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The Section of Nutrition and Metabolism (NME) comprises three highly integrated groups: 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 the Section is to provide robust evidence on the role of nutrition in cancer development that can be translated to clinical interventions and public health policy. NME aims to go beyond what may be considered as the traditional domains of nutrition in cancer research and to fully exploit methodological advances in –omics and molecular profiling techniques to implement an integrated, multidisciplinary programme of research. The overall strategic vision of NME is based on three major research themes: (i) understanding the role of obesity and metabolic dysfunction in cancer development; (ii) identification of biomarkers of diet and nutrition and their application within studies of cancer; and (iii) multimorbidity and biological pathways common to cancer, diabetes, and cardiovascular disease. Within these themes, NME focuses on a core set of cancer sites, primarily gastrointestinal cancers, as well as hormone-related cancers, such as breast cancer and endometrial cancer. A particular emphasis is placed on cancer types that have clear links to nutrition and metabolic abnormalities and for which much remains to be discovered about disease etiology.

Biomarkers Group (BMA)

Metabolic profiles and breast cancer risk

To identify novel pathways of breast cancer development, targeted metabolomics was applied to samples from incident breast cancer cases and matched controls from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. In women not using exogenous hormone therapy at baseline (n = 2248), concentrations of arginine, asparagine, and phosphatidylcholines were inversely associated with breast cancer risk, and the concentration of acylcarnitine C2 was positively associated (Figure 1) (His et al., 2019). These findings point to potentially novel pathways that involve dysregulated amino acid, lipid, and energy metabolism in breast cancer development.

Inflammation biomarkers and thyroid cancer

Inflammation has been hypothesized to represent an etiological pathway for thyroid cancer development, but epidemiological data are limited. In a case–control study nested within EPIC, which included 475 first primary incident thyroid cancer cases and 1016 matched controls, adiponectin levels were inversely associated with risk of thyroid cancer in women but not in men. Interleukin-10 levels were positively associated with risk of thyroid cancer in women only (Dossus et al., 2018).

Coffee biomarkers and risk of liver cancer

Coffee drinking is associated with a lower risk of liver cancer, but the biological basis of this relationship is not understood. To advance knowledge in this area, 11 coffee metabolites were identified in blood from 451 subjects from the EPIC cohort (Rothwell et al., 2019a). In collaboration with the United States National Cancer Institute, BMA identified novel associations between coffee-related metabolites and liver cancer in two case–

Figure 1. Odds ratios (ORs) and permutation-based stepdown minP adjusted *P* values for associations between metabolites and risk of breast cancer in hormone non-users (1124 cases and 1124 controls). ORs are estimated per standard deviation (SD) increase in log-transformed metabolite concentrations, from logistic regression conditioned on matching variables. Adjusted *P* values greater than 0.05 (dashed line) were considered to be statistically significant after correction for multiple tests. PC, phosphatidylcholine; SM, sphingomyelin. Reproduced from His et al. (2019). CC BY 3.0 IGO.

