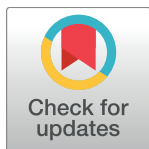


RESEARCH ARTICLE

Nutritional quality of food as represented by the FSAm-NPS nutrient profiling system underlying the Nutri-Score label and cancer risk in Europe: Results from the EPIC prospective cohort study

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Data Availability Statement: EPIC data and biospecimens are available to investigators in the context of research projects that are consistent with the legal and ethical standard practices of IARC/WHO and the EPIC Centres. The use of a random sample of anonymized data from the EPIC study can be requested by contacting epic@iarc.fr. For information on EPIC data access policy and on how to submit an application for gaining access to

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EPIC data and/or biospecimens, please follow the instructions at <http://epic.iarc.fr/access/index.php>.

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Abbreviations: AICR, American Institute for Cancer Research; BMI, body mass index; DI, Dietary Index; EPIC, European Prospective Investigation into Cancer and Nutrition; EU, European Union; FFQ, food frequency questionnaire; FSA-NPS, Nutrient Profiling System of the British Food Standards Agency (original version); FSAm-NPS, Nutrient Profiling System of the British Food Standards Agency (modified version); HCSP, High Council for Public Health; HR, hazard ratio; ICD-O, International Classification of Diseases for Oncology; NACRe, Network for Nutrition And Cancer Research; ONQI-f, Overall Nutritional

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Abstract

Background

Helping consumers make healthier food choices is a key issue for the prevention of cancer and other diseases. In many countries, political authorities are considering the implementation of a simplified labelling system to reflect the nutritional quality of food products. The Nutri-Score, a five-colour nutrition label, is derived from the Nutrient Profiling System of the British Food Standards Agency (modified version) (FSAm-NPS). How the consumption of foods with high/low FSAm-NPS relates to cancer risk has been studied in national/regional cohorts but has not been characterized in diverse European populations.

Methods and findings

This prospective analysis included 471,495 adults from the European Prospective Investigation into Cancer and Nutrition (EPIC, 1992–2014, median follow-up: 15.3 y), among whom there were 49,794 incident cancer cases (main locations: breast, $n = 12,063$; prostate, $n = 6,745$; colon-rectum, $n = 5,806$). Usual food intakes were assessed with standardized country-specific diet assessment methods. The FSAm-NPS was calculated for each food/beverage using their 100-g content in energy, sugar, saturated fatty acid, sodium, fibres, proteins, and fruits/vegetables/legumes/nuts. The FSAm-NPS scores of all food items usually consumed by a participant were averaged to obtain the individual FSAm-NPS Dietary Index (DI) scores. Multi-adjusted Cox proportional hazards models were computed. A higher FSAm-NPS DI score, reflecting a lower nutritional quality of the food consumed, was associated with a higher risk of total cancer (HR_{Q5} versus Q₁ = 1.07; 95% CI 1.03–1.10, P -trend < 0.001). Absolute cancer rates in those with high and low (quintiles 5 and 1) FSAm-NPS DI scores were 81.4 and 69.5 cases/10,000 person-years, respectively. Higher FSAm-NPS DI scores were specifically associated with higher risks of cancers of the colon-rectum, upper aerodigestive tract and stomach, lung for men, and liver and postmenopausal breast for women (all $P < 0.05$). The main study limitation is that it was based on an observational cohort using self-reported dietary data obtained through a single baseline food frequency questionnaire; thus, exposure misclassification and residual confounding cannot be ruled out.

Quality Index; WCRF, World Cancer Research Fund.

Conclusions

In this large multinational European cohort, the consumption of food products with a higher FSAm-NPS score (lower nutritional quality) was associated with a higher risk of cancer. This supports the relevance of the FSAm-NPS as underlying nutrient profiling system for front-of-pack nutrition labels, as well as for other public health nutritional measures.

Author summary

Why was this study done?

- Helping consumers make healthier food choices is a key challenge for the prevention of cancer and other chronic diseases, which is why in many countries, political authorities are considering the implementation of a simplified labelling system to reflect the nutritional quality of food products.
- The Nutri-Score, a five-colour nutrition label based on the Nutrient Profiling System of the British Food Standards Agency (modified version) (FSAm-NPS) score (calculated for each food/beverage using its 100-g content in energy, sugar, saturated fatty acids, sodium, fibres, proteins, and fruits/vegetables/legumes/nuts) has been selected by French authorities but remains optional per European labelling regulations.
- So far, scientific evidence regarding the relevance of the Nutri-Score (and the underlying FSAm-NPS score) has been obtained at national/regional level, thus expanding investigations to the European level is of importance.

What did the researchers do and find?

- This study is part of a comprehensive assessment of the FSAm-NPS validity as underlying nutrient profiling system for front-of-pack nutrition labels (as well as other public health nutritional measures) in Europe.
- Here, we conducted a prospective analysis of the association between the FSAm-NPS score of the food consumed (reflecting their nutritional quality) and cancer risk in the large and diverse European population that constitutes the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, including 471,495 adults from 10 European countries with 49,794 newly diagnosed cancer cases.
- The consumption of foods with higher FSAm-NPS scores, reflecting a lower nutritional quality, was associated with an increased risk of developing cancer (overall and several specific cancer sites).

What do these findings mean?

- These findings add support to the relevance of using the FSAm-NPS to grade the nutritional quality of food products as a basis for prevention strategies for cancer and other chronic diseases.

- These findings will play a role in communications about the merits of the Nutri-Score to consumers, healthcare professionals and economic operators, in the context of the ongoing European/international debate on nutritional labelling.

Introduction

About a third of the most common cancers in Western countries are estimated to be preventable through appropriate nutritional behaviours (World Cancer Research Fund [WCRF]/American Institute for Cancer Research [AICR]) [1]. If nutrition can be modified at the individual level and therefore targeted by public health policies, informing the general population to make healthy, evidence-based nutritional decisions remains an important challenge. Among the promising strategies proposed to promote a healthier dietary environment [2,3], simplified front-of-pack nutrition labels, providing summarized, easy-to-use information on the nutritional quality of food products, have the potential to help consumers make healthier food choices and to encourage the food industry to improve the nutritional quality of the food supply [4,5]. The Nutri-Score five-colour labelling system (see [S1 Fig](#)) [3] uses a modified version of the British Food Standards Agency Nutrient Profiling System (original version) (FSAm-NPS) [6,7], considered a promising nutrient profiling system for use in a broad international context [6,8], to categorize food products into 5 colours reflecting their nutritional quality (see examples in [S1 Text](#)). The FSAm-NPS was built in a perspective of prevention of a large range of chronic diseases. It allocates a score to a given food/beverage from its content per 100 g of energy, saturated fatty acids, sugar, sodium, dietary fibres, proteins, and fruit/vegetables/legumes/nuts. It was initially developed and validated in the United Kingdom, where it has been used for advertising regulation (Ofcom) [6,7,9] and was transposed in France (FSAm-NPS) [10–12].

Several studies support the scientific relevance and the potential public health impact of the use of the FSAm-NPS as a basis for public health nutrition policies [13–21] (reviewed in [22]). In particular, studies performed in the SU.VI.MAX and NutriNet-Santé cohorts have shown that a diet composed of food products with better FSAm-NPS scores (summarized with the FSAm-NPS Dietary Index [DI] [23,24]) would lead to more favourable health outcomes as regards weight gain [25], metabolic syndrome [26], cardiovascular diseases [27,28], and cancer incidence (total and breast) [29,30]. These results were promising albeit restricted to French populations and based on a relatively limited number of cases (especially to perform robust analyses by cancer sites).

In 2017, the Nutri-Score was selected by the French Ministry of Health as the official front-of-pack nutrition label to be implemented in France [31,32], an initiative officially commended by WHO Europe [33]. However, to comply with the European Union (EU) labelling regulations, appending the Nutri-Score on food products remains optional and therefore relies on voluntary uptake by food manufacturers. In 2018, a review of existing labelling schemes at the EU level is anticipated, and discussions regarding the possible implementation of a unique nutritional labelling system for all EU countries are expected to follow. Similar discussions are also ongoing in North and South America, Canada, and Australia. Scientific evidence regarding the relevance of this label (and the underlying FSAm-NPS score) at an international level is therefore of importance.

This study is part of a comprehensive assessment of the validity of the FSAm-NPS as underlying nutrient profiling system for front-of-pack nutrition labels as well as other public health nutritional measures in Europe. Specifically, it aimed at investigating the association between the FSAm-NPS DI and cancer risk in the large and diverse European population that constitutes the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

Methods

Study population: The EPIC cohort

EPIC (<http://epic.iarc.fr/>) is a multicentre prospective cohort study investigating metabolic, dietary, lifestyle, and environmental factors in relation to cancer and other chronic diseases. Between 1992 and 2000, more than 500,000 volunteers (25–70 years old) were recruited from 10 European countries (23 administrative centres): Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the UK. All participants gave written informed consent. The study was approved by the local ethics committees and by the Internal Review Board of the International Agency for Research on Cancer. Details of the study design, recruitment, and data collection have been previously published [34–36].

Of the 521,324 participants enrolled, 471,495 were included in the analyses (see flowchart in [S2 Fig](#) for exclusion details). In particular, from the 54,459 eligible invasive cancer cases, we excluded those diagnosed within the first 2 years of follow-up ($n = 4,665$) to allow sufficient delay between baseline dietary assessment and cancer diagnosis, thereby limiting reverse causality.

Baseline data collection

An extended and standardized phenotypic characterisation was performed for each participant upon enrolment. Questionnaires were used to collect sociodemographic information, educational level (collected and standardized for the whole cohort), personal and familial history of diseases, lifestyle (e.g., smoking, alcohol use, physical activity), and menstrual and reproductive history for women. Anthropometric measurements (e.g., height, weight, waist, and hip circumferences) were performed in all centres (except France, Oxford, and Norway: self-reported data).

Dietary intake assessment

Usual dietary intake was assessed for each individual at recruitment using country-specific and validated dietary questionnaires developed to capture the geographical specificity of an individual's diet. The type of dietary questionnaire used differed according to study centres and included: self- or interviewer-administered semiquantitative food frequency questionnaires (FFQs) with an estimation of individual average portions or with the same standard portion assigned to all subjects or diet history questionnaires combining an FFQ and 7-day dietary records [36]. The EPIC food composition database comprises more than 10,000 food and beverage items reflecting the specificities of each country [37].

