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Diet and cancer prevention: Contributions from the European Prospective Investigation into Cancer and Nutrition (EPIC) study

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ABSTRACT

We present the main findings observed to date from the European Prospective Investigation into Cancer and Nutrition (EPIC) on dietary factors associated with the most frequent cancer sites.

Methods: EPIC is a multicentre prospective study carried out in 23 centres in 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom, including 519,978 participants (366,521 women and 153,457 men), most aged 35–70 years.

Results: We observed the following significant associations: gastric cancer risk was inversely associated with high plasma vitamin C, some carotenoids, retinol and α -tocopherol, high intake of cereal fibre and high adhesion to Mediterranean diet, while red and processed meat were associated with increased risk. High intake of dietary fibre, fish, calcium, and plasma vitamin D were associated with a decreased risk of colorectal cancer, while red

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and processed meat intake, alcohol intake, body mass index (BMI) and abdominal obesity were associated with an increased risk. High intake of fruit and vegetables in current smokers were associated with a decreased risk of lung cancer. An increased risk of breast cancer was associated with high saturated fat intake and alcohol intake. In postmenopausal women, BMI was positively and physical activity negatively associated with breast cancer risk. High intake of dairy protein and calcium from dairy products and high serum concentration of IGF-I were associated with an increased risk of prostate cancer. These results contribute to scientific evidence for appropriate public health strategies and prevention activities aimed at reducing the global cancer burden.

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1. Introduction

In 2008, there were an estimated 3.2 million new cases of cancer and 1.7 million deaths from cancer in Europe. The fact than only 5-10% of all cancer cases are due to genetic defects and that the remaining 90-95% are due to lifestyle factors (including smoking, diet, alcohol, physical inactivity, obesity and sun exposure), infections and environmental pollutants provides major opportunities for preventing cancer.² Within the lifestyle factors, it is widely accepted that nutrition and related factors such as alcohol intake, obesity and physical activity, play an important role in cancer occurrence, possibly representing the most important contributors to cancer risk after smoking. However, in spite of decades of epidemiological investigation, scientific evidence on the relationship between several cancer sites and some foods and nutrients is still insufficient or inconsistent, frustrating the establishment of solid conclusions.3 The European Prospective Investigation into Cancer and Nutrition (EPIC) was specifically designed to investigate the relationship between diet and cancer and other chronic diseases, with the aim of making a significant contribution to the accumulated scientific knowledge by overcoming limitations of previous studies.

The aim of this article is to summarise the main initial findings published to date from the EPIC study, on the association between the most frequent tumours (colorectal, lung, breast, stomach, and prostate), and several selected food and nutrient factors that were significantly associated with these tumours. Other diet related factors such as alcohol, body mass index (BMI) and physical activity were also included. Results on other risk factors, as well as regarding other cancer site, can be found on the EPIC website: http://EPIC.IARC.fr/publi.php?but=New+Search.

2. Material and methods

EPIC is a multicentre prospective study aimed at investigating the relationships between diet, lifestyle, genetic and environmental factors and the incidence of cancer and other chronic diseases, carried out in 23 centres in 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom. The EPIC cohort^{4,5} consists of 519,978 participants (366,521 women and 153,457 men), most aged 35–70 years, recruited mostly between 1992 and 1998, usually from the general population residing in a given geographical area, town or province

(see Fig. 1). Exceptions were the French cohort comprising members of the health insurance agency for school employees, the Utrecht cohort and the Florence cohort comprising women attending breast cancer screening, part of the Italian and Spanish cohorts comprising blood donors and most of the Oxford cohort comprising vegetarian volunteers.

Diet over the previous 12 months was assessed at recruitment by validated country specific questionnaires^{6,7} designed to ensure high compliance and improved measurements of local dietary habits. They include: self-administered semiquantitative food-frequency questionnaires (with approximately 260 food items), diet history questionnaires (with more than 600 food items) administered by means of interviews, and semi-quantitative food-frequency questionnaires combined with dietary record.4 To calibrate the dietary measuring instruments and with the objective of correcting systematic errors produced by the over- or underestimation of food intakes, one 24-h recall was applied by means of a computerized program (EPIC-SOFT) in a sub-sample of 8% of the cohort.8 A wide range of information was collected on habits, lifestyles and medical history. Height, weight and waist and hip circumference were measured and 385,747 blood samples were obtained for biochemical, hormonal and genetic analyses; these were conserved mostly in liquid nitrogen. Incident cancer cases (more than 50,000 cases so far), continue to be identified by means of computerized links with populationbased cancer registries, except in France, Germany and Greece, where a combination of methods is undertaken, including monitoring health insurance records and hospitals registries as well as actively following up on participants. Nutrients are analysed by a standardised Food Composition Table (EPIC Nutrient Database ENDB) that was completed for the 10 participating countries.9 For this review, we selected results on food groups or subgroups, specific foods or nutrients, dietary patterns and related dietary factors, including alcohol intake, BMI and physical activity, that were significantly associated with common cancer sites (stomach, colorectal, lung, prostate and breast).

