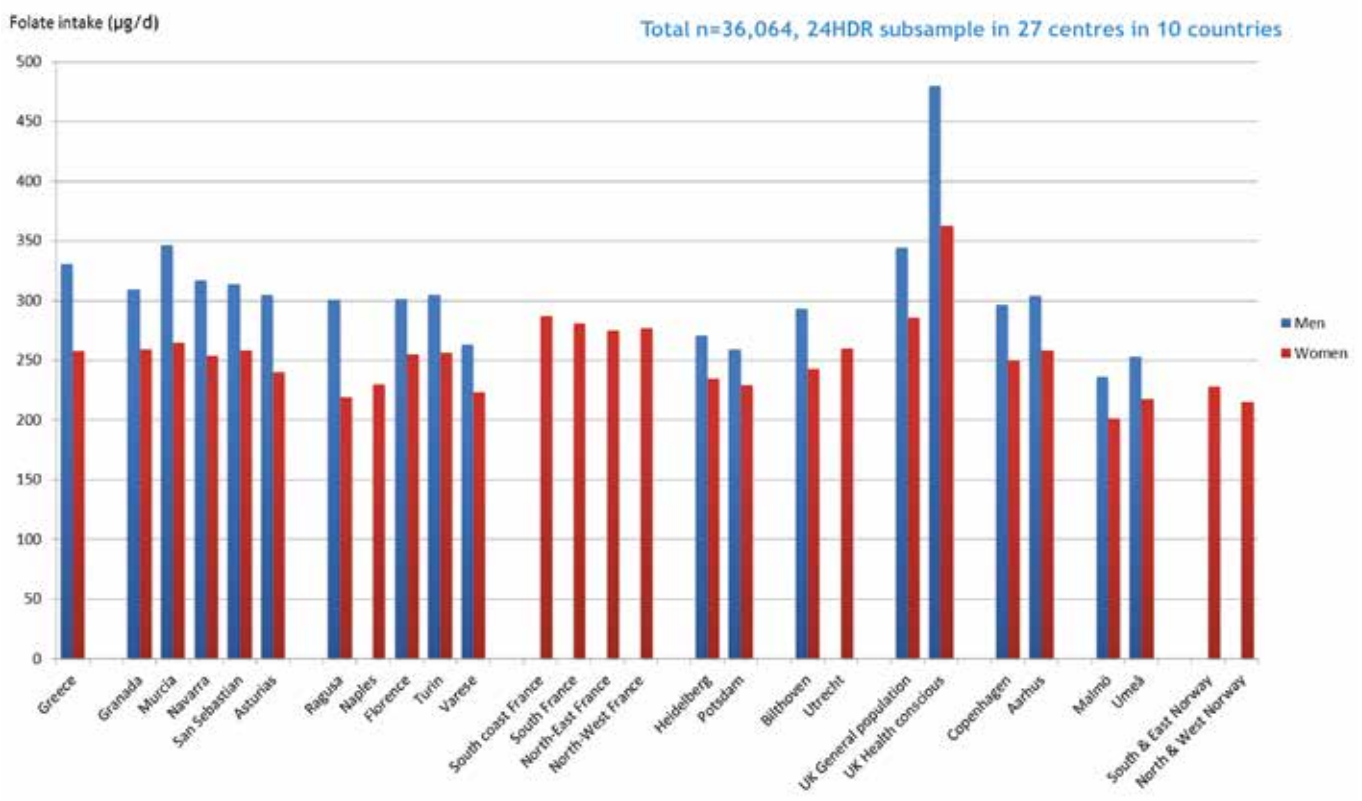
A better understanding of measurement errors is needed to improve the validity of dietary assessment tools. In the past biennium, three evaluation studies addressing complementary methodological questions were conducted. First, Freisling *et al.* (2012) confirmed that underreporting of protein and potassium intake is predicted by BMI and, for the first time, it was shown that underreporting is the same across countries. Second, Ferrari *et al.* (2013a) showed that acrylamide intake based on self-reported diet weakly correlates with biomarkers of acrylamide. Lastly, Crispim *et al.* (2012) concluded that group-level bias in protein and potassium intake collected with EPIC-Soft®-24-HDR does not vary across centres.

DEX also conducted an in-depth evaluation of measurement properties of new e-technologies in dietary assessment for large-scale epidemiological studies (Illner *et al.*, 2012).