FSAm-NPS DI computation

As described previously [7,10,12], the FSAm-NPS score is a modified version of the original FSA-NPS, with adaptations in the allocation of points for beverages, cheese, and added fats following recommendations from the French High Council for Public Health (HCSP) to ensure a high consistency of the FSAm-NPS score with nutritional recommendations, for labelling purposes [12].

The FSAm-NPS score was calculated for all foods and beverages in the EPIC food composition database as follows: points (0–10) are allocated for the content per 100 g in total sugars (g), saturated fatty acids (g), sodium (mg), and energy (kJ) (i.e., nutrients that should be consumed in limited amounts) and can be balanced by opposite points (0–5) allocated for dietary fibres (g), proteins (g), and fruits/vegetables/legumes/nuts (percent) (i.e., nutrients/components that should be promoted). The grids for point attribution are displayed in [S1 Text](#) (general rule and specific grids: sugars, energy, and fruits/vegetables/legumes/nuts for beverages, saturated fatty acids for added fats). The percentage of fruits/vegetables/legumes/nuts was derived using standard recipes. The FSAm-NPS score for each food/beverage is based on a unique discrete continuous scale ranging theoretically from –15 (most healthy) to +40 (least healthy). The universality of the FSAm-NPS components allows a computation for all existing foods/beverages, no matter the cultural diet structure in which they are included.

An individual consumes many different foods of contrasted nutritional quality, which synergistically influence his/her disease risk. When studying the association between food intakes and chronic diseases, all food items consumed have to be considered (and therefore all associated FSAm-NPS scores) and not just one single food. Therefore, in a second step, the FSAm-NPS DI was computed at the individual level as an energy-weighted mean of the FSAm-NPS scores of all foods and beverages consumed using the following equation [23] (FS_i: score of food/beverage i, E_i: energy intake from food/beverage i, n: number of food/beverage consumed):

$$\text{FSAm - NPS DI} = \frac{\sum_{i=1}^n (\text{FS}_i E_i)}{\sum_{i=1}^n E_i}$$

Higher FSAm-NPS DI therefore reflects lower nutritional quality in foods consumed. More details on FSAm-NPS and FSAm-NPS DI calculations can be found in [S1 Text](#).

Follow-up for cancer incidence and vital status

Incident cancer cases were identified through several methods, including record linkage with population-based cancer registries, health insurance records, pathology registries, and active follow-up of study subjects. Data on vital status were obtained from mortality registries, in combination with data collected through active follow-up. The end of follow-up/closure dates of the study period varied between 2009 and 2014 depending on the countries.

First primary invasive cancers were considered as cases in this study. Main cancer cases were coded according to the International Classification of Diseases for Oncology (ICD-O) [38] as follows: colorectal cancer (C18, C199, C209), bladder cancer (C67), kidney cancer (C649), upper aerodigestive tract cancers (oral cavity: C019, C02, C03, C04, C050, C06; oropharynx: C09, C10; hypopharynx: C13, C14; larynx: C32; esophagus: C15), lung cancer (C34), stomach cancer (C16), pancreas cancer (C25), liver cancer (C220), breast cancer (C50), endometrial cancer (C54), cervical cancer (C53), ovary cancer (C569), prostate cancer (C61).

Statistical analyses

All statistical analyses were pre-planned and followed the plan detailed in the project protocol that was submitted for funding application ([S2 Text](#)). Associations between the FSAm-NPS DI (continuous variable and sex-specific quintiles) and cancer risk overall and for specific cancer locations were characterized (hazard ratio [HR] and 95% CI) using multivariable Cox proportional hazards models with age as the primary time variable. We confirmed that the assumptions of proportionality were satisfied through examination of the log–log (survival) versus log–time plots. Tests for linear trends were performed with an ordinal coding of FSAm-NPS

DI quintiles (1, 2, 3, 4, 5). Participants contributed person-time to the model until their date of cancer diagnosis, their date of death, their date of emigration/loss to follow-up, or end-of-follow-up, whichever occurred first. Analysis by censoring the competing death event is the most appropriate way for HR estimation in evaluating exposure–disease associations [39,40]. For analyses of specific cancer sites, participants who reported a cancer other than the one under study were included and censored at the date of diagnosis (except basal cell skin carcinoma, which was not considered as cancer).

Analyses were performed for sexes combined and by sex. Models were stratified by age at recruitment (1-y intervals) and study centre [34] ('strata' option in proc phreg, SAS) and multivariable adjusted for other known risk factors for cancer: sex, body mass index (BMI), height, educational level, physical activity, smoking status and intensity, alcohol intake at recruitment, total energy intake, family history of breast and colorectal cancer, and, for women (subgroup analyses), menopausal status at baseline and whether they ever used hormonal treatment for menopause or oral contraception. For women-specific cancer locations (cancers of the reproductive system), models were further adjusted for age at menarche, age at first full-term pregnancy, age at menopause, and an interaction term between BMI and menopausal status. For these cancers, models were computed by menopausal status (pre-menopause/post-menopause): women contributed person-time to the 'pre-menopause model' until their age of menopause and to the 'post-menopause model' from their age of menopause. Detailed information about covariate categorization can be found in the table footnotes. Age at menopause was collected at baseline for postmenopausal women. If missing or if women were pre- or perimenopausal at baseline, then age at menopause was set at 55 years [41]. For analyses on cancers of the endometrium, cervix, and ovaries, we excluded women who declared a surgical menopause at baseline. When data on categorical covariates were missing, a 'missing class' was introduced in the model. If missing, height and weight were imputed with centre-, age-, and gender-specific average values. Sensitivity analyses were also performed using a 'complete cases' approach, excluding participants with missing data on covariates.

BMI was considered as a confounding factor in the analyses and thus was adjusted for in the models. However, BMI could also be considered as a potential intermediate factor, which was tested in a sensitivity analysis excluding BMI.

Unadjusted absolute rates were calculated as the number of cases per 10,000 person-years in the highest and the lowest quintiles, respectively, of the FSAm-NPS DI score.

All tests were two sided, and $P < 0.05$ was considered statistically significant. SAS version 9.4 (SAS Institute) was used for the analyses.

Results

After a median follow-up time of 15.3 y (between 1992–2000 and 2009–2014), 49,794 incident invasive cancer cases were recorded (cancer incidence by country is shown in [S1 Table](#)). The most common cancers were breast ($n = 12,063$), prostate ($n = 6,745$), colon-rectum ($n = 5,806$), and lung ($n = 3,654$).

Participants with a higher FSAm-NPS DI score, reflecting a diet of lower nutritional quality, were consistently more likely to have unhealthy dietary intakes, e.g., higher intakes of alcohol, energy and red and processed meat, lower intakes of dietary fibres, vegetables, fruit, fish, and lean meat ([Table 1](#)). Participants from France, Germany, the UK (Cambridge centre), and Sweden were more likely to score higher on the FSAm-NPS DI (i.e., to consume food products of lower nutritional quality) and thus to be classified in the 5th quintile, whereas participants from Greece, Italy, Spain, Norway, and the UK (Oxford centre, mainly 'health-conscious' participants, including a high proportion of vegetarians) were more likely to have lower scores.

Table 1. Baseline characteristics of participants overall and by quintiles of the FSAm-NPS DI, EPIC cohort, 1992–2014.

