Population and Prevention Science

Cancer Research

Cancer-Specific and General Nutritional Scores and Cancer Risk: Results from the Prospective NutriNet-Santé Cohort

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Abstract

Several national and international authorities have proposed nutritional and lifestyle recommendations with the aim of improving health of the general population. Scores of adherence to these recommendations can be calculated at the individual level. Here, we investigated the associations between four nutritional scores and overall, breast, prostate, and colorectal cancer risk in a large prospective population-based cohort: the cancer-specific World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) score, the Alternate Healthy Eating Index 2010 (AHEI-2010), a score based on adherence to the Mediterranean diet (MEDI-LITE), and the French National Nutrition Health Program-Guideline Score (PNNS-GS). This study included 41,543 participants aged $\geq$40 years from the NutriNet-Santé cohort (2009–2017). A total of 1,489 overall incident cancers were diagnosed. A one-point increment of the WCRF/AICR score was significantly associated with decreased overall [12%; 95% confidence interval (CI), 8%–16%; $P < 0.0001$], breast (14%; 95% CI, 6%–21%; $P = 0.001$), and prostate (12%; 95% CI, 0%–22%; $P = 0.05$) cancer risks. Hazard ratio for colorectal cancer risk was 0.86 (95% CI, 0.72–1.03; $P = 0.09$). The PNNS-GS score was associated with reduced colorectal cancer risk ($P = 0.04$) and AHEI-2010 was associated with reduced overall cancer risk ($P = 0.03$). The WCRF/AICR score performed best. Compared with other tested scores, it included a stronger penalty for alcohol, which is a major risk factor for several cancer sites. Better adherence to nutritional recommendations, especially those designed for cancer prevention, could substantially contribute to decreased cancer incidence.

Significance: This large prospective population-based cohort study suggests that following dietary recommendations such as the ones proposed by the World Cancer Research Fund/American Institute for Cancer Research could significantly contribute to cancer prevention. *Cancer Res; 78(15); 4427–35. ©2018 AACR.*

Introduction

Cancers represent a worldwide and increasing public health, social and economic burden. In 2012, 14 million new cases of cancers were diagnosed, mainly affecting prostate, breast, lung and colon-rectum (1). Cancers are a leading cause of overall and premature deaths (2). In France, the National Cancer Institute (INCa) estimated that 80,000 deaths could be prevented each year by taking individual or collective prevention measures (3). Numerous environmental risk factors related to cancer have been identified in the past few decades, among which nutrition. In particular, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) estimated that in developed countries around 35% of breast cancers and 45% of colorectal cancers could be avoided by a better adherence to nutritional recommendations (4).

Given the stakes involved in the prevention of pathologies through food and nutrition, the development of nutrition policies has emerged as a public health priority at international (5, 6) and national (7) levels. Nutritional and lifestyle recommendations have been implemented to optimize primary prevention, either targeting a particular pathology or aiming at the prevention of chronic pathologies overall. Individual indexes have been developed during the last decades to estimate the adherence to such guidelines (8).

The present study investigated three validated and widely used scores (the WCRF/AICR score (9), the Alternate Healthy Eating Index (AHEI)-2010 (10) and the French Nutrition and Health Program-Guidelines Score (PNNS-GS; ref. 11), and one relatively recent score focusing on the adherence to a Mediterranean diet (the MEDI-LITE score; ref. 12). The WCRF/AICR score is based on the recommendations on diet, physical activity, and weight management for cancer prevention established in 2007 (6). The AHEI-2010 score provides an estimate of the quality of the diet by incorporating current knowledge on foods/nutrients predictive of the risk of chronic diseases (10). The MEDI-LITE score was developed upon an extended review of the literature and it

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assesses the adherence to a Mediterranean diet (12). Finally, the PNNS-GS score describes the overall quality of the diet for each individual according to the recommendations of the French Nutrition and Health Program (11).

Some prospective epidemiological studies have examined the relationship between these nutritional scores and cancer incidence and have shown promising results with a higher adherence to the corresponding nutritional recommendations indeed associated with decreased risk of cancer at several locations [e.g. (refs. 9, 13–22) for the WCRF/AICR score, or (refs. 10, 23–27) for the AHEI-2010 score]. However, these studies need to be replicated in other study populations or countries with different risks and dietary patterns. Besides, although the WCRF/AICR score was specifically designed in a context of cancer prevention, the three other scores (AHEI-2010, MEDI-LITE and PNNS-GS) are not cancer specific; thus, it is interesting to compare the strength of their association with cancer risk in a same population study.

Thus, this study aimed at investigating the association between these four nutritional scores and cancer risk in middle-aged French adults from the prospective NutriNet-Santé cohort.

Patients and Methods

The NutriNet-Santé cohort

The NutriNet-Santé study is a French ongoing web-based cohort launched in 2009 with the objective to investigate the associations between nutrition and health as well as the determinants of dietary behaviors and nutritional status. This cohort has been previously described in details (28). Participants aged over 18 years with access to the Internet are continuously recruited by vast multimedia campaigns. All questionnaires are completed online using a dedicated website (www.etude-nutrinet-sante.fr). The NutriNet-Santé study is conducted according to the Declaration of Helsinki guidelines. It was approved by the Institutional Review Board of the French Institute for Health and Medical Research (IRB Inserm n°0000388FWA00005831) and the "Commission Nationale de l'Informatique et des Libertés" (CNIL n°908450/n°909216). It is registered at clinicaltrials.gov as NCT03335644. Before starting the study, all participants signed an electronic informed consent via the online platform. This procedure is appropriate for web-cohorts and has been validated by the above mentioned ethical and regulatory instances.