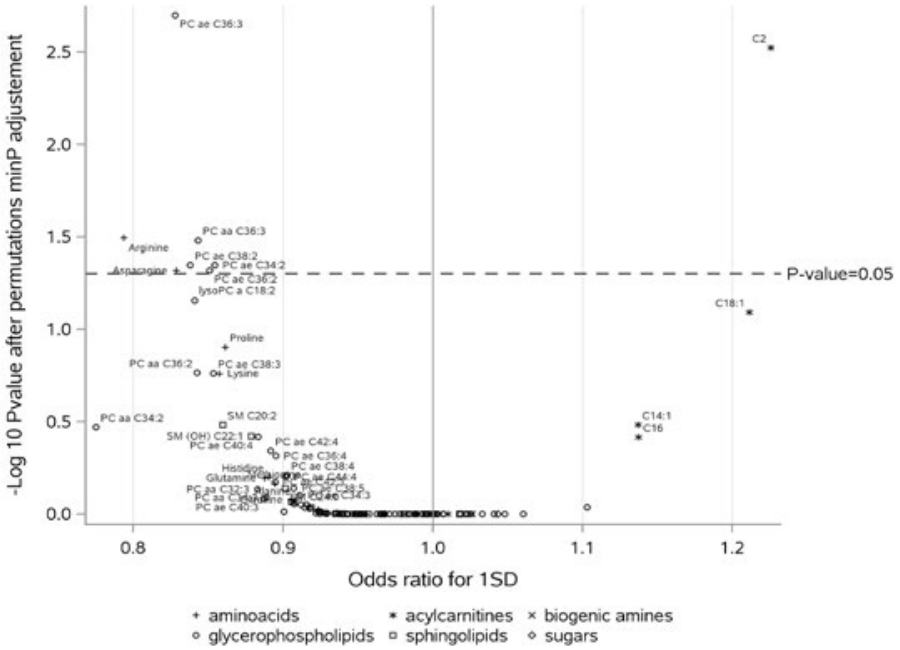
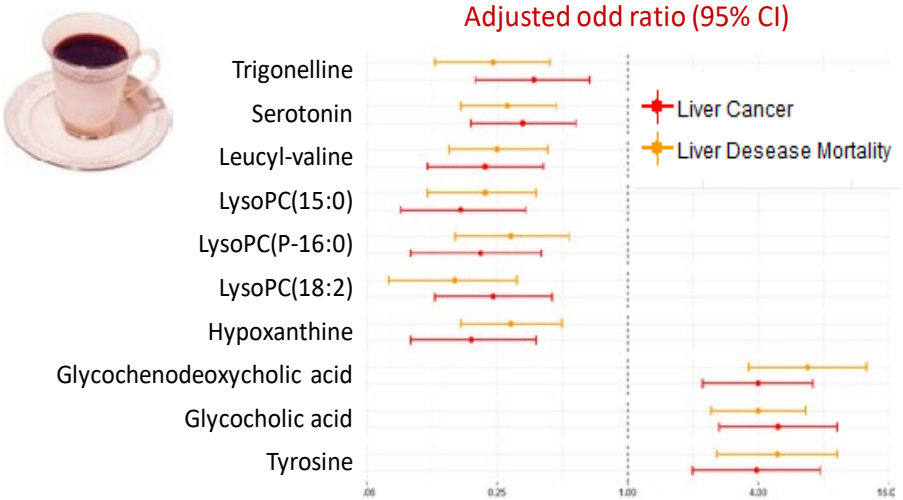


Figure 2. Odds ratios and 95% confidence intervals (CIs) for incident liver cancer and liver disease death comparing men in the 90th and 10th percentiles in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention cohort, for 10 metabolites associated with coffee intake. Compiled from Loftfield E, Rothwell JA, Sinha R, Keski-Rahkonen P, Robinot N, Albanes D, et al. (2019). Prospective investigation of serum metabolites, coffee drinking, liver cancer incidence, and liver disease mortality. J Natl Cancer Inst. djz122. https://doi.org/10.1093/jnci/djz122 PMID:31168595.



control studies nested within the EPIC and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention cohorts, indicating common mechanisms that may explain the lower risk of liver cancer in coffee drinkers (Figure 2).

Wholegrain intake and intestinal serotonin production

Wholegrain intake is associated with a decreased risk of colorectal cancer, but the underlying mechanisms are not well understood. A BMA study aimed to characterize the metabolic effects of wholegrain intake by performing untargeted metabolomic analyses in a clinical dietary intervention. Among various metabolic changes, decreased plasma concentrations of serotonin were identified after consumption of wholegrain rye, compared with controls. In agreement with these results, a decrease was observed in serotonin concentrations in the colonic mucosa of mice fed a meal supplemented with rye bran or wheat fibres (Figure 3). These results suggest that decreased peripheral serotonin production may represent a link between the effects of wholegrain consumption and the risk of colorectal cancer (Keski-Rahkonen et al., 2019).

Polyphenols and risk of colon cancer

Polyphenols are major antioxidants in the diet, known for their antimutagenic and anticarcinogenic properties. A novel and highly sensitive assay based on mass spectrometry was developed to measure 37 polyphenols in blood samples (Achaintre et al., 2018). The assay was applied in a nested case–control study in the EPIC cohort to evaluate the relationship between pre-diagnostic plasma levels of polyphenols and risk of colon cancer (Murphy et al., 2018a). Two polyphenols were significantly associated with risk of colon cancer, including equol, a metabolite that is formed from soy isoflavones by the gut microbiota and is known for its estrogenic properties (Figure 4).

Figure 3. (A) Serotonin in fasting plasma after two 4-week intervention periods in crossover design. (B) Tissue serotonin in the intestines of mice fed similar high-fat diets containing different sources of dietary fibre for 9 weeks: powdered cellulose (*n* = 14), rye bran flour (*n* = 11), or wheat aleurone (*n* = 9) with matched calorie density, macronutrient, and dietary fibre content. (A) © IARC (B) © Keski-Rahkonen et al. (2019), by permission of Oxford University Press.

