Section of Nutrition and Metabolism (NME)

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Diet, nutrition, metabolic/hormonal imbalances, excess energy consumption, obesity, and physical inactivity are thought to be important contributors to increasing cancer incidence rates worldwide. However, the mechanisms of action of these factors remain poorly understood. In addition, the contributing influences of dietary transitions from traditional diets to diets typical of industrialized countries, which is taking place in low- and middle-income countries (e.g. in Latin America), and of exposures in fetal life or early infancy are not well studied. Thus, the main objective of the Section of Nutrition and Metabolism (NME) is to address these issues by evaluating the association of diet, dietary patterns, nutrition, physical activity, and energy imbalance with cancer risk in high-income and medium-to-low-income countries using cohort and case–control designs or human intervention studies. The emphasis is on improving the assessment of dietary exposures through standardized dietary methodologies relevant to international study settings; applying biomarkers and metabolomics to study cellular, biochemical, and physiological changes; and consideration of gene–environment interactions. The translation of findings into public health recommendations for cancer prevention is of major importance to the Section.

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The activities of the Biomarkers Group (BMA) have shown a significant development over the 2014–2015 biennium, with the recruitment of three new technicians and three postdoctoral researchers, the relocation of the BMA laboratory and offices to the tower building with a larger space, and the acquisition of two new mass spectrometers and a robot for sample handling.

Several methods based on mass spectrometry have been developed to analyse the metabolome in blood and urine samples (polyphenols, sex steroids, and intermediate metabolism). Methodological studies on the application of these methods to epidemiological studies have been performed (Carayol et al., 2015). The methods were applied to a prospective study on the etiology of hepatocellular carcinoma, in collaboration with the Nutritional Epidemiology Group (NEP), and studies on breast cancer are in progress.

Standard operating procedures were developed to analyse the metabolome on a broader scale (> 3000 metabolites detected) in urine and plasma samples by high-resolution mass spectrometry (Edmands et al., 2014, 2015). These methods were used to characterize the food metabolome (Scalbert et al., 2014) and to identify novel dietary biomarkers (coffee, tea, red wine, citrus fruits, and apples) in a cross-sectional study in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (Figure 1) (Edmands et al., 2015). A new database is being developed called Exposome-Explorer, which includes detailed information on all known dietary biomarkers.

A new food composition table for all known polyphenols was built within the EPIC study, in collaboration with the Dietary Exposure Assessment Group (DEX), and was used to calculate the intake of more than 400 polyphenols in the EPIC cohort (Figure 2). In parallel, a new analytical method was developed to measure the levels of 34 polyphenol biomarkers in urine. The method was applied to 24-hour urine samples collected from 475 subjects in the EPIC cohort. High correlations were observed between polyphenol biomarkers and intake measurements, showing the high quality of the new food composition table. Studies on reproductive and menstrual factors, as well as on energy and macronutrient intake and the risk of differentiated thyroid cancer, have been undertaken within the EPIC cohort (Zamora-Ros et al., 2015a), and circulating inflammatory factors and sex steroids are currently being analysed in the same studies. Associations between growth factors, adipokines, and body size in young Mexican women have been investigated in the Mexican Teachers' Cohort, in collaboration with NEP (Rinaldi et al., 2014a, 2015) to assess whether different adipose tissues are associated with different metabolic alterations.

A method based on gas chromatography has been validated to determine in plasma/serum 60 fatty acids from dietary sources and endogenous metabolism. It is currently being applied to large epidemiological studies, in collaboration with NEP.

Figure 1. Heat map showing clusters of signals detected by high-resolution mass spectrometry and associated with the consumption of six specific foods, in 475 urine samples collected in the European Prospective Investigation into Cancer and Nutrition (EPIC) cross-sectional study. Numbers indicate metabolites identified as best predictors of intake. Reprinted with permission from Edmands et al. (2015).

