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The Section of Nutrition and Metabolism (NME) comprises the Biomarkers Group (BMA), the Nutritional Epidemiology Group (NEP), and the Nutritional Methodology and Biostatistics Group (NMB). The Section combines large-scale population-based studies with laboratory and biostatistical expertise to identify causal links between nutrition, metabolic factors, and cancer. The goal of NME is to provide robust evidence on the role of nutrition in cancer development that can translate to clinical interventions and public health policy.

After the retirement of Dr Isabelle Romieu and the arrival of Dr Marc Gunter in February 2016, the Section was reorganized to align with its new research priorities. Greater emphasis has been placed on conducting molecular research that integrates omics data, including metabolomics, hormone measurements, genomics, and epigenomics within population-based cohorts in Europe as well as in low- and middle-income countries. NME also benefits from extensive international collaborations and leads projects in international consortia comprising millions of study participants. Major research themes within the Section include understanding the biological basis for the link between obesity, metabolic dysfunction, and cancer; identifying nutritional biomarkers and metabolic fingerprints of diet through interventions and observational studies and studying their relationship with cancer; and studies on multimorbidity that identify common pathways underlying the development of cancer, diabetes, and cardiovascular disease.

Biomarkers Group (BMA)

Biomarkers of meat consumption

A human intervention study was conducted in collaboration with Imperial College London and University College Dublin to identify biomarkers of meat and fish intake using a metabolomic approach based on high-resolution mass spectrometry (Cheung et al., 2017). Several compounds detected in urine or blood were found to be highly specific for intake of chicken (3-methylhistidine and anserine), fish (trimethylamine-*N*-oxide), and red meat (acylcarnitines and carnosine). These markers were also found to accurately predict intake of the same foods in 475 subjects from the European Prospective Investigation

into Cancer and Nutrition (EPIC) cross-sectional study (Figure 1).

Exposome-Explorer

Exposome-Explorer, a new database on biomarkers of exposure to environmental risk factors, was developed and is available in the public domain (Figure 2) (Neveu et al., 2017). This database contains detailed information collected from peer-reviewed publications on the nature of 692 dietary and pollutant biomarkers, more than 10 000 concentration values in various populations, and data on correlations with food intake and on biological reproducibility over time. This database also enables the comparison of the performance of biomarkers of exposure for various dietary factors – information that can be used to define panels of biomarkers for dietary-wide association studies on cancer.

Biomarkers of mammographic density

Associations between circulating leptin and adiponectin and mammographic density were evaluated in Mexican premenopausal women from the large Mexican Teachers' Cohort. Leptin and

Figure 1. Correlation heat map of the 18 biomarkers associated with meat and fish intake in the European Prospective Investigation into Cancer and Nutrition (EPIC) cross-sectional study. The size and colour of the circles indicate the magnitude of correlation between biomarkers. Reproduced with permission from Cheung et al. (2017).