Data collection

At inclusion, participants fulfilled a set of five questionnaires related to socio-demographic and lifestyle characteristics (ref. 29; e.g., occupation, educational level, smoking status, alcohol consumption, number of children), anthropometrics (refs. 30, 31; e.g., height, weight), dietary intakes (see below), physical activity (validated IPAQ questionnaire; ref. 32), and health status (e.g., personal and family history of diseases, medication use including hormonal treatment for menopause and oral contraception, menopausal status). Age at menopause was determined using the yearly health status questionnaires available during follow-up.

Dietary data. Usual dietary intakes were assessed every 6 months through series of three non-consecutive validated web-based 24 hours-dietary records, randomly assigned over a two2-week period (2 weekdays and one weekend day; 33–35). Participants used a dedicated interface of the study website to declare all foods and beverages consumed during a 24 hours-period: three main meals (breakfast, lunch, dinner) or any other eating occasion. Portion sizes were estimated using validated photographs (36). Mean daily energy, alcohol and nutrient intakes were estimated using a published French food composition table (>3,300 items; ref. 37). Amounts consumed from composite dishes were estimated using French recipes validated by food and nutrition professionals. Dietary underreporting was identified on the basis of the method proposed by Black, using the basal metabolic rate and Goldberg cutoff, and under-energy reporters were excluded (38). The NutriNet-Santé web-based dietary records have been validated against blood and urinary biomarkers (showing satisfying correlations for nutrients of interest in the present study, for example, protein, sodium, n-3 polyunsaturated fatty acid, eicosapentaenoic acid and docosahexaenoic acid intake, with correlations of 0.6, 0.5, 0.3, 0.4 and 0.4 for men and 0.6, 0.4, 0.4, 0.4 and 0.4 for women, respectively; refs. 33, 35) and compared with an interview by a trained dietician (range of intra-class correlation coefficients for food groups = 0.5–0.9/range of energy-adjusted Pearson's correlations for nutrients = 0.6–0.9; ref. 34). For each subject, usual dietary intakes were estimated as the mean intakes across all the 24 hours-dietary records available in their first 2 years of each participant's follow-up.

Scores computation

A summary of all components, cutoff points and scoring of the four nutritional scores is presented in Supplementary Table S1. For all these scores, a higher value corresponded to a better fit with the corresponding recommendations.

WCRF/AICR. An index score reflecting concordance with the WCRF/AICR recommendations for cancer prevention was constructed (WCRF/AICR score; ref. 9). For each of the eight recommendations, one point was assigned when the recommendation was met. An intermediate category (0.5 points) was created for the subjects who partially met the recommendation, to appraise a higher proportion of variability in the population. All other individuals received zero point. Some recommendations had several sub-recommendations: in that case, each sub-recommendation was scored and the component score was the average of the sub-recommendation scores. Points obtained for each component were summed to calculate a single score for each study participant. The maximum score was eight.

AHEI-2010. The AHEI-2010 score was calculated from 10 of the 11 components used in the AHEI calculation (10) because *trans* fats were not available in the food composition table. It has been developed in a U.S. context and aimed to estimate the nutritional quality of the diet. It was based on foods and nutrients involved in the etiology of chronic disease risk. Each component contributed 0 (recommendation not met) to 10 points (recommendation fully met) to the total score. Intermediate inputs were assessed proportionally between 0 and 10. All points of the components were summed to obtain the AHEI-2010 score which ranged from 0 to 100.

MEDI-LITE. The MEDI-LITE score included nine components. It was designed to evaluate the level of adherence to the Mediterranean diet (12). For typical food groups in the Mediterranean diet, two points were assigned to the highest consumption category, one point for the middle category and zero for the lowest category. Conversely, for food groups not typical of the Mediterranean diet, two points were awarded for the lowest category, one point for the average category and zero point for the highest consumption category. For alcohol, two points were awarded to the average category, one point to the lowest category and zero to the highest category of consumption. For olive oil, two points were attributed for regular use, one point for frequent use and zero point for occasional use. The final score ranged from 0 to 18 points.

PNNS-GS. This score was calculated from 13 components. It represented the level of adherence to the French nutritional guidelines of the Nutrition and Health program (11). Eight components referred to adequation, four to moderation and to physical activity level. At least one point was attributed when the participant's consumption was in accordance with the recommendation. For most components, intermediate points were allocated to subjects who did not fully meet the recommendation but came close. Beneficial supplementary points were allocated to people with high consumption of fruits and legumes, low consumption of salt, and high physical activity level. Penalties were allocated to high consumer of salt or of sugar. Conversely, points were deducted for people with energy consumption above their estimated need. If reported energy intake was 5% or more higher than the calculated energy need, the total score was reduced by the same proportion. Consequently, the overall score could be negative (due to the penalty) and went up to 15 points.