3. Results

3.1. Gastric cancer

A negative but insignificant association for total vegetable intake and onion and garlic intake was observed for intestinal gastric cancer. ¹⁰ A negative but insignificant association

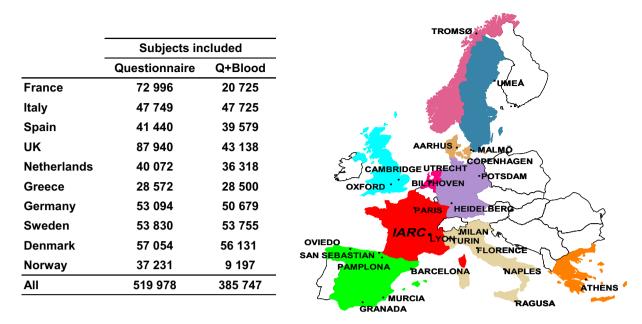


Fig. 1 - Collaborating centres and cohort subjects.

between citrus fruit intake and the cardia site was found, while no association was observed with the non-cardia site. No evidence of association between fresh fruit intake and gastric cancer (GC) risk was observed. However, in a nested-case–control study, ¹¹ the plasma level of vitamin C was significantly and inversely associated with GC risk, while dietary vitamin C was not associated (Table 1). Likewise, in another nested case–control study, ¹² the highest versus lowest quartiles of plasma of some carotenoids (β -cryptoxanthin and zeaxantin), retinol and α -tocopherol were significantly and negatively associated with GC risk (Table 1).

In the analysis of the effect of different types of meat intake, there was a significant and positive association between non-cardia gastric cancer and the intake of total meat, red meat, and processed meat¹³ (Table 2). The association with total meat was strong for *Helicobacter pylori* infected subjects, whereas no association was observed in uninfected subjects. For gastric cardia cancer, no association was observed with total, red or processed meat.

Cereal fibre intake, however, was associated with reduced risk of GC, ¹⁴ unlike total fruit or vegetable fibre (Table 1). For the first time, a strong and significant negative association between adherence to a traditional Mediterranean diet and GC risk¹⁵ was also found. Based on a relative Mediterranean score, incorporating nine key components of the Mediterranean dietary pattern (high intake of fruit and vegetables (F&V), cereals, fish, olive oil, legumes, moderate intake of alcohol and low intake of meat and dairy products), a significant reduction of 33% in GC risk was observed when comparing high versus low adherence (Table 1).

3.2. Colorectal cancer (CRC)

A significant negative association between dietary fibre and CRC risk was observed ¹⁶ (Table 1). The calibrated relative risk was 0.58 when comparing the highest quintile (mean 35 g/d) versus the lowest (mean 15 g/d). No food source of fibre

(cereal, vegetables or fruits) was more protective than another. Subsequently, it was suggested that the EPIC results could be confounded by the lack of adjustment of folate intake in the model, ¹⁷ causing a discrepancy between results from the EPIC study and results from other cohorts. The analysis was thus repeated ¹⁸ based on more cases and adjusting for folate intake. The results were the same, confirming the protective effect of fibre intake in this European population.

The analysis of usual F&V intake¹⁹ revealed a weak inverse association with risk, mainly for colon cancer and particularly after excluding the first 2 years of follow-up (Table 1). The association between F&V intake and colorectal cancer risk was modified by smoking status, requiring further investigation. In a nested-case-control study from the EPIC study, aimed at assessing the effect of serum vitamin D and CRC²⁰ (one of the largest in the world and the first in the European population) we found a strong inverse association between pre-diagnostic circulating vitamin D concentration (25-(OH) D) and risk of CRC (Table 1). Subgroup analysis showed that this association is restricted to colon cancer but not rectal cancer. High intake of calcium was also associated with a lower CRC risk, but dietary vitamin D was not associated, suggesting a relevant role of endogenous formation of vitamin D.