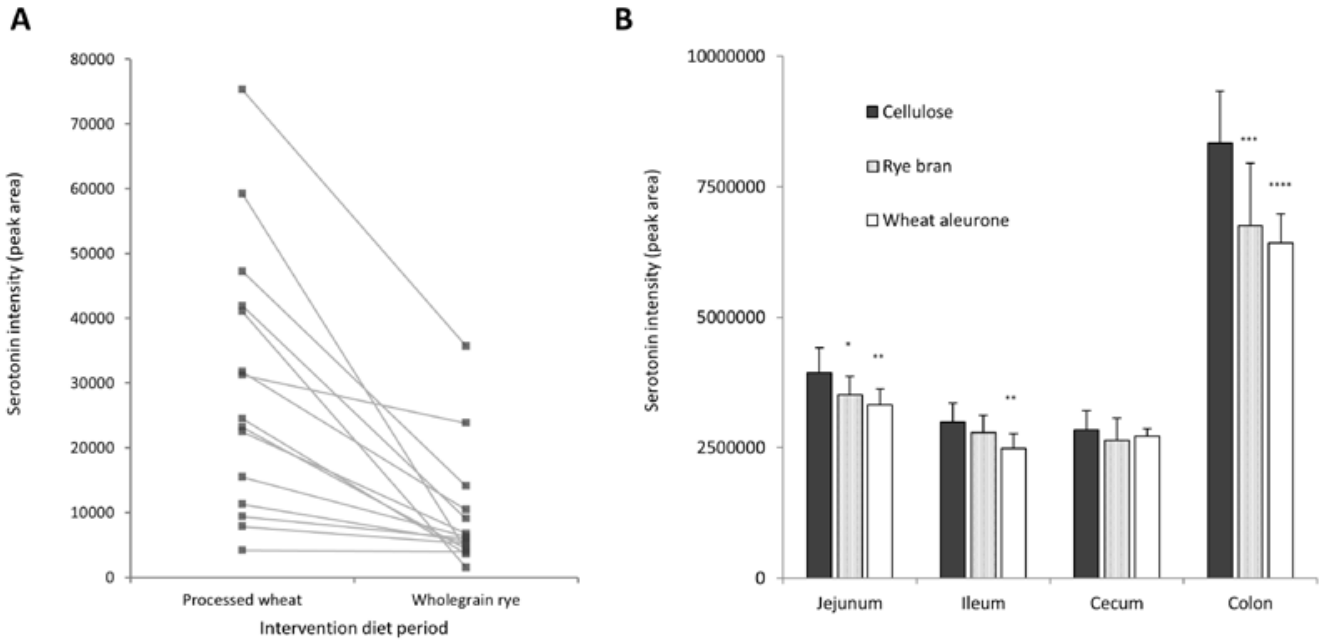
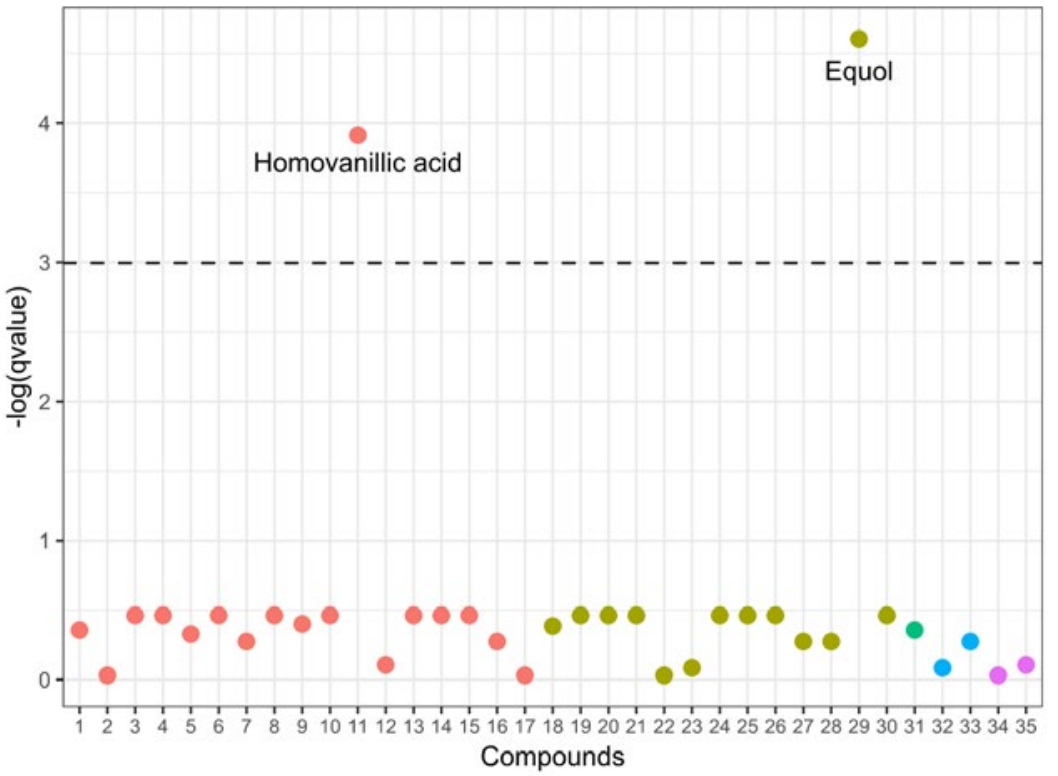