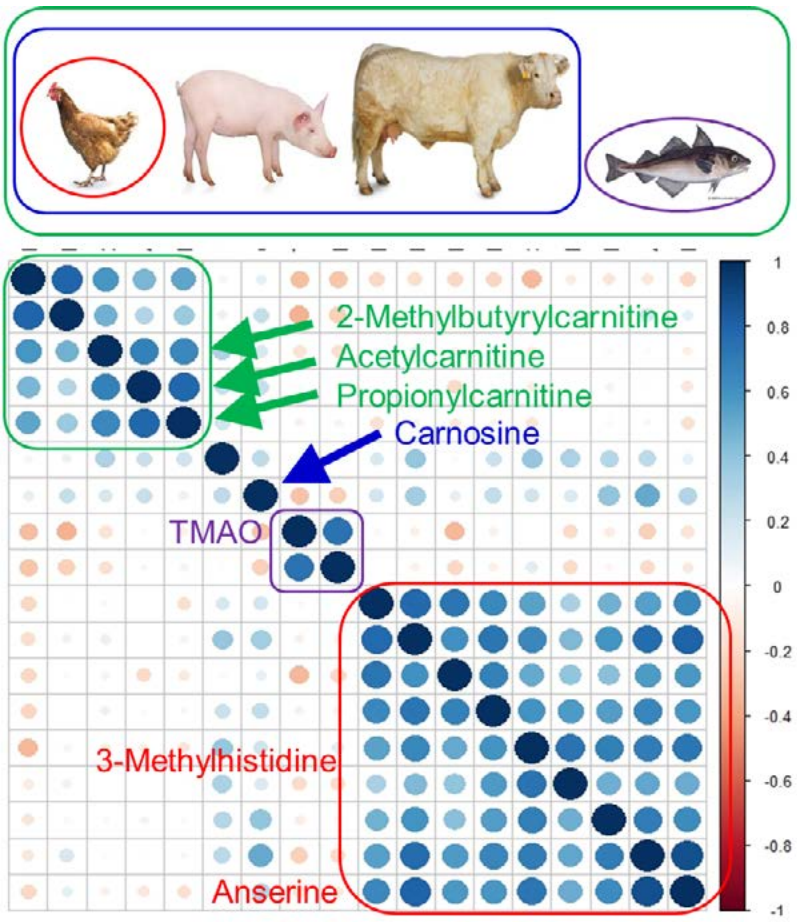
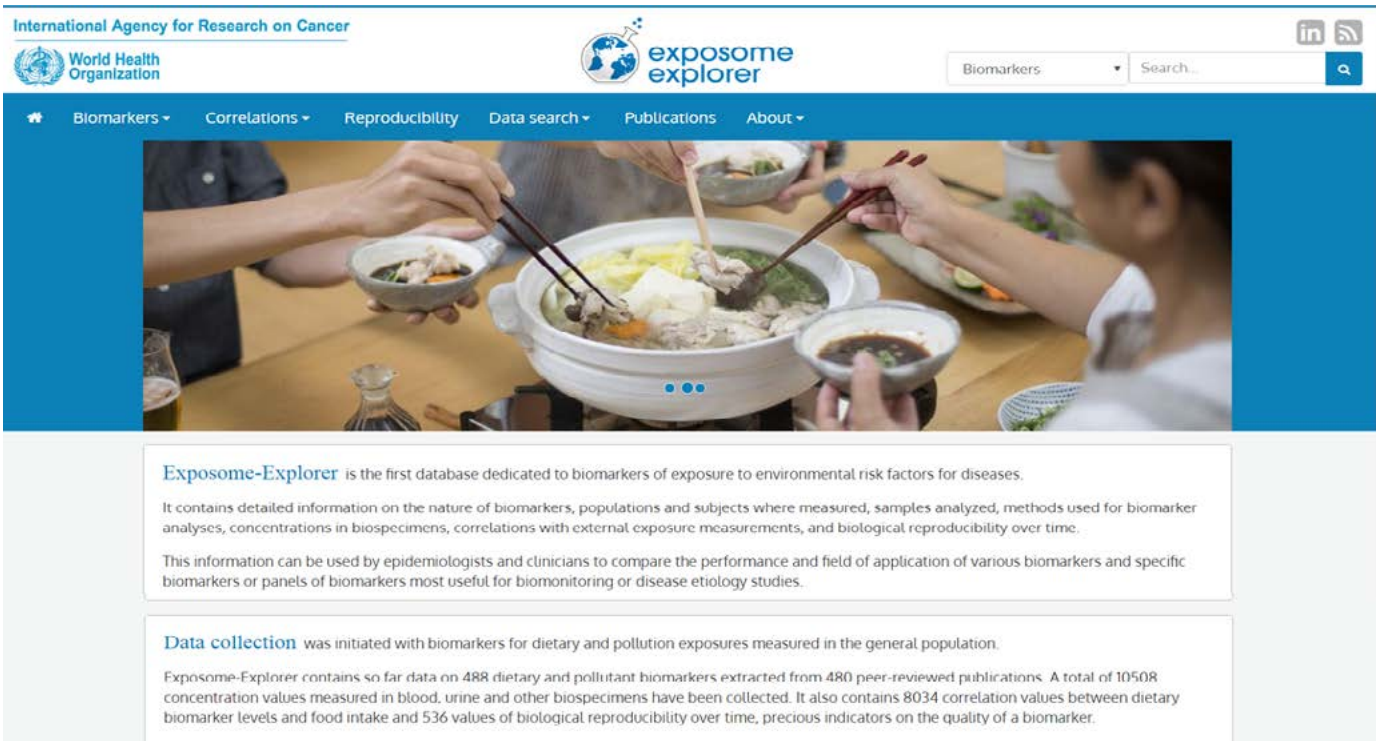