Studies on dietary exposure (including biomarkers of diet)

Descriptive analyses of dietary exposure have been published, such as the first standardized comparison of dietary folate intake across 10 European countries (Park *et al.*, 2012a) (Figure 2), and dietary acrylamide exposure in the EPIC study (Freisling *et al.*, 2013a) and their related biomarkers (Park *et al.*, 2013a).

Figure 2. Mean intake of folate (µg/d) in men and women, stratified by centre ordered from south to north, adjusted for age, total energy intake, weight, and height, and weighted by season and day of recall. Source: Park *et al.* (2012a); reproduced with permission from Cambridge University Press.



Studies on diet and cancer and other, intermediate chronic diseases

DEX is also involved in projects concerning the role of diet and biomarkers of diet in relation to cancer (EPIC) and other chronic diseases, such as obesity and diabetes (EPIC-PANACEA and INTERACT projects). A particular focus is on industrial foods (industrial trans fatty acids, acrylamide, energy-dense foods, and foods with high glycaemic index/glycaemic load). This work is in collaboration with other researchers in NME.

Development and application of new methodologies to analyse dietary patterns

One of the Group's new research activities is dietary pattern analyses, which appear to be a promising approach for better depicting the complexities of diet and improving the understanding of its association with diseases, particularly cancer. DEX, in collaboration with other IARC researchers (in the Biostatistics Group and NEP) and external partners, has initiated a project on analysing nutrient and biological patterns in international studies; applications for supporting grants are being submitted and papers prepared for studies of colorectal cancer, breast cancer, and diabetes. Furthermore, a systematic review of peer-reviewed studies on diet quality indices applied to old age was recently published as an invited book chapter evaluating the impact of more than 40 factors from different domains (e.g. lifestyle, health, environment) on diet quality (Freisling *et al.*, 2013b).

Goals and projects for the next biennium

DEX plans to develop its activities within the recently launched LPC-BBMRI project, which aims to federate the largest European cohorts with biobanks under the framework of the already existing Biobanking and Biomolecular Research Infrastructure (BBMRI) network. DEX will also collaborate as a task leader in the first Joint Programming Initiative, A Healthy Diet for a Healthy Life (JPI HDHL), on Determinants of Diet and Physical Activity Choice (DEDIPAC).

More broadly, DEX intends to contribute to the new global strategies on diet-related NCDs. Indeed, one of the main challenges in implementing these strategies is the lack of reliable and standardized dietary methodologies and their supporting research infrastructures for measuring, monitoring, comparing the nutritional transitions, and investigating their association with diseases.

To fill this gap, DEX intends, as part of its strategic plan, to support the establishment of a new worldwide network of nutritional surveillance, with a particular but not exclusive focus on LMICs. Within IARC, as an integrated part of WHO and building on its regional offices and other partnerships, DEX aims to provide standardized dietary methodologies and support for the collection of more comparable dietary exposure data worldwide. This comprehensive dietary framework should serve multiple research, prevention, and risk assessment purposes at the national, regional, and international level.

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The overall objective of the Nutritional Epidemiology Group (NEP), in close interaction with DEX and BMA, is to determine the role of diet, under-/over-nutrition, hormonal factors, physical activity, and energy balance on cancer incidence and survival.

We recognize that the cancer process is a continuum, and that cancer and noncommunicable diseases (NCDs) share risk factors and underlying mechanisms with metabolic disorders, particularly metabolic syndrome and diabetes. Therefore, NEP works to implement a life-course approach to cancer etiology and to bring together information about early-life and mid-life exposures and determinants of healthy ageing. The Group uses modern epidemiological and statistical techniques tied to the use of biomarkers to explore metabolic alterations, along with the application of genetic, nutrigenomic, and epigenetic approaches.

Studies in high-resource settings: the European Prospective Investigation into Cancer and Nutrition (EPIC)

NEP plays a key role in the coordination and scientific management of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. It ensures the cyclic end-point/vital status update of the EPIC database, with the centralization of the most recent information on incident cancer events and mortality from collaborating centres. NEP is setting up a larger centralized database to include additional chronic disease end-points and updated exposure information. NEP also ensures delivery of updated project-specific databases to the EPIC working group network, including the preparation of data sets for nested case–control studies. The Group also provides support to the Laboratory Information Management System for the retrieval of biological samples, in collaboration with the IARC Laboratory Services and Biobank Group.