Case ascertainment

Participants self-declared health events through the yearly health status questionnaire, through a specific check-up questionnaire for health events (every three months) or at any time through a specific interface on the study website. For each incident cancer declared, participants were contacted by a physician of the team and asked to provide any relevant medical records. Whenever necessary, the study physicians contacted the physician of the patient and/or hospitals to collect additional information. Afterwards, all medical data were reviewed by a physician expert committee. Medical records were obtained for >90% of cancer cases. Because of the high validity of self-reports (95% of self-reported cancers for which a medical record was obtained were confirmed by our physicians), we included as cases all participants who self-reported incident cancers, unless they were identified as non-cases participants by a pathology report, in which case we classified them as non-cases. Besides, our research team was the first in France to obtain the authorization by Decree in the Council of State (n°2013-175) to link data from our cohorts to medico-administrative databases of the National health insurance (SNIIRAM database). Declared health events were, therefore, completed by the information from these databases, thereby limiting any potential bias due to people with cancer who may not report their disease to the study investigators. Last, an additional linkage to the French National cause-specific mortality registry (CépiDC) is used to detect death and potentially missed cancer cases for deceased participants. Cancer cases were classified using the International Chronic Diseases Classification, 10th Revision, Clinical Modification (ICD-10; ref. 39). In this study, all first primary cancers diagnosed between the inclusion and January 1, 2017 were considered as cases, except for basal cell skin carcinoma, which was not considered as cancer.

Statistical analyses

Up to January 1, 2017, 97,413 participants who had never suffered cancer prior to inclusion had completed at least three valid 24 hours-dietary records during the first 2 years of follow-up. Participants aged under 40 years were excluded (n = 44,061) due to a very low susceptibility to develop cancer. We also excluded people for whom the calculation of the four scores was impossible due to missing values in some of the components ($n = 11,809$). Thus, 41,543 subjects were included in the analyses. The flow chart for the selection of the population study is presented in Supplementary Fig. S1. Nutritional scores were considered as the primary exposure and were coded as continuous variables and sex-specific quintiles. For all covariates $\leq$5% of values were missing and were imputed to the modal value.

Multivariable Cox proportional hazard models were used with age as the primary time variable, to characterize the associations between each nutritional score and overall cancer risk by generating Hazard Ratios (HR) and 95% confidence intervals (95% CI). Distinct models were used to assess the associations between each nutritional score and breast, prostate, and colorectal cancer risks. In these models, participants with cancers of other locations than the one studied were censored at the date of diagnosis. Log–log (survival) versus log-time plots were generated to check for risk proportionality assumptions. Participants contributed person-time to the Cox model until the date of cancer diagnosis, the date of last completed questionnaire, the date of death or January 1, 2017, whichever occurred first. Breast cancer analyses were additionally stratified by menopausal status. For the latter, 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.

Multivariable models were adjusted for age (time-scale), height (cm, continuous), smoking status (never smokers, former smokers, current smokers), number of dietary records (continuous), energy intake without alcohol (kcal/d, continuous), family history of cancer among first-degree relatives (yes/no), higher education (none, <2 years, $\geq$2 years), body mass index (BMI; continuous variable; kg/m^2, continuous) and physical activity (high, moderate, low, calculated according to the IPAQ recommendations; ref. 40). Adjustment for BMI and physical activity were not performed for scores in which they were included as components (Supplementary Table S1). For breast cancer, models were additionally adjusted for the number of biological children (continuous), menopausal status at baseline (pre/post-menopause), hormonal treatment for menopause (yes/no) and oral contraception (yes/no). Tests for linear trends were performed across categories with the use of the ordinal value of the corresponding variable. Furthermore, sensitivity analyses were performed by excluding cases diagnosed in the first 2 years of follow-up and participants with a less than 2-year follow-up period.

Last, to compare predictive performance of each nutritional score, NRI (Net Reclassification Improvement) indexes (41) were calculated. This indicator aimed at comparing the predictive performance of the models when each score was added, compared with the reference model based on known risk factors only, as defined above. Because the reference model was not the same for each score, it has been adapted according to the components already included in each model (as detailed in the footnotes to Supplementary Table S2).

A $P \leq 0.05$ was considered statistically significant. All analyses were carried out with SAS software (version 9.4; SAS Institute Inc.).

Results

Between May 2009 and January 1, 2017 (164,052 person-years), 1,489 overall incident cancer cases were diagnosed, among which 488 breast cancers (119 premenopausal and 369 postmenopausal breast cancers), 222 prostate cancers (11.5% of aggressive prostate cancer [Gleason ≥7]), and 118 colorectal cancers. Baseline characteristics of participants are described in Table 1. Mean age at diagnosis was 61.6 years (SD = 8.6) and mean baseline-to-diagnosis time was 3.0 years (SD = 1.9). Mean number of dietary records per subjects over their first two years of follow-up was 6.4 (SD = 2.9).