Figure 2. Screenshot of the homepage of the Exposome-Explorer website (http://exposome-explorer.iarc.fr/).



adiponectin are adipose tissue-derived cytokines that regulate cell proliferation and apoptosis. Variation in circulating levels of these cytokines has been linked to breast cancer development, but few studies have assessed their association with mammographic density – a marker for breast cancer risk. In this study, high leptin levels and the leptin/adiponectin ratio were found to be significantly associated with lower mammographic density in premenopausal women. These findings may shed light on potential mechanisms linking adiposity to lower risk of breast cancer in premenopausal women.

Thyroid cancer studies

One focus of BMA is exploring the etiology of thyroid cancer, which is the most common endocrine malignancy worldwide. Following on from a series of studies that examined hormonal factors in relation to thyroid cancer risk in EPIC, BMA explored the association between various dietary factors and thyroid cancer development. No significant associations were observed for fish consumption overall or for any specific type of fish, or for fruits and vegetables; however, a positive borderline trend with intake of fruit juice was observed, possibly related to its high sugar content (Zamora-Ros et al., 2017a).

Dietary Exposure Assessment Group (DEX)

until June 2016

Global Nutrition Surveillance initiative

The Dietary Exposure Assessment Group (DEX) launched the Global Nutrition Surveillance initiative (GloboDiet) to support the collection of standardized dietary data worldwide for surveillance and research for prevention of cancer and other noncommunicable diseases. Seven European countries have already implemented GloboDiet in their national surveys, and the concept was subsequently expanded to other regions worldwide. Brazilian and Mexican versions of GloboDiet have been advanced or completed (Bel-Serrat et al., 2017) for local implementation, for example in the Brazilian Longitudinal Study of Adult Health (ELSA) cohort. For Africa, preparatory work has enabled the evaluation of the specific needs and constraints in applying GloboDiet in this region (Aglago et al., 2017a) and the proposal of new approaches for optimizing its implementation across Africa. IARC continues to support where possible the transfer of the GloboDiet methodology to interested users at the national level.

In addition, DEX pursued a series of activities on the compilation of new international nutrient databases (Nicolas et al., 2016), meal pattern analyses, and new approaches for analysing nutrient patterns and their association with cancer and its risk factors (Freisling et al., 2016; Moskal et al., 2016), in close collaboration with the other Groups in NME.

Nutritional Epidemiology Group (NEP)