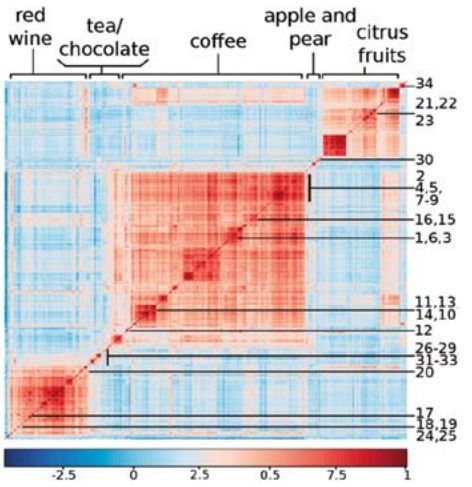
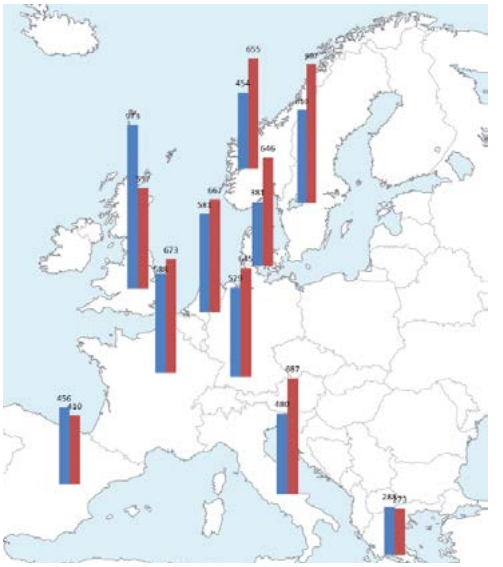


Figure 2. Polyphenol intake in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. Intake (in mg/day) is shown for the two main classes of polyphenols (flavonoids, blue bars; phenolic acids, red bars) in the 10 countries of the cohort. Compiled from Zamora-Ros R, Knaze V, Rothwell JA, Hémon B, Moskal A, Overvad K, et al. (2015). Dietary polyphenol intake in Europe: the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Eur J Nutr. http://dx.doi.org/10.1007/s00394-015-0950-x PMID:26081647.



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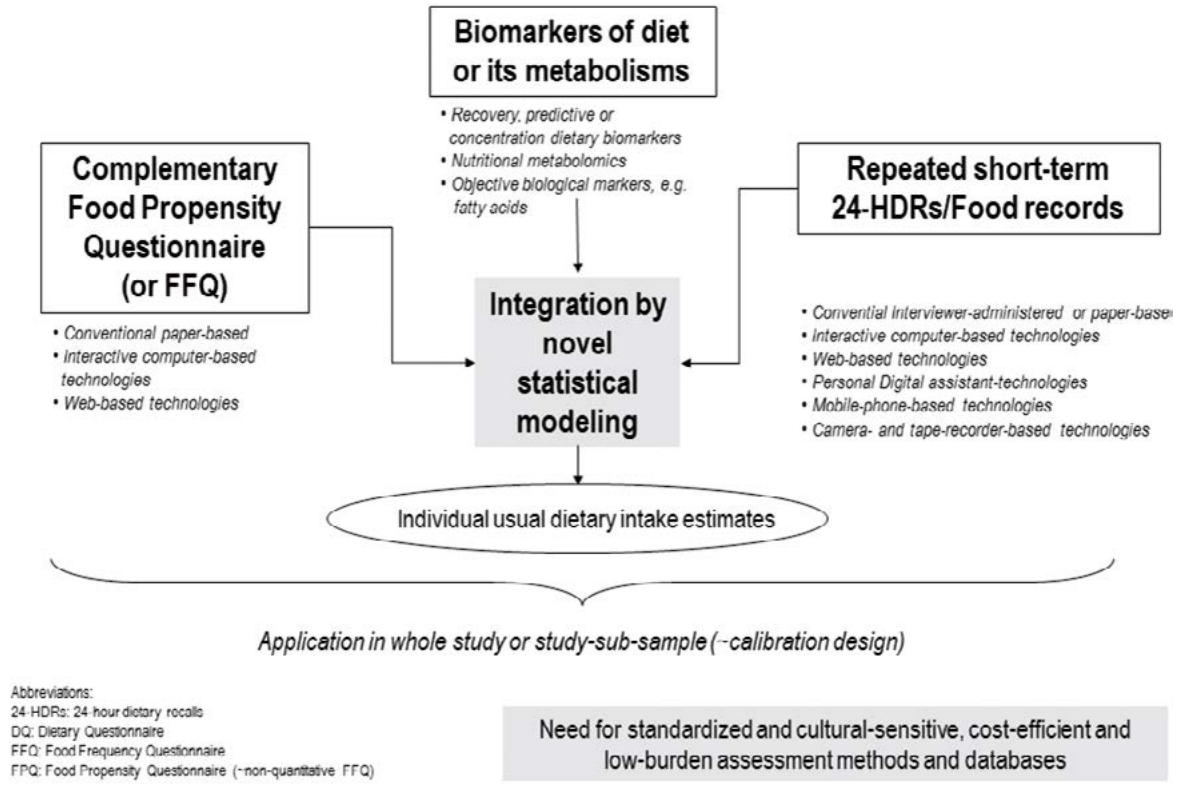
IARC-WHO Global Nutrition Surveillance initiative (GloboDiet)