Regarding meat intake (Table 2), the positive association between red and processed meat intake and CRC risk was confirmed. There was a 35% increase in CRC risk when more than 160 g/d of red and processed meat intake was compared with less than 20 g/d. In addition, the increase in CRC risk associated with high red and processed meat was higher in the group with low fibre intake than in the group with high fibre intake. On the other hand, fish intake (Table 1) was inversely associated with the risk of CRC cancer (31% decrease risk when more than 80 g/d of fish intake was compared with less than 10 g/d). The decreased risk associated with low versus high fish intake was independent of the levels of red and processed meat intake.

Table 1 – Foods and nutrients that were significantly associated with a reduced risk of most frequent	tumours in the EPIC
study.	

Tumour site	No. of cases (mean follow-up)	Results hazard [95% confidence interval (CI)]	Reference
Stomach	215 cases/416 controls	Plasma vit C odds ratio (OR) = 0.55 (0.31–0.97) p for trend 0.043	Jenab M. Carcinogenesis 2006 ¹¹
	244 cases/645 controls	Plasma β -cryptoxanthin OR = 0.53 (0.30–0.94) p for trend 0.006 Plasma zeaxanthin OR = 0.39 (0.22–0.69) p for trend 0.005 Plasma retinol OR = 0.55 (0.33–0.93) p for trend 0.005 Plasma α -tocopherol OR = 0.59 (0.37–0.94) p for trend 0.022 Highest versus lowest levels	Jenab M. BJC 2006 ¹²
	312 cases (8.9 years)	Cereal fibre HR 0.69 (0.48–0.99) p for trend 0.01 Highest versus lowest	Mendez M. Int J Can 2007 ¹⁴
	449 cases (8.9 years)	Adherence to Mediterranean diet HR = 0.67 (= .47–0.94) p for trend 0.020 Highest versus lowest	Buckland G. Am J Clin Nutr 2010 ¹⁵
Colorectal	1065	Dietary fibre: Calibrated HR = 0.58 (0.41–0.85) highest versus lowest	Bingham S. Lancet 2003 ¹⁶
	1721 (6.2 years)	Dietary fibre adjusted also for folate intake HR = 0.79 (0.63–0.99) p for trend 0.01, highest versus lowest	Bingham S. CEB&P 2005 ¹⁸
	1329 cases (4.8 years)	Fish calibrated HR = 0.46 (0.27–0.77) p for trend 0.003 per 100 g/d increase	Norat T. J Natl Cancer Inst 2005 ²¹
	2819 cases (8.8 years)	Fruit and vegetables calibrated HR = 0.94 (0.89–0.99) p for trend 0.02 per 100 g daily increase (after excluding cases diagnosed in the first 2 years of follow-up)	van Duijnhoven. AJCN 2009 ¹⁹
	1248 cases/1248 controls	Plasma vit D (25-(OH)D) OR = 0.77 (0.56–1.06) p for trend <0.001 highest versus lowest Dietary calcium intake RR = 0.69 (0.50–0.96) p for trend 0.016 highest versus lowest	Jenab M. BMJ 2010 ²⁰
Lung	860	Total fruit: HR = 0.60 (0.46–0.78) p for trend 0.0099 highest versus lowest	Miller A. Int J Cancer 2004 ²⁴
	1,126 (6.4 years)	Total vegetables in current smokers: calibrated HR = 0.78 (0.62–0.98) per 100 g/d increase	Linseisen J. Int J Cancer 2007 ²⁵
	1,830 (8.7 years)	Total F&V calibrated = HR 0.94 (0.89–0.99) per 100 g/d increase Total F&V in current smokers: calibrated HR = 0.93 (0.90–0.97) per 100 g/daily increase	Büchner FL. CC&C 2010 ²⁶

There was also a positive association between high alcohol intake and CRC risk.²² A significant increase of 8% was observed for 15 g daily increase of alcohol intake. The risk was higher for cancer of the rectum than distal and proximal colon cancer, and higher for beer than wine, although both types of alcoholic drinks increased the risk. Body weight and BMI were significantly associated with CRC in men but not in women,²³ while indicators of abdominal obesity were related to colon cancer risk in both sexes (Table 2). The association of abdominal obesity in postmenopausal women may vary depending on hormone replacement therapy (HRT).