Fatty acid metabolism and breast cancer

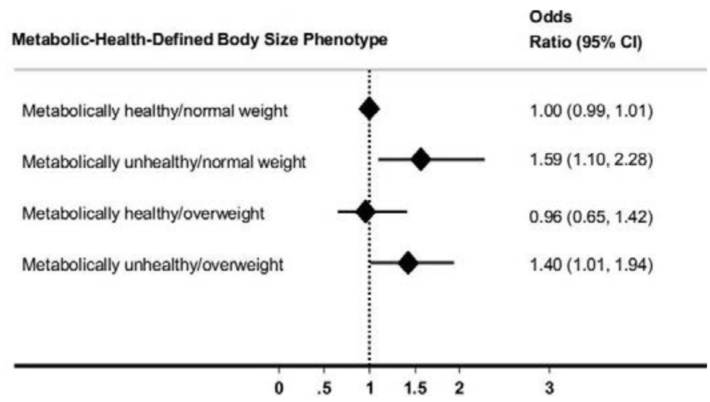
In a case–control study nested within EPIC, 60 plasma phospholipid fatty acids were measured by gas chromatography in 2982 incident breast cancer case–control pairs. Levels of palmitoleic acid were positively associated with risk of breast cancer, and higher levels of industrial trans-fatty acids were specifically associated with estrogen receptor (ER)-negative breast tumours. These findings suggest that increased de novo lipogenesis, acting through increased synthesis of palmitoleic acid, could be a relevant metabolic pathway for breast tumorigenesis (Chajès et al., 2017).

Metabolically defined body size phenotypes and colorectal cancer

Obesity is a metabolically heterogeneous condition, and although metabolic abnormalities such as hyperinsulinaemia are common in obesity, not all obese individuals exhibit elevated insulin levels. Furthermore, a subset of individuals of normal weight are hyperinsulinaemic. In a nested case–control study within EPIC comprising 750 case–control pairs, we found that lean individuals with elevated insulin levels were at equivalent elevated risk of colorectal cancer as their obese hyperinsulinaemic counterparts. Conversely, metabolically healthy obese

individuals did not have excess risk of colorectal cancer (Figure 3). These findings suggest that metabolic health defined by insulin sensitivity may be an important and etiologically relevant phenotype for colorectal cancer, rather than obesity per se (Murphy et al., 2016a).

Figure 3. Association of metabolically defined body size subtypes with risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). Figure compiled from Murphy et al. (2016a).



Coffee drinking and mortality

The association of coffee drinking with cause-specific mortality was investigated in EPIC, where 41 693 deaths have occurred following a mean follow-up of 16 years. Compared with non-consumers, consumers in the highest quartile of coffee consumption experienced lower all-cause mortality: 12% lower for men, and 8% lower for women. Inverse associations were particularly pronounced for digestive disease and cardiovascular mortality. Coffee consumption was also associated with a healthier liver enzyme profile, defined by lower serum alkaline phosphatase, alanine transaminase, and aspartate transaminase, lower C-reactive protein, and better glucose control (Gunter et al., 2017).