Associations between each nutritional score and overall, breast, prostate and colorectal cancer risk are presented in Tables 2–5 and associations for standardized score are summarized in Fig. 1. A one-point increment of the WCRF/AICR score was associated with a 12% decrease in overall cancer risk (95% CI, 8%–16%; $P <$ 0.0001), a 14% [95% CI, 6%–21%] decrease in breast cancer risk ($P = 0.001$), and a 12% [95% CI, 0%–22%] decrease in prostate cancer risk ($P = 0.05$). HR for colorectal cancer risk was 0.86 ($P =$ 0.09). Regarding breast cancer risk and the WCRF/AICR score, similar trends were observed when models were restricted to postmenopausal women (17%; 95% CI, 8%–25%; decrease $P = 0.003$). The association was not significant in premenopausal women only, as statistical power was more limited (119 cases; HR, 0.98; 95% CI, 0.81–1.17; $P = 0.86$). A ten-point increment of the AHEI-2010 score was associated with a 5% (95% CI, 1%–10%)

Table 1. Baseline characteristics of study participants, NutriNet-Santé Cohort, France, 2009–2017[a]

	All (*n* = 41,543)	Non-cases (*n* = 40,054)	Incident cancers (*n* = 1,489)	*P*[b]
Age, years	54.6 ± 8.7	54.4 ± 8.7	58.4 ± 8.5	<0.0001
Sex (men)	11018 (26.5)	10514 (26.3)	504 (33,9)	<0.0001
Educational level				0.047
<High-school degree	10905 (26.3)	10480 (26.1)	425 (28.5)	
≥High-school degree to <2 y after high-school degree	6605 (15.9)	6357 (15.9)	248 (16.7)	
≥2 y after high-school degree	24033 (57.8)	23217 (58.0)	816 (54.8)	
Smoking status				0.0007
Never smokers	18375 (44.2)	17748 (44.3)	627 (42.1)	
Former smokers	18110 (43.6)	17396 (43.4)	714 (48.0)	
Current Smokers	5058 (12.2)	4910 (12.3)	148 (9.9)	
Physical activity[c]				0.2
Low (irregular)	9056 (21.8)	8759 (21.9)	297 (20.0)	
Moderate (<1 h/day walking or equivalent)	16510 (39.7)	15899 (39.7)	611 (41.0)	
High (≥1 h/day walking or equivalent)	15977 (38.5)	15396 (38.4)	581 (39.0)	
BMI, kg/m^2	24.5 ± 4.5	24.5 ± 4.6	25.0 ± 4.3	0.0003
Weight status				<0.0001
Underweight (BMI < 18 kg/m^2)	1188 (2.8)	1151 (2.9)	37 (2.5)	
Normal-weight (18 ≤ BMI < 25 kg/m^2)	24964 (60.1)	24153 (60.3)	811 (54.5)	
Overweight (25 ≤ BMI < 30 kg/m^2)	10875 (26.2)	10413 (26.0)	462 (31,0)	
Obese (BMI ≥ 30 kg/m^2)	4516 (10.9)	4337 (10.8)	179 (12,0)	
Height, cm	166.5 ± 8.3	166.4 ± 8.3	167.5 ± 8.2	<0.0001
Family history of cancer (yes)[d]	20300 (48.9)	19473 (48.6)	827 (55.5)	<0.0001
Number of biological children	1.9 ± 1.1	1.9 ± 1.1	1.9 ± 1.1	0.9
Menopausal status				<0.0001
Premenopause	12157 (39.8)	11872 (40.2)	285 (28.9)	
Perimenopause	3084 (10.1)	2982 (10.1)	102 (1.4)	
Postmenopause	15284 (50.1)	14686 (49.7)	598 (60.7)	
Oral contraception (yes)[e]	2582 (21.2)	2521 (21.2)	61 (21.4)	0.9
Hormonal treatment for menopause (yes)[f]	3256 (17.7)	3105 (17.6)	151 (21.6)	0.007
Energy intake (without alcohol), kcal/day	1895.9 ± 463.9	1894.3 ± 464	1939.5 ± 444.6	0.0002
Alcohol intake, g/day	9.4 ± 12.6	9.3 ± 12.6	11.8 ± 14.2	<0.0001
WCRF/AICR score	4.8 ± 1.1	4.8 ± 1.1	4.6 ± 1.1	<0.0001
AHEI-2010 score	47.8 ± 11.6	47.8 ± 11.6	48.1 ± 11.1	0.2
MEDI-LITE score	8.4 ± 2.3	8.4 ± 2.3	8.5 ± 2.3	0.1
PNNS-GS score	9.3 ± 1.8	9.3 ± 1.8	9.5 ± 1.8	<0.0001

Abbreviations: WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research; AHEI, Alternate Healthy Eating Index; MEDI-LITE, Mediterranean diet based on literature; PNNS-GS, The Nutrition and Health Program – Guideline Score (Programme National Nutrition Santé-Guideline Score).

[a]Values are presented as means ± SDs or *N* (%).

[b]*P* values for the comparison between cases/non-cases using χ^2 tests or Fisher tests as appropriate. All statistical tests were two-sided.

[c]The highest category corresponds to participants who practiced vigorous-intensity activity on at least 3 days during the week and accumulated at least 1,500 MET-min/wk, or 7 days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum of at least 3,000 MET-min/wk. The category of moderate physical activity corresponds to any one of the following three criteria: 3 or more days of vigorous activity of at least 20 minutes per day or 5 or more days of moderate-intensity activity or walking of at least 30 minutes per day, or 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum of at least 600 MET-min/wk. The lowest category concerns participants with the lowest level of physical activity, who did not meet criteria of the categories "high" or "moderate."

[d]Among first-degree relatives.

[e]Among premenopausal women (*n* = 12,157).

[f]Among postmenopausal women (*n* = 18,368).