International nutrition surveillance systems to monitor trends and better understand the nutrition transition and its association with the global burden of noncommunicable diseases (NCDs) are currently lacking. To address this gap, the Dietary Exposure Assessment Group (DEX) launched the IARC-WHO Global Nutrition Surveillance initiative in 2014–2015, with the aim of collecting standardized dietary data worldwide, using DEX methodologies, to support dietary surveillance, research, and prevention of cancer and other NCDs, and ultimately to promote more concerted prevention and research action plans. The GloboDiet-Europe consortium, involving seven countries using the DEX methodology in their national surveys (Austria, Belgium, France, Germany, Malta, the Netherlands, and Switzerland), has been developed as a proof of concept of the global initiative, and the legal consortium framework to support it is being explored. In parallel, pilot initiatives have been pursued in other regions worldwide (Latin America, Asia, and Africa). Korean (Park et al., 2015), Mexican, and Brazilian versions of GloboDiet have been completed, and road maps for their local validation and implementation are advanced. In Africa, an inventory, conducted as a prerequisite of any implementation, highlighted a lack of comparable dietary assessment methods and support infrastructure for research across the 18 countries represented, and elucidated specific needs and obstacles for implementation.

DEX, as part of its advanced methodological research on improving dietary assessment (Freisling and Slimani, 2015; Leclercq et al., 2015; Julián-Almárcegui et al., 2015; Slimani et al., 2015) and its contribution to the transfer of knowledge and training (Figure 1), and through partnerships and grant projects (e.g. Determinants, Intake, Status, Health [EuroDISH]; Biobanking and Biomolecular Resources Research Infrastructure – Large Prospective Cohorts [BBMRI-LPC]; Determinants of Diet and Physical Activity [DEDIPAC]; and Pilot Study for the Assessment of Nutrient Intake and Food Consumption Among Kids in Europe [PANCAKE]), has led the development of a strong virtual research environment/research infrastructure (GloboDiet-VRE/RI) concept. GloboDiet-VRE/RI aims to support the GloboDiet initiative, as well as new international targeted tools (e.g. tools targeted to children validated in the PANCAKE project) (Freisling et al., 2015; Ocké et al., 2015) and validation against biomarkers of WHO health indicators obtained with GloboDiet (e.g. sodium intakes) (De Keyzer et al., 2015a). This GloboDiet-VRE will feed into the European Strategy Forum on Research Infrastructures (ESFRI) road map of implementation of a pan-European Union interfaced food and nutrient intake RI.

New approaches to analyse nutrient patterns in international study settings have been initiated by DEX in collaboration with the Nutritional Epidemiology Group (NEP), starting with a first European-wide nutrient patterns analysis (Moskal et al., 2014). These patterns were shown to be associated with moderate but significant long-term differences in weight gain in adults.

Figure 1. Towards an integrated approach to measure diet in international epidemiological studies. Reprinted from Illner AK, Freisling H, Boeing H, Huybrechts I, Crispim SP, Slimani N (2012). Review and evaluation of innovative technologies for measuring diet in nutritional epidemiology. Int J Epidemiol. 41(4):1187–203. http://dx.doi.org/10.1093/ije/dys105 PMID:22933652, by permission of Oxford University Press.