Figure 4. Associations between log2-transformed polyphenol concentrations and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Compiled from Murphy et al. (2018a).



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

NME is coordinating 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).

Patients attending the breast unit at Chris Hani Baragwanath Hospital, Johannesburg, South Africa. © IARC.

Preliminary analyses from PRECAMA showed that reproductive factors are differentially associated with breast cancer subtypes in young Latin American women: an older age at first full-term pregnancy and at last pregnancy were associated with an increased risk of estrogen receptor-positive (ER+) tumours; pregnancy, number of childbirths, and history of breastfeeding were inversely associated with the risk of ER+ tumours; and older age at menarche and longer duration of breastfeeding were inversely associated with risk of estrogen receptor-negative (ER−) tumours.

Results from the SABC study showed that 91% of the study population had at least one metabolic condition (e.g. adiposity, hypertension, or impaired glucose) or another comorbidity (e.g. depression or HIV), highlighting the need to address the chronic noncommunicable disease epidemic in South Africa and to coordinate multidisciplinary care.

Analyses of food intake suggested that consumption of fresh fruit was associated with a lower risk of breast cancer in premenopausal women, whereas consumption of savoury food was associated with a higher risk in postmenopausal women (Romieu et al., 2018; Ayeni et al., 2019; Jacobs et al., 2019).

Nutritional Epidemiology Group (NEP)

Fish, long-chain fatty acids, and colorectal cancer

The link between fish and marine n-3 long-chain polyunsaturated fatty acid (LC-PUFA) intake and colorectal cancer is uncertain. NEP has examined how fish consumption and dietary and circulating levels of n-3 LC-PUFA are associated with colorectal cancer risk in the EPIC cohort. Compared with individuals consuming very little fish, those eating the highest levels had a 12% lower risk of colorectal cancer over a 16-year follow-up period. Similarly, those in the highest category of intake of n-3 LC-PUFA had a 14% lower risk of colorectal cancer compared with individuals with the lowest intakes. Regular consumption of fish may lower the risk of colorectal cancer, possibly through exposure to n-3 LC-PUFA. Following international recommendations for fish and n-3 LC-PUFA intake may reduce an individual's risk of colorectal cancer (Aglago et al., 2019).

Energy balance, metabolic health, and liver cancer

NEP has previously shown that an increased risk of hepatocellular carcinoma is associated, in part, with unhealthy lifestyle patterns, such as being physically inactive (Baumeister et al., 2019). Unhealthy lifestyle factors may act collectively to weaken the protective barrier functionality of the gut, hence increasing the exposure of the liver to environmental carcinogens, or may

cause perturbations in the metabolism of bile acids, further exposing the liver to carcinogenic compounds. Poor dietary habits may also lead to lower blood levels of micronutrients, such as selenium and zinc, both of which have been shown to be associated with a higher risk of hepatocellular cancer. Overall, numerous clear metabolic differences have been observed between cases of hepatocellular cancer and controls, assessed using high-resolution liquid chromatography–mass spectrometry metabolomic methods in collaboration with BMA.