Table 2. HRs [95% CIs] for the association between the WCRF/AICR score and cancer risk, NutriNet-Santé Cohort, France, 2009–2017 ($n = 41,543$)[a]

	Continuous score (1-point increment)	P	Quintiles of the WCRF/AICR score					P
			1	2	3	4	5	
Score range (min–max)								
Men			0.75–3.50	3.75–4.25	4.50–4.75	5.00–5.50	5.75–8.00	
Women			0.75–3.75	4.00–4.50	4.75–5.00	5.25–5.75	6.00–8.00	
Overall cancer								
All (cases/non-cases)	1489/40,054		313/7,255	358/9,181	281/7,275	328/9,389	209/6,954	
HR [95% CI]	0.88 [0.84–0.92]	<0.0001	1 [reference]	0.87 [0.75–1.01]	0.85 [0.72–1.00]	0.76 [0.65–0.89]	0.66 [0.55–0.79]	<0.0001
Breast cancer								
Women (cases/non-cases)	488/30,037		101/5,477	117/6,890	105/5,559	103/7,030	62/5,081	
HR [95% CI]	0.86 [0.79–0.94]	0.001	1 [reference]	0.89 [0.68–1.16]	0.97 [0.73–1.28]	0.75 [0.56–0.99]	0.64 [0.46–0.89]	0.004
Prostate cancer								
Men (cases/non-cases)	222/10,796		50/1,940	54/2,478	39/1,853	46/2,538	33/1,987	
HR [95% CI]	0.88 [0.78–1.00]	0.05	1 [reference]	0.76 [0.52–1.12]	0.72 [0.47–1.10]	0.60 [0.40–0.91]	0.54 [0.34–0.86]	0.004
Colorectal cancer								
All (cases/non-cases)	118/41,425		24/7,544	32/9,507	15/7,541	31/9,686	16/7,147	
HR [95% CI]	0.86 [0.72–1.03]	0.09	1 [reference]	0.98 [0.58–1.67]	0.56 [0.29–1.08]	0.86 [0.50–1.48]	0.58 [0.30–1.12]	0.1

Abbreviation: WCRF/AICR, World Cancer Research Fund/American Institute for Cancer Research.
[a]Analyses were performed by using hazard proportional Cox regression model, adjusted for age (time-scale), sex, educational level (<high-school degree, ≥high-school degree to <2 years after high-school degree, ≥2 years after high-school degree), smoking status (nonsmokers, former smokers, smokers), number of 24-hours dietary records (continuous), height (cm; continuous), and family history of cancer (yes/no). Models for women were further adjusted for the number of biological children (continuous), menopausal status at baseline (premenopausal, postmenopausal), hormonal treatment for menopause at baseline (yes/no), and oral contraception use at baseline (yes/no).

decrease in overall cancer risk ($P = 0.03$). A one-point increment of the PNNS-GS score was associated with a 11% (95% CI, 1%–20%) decrease in colorectal cancer risk ($P = 0.04$).

Sensitivity analyses excluding cases diagnosed during the first 2 years of follow-up revealed similar results for the WCRF/AICR score (for a one-point increment: 907 cases/39,868 non-cases, HR, 0.86; 0.81–0.92; $P < 0.0001$ for overall cancer; 285 cases/29,733 non-cases, HR, 0.84; 95% CI, 0.75–0.94; $P = 0.003$ for breast cancer; 128 cases/10,629 non-cases, HR, 0.83 (95% CI, 0.70–0.98; $P = 0.03$ for prostate cancer) and the AHEI-2010 score (907 cases/39,868 non-cases, HR for a ten-point increment = 0.93 (95% CI, 0.87–0.99; $P = 0.02$ for overall cancer). Results were also similar regarding PNNS-GS and colorectal cancer risk, although not significant due to loss of statistical power (71 cases/40,704 non-cases, HR for a one-point increment = 0.93 (95% CI, 0.80–1.06; $P = 0.3$). In addition, further analyses were performed on the WCRF/AICR score by removing each component one by one from the original score and including this component as a covariate in the model to evaluate the relative importance of each component on the overall cancer risk. Similar HRs were obtained when individual components of the WCRF/AICR score were alternately excluded from the overall score or when the "body fatness" and "physical activity" components were simultaneously excluded from the overall score, although some associations became non-statistically significant for prostate cancer (Supplementary Table S3).

Table 3. HRs [95% CIs] for the association between the AHEI-2010 score and cancer risk, NutriNet-Santé Cohort, France, 2009–2017 ($n = 41,543$)[a]

	Continuous score (10-point increment)	P	Quintiles of the AHEI-2010 score					P
			1	2	3	4	5	
Score range (min–max)								
Men			6.36–35.52	35.52–42.37	42.37–48.38	48.38–55.61	55.61–94.77	
Women			7.22–38.93	38.93–45.30	45.31–51.03	51.03–57.93	57.93–95.46	
Overall cancer								
All (cases/non-cases)	1,489/40,054		257/8,051	291/8,018	305/8,004	329/7,980	307/8,001	
HR [95% CI]	0.95 [0.90–0.99]	0.03	1 [reference]	0.93 [0.79–1.11]	0.91 [0.77–1.08]	0.93 [0.79–1.10]	0.87 [0.73–1.03]	0.1
Breast cancer								
Women (cases/non-cases)	488/30,037		84/6,021	91/6,014	109/5,996	105/6,000	99/6,006	
HR [95% CI]	0.95 [0.87–1.03]	0.2	1 [reference]	0.91 [0.68–1.23]	1.03 [0.77–1.37]	0.95 [0.71–1.27]	0.88 [0.65–1.19]	0.5
Prostate cancer								
Men (cases/non-cases)	222/10,796		32/2,171	42/2,162	55/2,149	48/2156	45/2,158	
HR [95% CI]	0.96 [0.85–1.08]	0.5	1 [reference]	0.93 [0.59–1.48]	1.14 [0.73–1.77]	0.90 [0.57–1.42]	0.82 [0.51–1.31]	0.3
Colorectal cancer								
All (cases/non-cases)	118/41,425		16/8,292	24/8,285	29/8,280	23/8,286	26/8,282	
HR [95% CI]	0.93 [0.79–1.10]	0.4	1 [reference]	1.19 [0.63–2.25]	1.30 [0.70–2.41]	0.95 [0.50–1.82]	1.04 [0.55–1.97]	0.7