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European Prospective Investigation into Cancer and Nutrition (EPIC)

The Nutritional Epidemiology Group (NEP) ensures the coordination of the European Prospective Investigation into Cancer and Nutrition (EPIC) by centralizing up-to-date cancer end-point/vital status data (Table 1), centralizing multiple end-points and updated exposure information, delivering project-specific databases to the EPIC network, and tracking biological sample retrieval/use.

Nutritional and lifestyle cancer predictors

Obesity

Maintaining a healthy weight is important for cancer prevention. NEP's analysis, in collaboration with the Dietary Exposure Assessment Group (DEX) and the Biomarkers Group (BMA), of circulating industrial trans fatty acids (biomarkers of highly processed foods) shows a positive association with weight gain over time (Chajès et al., 2015) and has been extended to countries in Latin America, the Middle East, and Africa.

Alcohol consumption and cancer

Higher lifetime alcohol consumption was identified as a major determinant of mortality (Ferrari et al., 2014). However, an inverse association was noted for papillary and follicular thyroid carcinomas (Sen et al., 2015). A consortium of worldwide cohorts was created to evaluate alcohol–cancer associations at less-studied anatomical sites.

Early environmental exposure, metabolic disorders, and cancer

NEP's study of fetal and childhood exposures and the incidence of intermediate cancer outcomes shows an influence of supplementation with docosahexaenoic acid (DHA) on methylation at *IGF2/H19* imprinted genes (Lee et al., 2014a) and an important role of breastfeeding on lowered adiposity and total cholesterol levels in childhood (Ramirez-Silva et al., 2015).

Breast cancer

NEP's work on dietary and lifestyle patterns has shown reduced breast cancer risk in women with nutrient patterns high in micronutrients originating from vegetables, fruits, and cereals, or women who score highly on a healthy lifestyle index (McKenzie et al., 2015). Further analysis showed a link between higher alcohol consumption and breast cancer of all receptor-based phenotypes, particularly among women consuming alcohol before their first full-term pregnancy (Figure 1) (Romieu et al., 2015).

Two nutrients of interest are dietary folate and fatty acids. Higher intake of dietary folate was associated with lower risk of estrogen receptor (ER)-negative breast cancers in premenopausal women (de Batlle et al., 2015). Preliminary biomarker-based results suggest different breast cancer risks for specific fatty acid subgroups (Pouchieu et al., 2014).

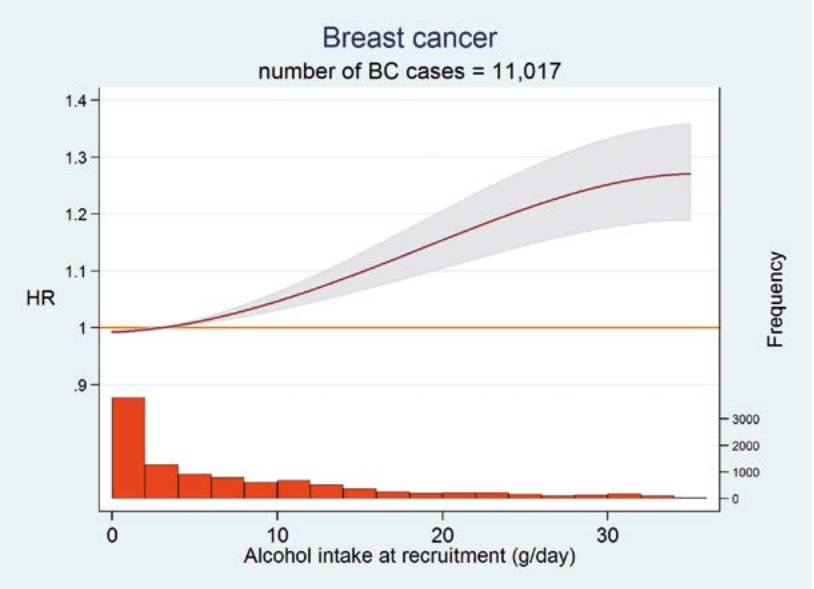
Studies on breast cancer in low- and middle-income countries

NEP collaborated with national institutions in Mexico in the large prospective Mexican Teachers' Cohort to explore

Table 1. Description of the European Prospective Investigation into Cancer and Nutrition (EPIC) study