3.3. Lung cancer

In the first analysis of F&V intake and lung cancer $risk^{24}$ (Table 1), a significant inverse association between fruit intake and lung cancer was observed, with a 40% reduction of risk for the highest quintile of intake relative to the lowest. On the other hand, we did not observe an association

between of intake vegetables or vegetable subtypes and lung cancer. In a second analysis based on more cases and with longer follow-up,²⁵ the same results were confirmed in the whole population. After stratifying by smoking status, we observed a significant negative association between vegetable intake and lung cancer risk in current smokers. Neither fruit nor vegetables were associated with the risk of lung cancer in never smokers. A third analysis, based on more cases and larger follow-up,²⁶ focused on the effect of F&V intake on histological subtypes of lung cancer, and no association between F&V intake in never smokers was found (Table 1). A weak and significant association was found in current smokers, although the effect associated with fruit was weaker than in the previous analysis.

3.4. Breast cancer

Overall F&V intake was not associated with reduced breast cancer risk,²⁷ nor was there any association for intake of total

Table 2 – Food and nutrients that were associated with	a significant increased risk of i	most frequent tumours in the EPIC
study.		

Tumour site	No. of cases (follow-up)	Results	Reference
Stomach	330 (6.5 years)	Total meat calibrated HR = 2.03 (1.28–3.22) per 100 g/d increase Red meat: calibrated HR = 1.31 (0.89–1.94) per 50 g/d increase Processed meat: calibrated HR = 1.64 (1.07–2.51) per 50 g/d increase	González CA. JNCI 2006 ¹³
Colorectal	1329 (4.8 years)	Red and processed meat intake calibrated HR = 1.55 (1.19–2.02) per 100 g /d increase. Red meat calibrated HR = 1.49 (0.91–2.43) per 100 g /d increase Processed meat calibrated HR = 1.70 (1.05–2.76) per 100 g /d increase	Norat T. JNCI 2005 ²¹
	984 colon (6.1 years)	BMI men: HR = 1.55 (1.12–2.15) <i>p</i> trend 0.006 WHR women HR = 1.46 (1.06–2.0) <i>p</i> for trend 0.01 (highest versus lowest)	Pischon T. JNCI 2006 ²³
	1833	Alcohol intake HR 1.08 (1.04–1.12) for 15 g/d increase	Ferrari P. Int J Can 2007 ²²
Breast	1879 (4.7 years) 4285 (6.4 years)	BMI postmenopausal women non-user of HRT HR 1.36 (1.06–1.75) p for trend 0.002 highest versus lowest Alcohol intake HR = 1.03 (1.01–.05) per 10 g/d increase	Lahmann P. Int J Can 2004 ³¹ Tjonneland A. CC&C 2007 ³⁰
	7119 (8.8 years)	Saturated fat intake HR = 1.13 (1.00–1.27) p for trend 0.038. Highest versus lowest	Sieri S. Am J Clin Nutr 2008 ²⁹
Prostate	630 cases/630 controls	IGF-I serum concentration OR = 1.39 (1.02–.89) highest versus lowest third	Allen N. CEB&P 2007 ³³
	2727 (8.7 years)	Dairy protein intake calibrated HR = 1.32 (1.01–.72) p for trend 0.04 for an increase of 35 g /d Dairy calcium intake calibrated HR = 1.07 (1.00–.14) p for trend 0.04 for an increase of 0.3 g /d	Allen N. BJC 2008 ³⁵

vegetables, total fruits, fruit and vegetable juices, or six specific vegetable subgroups. Although the period of follow-up was limited, these results suggest that total F&V intake is not associated with the risk of breast cancer. In a subsequent analysis based on more cases and larger follow-up, ²⁸ dietary intake of beta-carotene, vitamin C and vitamin E were not related to breast cancer risk in either pre or postmenopausal women, although in a subgroup analysis, there was a significant negative association of high intake of beta-carotene and vitamin C and breast cancer risk in postmenopausal women using exogenous hormones (Table 1).

Regarding the effect of dietary fat²⁹ using a standard energy-adjusted model, a significant 13% increase in risk was found for the highest quintile of saturated fat intake compared with the lowest quintile (Table 2). The effect was somewhat similar for the density and partition energy-adjusted models, but it was not significant using the residual energy-adjusted model. The association was stronger for postmenopausal women who never used hormone therapy. No significant association between breast cancer and total, monounsaturated or polyunsaturated fat intake was found.