Consumption of soft drinks and mortality

The association between total, sugar-sweetened, and artificially sweetened soft drinks consumption and subsequent total and cause-specific mortality was evaluated in 451 743 individuals from the EPIC cohort. Compared with those consuming less than 1 glass per month, individuals drinking 2 or more glasses per day of total soft drinks had a 17% higher risk of all-cause mortality. For consumers of sugar-sweetened soft drinks, the risk of premature death was elevated by 8%; for artificially sweetened soft drinks, the risk was increased by 26%. These results support public health campaigns aimed at limiting the consumption of soft drinks.

Physical activity and breast and colorectal cancer: genetic studies

Epidemiological studies have consistently observed inverse relationships between physical activity and risks of breast cancer and colorectal cancer, but they have generally relied on self-reported measures of physical activity, which may be prone to bias. NEP examined the associations between genetic variants associated with physical activity and risk of breast cancer (122 977 breast cancer cases and 105 974 controls) and of colorectal cancer (58 221 colorectal cancer cases and 67 694 controls). An increment of one standard deviation in genetically predicted average physical activity was associated with a 41% lower risk of breast cancer and a 34% lower risk of colorectal cancer. These results support a potentially causal relationship between higher physical activity levels and lower risks of breast cancer and colorectal cancer.

Nutritional Methodology and Biostatistics Group (NMB)

Alcohol and cancer

The association between alcohol consumption and cancer risk is still ambiguous for certain cancer sites, and the underlying biological pathways are not understood. Within the EPIC study, alcohol intake was associated with risk of pancreatic cancer (Naudin et al., 2018). Using novel statistical methodology to examine potential mechanisms, NMB found that concentrations of specific sex hormones did not have a major role in the relationship between alcohol intake and risk of breast cancer. The application of –omics to understand the link between alcohol consumption and cancer is also a promising area of study within the Group. With metabolomics data from EPIC participants, alcohol consumption was significantly associated with several lipid metabolites, and with specific acylcarnitines and amino acids (van Roekel et al., 2018). With epigenetic data, dietary folate and alcohol intake were associated with genomic regions with tumour suppressor activity, such as the *GSDMD* and *HOXA5* genes, supporting the hypothesis that epigenetic mechanisms may have a role in folate and alcohol metabolism and their relation to cancer (Perrier et al., 2019). These results may prove useful in future research aiming to elucidate the mechanisms of the effects of alcohol consumption in relation to several cancer sites (van Roekel et al., 2018).

Health indicators and cancer

A healthy lifestyle indicator (HLI) – a function of baseline body mass index (BMI), smoking status, alcohol intake, level of physical activity, and adherence to a healthy diet – was found to be strongly inversely associated with risk of pancreatic cancer in the EPIC cohort. Also within the EPIC cohort, HLI was inversely related to the risk of developing more than one chronic condition among cancer, cardiovascular disease, and type 2 diabetes. These findings emphasize the need for primary and tertiary prevention with guidelines targeting several lifestyle/nutritional behaviours at once. With molecular data, metabolic signatures of the HLI were strongly inversely related to the risk of hepatocellular carcinoma (Assi et al., 2018a). Circulating levels and genetic predictors of bilirubin, a metabolite with antioxidant properties, were positively associated with risk of colorectal cancer in men; an inverse association was observed in women. Nut consumption may play a role in reducing the risk of individual cancer types, specifically colorectal cancer, possibly through weight control during adulthood (Freisling et al., 2018).

Statistical methodology

Modern cancer epidemiology increasingly requires the development of ad hoc methodology to comprehensively address the challenges raised by sets of complex data. The predictive ability of established risk factors for breast cancer was evaluated in risk prediction models for ER+ and ER− tumours in the Women's Health Initiative and EPIC cohorts (Li et al., 2018a). Causal mediation analysis, used to investigate biological processes underlying the carcinogenic effect of specific risk factors, showed that sex hormones partly mediated the association between obesity and breast cancer.

Specific signatures of metabolomics data were observed to mediate, in part, the association between alcohol intake, obesity, and hepatocellular carcinoma (Assi et al., 2018b). Statistical methods for the normalization of –omics data were evaluated (Perrier et al., 2018, 2019) using tools for the pre-processing and analysis of large-dimension data previously developed within NMB (the principal component partial R-square technique). Penalized approaches can yield more accurate estimates by properly accounting for specific structures of large-dimension data, and were shown to be particularly useful in identifying and evaluating heterogeneity in subgroup analyses, under graphical models (Ballout and Viallon, 2019), or under conditional and multinomial logistic regression models.