Abbreviation: AHEI, Alternate Healthy Eating Index.
[a]Analyses were performed by using hazard proportional Cox regression model, adjusted for age (time-scale), sex, educational level (<high-school degree, ≥high-school degree to <2 years after high-school degree, ≥2 years after high-school degree), smoking status (nonsmokers, former smokers, smokers), number of 24-hours dietary records (continuous), height (cm; continuous), family history of cancer (yes/no), body mass index (kg/m^2; continuous), physical activity (high, moderate, low, computed following IPAQ recommendations), and energy intake (without alcohol, g/d, continuous). Models for women were further adjusted for the number of biological children (continuous), menopausal status at baseline (premenopausal, postmenopausal), hormonal treatment for menopause at baseline (yes/no), and oral contraception use at baseline (yes/no).

Table 4. HRs [95% CIs] for the association between the MEDI-LITE score and cancer risk, NutriNet-Santé Cohort, France, 2009–2017 ($n = 41{,}543$)[a]

	Continuous score (1-point increment)	P	Quintiles of the MEDI-LITE score 1	2	3	4	5	P
Score range (min–max)								
Men			0–6	7–7	8–8	9–10	11–16	
Women			1–6	7–7	8–9	10–10	11–16	
Overall cancer								
All (cases/non-cases)	1,489/40,054		285/8,380	197/5,568	404/11,528	312/7,135	291/7,443	
HR [95% CI]	0.99 [0.97–1.01]	0.4	1 [reference]	0.94 [0.78–1.13]	0.93 [0.80–1.09]	1.00 [0.85–1.18]	0.95 [0.80–1.13]	0.8
Breast cancer								
Women (cases/non-cases)	488/30,037		82/6,072	67/4,136	162/10,022	69/4,261	108/5,546	
HR [95% CI]	1.01 [0.97–1.05]	0.8	1 [reference]	1.07 [0.77–1.48]	1.01 [0.77–0.32]	0.96 [0.69–1.33]	1.13 [0.84–1.53]	0.6
Prostate cancer								
Men (cases/non-cases)	222/10,796		38/2,473	32/1,530	37/1711	74/3,043	41/2,039	
HR [95% CI]	0.98 [0.93–1.04]	0.5	1 [reference]	1.16 [0.72–1.86]	1.12 [0.71–1.76]	1.14 [0.77–1.70]	0.95 [0.61–1.50]	0.9
Colorectal cancer								
All (cases/non-cases)	118/41,425		13/6,553	31/9,147	35/11,568	14/5,168	25/8,989	
HR [95% CI]	0.96 [0.89–1.03]	0. 3	1 [reference]	1.48 [0.77–2.83]	1.21 [0.64–2.31]	1.06 [0.49–2.28]	1.02 [0.51–2.04]	0.5

Abbreviation: MEDI-LITE, Mediterranean diet based on the literature.

[a]Analyses were performed by using hazard proportional Cox regression model, adjusted for age (time-scale), sex, educational level (<high-school degree, ≥high-school degree to <2 years after high-school degree, ≥2 years after high-school degree), smoking status (nonsmokers, former smokers, smokers), number of 24-hours dietary records (continuous), height (cm; continuous), family history of cancer (yes/no), body mass index (kg/m^2; continuous), physical activity (high, moderate, low, computed following IPAQ recommendations), and energy intake (without alcohol, g/d, continuous). Models for women were further adjusted for the number of biological children (continuous), menopausal status at baseline (premenopausal, postmenopausal), hormonal treatment for menopause at baseline (yes/no), and oral contraception use at baseline (yes/no).

Table 5. HRs [95% CIs] for the association between the PNNS-GS score and cancer risk, NutriNet-Santé Cohort, France, 2009–2017 ($n = 41{,}543$)[a]