	All	Sex-specific quintiles of the FSAm-NPS DI score				
	(n = 471,495)	Q1 (n = 94,323)	Q2 (n = 94,341)	Q3 (n = 94,375)	Q4 (n = 94,278)	Q5 (n = 94,178)
	N (%) ^a Mean ± SD	N (%) ^a Mean ± SD	N (%) Mean ± SD	N (%) Mean ± SD	N (%) Mean ± SD	N (%) Mean ± SD
FSAm-NPS DI	6.0 ± 2.1	3.0 ± 1.0	4.8 ± 0.36	5.9 ± 0.33	7.1 ± 0.37	8.9 ± 1.1
Age, years	51.2 ± 9.9	51.6 ± 10.1	51.1 ± 9.8	50.8 ± 9.8	51.1 ± 9.9	51.2 ± 10.1
Sex						
Male	140,729 (29.8)	28,165 (29.9)	28,164 (29.8)	28,170 (29.8)	28,141 (29.8)	28,089 (29.8)
Female	330,766 (70.1)	66,158 (70.1)	66,177 (70.1)	66,205 (70.1)	66,137 (70.1)	66,089 (70.2)
Country						
Denmark	54,241 (11.5)	8,197 (8.7)	10,164 (10.8)	12,043 (12.8)	12,841 (13.6)	10,996 (11.7)
France	66,766 (14.2)	2,295 (2.4)	6,173 (6.5)	11,956 (12.7)	19,976 (21.2)	26,366 (28.0)
Greece	25,868 (5.5)	10,486 (11.1)	9,775 (10.4)	4,196 (4.4)	1,171 (1.2)	240 (0.25)
Germany	48,066 (10.2)	4,254 (4.5)	7,054 (7.5)	10,281 (10.9)	12,841 (13.6)	13,636 (14.5)
Italy	44,125 (9.4)	9,367 (9.9)	13,487 (14.3)	10,819 (11.5)	7,005 (7.4)	3,447 (3.7)
Norway	33,691 (7.1)	10,273 (10.9)	10,189 (10.8)	7,490 (7.9)	4,079 (4.3)	1,660 (1.8)
Spain	39,744 (8.4)	21,356 (22.6)	8,615 (9.1)	5,011 (5.3)	2,905 (3.1)	1,857 (2.0)
Sweden	48,078 (10.2)	7,176 (7.6)	8,966 (9.5)	9,954 (10.5)	10,277 (10.9)	11,705 (12.4)
The Netherlands	36,211 (7.7)	3,469 (3.7)	7,268 (7.7)	9,640 (10.2)	9,524 (10.1)	6,310 (6.7)
United Kingdom	74,705 (15.8)	17,450 (18.5)	12,650 (13.4)	12,985 (13.8)	13,659 (14.5)	17,961 (19.1)
Educational level ^b						
Longer education (including university degree), yes	112,434 (23.8)	19,000 (20.1)	20,592 (21.8)	23,109 (24.5)	25,162 (26.7)	24,571 (26.1)
Smoking status						
Never	203,399 (43.1)	46,448 (49.2)	41,869 (44.4)	39,852 (42.2)	38,556 (40.9)	36,674 (38.9)
Current	131,993 (28.0)	20,653 (21.9)	24,789 (26.3)	26,703 (28.3)	28,443 (30.2)	31,405 (33.3)
Former	120,577 (25.6)	24,486 (26.0)	24,619 (26.1)	24,648 (26.1)	24,102 (25.6)	22,722 (24.1)
Current/Former, missing	7,682 (1.6)	1,145 (1.2)	1,352 (1.4)	1,611 (1.7)	1,785 (1.9)	1,789 (1.9)
Unknown	7,844 (1.7)	1,591 (1.7)	1,712 (1.8)	1,561 (1.6)	1,392 (1.5)	1,588 (1.7)
Physical activity (Cambridge index)						
Inactive	98,710 (20.9)	24,186 (25.6)	20,624 (21.9)	18,049 (19.1)	17,103 (18.1)	18,748 (19.9)
Moderately inactive	155,211 (32.9)	28,293 (30.0)	29,821 (31.6)	31,184 (33.0)	32,719 (34.7)	33,194 (35.2)
Moderately active	124,377 (26.4)	23,994 (25.4)	25,415 (26.9)	25,172 (26.7)	25,086 (26.6)	24,710 (26.2)
Active	84,444 (17.9)	16,531 (17.5)	16,721 (17.7)	17,981 (19.0)	17,353 (18.4)	15,858 (16.8)
Missing	8,753 (1.9)	1,319 (1.4)	1,760 (1.9)	1,989 (2.1)	2,017 (2.1)	1,668 (1.8)
BMI ^c , kg/m ²	25.4 ± 4.3	26.3 ± 4.5	25.8 ± 4.3	25.4 ± 4.2	25.0 ± 4.1	24.7 ± 4.1
Height ^c , cm	166.0 ± 9.0	164.5 ± 8.8	165.6 ± 9.0	166.4 ± 9.0	166.7 ± 9.0	166.7 ± 8.9
Family history of breast cancer, yes ^d	14,171 (3.0)	2,600 (18.3)	2,608 (18.4)	2,857 (20.2)	3,030 (21.4)	3,076 (21.7)
Family history of colorectal cancer, yes ^d	9,641 (2.0)	1,906 (19.8)	1,355 (14.0)	1,609 (16.7)	2,106 (21.8)	2,665 (27.6)
Energy intake, kcal/d ^e	1,997 (1,631–2,437)	1,750 (1,435–2,152)	1,905 (1,573–2,320)	1,988 (1,647–2,399)	2,094 (1,738–2,508)	2,256 (1,865–2,708)
Alcohol intake, g/d ^e	5.3 (0.93–14.9)	2.9 (0.35–11.9)	4.6 (0.82–13.3)	5.6 (1.1–15.2)	6.7 (1.5–16.5)	6.9 (1.5–17.1)
Dietary fibres intake, g/d ^e	21.8 (17.4–27.0)	24.2 (19.4–30.4)	22.5 (18.1–27.6)	21.7 (17.5–26.7)	21.2 (16.9–26.0)	19.9 (15.7–24.5)
Vegetables intake, g/d ^e	175.4 (109.9–276.6)	219.6 (134.3–340.8)	184.0 (115.7–294.1)	166.3 (107.1–260.3)	160.1 (103.7–248.3)	156.3 (98.0–242.1)
Fruits, nuts and seeds intake, g/d ^e	200.6 (111.6–322.3)	288.1 (174.3–436.0)	235.6 (132.6–356.9)	195.1 (111.6–308.9)	171.5 (98.5–272.3)	143.2 (79.8–233.1)
Dairy products intake, g/d ^e	277.2 (160.7–444.7)	267.5 (144.7–445.2)	282.4 (163.1–461.6)	293.6 (173.0–464.7)	284.4 (168.3–445.8)	258.7 (153.1–401.2)
Fish and shellfish intake, g/d ^e	28.0 (13.8–49.7)	32.9 (15.0–63.5)	28.5 (14.4–52.9)	27.3 (13.6–48.6)	26.4 (13.0–44.7)	25.3 (12.6–42.2)
Red meat intake, g/d ^e	34.8 (16.1–63.1)	26.5 (10.1–50.4)	34.4 (16.7–60.8)	37.5 (18.0–66.3)	40.3 (19.0–69.3)	37.0 (17.4–66.4)

(Continued)

Table 1. (Continued)

	All	Sex-specific quintiles of the FSAm-NPS DI score				
	(n = 471,495)	Q1 (n = 94,323)	Q2 (n = 94,341)	Q3 (n = 94,375)	Q4 (n = 94,278)	Q5 (n = 94,178)
	N (%) ^a Mean ± SD	N (%) ^a Mean ± SD	N (%) Mean ± SD	N (%) Mean ± SD	N (%) Mean ± SD	N (%) Mean ± SD
Poultry intake, g/d ^c	15.0 (6.0–27.3)	16.1 (6.3–35.4)	15.9 (6.4–28.1)	15.0 (6.3–25.9)	13.7 (5.2–24.6)	11.8 (3.2–22.5)
Processed meat intake, g/d ^c	24.2 (10.5–43.8)	12.9 (3.1–27.4)	19.8 (7.6–36.3)	25.5 (12.4–43.8)	30.5 (16.1–50.9)	35.8 (18.6–60.1)
Age at menarche (years) ^f						
≤12	116,661 (35.3)	23,724 (35.9)	23,455 (35.4)	23,186 (35.0)	23,070 (34.9)	23,226 (35.1)
13–14	152,508 (46.1)	29,612 (44.8)	30,254 (45.7)	30,739 (46.4)	30,922 (46.7)	30,981 (46.9)
≥15	50,873 (15.4)	10,306 (15.6)	10,018 (15.1)	10,023 (15.1)	10,265 (15.5)	10,261 (15.5)
Missing	10,724 (3.2)	2,516 (3.8)	2,450 (3.7)	2,257 (3.4)	1,880 (2.8)	1,621 (2.4)
Age at first full-term pregnancy (years) ^f						
Nulliparous	47,901 (14.5)	10,683 (16.1)	9,057 (13.7)	9,261 (14.0)	9,108 (13.8)	9,792 (14.8)
≤21	60,915 (18.4)	12,644 (19.1)	12,765 (19.3)	12,246 (18.5)	11,623 (17.6)	11,637 (17.6)
22–30	180,029 (54.4)	34,969 (52.9)	36,022 (54.4)	36,160 (54.6)	36,786 (55.6)	36,092 (54.6)
>30	27,077 (8.2)	5,120 (7.7)	5,485 (8.3)	5,573 (8.4)	5,627 (8.5)	5,272 (8.0)
Missing	14,844 (4.5)	2,742 (4.1)	2,848 (4.3)	2,965 (4.5)	2,993 (4.5)	3,296 (5.0)
Menopausal status ^f						
Premenopause	115,631 (35.0)	22,199 (33.5)	23,011 (34.8)	23,686 (35.8)	23,177 (35.0)	23,558 (35.6)
Perimenopause	63,242 (19.1)	11,256 (17.0)	12,297 (18.6)	12,650 (19.1)	13,272 (20.1)	13,767 (20.8)
Postmenopause	142,368 (43.0)	30,326 (45.8)	28,833 (43.6)	28,011 (42.3)	27,959 (42.3)	27,239 (41.2)
Surgical postmenopause	9,525 (2.9)	2,377 (3.6)	2,036 (3.1)	1,858 (2.8)	1,729 (2.6)	1,525 (2.3)
Ever use of oral contraception (yes) ^f	189,288 (57.2)	32,555 (49.2)	34,986 (52.9)	38,689 (58.4)	41,060 (62.1)	41,998 (63.5)
Ever use of hormonal treatment for menopause (yes) ^f	79,929 (24.2)	14,562 (22.0)	15,275 (23.1)	16,478 (24.9)	17,056 (25.8)	16,558 (25.0)

^a Percentages are given in column.

^b Not specified for N = 16,701 (3.5%).

^c Missing BMI for N = 83,938 (17.8%), missing height for 82,875 (17.6%). When missing, height and weight were imputed with centre-, age-, and gender-specific average values.

^d Among first-degree relatives.

^e Values are median (interquartile range) for all dietary variables.

^f In women only.

Abbreviations: BMI, body mass index; DI, Dietary Index; EPIC, European Prospective Investigation into Cancer and Nutrition; FSAm-NPS, Nutrient Profiling System of the British Food Standards Agency (modified version).

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Participants from Denmark and the Netherlands were more likely to have middle-range scores falling within the 2nd to the 4th quintile (Table 1).

Associations between the FSAm-NPS DI (continuous score and sex-specific quintiles) and cancer risk for different cancer types are displayed in Table 2 (overall) and Table 3 (by sex).

A higher FSAm-NPS DI score was associated with a higher risk of total cancer (HR_{Q5} versus Q₁ = 1.07; 95% CI 1.03–1.10, P-trend < 0.001). The absolute rates in those with high and low FSAm-NPS DI scores were 81.4 (men: 115.9; women: 66.6) and 69.5 (men: 89.6; women: 61.1) cases per 10,000 person-years, respectively.

Regarding specific cancer types, a higher FSAm-NPS DI was associated with a higher risk of colorectal cancer (HR_{Q5} versus Q₁ = 1.11 (1.01–1.22), P-trend = 0.02), especially in women (P-interaction = 0.04). A higher FSAm-NPS DI was also associated with a higher liver cancer risk in women (HR_{Q5} versus Q₁ = 2.33 (1.23–4.43), P-trend = 0.008, P-interaction = 0.04) and

Table 2. Associations between the FSAm-NPS DI and cancer risk (total cancer and specific cancer types), from multivariable Cox proportional hazards models, EPIC cohort, 1992–2014.