Nutritional and lifestyle predictors of cancer in EPIC

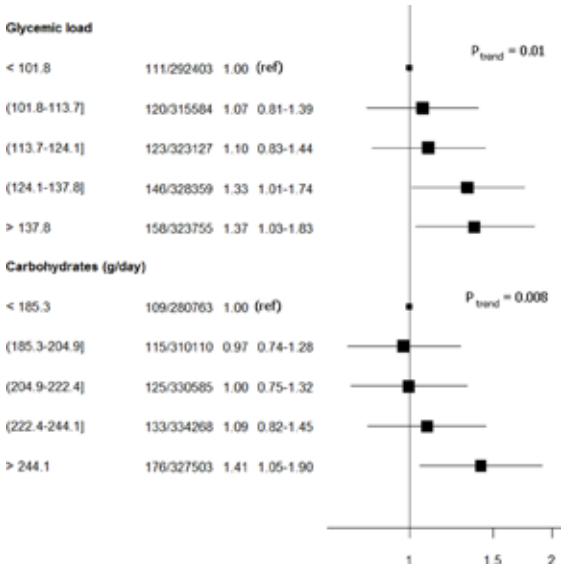
Breast cancer

NEP considers that analysis of breast cancer phenotypes based on homogenous groupings by hormonal receptor status will lead to a clearer etiological understanding of dietary/metabolic risk factors. NEP has recently shown that: carbohydrate-rich diets are significantly related to increased breast cancer risk among postmenopausal women with estrogen receptor-negative (ER-) and ER-/progesterone-negative (PR-) tumours, but not those with receptor-positive tumours (Romieu *et al.*, 2012a) (Figure 1A); higher vegetable-source dietary fibre intake is significantly related to lower breast cancer risk in pre/postmenopausal women, with a stronger association in ER- and ER-/PR- tumours (Ferrari *et al.*, 2013b) (Figure 1B); dietary flavonoids/lignans and circulating vitamin D are not related to breast cancer risk (Zamora-Ros *et al.*, 2013b); and moderate to high levels of physical activity are strongly inversely associated with breast cancer risk, particularly in ER+/PR+ tumours (Steindorf *et al.*, 2013).

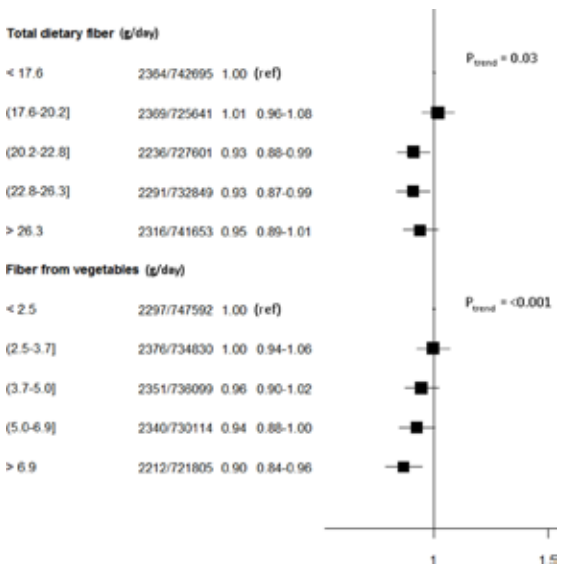
A nutrient of key interest is folate, which affects both genetic and epigenetic pro-carcinogenic processes (Teegarden *et al.*, 2012). NEP received funding (INCa/La Ligue Contre le Cancer/Fondation de France/WCRF) to determine the role of folate and other B vitamins on breast cancer risk using dietary information and biomarkers of one-carbon metabolism, and incorporating genetic factors and genome-wide DNA methylome profiling. Analyses are still under way, but preliminary results suggest a protective effect of dietary folate on breast cancer among women with high alcohol consumption.

Figure 1. (A) Associations with risk of breast cancer in postmenopausal women with estrogen receptor (ER)-negative tumours, in the EPIC study: glycaemic load and carbohydrate intake. Figure compiled from Romieu *et al.* (2012a). (B) Associations with risk of breast cancer in postmenopausal women with ER-negative tumours, in the EPIC study: dietary fibre intake, total and from vegetable sources. Source: Ferrari *et al.* (2013b); reproduced with permission from the publisher.