The association between alcohol intake and breast cancer risk was also confirmed.³⁰ For European women, a 3% increase in breast cancer risk was observed per 10 g recent daily increase in alcohol intake (Table 2). Moreover, the EPIC study confirmed the association of body size and breast cancer risk

in postmenopausal women.³¹ In postmenopausal women not taking HRT, BMI was a significant predictor of breast cancer risk, while indicators of abdominal obesity were not related to excess risk when adjusted for BMI (Table 2). EPIC also provides additional evidence for the protective effect of physical activity and breast cancer risk.³² Increasing physical activity (specifically combined recreational and household activities) was associated with a significant reduced risk of breast cancer in postmenopausal women (Table 1).

3.5. Prostate cancer

Results from EPIC have shown a positive association between the serum concentration of insulin-like growth factor I (IGF-I) and the risk of prostate cancer³³ (Table 2). EPIC analyses have also shown that men who consume the most dairy protein and calcium have relatively high blood levels of IGF-I.³⁴ Consistent with this, high intake of dairy protein and calcium from dairy products were associated with an increased risk of prostate cancer³⁵ (Table 2).

The results of EPIC analyses on prostate cancer risk in relation to other dietary factors, including serum biomarkers, were largely null. For example, the EPIC study did not find an association between prostate cancer incidence and total fruit and vegetable intake. Some potentially important associations were observed in the subgroup of men diagnosed

with relatively advanced disease, and further work is now required on some nutritional biomarkers such as carotenoids, folate, vitamin B12 and phyto-oestrogens.

4. Discussion

EPIC studies found that gastric cancer risk is significantly and inversely associated with plasma pre-diagnostic circulating level of vitamin C, some carotenoids (β -cryptoxantin and zeaxantin) retinol and α -tocopherol. Furthermore, high intake of cereal fibre was also significantly associated with a reduced risk of gastric cancer. Intake of total, red and processed meat, on the other hand, was associated with an increased risk for gastric cancer, mainly for the non-cardia site and in those infected by Helicobacter pylori. Adhesion to the traditional Mediterranean diet was strongly associated with a reduction of gastric cancer risk, illustrating the relevance of dietary factors in gastric cancerogenesis. There is a strong and significant protective effect for fruit and vegetables intake, according to a meta-analysis and expert evaluation³ in case-control studies, although cohort studies failed to confirm a significant association. Evidence from EPIC regarding the increased risk of gastric cancer associated with processed meat is consistent with the most recent evidence. A meta-analysis of case-control and cohort studies³⁷ found a significant positive association between the risk of gastric cancer and high intake of processed meat.

Results from the EPIC study have, up to now, shown a significant negative association between colorectal cancer and high intake of dietary fibre, fish intake, calcium intake, prediagnostic circulating plasma vitamin D as well as a weak but significant association with F&V intake mainly for colon cancer. On the contrary, red and processed meat intake, alcohol intake, BMI in men and waist circumference and waist-to-hip ratio in both sexes were associated with a significant increased risk of CRC. Based on a large body of epidemiological and experimental findings as well as on biological mechanisms, most dietary recommendations advise increased fibre intake to reduce the risk of CRC.

This traditional view has been challenged by results from recent prospective studies on CRC cancer³⁸ and randomized control trials on recurrence rates of adenomatous colorectal polyps in which no protective effect was observed. However, the protective association observed in EPIC is consistent throughout most of the European participant countries, with a clear dose response, constituting strong evidence that high fibre is associated with a decreased CRC risk in this European population. The WRCF&AICR report³ concluded that foods containing dietary fibre probably decrease the risk of CRC. Although this report recognised that there is only limited evidence linking F&V intake with decreased risk of CRC, a recent meta-analysis based on 14 prospective studies and 5,838 cases³⁹ found a significant negative association (26% reduction of risk comparing 800 g/d versus 200 g/d of F&V intake) with distal colon cancer. The EPIC results support the hypotheses of the protective role of calcium on CRC risk (probably associated with a decrease of CRC risk according to the WRCF&AICR report) and add important evidence on the effect of vitamin D, which has a key function in the maintenance of calcium homoeostasis. According to the conclusion of the WRCF&AICR report, there is convincing evidence that red meat, processed meat, alcoholic drinks, body fat and abdominal fat increase the risk of CRC.