	Continuous score (1-point increment)	P	Quintiles of the PNNS-GS score 1	2	3	4	5	P
Score range (min–max)								
Men			0.12–7.75	7.75–8.78	8.80–9.75	9.80–10.75	10.80–14.30	
Women			1.00–7.80	7.80–9.05	9.05–9.80	9.81–10.80	10.81–14.50	
Overall cancer								
All (cases/non-cases)	1489/40054		260/8110	285/7732	268/8266	312/7943	364/8003	
HR [95% CI]	0.97 [0.95–1.01]	0.1	1 [reference]	0.99 [0.84–1.18]	0.79 [0.66–0.94]	0.85 [0.72–1.01]	0.89 [0.76–1.06]	0.08
Breast cancer								
Women (cases/non-cases)	488/30037		88/6086	93/5888	87/6109	98/6027	122/5927	
HR [95% CI]	1.00 [0.95–1.05]	0.9	1 [reference]	0.98 [0.73–1.32]	0.81 [0.60–1.09]	0.84 [0.62–1.13]	0.96 [0.72–1.28]	0.6
Prostate cancer								
Men (cases/non-cases)	222/10796		35/2161	38/1998	46/2292	44/2086	59/2259	
HR [95% CI]	0.97 [0.89–1.05]	0.4	1 [reference]	0.88 [0.55–1.40]	0.85 [0.55–1.34]	0.74 [0.47–1.17]	0.83 [0.54–1.28]	0.3
Colorectal cancer								
All (cases/non-cases)	118/41425		22/8348	20/7997	25/8509	28/8227	23/8344	
HR [95% CI]	0.89 [0.80–1.00]	0.04	1 [reference]	0.76 [0.41–1.39]	0.76 [0.43–1.36]	0.76 [0.43–1.34]	0.54 [0.30–0.99]	0.07

Abbreviation: PNNS-GS, The Nutrition and Health Program—Guideline Score (Programme National Nutrition Santé-Guideline Score).

[a]Analyses were performed by using hazard proportional Cox regression model, adjusted for age (time-scale), sex, educational level (<high-school degree, ≥high-school degree to <2 years after high-school degree, ≥2 years after high-school degree), smoking status (nonsmokers, former smokers, smokers), number of 24-hours dietary records (continuous), height (cm; continuous), and family history of cancer (yes/no), and body mass index (kg/m^2, continuous). Models for women were further adjusted for the number of biological children (continuous), menopausal status at baseline (premenopausal, postmenopausal), hormonal treatment for menopause at baseline (yes/no), and oral contraception use at baseline (yes/no).

NRI results were broadly consistent with main results from Cox models: They also suggested a better predictive performance of the WCRF/AICR score compared with the other "general" scores (e.g., for overall cancer: P value $_{\text{WCRF/AICR}} < 0.0001$; P value $_{\text{AHEI-2010}} = 0.9$; P value MEDI-LITE $= 0.5$; P value $_{\text{PNNS-GS}} = 0.09$, Supplementary Table S2).

Discussion

This study showed that a better adherence to the WCRF/AICR recommendations was associated with a significant cancer risk reduction (12% for overall cancer, 14% for breast cancer, and 12% for prostate cancer, for an increment of one point of the score). Results of the sensitivity analyses suggest that these strong and consistent associations were not driven by one specific component but rather by a synergistic contribution of the different components of the score. The other scores tested—not specifically designed for cancer prevention, were less clearly associated with cancer risk.

Consistent with our findings, a study conducted in the large European Prospective Investigation into Cancer and Nutrition (EPIC) cohort showed that a one-point increase in the

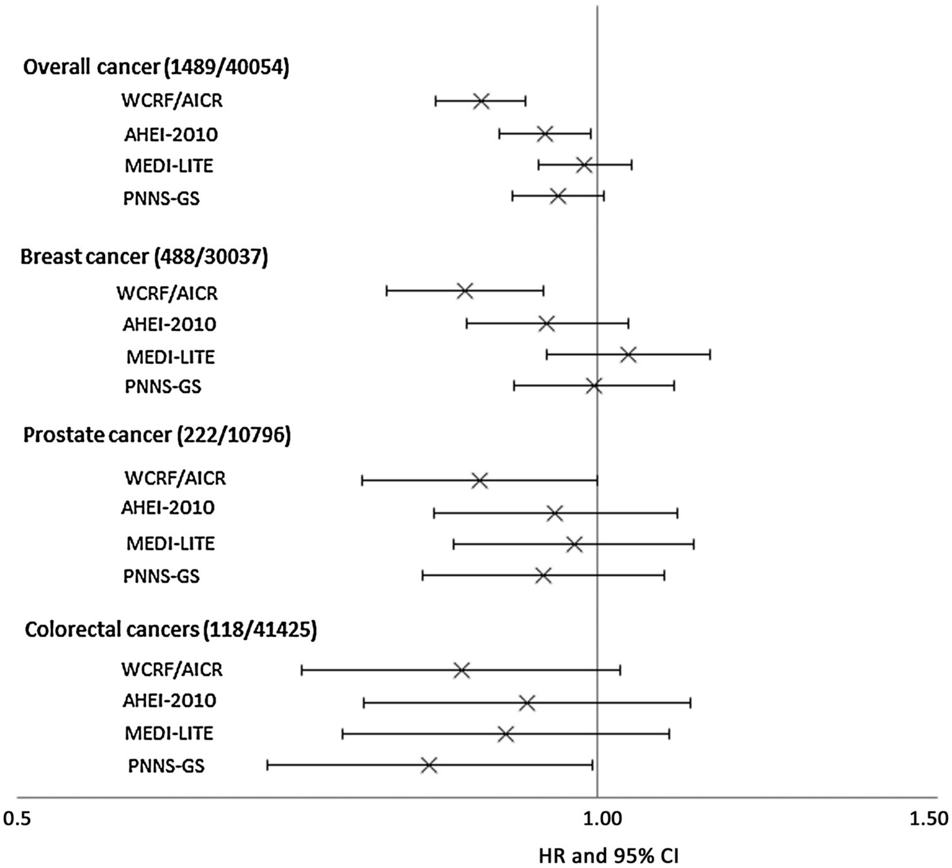

Figure 1.
Association between WCRF/AICR, AHEI-2010, MEDI-LITE, and PNNS-GS nutritional scores and incident cancer risks, NutriNet-Santé Cohort, France, 2009–2017 (n = 41,543). For graphic representation, scores have been standardized by dividing each score by its SD. Results are presented for an increment of one point of this variable.