	FSAm-NPS DI							
	Per 2-point increment	P-trend	Q1	Q2	Q3	Q4	Q5	P-trend
FSAm-NPS DI range (men/women)			−6.0–4.3/ −4.3–4.1	4.3–5.5/ 4.1–5.3	5.5–6.6/ 5.3–6.4	6.6–7.9/ 6.4–7.7	7.9–17.6/ 7.7–18.9	
Total cancer								
All (cases/person-years)	49,794/6,635,062		9454/1,360,371	9482/1,327,943	9865/1,326,951	10,371/1,315,230	10,622/1,304,567	
Sex-adjusted model—HR (95% CI) ^a	1.04 (1.03–1.05)	<0.001	1.00 (ref)	1.03 (1.00–1.06)	1.05 (1.02–1.08)	1.09 (1.05–1.12)	1.12 (1.08–1.15)	<0.001
Multi-adjusted model 1—HR (95% CI) ^b	1.02 (1.01–1.03)	<0.001	1.00 (ref)	1.02 (0.99–1.05)	1.03 (1.00–1.06)	1.06 (1.03–1.09)	1.07 (1.03–1.10)	<0.001
Colorectal cancer								
All (cases/person-years)	5806/6,639,343		1144/1,361,188	1150/1,328,771	1152/1,327,731	1195/1,316,126	1165/1,305,527	
Sex-adjusted model—HR (95% CI)	1.03 (1.00–1.06)	0.03	1.00 (ref)	1.07 (0.99–1.17)	1.07 (0.98–1.17)	1.11 (1.02–1.22)	1.11 (1.01–1.21)	0.02
Multi-adjusted model 1—HR (95% CI)	1.03 (1.00–1.06)	0.03	1.00 (ref)	1.07 (0.99–1.17)	1.07 (0.98–1.17)	1.12 (1.02–1.22)	1.11 (1.01–1.22)	0.02
Bladder cancer								
All (cases/person-years)	1382/6,639,748		278/1,361,289	243/1,328,835	289/1,327,804	270/1,316,200	302/1,305,620	
Sex-adjusted model—HR (95% CI)	1.06 (1.00–1.12)	0.04	1.00 (ref)	0.97 (0.81–1.16)	1.18 (0.98–1.40)	1.09 (0.90–1.31)	1.15 (0.96–1.39)	0.08
Multi-adjusted model 1—HR (95% CI)	1.02 (0.96–1.08)	0.6	1.00 (ref)	0.96 (0.80–1.14)	1.14 (0.95–1.36)	1.03 (0.85–1.24)	1.03 (0.85–1.25)	0.6
Kidney cancer								
All (cases/person-years)	926/6,639,740		211/1,361,288	155/1,328,832	178/1,327,788	181/1,316,203	201/1,305,629	
Sex-adjusted model—HR (95% CI)	1.09 (1.02–1.16)	0.02	1.00 (ref)	0.78 (0.63–0.97)	0.94 (0.76–1.16)	1.02 (0.82–1.26)	1.22 (0.98–1.52)	0.01
Multi-adjusted model 1—HR (95% CI)	1.07 (1.00–1.15)	0.06	1.00 (ref)	0.78 (0.63–0.96)	0.93 (0.75–1.15)	0.99 (0.80–1.24)	1.17 (0.93–1.46)	0.04
Upper aerodigestive tract cancers^c								
All (cases/person-years)	1,176/6,639,705		219/1,361,297	198/1,328,828	228/1,327,796	227/1,316,185	304/1,305,600	
Sex-adjusted model—HR (95% CI)	1.16 (1.09–1.23)	<0.001	1.00 (ref)	1.00 (0.82–1.22)	1.13 (0.93–1.38)	1.11 (0.91–1.36)	1.52 (1.25–1.84)	<0.001
Multi-adjusted model 1—HR (95% CI)	1.07 (1.01–1.14)	0.03	1.00 (ref)	0.96 (0.78–1.17)	1.04 (0.85–1.27)	0.98 (0.79–1.20)	1.21 (0.99–1.48)	0.06
Lung cancer								
All (cases/person-years)	3654/6,639,528		640/1,361,259	684/1,328,795	702/1,327,764	782/1,316,159	846/1,305,551	
Sex-adjusted model—HR (95% CI)	1.16 (1.12–1.20)	<0.001	1.00 (ref)	1.11 (0.99–1.24)	1.17 (1.04–1.31)	1.34 (1.19–1.50)	1.57 (1.40–1.76)	<0.001
Multi-adjusted model 1—HR (95% CI)	1.01 (0.97–1.04)	0.7	1.00 (ref)	1.05 (0.94–1.17)	1.03 (0.92–1.16)	1.09 (0.97–1.22)	1.06 (0.94–1.20)	0.3
Stomach cancer								
All (cases/person-years)	963/6,639,770		216/1,361,290	200/1,328,838	185/1,327,802	165/1,316,207	197/1,305,631	
Sex-adjusted model—HR (95% CI)	1.13 (1.06–1.21)	0.0004	1.00 (ref)	1.07 (0.88–1.31)	1.10 (0.89–1.36)	1.08 (0.86–1.34)	1.39 (1.12–1.74)	0.01
Multi-adjusted model 1—HR (95% CI)	1.10 (1.02–1.18)	0.01	1.00 (ref)	1.06 (0.87–1.29)	1.08 (0.87–1.33)	1.02 (0.82–1.29)	1.25 (0.99–1.58)	0.1
Pancreas cancer								
All (cases/person-years)	1244/6,639,760		260/1,361,295	240/1,328,830	251/1,327,800	254/1,316,205	239/1,305,630	
Sex-adjusted model—HR (95% CI)	1.00 (0.95–1.06)	0.9	1.00 (ref)	0.96 (0.80–1.15)	1.01 (0.84–1.22)	1.04 (0.86–1.25)	1.02 (0.84–1.24)	0.6
Multi-adjusted model 1—HR (95% CI)	0.98 (0.92–1.04)	0.4	1.00 (ref)	0.94 (0.79–1.13)	0.98 (0.82–1.18)	0.99 (0.82–1.20)	0.94 (0.77–1.15)	0.7
Liver cancer								
All (cases/person-years)	338/6,639,776		71/1,361,289	64/1,328,835	60/1,327,811	70/1,316,211	73/1,305,629	
Sex-adjusted model 1—HR (95% CI)	1.10 (0.98–1.24)	0.1	1.00 (ref)	0.96 (0.68–1.36)	1.02 (0.71–1.47)	1.26 (0.87–1.81)	1.36 (0.94–1.98)	0.046
Multi-adjusted model 1—HR (95% CI)	1.05 (0.93–1.18)	0.5	1.00 (ref)	0.92 (0.65–1.31)	0.95 (0.66–1.38)	1.15 (0.79–1.67)	1.18 (0.80–1.74)	0.2
Prostate cancer								
Men (cases/person-years)	6745/1,978,301		1192/400,545	1162/393,399	1365/397,646	1471/395,278	1555/391,434	
Unadjusted model—HR (95% CI) ^d	1.02 (1.00–1.05)	0.1	1.00 (ref)	0.99 (0.91–1.07)	1.05 (0.96–1.14)	1.05 (0.97–1.15)	1.06 (0.97–1.15)	0.08
Multi-adjusted model 1—HR (95% CI)	1.03 (1.00–1.06)	0.04	1.00 (ref)	0.99 (0.91–1.07)	1.05 (0.97–1.15)	1.06 (0.97–1.16)	1.07 (0.98–1.17)	0.04
Breast cancer								
Women (cases/person-years)	12,063/4,659,777		2093/960,453	2303/935,107	2403/929,855	2628/920,557	2636/913,805	
Unadjusted model—HR (95% CI)	1.03 (1.01–1.05)	0.01	1.00 (ref)	1.05 (0.99–1.12)	1.04 (0.98–1.11)	1.09 (1.02–1.16)	1.08 (1.01–1.15)	0.01
Multi-adjusted model 2—HR (95% CI) ^e	1.02 (1.00–1.04)	0.05	1.00 (ref)	1.04 (0.98–1.11)	1.03 (0.97–1.10)	1.07 (1.01–1.14)	1.06 (0.99–1.14)	0.05
Endometrial cancer^f								
Women (cases/person-years)	1,763/4,529,816		401/926,746	377/907,086	344/904,957	361/897,398	280/893,630	
Unadjusted model—HR (95% CI)	0.95 (0.91–1.00)	0.06	1.00 (ref)	1.00 (0.87–1.16)	0.94 (0.81–1.09)	1.03 (0.88–1.20)	0.85 (0.72–1.00)	0.1
Multi-adjusted model 2—HR (95% CI)	0.98 (0.93–1.03)	0.4	1.00 (ref)	1.02 (0.88–1.18)	0.98 (0.84–1.14)	1.09 (0.93–1.27)	0.91 (0.76–1.08)	0.6
Cervical cancer^f								

(Continued)

Table 2. (Continued)

	FSAm-NPS DI							
	Per 2-point increment	P-trend	Q1	Q2	Q3	Q4	Q5	P-trend
Women (cases/person-years)	305/4,529,956		66/926,769	71/907,109	62/904,989	60/897,436	46/893,652	
Unadjusted model—HR (95% CI)	1.04 (0.92–1.17)	0.5	1.00 (ref)	1.18 (0.84–1.66)	1.11 (0.77–1.59)	1.20 (0.83–1.75)	1.01 (0.67–1.52)	0.8
Multi-adjusted model 2—HR (95% CI)	1.05 (0.93–1.18)	0.5	1.00 (ref)	1.20 (0.85–1.70)	1.12 (0.78–1.62)	1.23 (0.84–1.80)	1.02 (0.67–1.56)	0.8
Ovary cancer^f								
Women (cases/person-years)	1,273/4,529,820		268/926,740	235/907,088	264/904,948	253/897,412	253/893,632	
Unadjusted model—HR (95% CI)	1.04 (0.98–1.10)	0.2	1.00 (ref)	0.92 (0.77–1.11)	1.06 (0.89–1.27)	1.05 (0.87–1.26)	1.08 (0.89–1.30)	0.2
Multi-adjusted model 2—HR (95% CI)	1.04 (0.98–1.11)	0.2	1.00 (ref)	0.93 (0.78–1.11)	1.07 (0.90–1.28)	1.06 (0.88–1.28)	1.08 (0.89–1.31)	0.2

^a Sex-adjusted models were stratified for centre and age at recruitment (1-y intervals, time-scale) and adjusted for sex.

^b Multi-adjusted model 1 was stratified for centre and age at recruitment (1-y intervals, time-scale) and adjusted for sex, BMI (continuous), height (continuous), baseline alcohol intake (g/d), physical activity (Cambridge index: active; moderately active; moderately inactive; inactive; missing), smoking status and intensity of smoking (current, 1–15 cigarettes/d; current, 16–25 cigarettes/d; current, 26+ cigarettes/d; current, pipe/cigar/occasional; current/former, missing; former, quit 11–20 y; former, quit 20+ y; former, quit ≤10 y; never; unknown), family history of breast cancer (total and breast cancer models), family history of colorectal cancer (total and colorectal cancer models), educational level (longer education [including university degree]; secondary school; primary school completed; not specified), baseline energy intake (kcal/d).

^c Upper aerodigestive tract cancers: cancers of the oral cavity, oropharynx, hypopharynx, larynx, and oesophagus.

^d Unadjusted models were stratified for centre and age at recruitment (1-y intervals, time-scale).