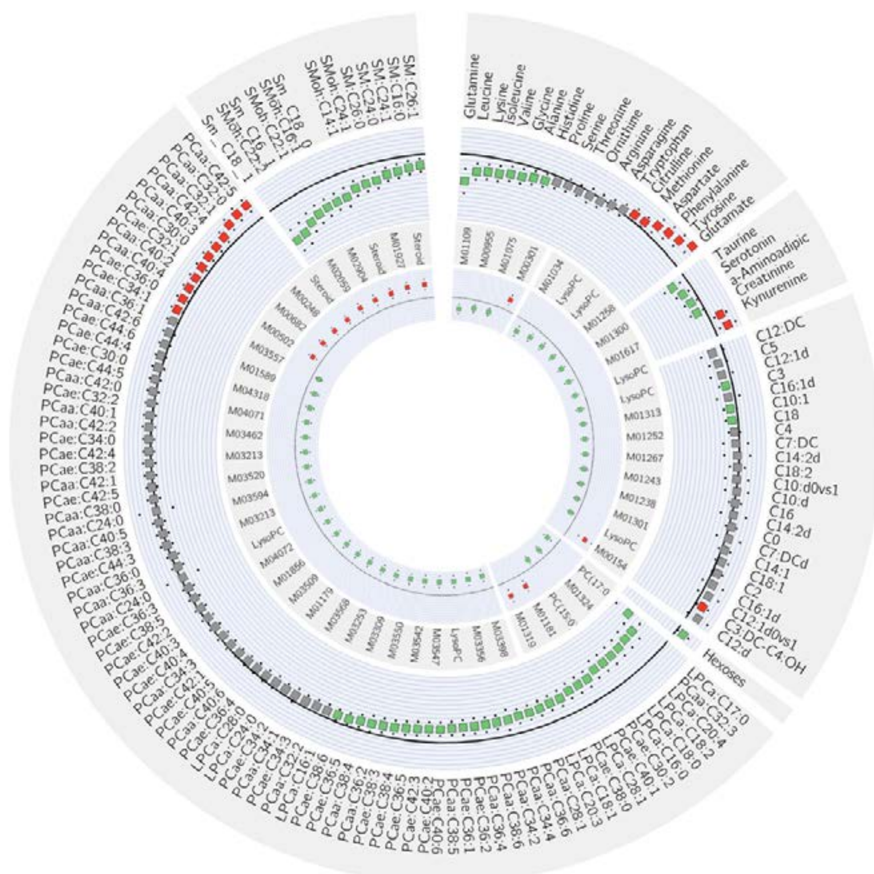
Metabolomics and liver cancer

Our previous research has shown that unhealthy lifestyle exposures have a diverse range of metabolic consequences. To explore these in more detail, in collaboration with BMA, we applied mass spectrometry-based metabolomics to pre-diagnostic blood samples taken from hepatocellular cancer cases and matched controls. Our findings show that development of hepatocellular cancer is associated with liver dysfunction, marked alterations in amino acid levels, and alterations in bile acid and bilirubin metabolism (Figure 4) (Stepien et al., 2016a, 2016b).

Microbial exposures and colorectal cancer

Within a prospective analysis in EPIC, we showed that unhealthy lifestyle exposures can alter gut barrier function, allowing leakage of toxic bacterial metabolites into the systemic circulation, and possibly even bacterial translocation (Kong et al., 2016). In a follow-up study in the same population, we observed statistically significant higher levels of circulating antibodies to *Streptococcus gallolyticus* subspecies *gallolyticus* (SGG), a commensal bacterium that can induce infective endocarditis and can directly colonize colorectal tissue.

Figure 4. Metabolites linked to higher (red) or lower (green) risk of hepatocellular carcinoma. Figure compiled from Stepien et al. (2016a).



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

Together with BMA, NEP coordinates three new studies on breast cancer in low- and middle-income countries, specifically in Morocco (Determinants of Breast Cancer in Morocco; EDSMAR), South Africa (South Africa Breast Cancer; SABC), and Latin America (Molecular Subtypes of Premenopausal Breast Cancer in Latin American Women; PRECAMA).

Within these studies, the recruitment of cases and matched controls is complete or ongoing. Questionnaire data are being collected, as well as blood and tumour tissue and, for EDSMAR, urine, stool samples, and adipose tissue.

Preliminary analyses in PRECAMA have revealed associations of breast cancer with reproductive factors concordant with data from other regions and an inverse association between adiposity measures and breast cancer. Tumour mutation analyses are currently under way, in collaboration with MMB.

Nutritional Methodology and Biostatistics Group (NMB)