(A)



(B)



Another important group of nutrients are fatty acid biomarkers. Recent results from the E3N-EPIC cohort show a strong positive association between trans fatty acid isomers originating from industrial processes and breast cancer risk. In collaboration with BMA, NEP has extended this project to the full EPIC cohort (5000 breast cancer cases), using updated methodology to quantify 60 fatty acids, including 15 transisomers.

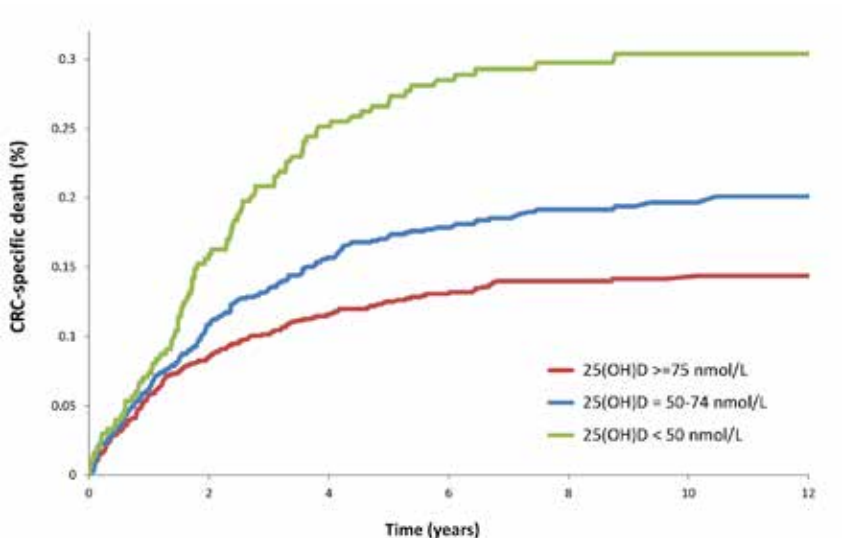
Colorectal cancer

The Group has shown that maintaining healthy dietary habits, such as higher dietary fibre intake (Murphy *et al.*, 2012) and adherence to a Mediterranean diet (Bamia *et al.*, 2013), is associated with decreased colorectal cancer risk, whereas higher adult weight gain, particularly abdominal obesity, is positively associated (Aleksandrova *et al.*, 2013b). Accordingly, measures of selected circulating obesity markers showed decreased risk with higher concentrations of adiponectin (Aleksandrova *et al.*, 2012a) and soluble leptin receptor (Aleksandrova *et al.*, 2012b). A further analysis showed that these biomarkers, along with high-density lipoprotein (HDL), account for a large proportion of the association between abdominal obesity and colorectal cancer risk (Aleksandrova *et al.*, 2013a). Fatty acid biomarkers were analysed in the French E3N-EPIC cohort study, showing an increased risk of advanced adenoma with higher oleic acid levels, and a decreased risk with higher levels of long-chain polyunsaturated fatty acids (PUFAs), indicating altered fatty acid metabolism (Cottet *et al.*, 2013). Colorectal cancer analyses are currently under way, and NEP is also leading a project on determinants of colorectal cancer survival. The initial findings suggest longer survival in those with higher baseline vitamin D concentration (Fedirko *et al.*, 2012a) (Figure 2). Current projects include investigations of body iron status, advanced glycation end-products, and colonic barrier function.

Hepatocellular carcinoma

Research showed that abdominal obesity (Schlesinger *et al.*, 2013a) and presence of diabetes (Schlesinger *et al.*, 2013b) are associated with increased hepatocellular carcinoma risks, as are lower intakes of dietary fibre (Fedirko *et al.*, 2013b), fish (Fedirko *et al.*, 2013c), and flavonoids and antioxidant nutrients (Zamora-Ros *et al.*, 2013a), and higher total sugar intake (Fedirko *et al.*, 2012b). Further detailed analyses, particularly with biomarker measures, are in progress.

Figure 2. Adjusted cumulative incidence curve of colorectal cancer-specific mortality by pre-defined levels of pre-diagnostic 25-hydroxyvitamin D [25(OH)D] (< 50, deficient; 50–74, insufficient; ≥ 75 nmol/L, sufficient vitamin D status, on the basis of proposed levels of vitamin D deficiency/insufficiency). Source: Fedirko *et al.* (2012a); reproduced with permission from American Association for Cancer Research.