^e Multi-adjusted model 2: Multi-adjusted model 1 further adjusted for an interaction term between BMI and menopausal status, menopausal status (premenopausal, perimenopausal, postmenopausal, surgical), ever use of oral contraception (yes, no, missing), ever use of hormonal treatment for menopause (yes, no, missing), age at menarche (≤12 y, 13–14 y, ≥15 y, missing), age at first full-term pregnancy (nulliparous, ≤21 y, 22–30 y, >30 y, missing) and age at menopause (<50 y, ≥50 y).

^f Women who declared a surgical menopause at baseline were excluded.

Abbreviations: BMI, body mass index; DI, Dietary Index; EPIC, European Prospective Investigation into Cancer and Nutrition; FSAm-NPS, Nutrient Profiling System of the British Food Standards Agency (modified version); HR, hazard ratio.

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a higher lung cancer risk in men (HR_{Q5} versus Q₁ = 1.26 (1.06–1.51), *P*-trend = 0.02) although the interaction with sex was not significant for lung cancer (*P*-interaction = 0.3). If only borderline nonsignificant trends were observed when comparing the highest and the lowest quintiles of the FSAm-NPS DI, 2-point increment in the FSAm-NPS DI score was associated with higher risks of stomach cancer (HR per 2-point increment = 1.10 (1.02–1.18), *P*-trend = 0.01) and of cancers of the upper aerodigestive tract (HR per 2-point increment = 1.07 (1.01–1.14), *P*-trend = 0.03). A borderline significant association was also observed for kidney cancer (HR_{Q5} versus Q₁ = 1.17 (0.93–1.46), *P*-trend = 0.04). No association was observed for cancers of the bladder (*P*-trend = 0.6) and pancreas (*P*-trend = 0.7).

For sex-specific cancers of the reproductive system, a higher FSAm-NPS DI score was associated with a higher risk of postmenopausal breast cancer (HR_{Q5} versus Q₁ = 1.08 (1.00–1.16), *P*-trend = 0.03, [S2 Table](#)) and a borderline significant higher risk of prostate cancer (HR_{Q5} versus Q₁ = 1.07 (0.98–1.17), *P*-trend = 0.04, [Table 2](#)). No association was detected for cancers of the endometrium, uterine cervix, or ovaries ([Table 2](#)). Similar results were observed for overall cancer risk when complete cases models were used (40,945 cases/5,201,091 person-years, HR_{Q5} versus Q₁ = 1.07 (1.03–1.11), *P*-trend < 0.001) and when models were not adjusted for BMI (HR_{Q5} versus Q₁ 95% CI 1.07 [1.03–1.10], *P*-trend < 0.001).

Discussion

In this large multinational European cohort, participants with the highest FSAm-NPS DI scores, i.e., those consuming on average food products with a lower nutritional quality, were at higher risk of developing cancer overall. Stronger associations were observed for colorectal,

upper aerodigestive tract, and stomach cancers, for lung cancer in men, and for liver and postmenopausal breast cancers in women.

To our knowledge, this study was the first effort to investigate the association between the FSAm-NPS DI and disease in a large European cohort. Consistent with our results, previous studies performed in the SU.VI.MAX and NutriNet-Santé cohorts reported higher risks for total and breast cancers with higher FSAm-NPS DI scores [29,30]. However, these studies exhibited limited statistical power to investigate the relationships for other specific cancer types.

With a different approach, using the original FSA-NPS score and the Ofcom regulation threshold [9] to categorize food/beverage as 'healthier' or 'less healthy', Masset and colleagues observed a lower all-cause and cancer mortality associated to the intake of a greater variety of 'healthier' food items in the Whitehall II cohort [42], and, recently, Mytton and colleagues observed a higher all-cause mortality associated to the consumption of 'less healthy' food items in EPIC-Norfolk [43].

The comparison between other dietary scores and the FSAm-NPS DI is not straightforward. Indeed, the FSAm-NPS DI is a dietary score based on a nutrient profiling system at the level of food products, obtained following a two-step process. First, all food and beverage items are assigned a score according to their nutritional quality (FSAm-NPS). Then, an individual index, the FSAm-NPS DI, is computed at the individual level (mainly for research purposes) by calculating a weighted mean of the FSAm-NPS scores of all food/beverages consumed by this individual. In contrast, usual dietary scores are obtained directly at the individual level, allocating points based on the consumption of foods/food groups or nutrients relevant for overall or specific chronic disease risk (e.g., Mediterranean diet score [44], WCRF/AICR adherence score [45], Alternate Healthy Eating Index [46]). Therefore, these scores relate more to individual eating behaviours than to the intrinsic nutritional quality of the foods consumed, with objective to add support to dietary recommendations and/or be a basis for dietary guidelines. The FSAm-NPS was not designed to find the best predictive score for cancer risk but rather to serve as a basis for food nutritional labelling (such as the Nutri-Score) and other public health nutritional policies (e.g., advertising regulation) in order to improve the prevention of a large range of chronic diseases. As such, it has to be easily computable by industrial and public stakeholders (thus including only items generally present in the nutritional facts of all food labels). Hence, our objective was not to compare the FSAm-NPS DI score to other existing dietary scores but to specifically assess the relevance of the use of the FSAm-NPS score to grade the nutritional quality of food products in the framework of public health policies aiming at reducing cancer risk.

To our knowledge, the Overall Nutritional Quality Index (ONQI-f) is the only other dietary score based on a nutrient profiling system at the food level that has been translated at the individual level and then studied in relation to health outcomes so far [47]. In a study performed in the Nurses' Health Study and the Health Professionals Follow-up Study, Chiuve and colleagues observed that a higher ONQI-f (reflecting a higher overall nutritional quality of the diet), was associated with a lower risk of cardiovascular diseases, diabetes, and mortality but was not associated with cancer risk. Nonetheless, it is important to note that the ONQI-f is based on 30 nutrients (from macronutrients such as fat, protein, or glycaemic load to micronutrients such as folate, vitamin D, zinc, iron, or omega 3 fatty acids but also polyphenols [flavonoids]), among which few have shown a consistent association with cancer risk, which may have weakened its relevance for the cancer outcome.

In contrast, the FSAm-NPS score relies on a limited number of components for which information is readily available on food packaging; in addition, most of these components have been proposed to be involved in cancer development in epidemiological and mechanistic

Table 3. Associations between the FSAm-NPS DI and cancer risk (total cancer and specific cancer types) by sex strata, from multivariable Cox proportional hazards models, EPIC cohort, 1992–2014.

	FSAm-NPS DI							P-trend
	2-point increment	P-trend	Q1	Q2	Q3	Q4	Q5	
FSAm-NPS DI range (men/women)			–6.0–4.3/ –4.3–4.1	4.3–5.5/ 4.1–5.3	5.5–6.6/ 5.3–6.4	6.6–7.9/ 6.4–7.7	7.9–17.6/ 7.7–18.9	
Total cancer								
P-interaction		0.4						0.6
Men (cases/person-years)	19,711/1,977,015		3585/ 400,287	3494/393,163	3838/397,419	4259/395,015	4535/391,131	
Unadjusted model—HR (95% CI) ^a	1.05 (1.03–1.06)	<0.001	1.00 (ref)	1.03 (0.98–1.08)	1.07 (1.02–1.12)	1.12 (1.07–1.18)	1.15 (1.09–1.20)	<0.001
Multi-adjusted model—HR (95% CI) ^b	1.03 (1.01–1.04)	0.002	1.00 (ref)	1.01 (0.97–1.06)	1.04 (0.99–1.10)	1.08 (1.03–1.14)	1.07 (1.02–1.13)	0.001
Women (cases/person-years)	30,083/4,658,047		5869/ 960,083	5988/934,780	6027/929,532	6112/920,215	6087/913,437	
Unadjusted model—HR (95% CI)	1.03 (1.02–1.05)	<0.001	1.00 (ref)	1.03 (1.00–1.07)	1.04 (1.00–1.08)	1.07 (1.03–1.11)	1.11 (1.06–1.15)	<0.001
Multi-adjusted model—HR (95% CI)	1.02 (1.01–1.03)	0.001	1.00 (ref)	1.02 (0.99–1.06)	1.03 (0.99–1.06)	1.05 (1.01–1.09)	1.07 (1.03–1.11)	0.001
Colorectal cancer								
P-interaction		0.04						0.04
Men (cases/person-years)	2506/1,978,384		489/400,529	463/393,421	485/397,669	542/395,305	527/391,460	
Unadjusted model—HR (95% CI) ^a	1.02 (0.98–1.07)	0.3	1.00 (ref)	1.05 (0.92–1.20)	1.05 (0.92–1.21)	1.12 (0.98–1.29)	1.06 (0.92–1.22)	0.3
Multi-adjusted model—HR (95% CI) ^b	1.03 (0.98–1.07)	0.2	1.00 (ref)	1.05 (0.92–1.20)	1.05 (0.91–1.20)	1.12 (0.98–1.29)	1.07 (0.92–1.24)	0.2
Women (cases/person-years)	3300/4,660,959		655/960,658	687/935,350	667/930,062	653/920,822	638/914,067	
Unadjusted model—HR (95% CI)	1.05 (1.01–1.08)	0.01	1.00 (ref)	1.10 (0.98–1.22)	1.10 (0.98–1.23)	1.12 (1.00–1.26)	1.18 (1.05–1.33)	0.01
Multi-adjusted model—HR (95% CI)	1.04 (1.00–1.08)	0.03	1.00 (ref)	1.09 (0.98–1.22)	1.10 (0.98–1.23)	1.12 (0.99–1.26)	1.17 (1.03–1.32)	0.02
Bladder cancer								
P-interaction		0.8						0.6
Men (cases/person-years)	987/1,978,521		197/400,572	170/393,445	199/397,688	202/395,333	219/391,484	
Unadjusted model—HR (95% CI) ^a	1.08 (1.01–1.16)	0.02	1.00 (ref)	1.00 (0.81–1.24)	1.20 (0.96–1.49)	1.20 (0.96–1.50)	1.20 (0.96–1.50)	0.05
Multi-adjusted model—HR (95% CI) ^b	1.04 (0.97–1.11)	0.3	1.00 (ref)	0.98 (0.79–1.22)	1.14 (0.92–1.42)	1.12 (0.89–1.40)	1.05 (0.83–1.33)	0.5
Women (cases/person-years)	395/4,661,227		81/960,717	73/935,390	90/930,116	68/920,868	83/914,136	
Unadjusted model—HR (95% CI)	1.04 (0.94–1.16)	0.4	1.00 (ref)	0.96 (0.70–1.33)	1.24 (0.91–1.70)	0.96 (0.68–1.36)	1.19 (0.85–1.67)	0.4
Multi-adjusted model—HR (95% CI)	1.01 (0.91–1.12)	0.9	1.00 (ref)	0.94 (0.68–1.30)	1.20 (0.87–1.65)	0.91 (0.64–1.28)	1.07 (0.75–1.52)	0.8
Kidney cancer								
P-interaction		0.4						0.4
Men (cases/person-years)	522/1,978,557		119/400,579	76/393,450	90/397,692	112/395,339	125/391,497	
Unadjusted model—HR (95% CI) ^a	1.08 (0.99–1.18)	0.1	1.00 (ref)	0.70 (0.52–0.95)	0.84 (0.62–1.13)	1.02 (0.76–1.38)	1.13 (0.84–1.52)	0.07
Multi-adjusted model—HR (95% CI) ^b	1.05 (0.96–1.16)	0.3	1.00 (ref)	0.68 (0.51–0.92)	0.80 (0.59–1.08)	0.97 (0.72–1.31)	1.04 (0.77–1.42)	0.2
Women (cases/person-years)	404/4,661,183		92/960,709	79/935,383	88/930,096	69/920,864	76/914,131	
Unadjusted model—HR (95% CI)	1.11 (1.00–1.24)	0.04	1.00 (ref)	0.90 (0.66–1.23)	1.12 (0.83–1.52)	1.03 (0.74–1.43)	1.41 (1.02–1.96)	0.04