Sex	Country	Number of participants	Person-years	Number of incident cancers	Number of incident deaths
Women	France	74 523	1 420 115	9015	5723
	Italy	32 577	498 612	3561	1551
	Spain	25 808	479 249	2288	1528
	United Kingdom	60 967	1 007 559	7325	7669
	Netherlands	29 751	484 984	3579	3042
	Greece	16 614	181 903	770	1213
	Germany	30 255	411 560	2354	1453
	Sweden	30 328	552 306	4620	4668
	Denmark	29 875	490 930	5778	4110
	Norway	37 200	514 326	3802	1452
	Total	367 898	6 041 544	43 092	32 409
Men	France	—	—	—	—
	Italy	15 168	237 627	1829	1133
	Spain	15 629	284 030	2466	2155
	United Kingdom	26 917	424 843	4445	6396
	Netherlands	10 260	166 222	869	885
	Greece	11 947	121 475	740	1537
	Germany	22 833	311 217	2597	2590
	Sweden	23 494	413 112	4764	5455
	Denmark	27 178	428 296	6206	5886
	Norway	—	—	—	—
	Total	153 426	2 386 821	23 916	26 037

Figure 1. Dose–response curve of breast cancer (BC) risk with alcohol intake at recruitment. The dose–response curve is displayed up to 35 g/day, corresponding to the 99th percentile of the alcohol intake distribution. Reprinted with permission from Romieu et al. (2015).



predictors of mammographic density (Rinaldi et al., 2014a; Rice et al., 2015). Results from a multicentre case–control study conducted in Mexico show increased breast cancer risks with increasing body shape silhouette over the life course (Amadou et al., 2014a), high carbohydrate intake (Amadou et al., 2015), and lower scores on a healthy lifestyle index (Fanidi et al., 2015).

NEP leads a World Cancer Research Fund (WCRF)-funded study of dietary/lifestyle determinants of breast cancer in the understudied population of Soweto, South Africa, with structured collection of individual, clinical, and pathological information, biological specimens, and detailed anthropometry (DEXA/ultrasound). This study will provide relevant information on tumour subtype frequencies and specific risk factors for breast cancer incidence and survival.

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

NEP coordinates the PRECAMA project to explore risk factors for premenopausal breast cancer among Hispanic women in four Latin American countries (Chile, Colombia, Costa Rica, and Mexico). The standardized protocols (refined phenotyping, identification of endogenous or exogenous risk factors) and structured collection of individual, clinical, and pathological information and biological specimens were successful in the feasibility study (http://precama.iarc.fr). The main study is now under way, with Brazil also joining.

Colorectal cancer

Inverse associations with risk of colorectal cancer were observed with higher circulating selenoprotein P levels (a selenium status indicator) (Hughes et al., 2015), higher plasma alkylresorcinols (biomarkers of whole-grain intake), for the distal colon cancer only (Kyrø et al., 2014a), and lower endogenous energy excess, for rectal cancer only. Post-diagnosis survival of colorectal cancer patients was improved with lower pre-diagnostic general/abdominal adiposity (Fedirko et al., 2014a) or concordance with the WCRF/American Institute of Cancer Research (WCRF/AICR) cancer prevention guidelines (Romaguera et al., 2015).

Hepatocellular carcinoma

Associations with decreased risk of hepatocellular carcinoma were observed with higher consumption of monounsaturated fats (Duarte-Salles et al., 2015), vegetables (Bamia et al., 2015a), or coffee/tea (Bamia et al., 2015b) and with lower consumption of sugary drinks and of milk/cheeses (Duarte-Salles et al., 2014). Multiplatform metabolomic analyses identified distinct profiles between cases and matched controls (Fages et al., 2015), particularly with respect to levels of some amino acids.

Methodological research

NEP has developed statistical techniques to correct for measurement errors in episodically consumed foods (Agogo et al., 2014) and to evaluate individual-level and aggregate-level evidence of diet–disease associations using multilevel modelling (Sera and Ferrari, 2015). Analytical frameworks were conceptualized to explore major sources of variability in large-dimensional data (e.g. metabolomics; Fages et al., 2014) and to model the "meeting-in-the-middle" principle linking dietary/lifestyle exposures and cancer risks through metabolomics (Assi et al., 2015). The treelet transform was identified as an informative technique to investigate dietary patterns in breast cancer etiology.

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