Pancreatic and other cancers

The Group has recently been funded by INCa/ARC/WCRF to analyse fatty acid biomarkers in association with risk of pancreatic cancer, a highly fatal tumour for which studies to date indicate a potential association with dietary fat and some fat subtypes.

NEP has adapted statistical models for dietary pattern analyses (Fahey *et al.*, 2012) and is applying the approach to measures of dietary/lifestyle quality (e.g. the Healthy Eating Index and the Oxidative Balance Score).

Alcohol and cancer

NEP collaborated with the French Direction Générale de la Santé on an exhaustive evaluation of lifetime alcohol and tobacco use and overall/cause-specific mortality, using evidence from EPIC. Individuals consuming more than 5 drinks/day in men and more than 2.5 in women showed a 2–5 times higher risk of dying due to alcohol-related cancers (including cancers of the upper aerodigestive tract, liver, colorectum, and female breast) compared with subjects with lifetime consumption of less than one drink/week (Bergmann *et al.*, 2013). In the EPIC population, mortality rates were 1.5–3-fold larger for current smokers than never-smokers. Associations related to tobacco use were of similar magnitude for tobacco-related cancer, respiratory disease, and cardiovascular disease deaths (Bergmann *et al.*, 2013; Licaj *et al.*, 2013). Similar analyses on the incidence of NCDs are in progress. We also collaborated on a meta-analysis of low-dose alcohol consumption and cancer risk (Bagnardi *et al.*, 2013). NEP showed that genetic variability in alcohol metabolizing genes did not modulate the strong association between alcohol and colorectal cancer risk (Ferrari *et al.*, 2012a). For female cancers, no association was observed with alcohol intake and endometrial cancer (Fedirko *et al.*, 2013a); analyses on breast cancer and reproductive factors are in progress.

Studies on breast cancer in low- and middle-income countries

Breast cancer incidence and mortality are rising rapidly in LMICs. In collaboration with the National Institute

of Public Health (INSP) and the National Institute of Cancerology (INCAN) in Mexico, NEP is using large cohorts (the EsMaestra cohort of Mexican teachers) and multicentre case–control studies (the CAMA study) to identify the role of diet, physical activity, obesity, and metabolic disorders on breast cancer incidence and survival. Findings from the CAMA study show lower breast cancer risk associated with higher circulating vitamin D levels (Fedirko *et al.*, 2012b) (Figure 3) and higher intake of n-3 PUFA (Chajès *et al.*, 2012) – a finding that is being pursued with fatty acid biomarker measures.

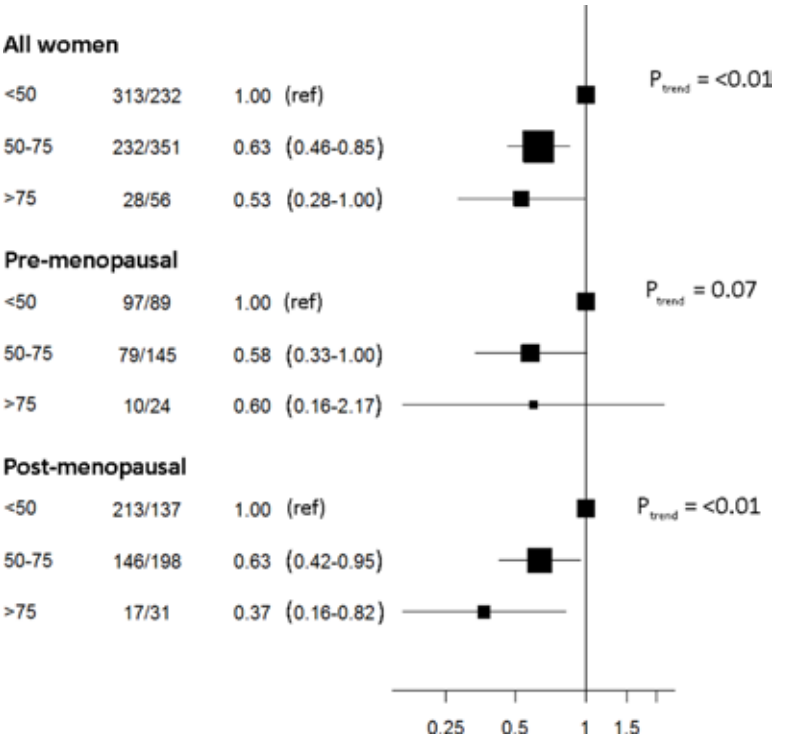
Higher breast cancer risks were observed in women reporting a diabetes diagnosis (Torres-Mejía *et al.*, 2012) and in women who reported increasing body shape silhouettes over their lifetime (Amadou *et al.*, 2013b). NEP plans to study interactions between fat distribution and genetics in breast cancer, following our recent meta-analysis that identified ethnicity as a key factor affecting the association of body size with premenopausal breast cancer (Amadou *et al.*, 2013b).