(Continued)

Table 3. (Continued)

	FSAm-NPS DI							
	2-point increment	P-trend	Q1	Q2	Q3	Q4	Q5	P-trend
Multi-adjusted model—HR (95% CI)	1.12 (1.01–1.25)	0.03	1.00 (ref)	0.92 (0.67–1.25)	1.15 (0.85–1.57)	1.06 (0.76–1.49)	1.45 (1.03–2.04)	0.03
Upper aerodigestive tract cancers^c								
P-interaction		0.9						0.8
Men (cases/person-years)	786/1,978,504		138/400,581	122/393,446	158/397,686	158/395,320	210/391,471	
Unadjusted model—HR (95% CI) ^a	1.19 (1.11–1.28)	<0.001	1.00 (ref)	1.03 (0.80–1.33)	1.28 (1.00–1.64)	1.22 (0.94–1.58)	1.61 (1.26–2.07)	<0.001
Multi-adjusted model—HR (95% CI) ^b	1.09 (1.01–1.18)	0.02	1.00 (ref)	0.97 (0.75–1.26)	1.14 (0.89–1.47)	1.03 (0.79–1.34)	1.25 (0.96–1.62)	0.08
Women (cases/person-years)	390/4,661,201		81/960,716	76/935,382	70/930,109	69/920,865	94/914,130	
Unadjusted model—HR (95% CI)	1.11 (1.01–1.22)	0.04	1.00 (ref)	1.01 (0.73–1.38)	0.94 (0.67–1.30)	1.00 (0.71–1.40)	1.46 (1.06–2.00)	0.04
Multi-adjusted model—HR (95% CI)	1.03 (0.93–1.14)	0.6	1.00 (ref)	0.96 (0.70–1.32)	0.87 (0.62–1.21)	0.88 (0.63–1.24)	1.16 (0.83–1.62)	0.5
Lung cancer								
P-interaction		0.5						0.3
Men (cases/person-years)	1876/1,978,425		297/400,564	336/393,426	343/397,670	415/395,313	485/391,452	
Unadjusted model—HR (95% CI) ^a	1.21 (1.15–1.27)	<0.001	1.00 (ref)	1.29 (1.10–1.52)	1.39 (1.17–1.65)	1.65 (1.39–1.96)	1.94 (1.64–2.31)	<0.001
Multi-adjusted model—HR (95% CI) ^b	1.04 (0.99–1.09)	0.2	1.00 (ref)	1.21 (1.02–1.43)	1.21 (1.02–1.44)	1.31 (1.10–1.60)	1.26 (1.06–1.51)	0.02
Women (cases/person-years)	1778/4,661,103		343/960,695	348/935,369	359/930,094	367/920,846	361/914,099	
Unadjusted model—HR (95% CI)	1.14 (1.09–1.20)	<0.001	1.00 (ref)	1.01 (0.87–1.18)	1.10 (0.94–1.28)	1.24 (1.06–1.44)	1.46 (1.24–1.71)	<0.001
Multi-adjusted model—HR (95% CI)	0.99 (0.95–1.04)	0.8	1.00 (ref)	0.94 (0.80–1.09)	0.95 (0.81–1.11)	0.99 (0.84–1.16)	0.97 (0.82–1.14)	0.9
Stomach cancer								
P-interaction		0.6						0.9
Men (cases/person-years)	535/1,978,569		115/400,585	106/393,454	101/397,693	97/395,342	116/391,495	
Unadjusted model—HR (95% CI) ^a	1.11 (1.01–1.22)	0.03	1.00 (ref)	1.14 (0.86–1.50)	1.20 (0.89–1.61)	1.18 (0.87–1.61)	1.39 (1.02–1.89)	0.06
Multi-adjusted model—HR (95% CI) ^b	1.08 (0.98–1.19)	0.1	1.00 (ref)	1.14 (0.86–1.50)	1.17 (0.87–1.58)	1.13 (0.82–1.55)	1.26 (0.91–1.73)	0.2
Women (cases/person-years)	428/4,661,201		101/960,706	94/935,384	84/930,109	68/920,866	81/914,136	
Unadjusted model—HR (95% CI)	1.17 (1.06–1.30)	0.002	1.00 (ref)	1.03 (0.77–1.37)	1.04 (0.77–1.41)	1.00 (0.72–1.39)	1.49 (1.08–2.06)	0.05
Multi-adjusted model—HR (95% CI)	1.12 (1.01–1.24)	0.04	1.00 (ref)	0.99 (0.74–1.33)	0.97 (0.72–1.33)	0.91 (0.65–1.27)	1.27 (0.91–1.79)	0.4
Pancreas cancer								
P-interaction		0.9						0.8
Men (cases/person-years)	526/1,978,561		98/400,580	92/393,450	110/397,696	121/395,338	105/391,496	
Unadjusted model—HR (95% CI) ^a	1.01 (0.92–1.11)	0.8	1.00 (ref)	0.92 (0.68–1.23)	1.05 (0.78–1.42)	1.10 (0.82–1.48)	0.97 (0.71–1.33)	0.7
Multi-adjusted model—HR (95% CI) ^b	0.98 (0.89–1.08)	0.7	1.00 (ref)	0.89 (0.66–1.20)	1.01 (0.75–1.37)	1.04 (0.77–1.41)	0.89 (0.64–1.22)	0.8
Women (cases/person-years)	718/4,661,199		162/960,715	148/935,380	141/930,103	133/920,867	134/914,134	
Unadjusted model—HR (95% CI)	1.01 (0.93–1.09)	0.9	1.00 (ref)	0.98 (0.78–1.23)	0.99 (0.78–1.25)	0.99 (0.78–1.27)	1.09 (0.85–1.40)	0.5
Multi-adjusted model—HR (95% CI)	0.97 (0.90–1.06)	0.5	1.00 (ref)	0.96 (0.77–1.21)	0.96 (0.76–1.22)	0.95 (0.74–1.22)	1.00 (0.77–1.30)	0.9

(Continued)

Table 3. (Continued)

	FSAm-NPS DI							P-trend
	2-point increment	P-trend	Q1	Q2	Q3	Q4	Q5	
Liver cancer								
P-interaction		0.07						0.04
Men (cases/person-years)	210/1,978,566		48/400,584	36/393,452	39/397,696	44/395,340	43/391,495	
Unadjusted model—HR (95% CI) ^a	1.00 (0.86–1.16)	0.9	1.00 (ref)	0.79 (0.51–1.23)	0.91 (0.57–1.44)	0.97 (0.61–1.54)	0.93 (0.57–1.50)	0.9
Multi-adjusted model—HR (95% CI) ^b	0.94 (0.80–1.10)	0.4	1.00 (ref)	0.74 (0.47–1.17)	0.82 (0.51–1.32)	0.88 (0.54–1.42)	0.79 (0.48–1.30)	0.6
Women (cases/person-years)	128/4,661,210		23/960,705	28/935,383	21/930,116	26/920,871	30/914,135	
Unadjusted model—HR (95% CI)	1.30 (1.08–1.57)	0.007	1.00 (ref)	1.40 (0.79–2.48)	1.31 (0.70–2.45)	1.95 (1.06–3.60)	2.64 (1.42–4.89)	0.002
Multi-adjusted model—HR (95% CI)	1.24 (1.02–1.51)	0.03	1.00 (ref)	1.35 (0.76–2.41)	1.23 (0.65–2.31)	1.80 (0.96–3.34)	2.33 (1.23–4.43)	0.008

^a Unadjusted models were stratified for centre and age at recruitment (1-y intervals, time-scale).

^b Multi-adjusted models were stratified for centre and age at recruitment (1-y intervals, time-scale) and adjusted for BMI (continuous), height (continuous), baseline alcohol intake (g/d), physical activity (Cambridge index: active; moderately active; moderately inactive; inactive; missing), smoking status and intensity of smoking (current, 1–15 cigarettes/d; current, 16–25 cigarettes/d; current, 26+ cigarettes/d; current, pipe/cigar/occasional; current/former, missing; former, quit 11–20 y; former, quit 20+y; former, quit ≤10 y; never; unknown), family history of breast cancer (total and breast cancer models), family history of colorectal cancer (total and colorectal cancer models), educational level (longer education [including university degree]; secondary school; primary school completed; not specified), baseline energy intake (kcal/d) + (women) menopausal status (premenopausal, perimenopausal, postmenopausal, surgical), ever use of oral contraception (yes, no, missing), ever use of hormonal treatment for menopause (yes, no, missing).

^c Upper aerodigestive tract cancers: cancers of the oral cavity, oropharynx, hypopharynx, larynx, and oesophagus.

Abbreviations: BMI, body mass index; DI, Dietary Index; EPIC, European Prospective Investigation into Cancer and Nutrition; FSAm-NPS, Nutrient Profiling System of the British Food Standards Agency (modified version); HR, hazard ratio.