EPIC results showed that high F&V intake in current smokers is significantly associated with a weak decreased risk of lung cancer. Our results regarding fruit are consistent with the epidemiological evidence: a pooled analysis of eight cohort studies⁴⁰ found a protective effect of fruit with a dose response relationship, but the effect was weaker and borderline significant for vegetables, without dose response. On the other hand, a pooled analysis focused on nutrients⁴¹ observed the protective association of β -cryptoxanthin, a carotenoid associated with citrus fruit intake. The WRCF&AICR report concluded that fruits and food containing carotenoids probably decrease the risk of lung cancer. Overall, this evidence suggests that high fruit intake may reduce the risk of lung cancer; vegetable intake may also have a role in smokers, but further evidence is needed. Despite these findings, the most effective measure by far for preventing lung cancer in smokers remains the cessation of smoking.

The EPIC study found a weak positive and significant association between breast cancer incidence and high saturated fat intake, as well as a clear positive association with alcohol intake, BMI and hip circumference in postmenopausal women who do not use HRT. Total F&V intake was not associated with breast cancer risk. Recent publication of a collaborative reanalysis of 53 epidemiological studies⁴² has provided solid evidence about the causal relationship between alcohol intake and breast cancer. An increase of 10 g of alcohol per day was associated with a 7% increase in risk of breast cancer, alcohol being the cause of about 4% of breast tumours in women from developed countries. The association between saturated and animal fat and breast cancer has been very controversial over the past 20 years. The most recent evidence from a meta-analysis of 14 cohort studies and 34 case-control studies has shown an increase of 19% in the risk of breast cancer for the highest level of intake of saturated fat. 43 Results from EPIC support the possibility of a weak but significant increased risk of breast cancer associated with high saturated fat intake. Increasing recreational and household physical activities, on the contrary, was associated with a significant reduced risk in postmenopausal women. According to the WRCF&AICR report, there is convincing evidence that body fat increased risk in postmenopausal women while physical activity probably decreased the risk.

The aetiology of prostate cancer is not well understood. The analyses in EPIC were designed to examine a range of current dietary hypotheses, looking at the possible roles of foods, nutrients and endogenous hormones. The clearest finding that has emerged from EPIC so far is a positive association between the serum concentration of IGF-I and the risk of prostate cancer. This association was confirmed in a pooled analysis of the data from EPIC and other studies worldwide. IGF-I levels were highly correlated with the intake of dairy protein and calcium, thus diet may influence the risk of prostate cancer by affecting IGF-I. Further research on this potentially important area is underway in EPIC.

High intake of dairy protein and calcium from dairy products was also associated with a significant increased risk of

prostate cancer. Results related with diets high in calcium are consistent with scientific evidence that indicated that this association is probable.³ Overall, results from EPIC suggest that diet may not have an important role in prostate carcinogenesis, although there are specific foods and nutrients that are significantly associated with the risk of prostate cancer.

The most important strengths of the EPIC study include its very large size to increase the study power, multiple populations with large variation in the incidence of cancers and with wide range of variation in dietary patterns, from Mediterranean diets (Greece, southern Italy, Spain, and south of France) to more Western style diets in the central and northern European countries. Other strengths include the availability of blood samples (collected in almost 80% of the subjects) to use as biomarkers of exposure and to study interactions between nutritional, hormonal and genetic factors, as well as dietary questionnaires with a relatively large and detailed number of food items, calibrated with one standardized 24-h diet recall.

The EPIC study also has potential limitations. Our results could be affected by measurement error in dietary intake, a common limitation of epidemiological studies. However, the wide range of dietary intake reported in the EPIC study, which increases the between-person variance in diet, probably minimizes the impact of measurement error. In addition, to correct for measurement error, a calibration approach was used, although the measurement error of the 24-h recall is not independent of that of dietary questionnaires.

In conclusion, these first results from the EPIC study on main food groups and nutrients and most frequent tumours represent a significant contribution to the existing body of evidence. In combination with data from other prospective studies, including studies using biological biomarkers, the study contributes to the scientific knowledge for appropriate public health policies and strategies aimed at reducing the global cancer burden. The authors hope that this evidence, as well as evidence from health policy research addressing the most suitable and effective ways to modify diet and physical activity patterns, may help to increase cancer prevention activities in strategic planning⁴⁵ for oncology.

Conflict on interest statement

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