WCRF/AICR score was associated with decreased risks of overall (5% [3%–7%]), breast (5% [3%–7%]), esophagus (16% [4%–27%]), liver (10 [1%–19%]), stomach (16% [9%–22%]), and colon-rectum (12% [9%–16%]) cancers (9). However, no association with prostate cancer was detected in this study (9). Other studies observed associations with overall (19), breast (14–16, 18, 21, 22), prostate (19), colorectal (13, 14, 19, 20, 42) and pancreatic (17) cancers. These results are largely supported by biological plausibility for each nutritional factor included in the score, as detailed in WCRF reports (6, 43) and a national report from the French Cancer Institute (44).

The AHEI-2010 score was associated with decreased overall (10), colorectal (in males; ref. 25), and prostate (27) cancer risks and cancer mortality (23, 24, 26) in several studies conducted in the United States.

The association between the PNNS-GS score and cancer risk was previously studied in the Supplementation in Vitamins and Minerals Antioxidants cohort (SU.VI.MAX), showing non-significant association overall (45).

To our knowledge, no previous study has investigated the association between the recent MEDI-LITE score and cancer risk. Nevertheless, several prospective studies investigating Mediterranean diets, using other dietary scores, have recently been meta-analyzed and suggest inverse associations with overall (12, 46–48), breast (49), prostate (49), and colorectal cancer risk (46, 47, 49).

These discrepancies between results of the different scores could be explained by the fact that the WCRF/AICR score was constructed specifically in a context of cancer prevention, whereas the other scores where not specific more general. The later scores include and/or emphasize certain nutritional factors for which the link with cancer has not been proven directly (e.g., olive oil, legumes). That could probably explain why these three scores are less related to cancer risk. Moreover, the WCRF/AICR score includes a strong penalty for alcohol, a major risk factor for several cancer sites (including breast; ref. 44), whereas other studied scores are less strict regarding alcohol which could explain nonsignificant associations. The MEDI-LITE is even more favorable to people with a moderate alcohol consumption compared with a lower consumption. Finally, BMI and physical activity are included in the WCRF/AICR score but not in all of the other studied scores while they are major risk/protective factors for cancer (44). However the WCRF/AICR score remained significantly inversely associated with cancer risk in this study, even when the BMI and physical activity components were both excluded from the score calculation.

Strengths of this study lie in its prospective design and its large sample size, along with a quantitatively precise dietary assessment of intakes. Besides, a large range of confounding factors was included in the analyses, thus limiting potential residual confounding bias. Nonetheless, a number of limitations need to be acknowledged. Indeed, as it is generally the case in volunteer-based cohorts, this study overrepresented women, health-conscious behaviors and higher socioprofessional and educational levels as compared with the general French population (50). Consequently, underrepresentation of unhealthy behaviors may have weakened the observed associations by limiting the contrast between extreme values of the scores. Another limitation of this study is the use of scores based on the sum of several risk factors, not all of which are associated with the risk of developing each type of cancer, which may have weakened observed associations. Moreover, two components could not be included in the score calculations in this study because corresponding data were not available: breastfeeding for the WCRF/AICR score and trans-fatty acids for the AHEI-2010 score. Therefore, the WCRF/AICR and AHEI-2010 scores that we have built may have underestimated the potential impact of adherence to these recommendations. Then, despite a multisource strategy for case ascertainment (combining validation of health events declared by participants, medicoadministrative databases from the health insurance, and national death registry), exhaustive detection of cancer cases cannot be guaranteed. Moreover when studying breast, prostate or colorectal cancers we could not adjust our analyses for family history of each specific cancer location, since the information was only available for family history of cancer in general. This point is being improved in the updated version of the NutriNet-Santé platform, which will collect details regarding family history of chronic diseases and will provide more accurate covariates for adjustment. Furthermore, French law is very restrictive regarding the collection of sensitive data such as the "racial" or ethnic origins. Thus, such information was not available in this cohort and related-residual confounding cannot be excluded. Last, statistical power was limited for colorectal cancers 118 cases), thus limiting our ability to detect some hypothesized associations. Also, we could not study the association with lung cancer due to a limited number of cases ($n = 60$); and the limited number of aggressive prostate cancers did not allow us to perform statistical analyses focusing strictly on aggressive malignancies.

To conclude, the results of this large prospective population-based cohort study suggest that following dietary recommendations, such as the ones proposed by the WCRF/AICR, could significantly contribute to cancer prevention.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Development of methodology: E. Kesse-Guyot, M. Touvier
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S. Hercberg, E. Kesse-Guyot, M. Touvier
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Lavalette, M. Adjibade, B. Srour, P. Latino-Martel, P. Fassier, M. Deschasaux, E. Kesse-Guyot, M. Touvier
Writing, review, and/or revision of the manuscript: C. Lavalette, M. Adjibade, B. Srour, L. Sellem, T. Fiolet, S. Hercberg, P. Latino-Martel, M. Deschasaux, E. Kesse-Guyot, M. Touvier
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