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studies. Inverse associations have been observed between dietary fibre intake and colorectal [48,49] and breast [48] cancer risk, fruit and vegetable intake and risk of cancers of the mouth/larynx/pharynx and lung [48,49], whereas positive associations have been observed between salt intake and stomach cancer risk [48,49] and sugar intake (as a contributor to glycaemic load) and endometrial cancer risk [49]. In addition, even though the evidence for an association between saturated fatty acid intake and breast cancer risk was classified as ‘limited-no conclusion’ in the last WCRF report, the corresponding meta-analysis did show a direct association [50]. Indirect associations may also be proposed between the FSAm-NPS components and cancer risk through an association with body fatness, a major risk factor for most cancer locations (oesophagus, stomach, pancreas, liver, colon-rectum, breast [postmenopausal], ovary, endometrium, prostate, and kidney) [48,49]. Indeed, FSAm-NPS components contribute to the energy density of foods, with energy, sugars, and saturated fatty acids as components of energy-dense foods and fibres and fruits and vegetables as components of low-energy foods.

In our study, nonsignificant results were observed for specific cancer types in men, women, or both, and most associations were weak compared to other studies exploring FSAm-NPS DI in relation with cancers (SU.VI.MAX: total cancer, 453 cases, HR_{Q5} versus Q₁ = 1.34 [1.00–1.81]); NutriNet-Santé, breast cancer, 555 cases: HR_{Q5} versus Q₁ = 1.52 [1.11–2.08] [29,30]). Although HR cannot be compared directly between our study and previous ones because of differences in population and methods, several hypotheses may be proposed to explain the rather weak associations observed here. Most centres participating in the EPIC cohort used an FFQ to assess dietary intakes. FFQs allow good estimations of usual dietary intakes but limit the discrimination of the nutritional quality of individual food products, especially when they

are collapsed into aggregated food groups. The use of FFQs may have contributed to a less accurate estimation of the individual FSAm-NPS DI scores and thus to a dilution of the potential effect [51], with weaker associations than the ones that could have been observed with the use of other dietary assessment methods (e.g., repeated 24-h dietary records as used in the SU.VI.MAX and NutriNet-Santé cohorts). Differences in effect size between studies and between cancer locations could also be partially explained by the differences in the number of cases; fewer cases may lead to less-accurate estimates of HRs. Finally, the differences in effect size between cancer locations and the nonsignificant results observed for some cancer sites may illustrate true different susceptibilities of cancer types to nutritional factors. For example, WCRF and AICR estimated that 47% of colorectal cancer may be prevented with nutrition compared to 19% for pancreatic cancers [1].

Strengths of this study include its large sample size, its prospective design, its long follow-up, and the inclusion of participants from different European countries with standardised data collection, especially for diet, offering a broad perspective on nutritional quality of dietary intakes in Europe. However, some limitations should be acknowledged. First, caution is needed regarding the extrapolation of these results to the entire European population or to other populations or ethnicities worldwide since this study included volunteers from 10 European countries involved in a long-term cohort study investigating the association between nutrition and health, with overall more health-conscious behaviours compared to the general population. Therefore, unhealthy dietary behaviours may have been underrepresented in this study, which may have weakened the observed associations by inducing a smaller contrast between high and low scores. Furthermore, in our models, we included all the participants with available dietary intake data but with potential missing data on other covariates replaced with a 'missing' class or imputation. Although this may have induced some bias, a complete cases model would lead to a selection towards more compliant participants in an already health-conscious population. Still, sensitivity analyses with a complete cases model provided similar results. In addition, this study used a single assessment of dietary intakes at baseline. Although diet may change over time, it is usually hypothesized that this estimation reflects general eating behavior throughout middle-aged adult life [52]. Diet measurement instruments are built to capture the usual dietary intakes of an individual but are still subject to imprecision and inaccuracy. Finally, this study was based on an observational cohort. Thus, even though our models included a large range of confounding factors, residual confounding cannot be entirely ruled out.

In conclusion, the results of this observational study performed on a large European cohort with diverse profiles and nutritional habits, suggest that the consumption of food products with higher FSAm-NPS scores (reflecting a lower nutritional quality) is associated with a higher risk of developing cancer. These studies complement published or ongoing studies specifically assessing the perception and understanding of the Nutri-Score (derived from FSAm-NPS score) and its actual impact on food choices [13–22]. Overall, this adds support to the relevance of the FSAm-NPS as underlying nutrient profiling system for the simplified nutrition label Nutri-Score, but also for other public health nutritional measures aiming to influence the nutritional quality of food choices at a national and potentially supranational level. This should be considered for ongoing and future debates at the EU level regarding the implementation of a unique food labelling system on the front of pack of food products. To date, the FSAm-NPS is the most validated nutrient-profiling system and the easiest to compute, with a limited number of components that are readily available on food packaging and an open/published algorithm. Future comparative studies may be carried on if other nutrient profiling systems with similar characteristics, and a corresponding score derived at the individual level are to be proposed. Appending a nutritional label like the Nutri-Score would be an additional tool to the

array of public health nutritional strategies. In particular, this would complement strategies setting the bases of a balanced diet mixing different types of food, by helping the consumers choose food products with a better nutritional profile, even among the same food category, and by highlighting food products for which a sensible consumption should be preferred.

Supporting information

S1 Fig. The Nutri-Score front-of-pack nutritional label (Santé Publique France).

(PDF)

S2 Fig. Participants' flowchart, EPIC cohort, 1992–2014. EPIC, European Prospective Investigation into Cancer and Nutrition.

(PDF)

S1 Table. Incident cancer cases and noncases by country, EPIC cohort, 1992–2014. EPIC, European Prospective Investigation into Cancer and Nutrition.

(PDF)

S2 Table. Associations between the FSAm-NPS DI and risk for cancers of the female reproductive system, by menopausal status, from multivariable Cox proportional hazards models, EPIC cohort, 1992–2014. DI, Dietary Index; EPIC, European Prospective Investigation into Cancer and Nutrition; FSAm-NPS, Nutrient Profiling System of the British Food Standards Agency (modified version).

(PDF)

S1 Text. FSAm-NPS score computation at food/beverage level, FSAm-NPS DI computation at individual level and link to the Nutri-Score (Santé Publique France). DI, Dietary Index; FSAm-NPS, Nutrient Profiling System of the British Food Standards Agency (modified version).

(PDF)

S2 Text. Analysis plan extracted from the project protocol submitted for funding application.

(PDF)

S1 STROBE Statement.

(PDF)

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References

1. WCRF/AICR. Cancer preventability estimates for food, nutrition, body fatness, and physical activity. WCRF/AICR. 2017. Available from: <http://www.wcrf.org/int/cancer-facts-figures/preventability-estimates/cancer-preventability-estimates-diet-nutrition>
2. Serra-Majem L. Moving forward in public health nutrition—the I World Congress of Public Health Nutrition. Introduction. *Nutr Rev*. 2009; 67 Suppl 1:S2–S6.
3. Hercberg S. Propositions pour un nouvel élan de la politique nutritionnelle française de santé publique dans le cadre de la stratégie nationale de santé. 1ère partie: mesures concernant la prévention nutritionnelle [in French]. 2013.

4. Hawley KL, Roberto CA, Bragg MA, Liu PJ, Schwartz MB, Brownell KD. The science on front-of-package food labels. *Public Health Nutr.* 2013; 16:430–9. <https://doi.org/10.1017/S1368980012000754> PMID: 22440538
5. Hersey JC, Wohlgenant KC, Arsenaault JE, Kosa KM, Muth MK. Effects of front-of-package and shelf nutrition labeling systems on consumers. *Nutr Rev.* 2013; 71:1–14. <https://doi.org/10.1111/nure.12000> PMID: 23282247
6. Arambepola C, Scarborough P, Rayner M. Validating a nutrient profile model. *Public Health Nutr.* 2008; 11:371–8. <https://doi.org/10.1017/S1368980007000377> PMID: 17605841
7. Rayner M, Scarborough P, Stockley P, Boxer A. Nutrient profiles: Development of Final Model. Final Report [online]. London, FSA. 2005.
8. Azais-Braesco V, Goffi C, Labouze E. Nutrient profiling: comparison and critical analysis of existing systems. *Public Health Nutr.* 2006; 9:613–22. PMID: 16923293
9. Rayner M, Scarborough P, Lobstein T. The UK Ofcom Nutrient Profiling Model: Defining 'healthy' and 'unhealthy' foods and drinks for TV advertising to children. London, OfCom. 2009.
10. Julia C, Kesse-Guyot E, Touvier M, Mejean C, Fezeu L, Hercberg S. Application of the British Food Standards Agency nutrient profiling system in a French food composition database. *Br J Nutr.* 2014; 112:1699–705. <https://doi.org/10.1017/S0007114514002761> PMID: 25277084
11. Anses. Evaluation de la faisabilité du calcul d'un score nutritionnel tel qu'élaboré par Rayner et al. Rapport d'appui scientifique et technique. Paris: Anses. 2015.
12. Haut Conseil de la Santé Publique. Opinion on information regarding the nutritional quality of foodstuffs. HCSP. 2015. Available from: <http://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=519>
13. Ducrot P, Mejean C, Julia C, Kesse-Guyot E, Touvier M, Fezeu L, et al. Effectiveness of Front-Of-Pack Nutrition Labels in French Adults: Results from the NutriNet-Sante Cohort Study. *PLoS ONE.* 2015; 10(10):e0140898. <https://doi.org/10.1371/journal.pone.0140898> PMID: 26509679
14. Ducrot P, Mejean C, Julia C, Kesse-Guyot E, Touvier M, Fezeu LK, et al. Objective Understanding of Front-of-Package Nutrition Labels among Nutritionally At-Risk Individuals. *Nutrients.* 2015; 7:7106–25. <https://doi.org/10.3390/nu7085325> PMID: 26305255
15. Ducrot P, Julia C, Mejean C, Kesse-Guyot E, Touvier M, Fezeu LK, et al. Impact of Different Front-of-Pack Nutrition Labels on Consumer Purchasing Intentions: A Randomized Controlled Trial. *Am J Prev Med.* 2016; 50:627–36. <https://doi.org/10.1016/j.amepre.2015.10.020> PMID: 26699246
16. Julia C, Kesse-Guyot E, Ducrot P, Peneau S, Touvier M, Mejean C, et al. Performance of a five category front-of-pack labelling system—the 5-colour nutrition label—to differentiate nutritional quality of breakfast cereals in France. *BMC Public Health.* 2015; 15:179. <https://doi.org/10.1186/s12889-015-1522-y> PMID: 25885583
17. Julia C, Ducrot P, Peneau S, Deschamps V, Mejean C, Fezeu L, et al. Discriminating nutritional quality of foods using the 5-Color nutrition label in the French food market: consistency with nutritional recommendations. *Nutr J.* 2015; 14:100. <https://doi.org/10.1186/s12937-015-0090-4> PMID: 26416389
18. Julia C, Blanchet O, Mejean C, Peneau S, Ducrot P, Alles B, et al. Impact of the front-of-pack 5-colour nutrition label (5-CNL) on the nutritional quality of purchases: an experimental study. *Int J Behav Nutr Phys Act.* 2016; 13:101. <https://doi.org/10.1186/s12966-016-0416-4> PMID: 27645372
19. Julia C, Hercberg S. Research and lobbying conflicting on the issue of a front-of-pack nutrition labelling in France. *Arch Public Health.* 2016; 74:51. <https://doi.org/10.1186/s13690-016-0162-8> PMID: 27933143
20. Julia C, Mejean C, Peneau S, Buscail C, Alles B, Fezeu L, et al. The 5-CNL Front-of-Pack Nutrition Label Appears an Effective Tool to Achieve Food Substitutions towards Healthier Diets across Dietary Profiles. *PLoS ONE.* 2016; 11(6):e0157545. <https://doi.org/10.1371/journal.pone.0157545> PMID: 27322033
21. Julia C, Peneau S, Buscail C, Gonzalez R, Touvier M, Hercberg S, et al. Perception of different formats of front-of-pack nutrition labels according to sociodemographic, lifestyle and dietary factors in a French population: cross-sectional study among the NutriNet-Sante cohort participants. *BMJ Open.* 2017; 7:e016108. <https://doi.org/10.1136/bmjopen-2017-016108> PMID: 28619781
22. Julia C, Hercberg S. Development of a new front-of-pack nutrition label in France: the five-colour Nutri-Score. *Public Health Panorama.* 2017; 3:712–25.
23. Julia C, Touvier M, Mejean C, Ducrot P, Peneau S, Hercberg S, et al. Development and validation of an individual dietary index based on the British Food Standard Agency nutrient profiling system in a French context. *J Nutr.* 2014; 144:2009–17. <https://doi.org/10.3945/jn.114.199679> PMID: 25411035
24. Julia C, Mejean C, Touvier M, Peneau S, Lassale C, Ducrot P, et al. Validation of the FSA nutrient profiling system dietary index in French adults—findings from SUVIMAX study. *Eur J Nutr.* 2016; 55:1901–10. <https://doi.org/10.1007/s00394-015-1006-y> PMID: 26293977