from July 2016

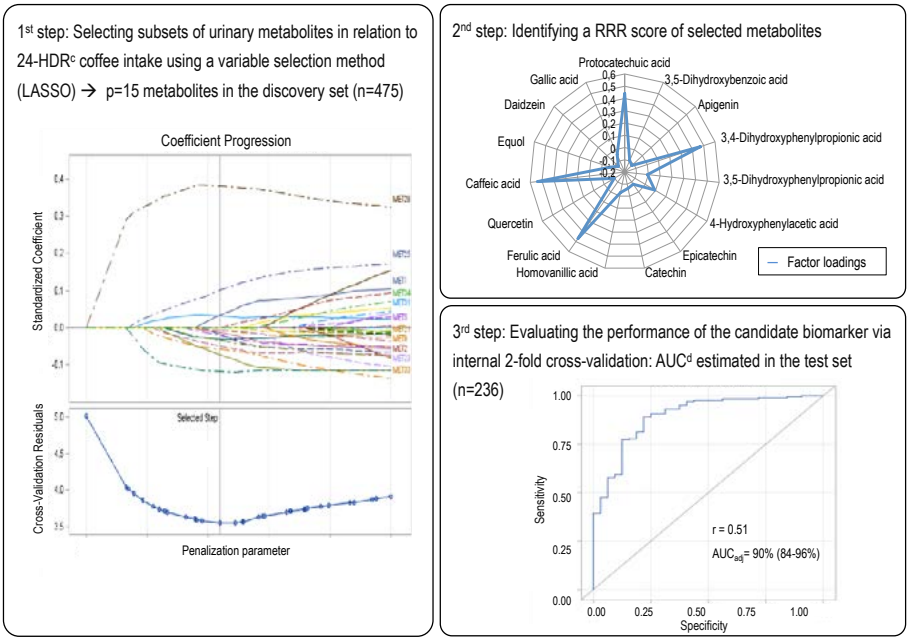
Alcohol and cancer

The Nutritional Methodology and Biostatistics Group (NMB) coordinates a large pooled analysis within the National Cancer Institute (NCI) Cohort Consortium, including data from 36 cohort studies and more than 2.7 million participants to comprehensively investigate the role of alcohol consumption and drinking patterns on risk of cancer. A systematic review of current epidemiological evidence on the relationship between alcohol intake and risk of oesophageal cancer was conducted, evaluating putative mechanisms and genetic susceptibility markers (Matejcic et al., 2017a). Furthermore, a study in EPIC including 1802 cases of urothelial cell carcinoma showed that baseline and lifetime intakes of alcohol were not associated with risk of urothelial cell carcinoma (Botteri et al., 2017). An analysis investigating the interaction between dietary fibre and alcohol intake in EPIC showed that high fibre intake can potentially mitigate the positive association of alcohol intake with risk of breast cancer (Romieu et al., 2017a).

Statistical methodology

A novel algorithm combining dimension reduction and variable selection methods was developed to identify urinary polyphenol metabolite patterns through the application of the least absolute shrinkage and selection operator (LASSO) and reduced rank regression (RRR) (Figure 5) (Noh et al., 2017). An analytical framework to model the "meeting-in-the-middle" principle demonstrated the utility of modelling metabolite profiles compared with questionnaire-based data in relating a healthy lifestyle index score to risk of hepatocellular carcinoma. Study design and statistical considerations to evaluate the validity of dietary biomarkers were extensively described and discussed (Ferrari, 2017). The estimation of specific quantiles of the distribution of laboratory data is greatly hindered by

Figure 5. A novel algorithm combining variable selection (least absolute shrinkage and selection operator [LASSO]) with dimension reduction (reduced rank regression [RRR]) to identify urinary polyphenol metabolite patterns. 24-HDR, 24-hour dietary recall; AUC, area under the curve. Figure compiled from Noh et al. (2017).



the presence of observations below the limit of detection, leading to left-censored data. Two different model-averaged quantile estimators derived from semi-nonparametric extensions of the log-normal distribution were defined and compared through simulations and then illustrated using data on cadmium concentration in food products (Nysen et al., 2016).

Obesity, dietary patterns, and cancer

In a treelet transform analysis, which combines features for dimension reduction with a clustering technique for individual nutrients, a treelet transform component reflecting plant-based nutrients was inversely associated with breast cancer risk (Assi et al., 2016). The healthy lifestyle index score – reflecting smoking, alcohol consumption, physical activity, body mass index, and healthy diet – was related to the risk of cancer, overall and by major subgroups (McKenzie et al., 2016b). A comparison of different measurements of adiposity was shown to predict risk of obesity-related cancer in older adults in a similar manner (Freisling et al., 2017).