Since mammographic density is a strong predictor of breast cancer, understanding the link between breast cancer risk factors and mammographic density could provide better insight into mechanisms underlying breast cancer development and help identify women at higher risk. In the large EsMaestras cohort, mammographic density was positively related to metabolic syndrome (Rice *et al.*, 2013b) and early adult body fatness (Rice *et al.*, 2013a), but no association was observed with circulating levels of growth hormone.

Molecular Subtypes of Premenopausal Breast Cancer in Latin American Women (PRECAMA): a multicentre population-based case–control study

Recently, the Group initiated a multicentre population study to determine risk factors for premenopausal breast cancer among Hispanic women, a culturally and genetically heterogeneous group. Detailed classification of tumour subtypes will help to refine the phenotype and improve the identification of specific endogenous and exogenous factors as well as to disentangle their interplay with regard to breast cancer. A feasibility study has been started with structured collection of individual, clinical, and pathological information and of biological specimens in four Latin American countries (Chile, Colombia, Costa Rica, and Mexico) in collaboration with national institutions, the Fred Hutchinson Cancer Research Center, and the Pan American Health Organization. Our efforts to establish the infrastructure for such a large, multicentre study in Latin America will enhance the potential of these countries to participate in international cancer research partnerships.

Figure 3. Serum 25-hydroxyvitamin D [25(OH)D] blood levels and breast cancer risk in Mexican women. Figure compiled from Fedirko *et al.* (2012b).



Influence of diet, physical activity, and body size on breast cancer in South Africa: a study of African women in transition

NEP recently obtained WCRF funding to develop a study of dietary/lifestyle determinants of breast cancer in the understudied population of Soweto, Johannesburg, South Africa. The study includes structured collection of individual, clinical, and pathological information along with biological specimens and detailed information on anthropometry (DEXA/ultrasound). It will provide relevant information on tumour subtype frequencies and specific risk factors that affect breast cancer incidence and survival.

Early environmental exposure, metabolic disorders, and cancer

NEP has established the Latin American Birth Cohort Consortium on Healthy Growth (LABCGD) composed of three cohorts from Brazil, Chile, and Mexico. We are evaluating the role of fetal and childhood exposures and the incidence of intermediate outcomes, child growth pattern, obesity and metabolic syndrome, and epigenetic changes. These outcomes are potentially relevant to future cancer risks. Thus, NEP intends to expand the consortium to other birth cohorts.

In collaboration with other IARC Groups (BMA, EGE, MMB), INSP (Mexico), and Emory University, recent NEP findings from the Mexican component

of the LABCGD show an influence of docosahexaenoic acid (DHA) supplementation on immune response and modulation of global methylation levels and Th1/Th2 response in infants of mothers who smoke (Lee *et al*., 2013a).

Determinants of healthy ageing

NEP has a leading role in the CHANCES FP7 project, which brings together 14 cohorts for pooled analyses of determinants of cancer risk and survival in elderly populations. We initiated specific projects within CHANCES (socioeconomic status, body size, alcohol intake) and collaborate with groups in the CHANCES network on several other projects (dietary patterns, vitamin D levels, disability-adjusted life years). The Group is also exploring determinants of healthy ageing using the existing EPIC resources.

Nutritional metabolomics

In collaboration with BMA and a leading nuclear magnetic resonance (NMR) metabolomics centre in Lyon http://www.ens-lyon.fr/crmn/crmn/index.html, NEP is conducting a series of metabolomic studies within EPIC on pancreatic, hepatocellular, and biliary tract cancers. Studies on other cancer sites are planned.

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