25. Julia C, Ducrot P, Lassale C, Fezeu L, Mejean C, Peneau S, et al. Prospective associations between a dietary index based on the British Food Standard Agency nutrient profiling system and 13-year weight gain in the SU.VI.MAX cohort. *Prev Med.* 2015; 81:189–94. <https://doi.org/10.1016/j.ypmed.2015.08.022> PMID: 26348449
26. Julia C, Fezeu LK, Ducrot P, Mejean C, Peneau S, Touvier M, et al. The Nutrient Profile of Foods Consumed Using the British Food Standards Agency Nutrient Profiling System Is Associated with Metabolic Syndrome in the SU.VI.MAX Cohort. *J Nutr.* 2015; 145:2355–61. <https://doi.org/10.3945/jn.115.213629> PMID: 26290007
27. Adriouch S, Julia C, Kesse-Guyot E, Mejean C, Ducrot P, Peneau S, et al. Prospective association between a dietary quality index based on a nutrient profiling system and cardiovascular disease risk. *Eur J Prev Cardiol.* 2016; 23:1669–76. <https://doi.org/10.1177/2047487316640659> PMID: 27000099
28. Adriouch S, Julia C, Kesse-Guyot E, Ducrot P, Peneau S, Mejean C, et al. Association between a dietary quality index based on the food standard agency nutrient profiling system and cardiovascular disease risk among French adults. *Int J Cardiol.* 2017; 234:22–7. <https://doi.org/10.1016/j.ijcard.2017.02.092> PMID: 28258849
29. Deschasaux M, Julia C, Kesse-Guyot E, Lecuyer L, Adriouch S, Mejean C, et al. Are self-reported unhealthy food choices associated with an increased risk of breast cancer? Prospective cohort study using the British Food Standards Agency nutrient profiling system. *BMJ Open.* 2017; 7:e013718. <https://doi.org/10.1136/bmjopen-2016-013718> PMID: 28600360
30. Donnenfeld M, Julia C, Kesse-Guyot E, Mejean C, Ducrot P, Peneau S, et al. Prospective association between cancer risk and an individual dietary index based on the British Food Standards Agency Nutrient Profiling System. *Br J Nutr.* 2015; 114:1702–10. <https://doi.org/10.1017/S0007114515003384> PMID: 26393396
31. Journal Officiel de la République Française. Arrêté du 31 octobre 2017 fixant la forme de présentation complémentaire à la déclaration nutritionnelle recommandée par l'Etat en application des articles L. 3232–8 et R. 3232–7 du code de la santé publique (in French). *JORF n°0257 2017.* Available from: <https://www.legifrance.gouv.fr/eli/arrete/2017/10/31/SSAP1730474A/jo/texte>
32. Julia C, Etile F, Hercberg S. Front-of-pack Nutri-Score labelling in France: an evidence-based policy. *Lancet Public Health.* 2018; 3:e164. [https://doi.org/10.1016/S2468-2667\(18\)30009-4](https://doi.org/10.1016/S2468-2667(18)30009-4) PMID: 29483002
33. WHO Europe. France becomes one of the first countries in Region to recommend colour-coded front-of-pack nutrition labelling system. *World Health Organization-Europe Office.* 2017. Available from: <http://www.euro.who.int/en/countries/france/news/news/2017/03/france-becomes-one-of-the-first-countries-in-region-to-recommend-colour-coded-front-of-pack-nutrition-labelling-system>
34. Ferrari P, Day NE, Boshuizen HC, Roddam A, Hoffmann K, Thiebaut A, et al. The evaluation of the diet/disease relation in the EPIC study: considerations for the calibration and the disease models. *Int J Epidemiol.* 2008; 37:368–78. <https://doi.org/10.1093/ije/dym242> PMID: 18180242
35. Riboli E, Kaaks R. The EPIC Project: rationale and study design. *European Prospective Investigation into Cancer and Nutrition.* *Int J Epidemiol.* 1997; 26 Suppl 1:S6–14.
36. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr.* 2002; 5:1113–24. <https://doi.org/10.1079/PHN2002394> PMID: 12639222
37. Slimani N, Deharveng G, Unwin I, Southgate DA, Vignat J, Skeie G, et al. The EPIC nutrient database project (ENDB): a first attempt to standardize nutrient databases across the 10 European countries participating in the EPIC study. *Eur J Clin Nutr.* 2007; 61:1037–56. <https://doi.org/10.1038/sj.ejcn.1602679> PMID: 17375121
38. International Classification of Diseases for Oncology, Third Edition, First Revision. Geneva: World Health Organization; 2013.
39. Andersen PK, Geskus RB, de WT, Putter H. Competing risks in epidemiology: possibilities and pitfalls. *Int J Epidemiol.* 2012; 41:861–70. <https://doi.org/10.1093/ije/dyr213> PMID: 22253319
40. Ferrari P, Licaj I, Muller DC, Kragh AP, Johansson M, Boeing H, et al. Lifetime alcohol use and overall and cause-specific mortality in the European Prospective Investigation into Cancer and nutrition (EPIC) study. *BMJ Open.* 2014; 4:e005245. <https://doi.org/10.1136/bmjopen-2014-005245> PMID: 24993766
41. Muka T, Asllanaj E, Avazverdi N, Jaspers L, Stringa N, Milic J, et al. Age at natural menopause and risk of type 2 diabetes: a prospective cohort study. *Diabetologia.* 2017; 60:1951–60. <https://doi.org/10.1007/s00125-017-4346-8> PMID: 28721436
42. Masset G, Scarborough P, Rayner M, Mishra G, Brunner EJ. Can nutrient profiling help to identify foods which diet variety should be encouraged? Results from the Whitehall II cohort. *Br J Nutr.* 2015; 113:1800–9. <https://doi.org/10.1017/S000711451500094X> PMID: 25898932
43. Mytton OT, Forouhi NG, Scarborough P, Lentjes M, Luben R, Rayner M, et al. Association between intake of less-healthy foods defined by the United Kingdom's nutrient profile model and cardiovascular

- disease: A population-based cohort study. *PLoS Med.* 2018; 15(1):e1002484. <https://doi.org/10.1371/journal.pmed.1002484> PMID: 29300725
44. Schwingshackl L, Hoffmann G. Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies. *Cancer Med.* 2015; 4:1933–47. <https://doi.org/10.1002/cam4.539> PMID: 26471010
 45. Romaguera D, Vergnaud AC, Peeters PH, van Gils CH, Chan DS, Ferrari P, et al. Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. *Am J Clin Nutr.* 2012; 96:150–63. <https://doi.org/10.3945/ajcn.111.031674> PMID: 22592101
 46. Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, et al. Alternative dietary indices both strongly predict risk of chronic disease. *J Nutr.* 2012; 142:1009–18. <https://doi.org/10.3945/jn.111.157222> PMID: 22513989
 47. Chiuve SE, Sampson L, Willett WC. The association between a nutritional quality index and risk of chronic disease. *Am J Prev Med.* 2011; 40:505–13. <https://doi.org/10.1016/j.amepre.2010.11.022> PMID: 21496749
 48. Latino-Martel P, Cottet V, Druesne-Pecollo N, Pierre FH, Touillaud M, Touvier M, et al. Alcoholic beverages, obesity, physical activity and other nutritional factors, and cancer risk: a review of the evidence. *Crit Rev Oncol Hematol.* 2016; 99:323.
 49. WCRF/AICR. Continuous Update Project Reports and associated Systematic Literature Review—(2007–2017): The Associations between Food, Nutrition and Physical Activity and the Risk of Cancer. Washington, DC: AICR; 2017.
 50. WCRF/AICR. Systematic Literature Review—Continuous Update Project Report: The Associations between Food, Nutrition and Physical Activity and the Risk of Breast Cancer. Washington, DC: AICR; 2017.
 51. Schatzkin A, Kipnis V, Carroll RJ, Midthune D, Subar AF, Bingham S, et al. A comparison of a food frequency questionnaire with a 24-hour recall for use in an epidemiological cohort study: results from the biomarker-based Observing Protein and Energy Nutrition (OPEN) study. *Int J Epidemiol.* 2003; 32:1054–62. PMID: 14681273
 52. Willett WC. *Nutritional Epidemiology*, 2nd ed. New York: Oxford University Press; 1998.