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Research Article

Cancer Prevention Research

Association between Five Lifestyle Habits and Cancer Risk: Results from the E3N Cohort

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Abstract

Although some modifiable lifestyle characteristics have been associated with decreased cancer risk, little is known about their combined effect or about the proportion of cancer cases that could be prevented by improving lifestyle behaviors. We aimed to quantify the association between lifestyle habits and all-site and site-specific cancer risk in middle-aged women. The study included 64,732 women from the French E3N prospective cohort, ages 43 to 68 years at baseline. During a 15-year follow-up period, 6,938 cases of invasive cancer were diagnosed. We defined an index that aggregated five lifestyle characteristics: smoking, body mass index, alcohol consumption, fruit and vegetable consumption, and physical activity. Proportional hazard Cox regressions were performed to evaluate the association between lifestyle and cancer risk and to estimate multivariate HRs and their 95% confidence intervals (CI). In addition, population-attributable fractions were used to estimate the proportion of cancer cases that could be prevented by healthier behaviors. A significant decrease in all-site cancer risk was observed and was associated with a healthy lifestyle (HR, 0.81; 95% CI, 0.73–0.89 when comparing the highest with the lowest health index category; P_{trend} across categories < 0.01). Combining all five characteristics would have prevented 6.3% (2.2%–10.3%) of any-site, 6.3% (0.5%–12.1%) of postmenopausal breast, and 47.5% (26.8%–64.1%) of lung cancers. In conclusion, compliance with only five modifiable lifestyle behaviors could prevent a significant number of cancers, notably postmenopausal breast and lung cancers. *Cancer Prev Res; 7(5); 516–25. ©2014 AACR.*

Introduction

Cancer is the primary cause of death in developed countries and is the second-most common cause of death in developing countries (1). Among women, the global cancer incidence was 164.4 for 100,000 women-years in 2008 (137.2 in less-developed regions and 226.3 in more-developed regions), and in France, cancer incidence reached 254.9 for 100,000 women-years in 2008 (1). Lifestyle characteristics, such as not smoking, maintaining a normal weight, limiting alcohol intake, adopting specific dietary habits such as a high fruit and vegetable consumption, and exercising regularly have been associated with decreased mortality (2) and a decreased risk of cancer (2), cardiovascular disease (3, 4), and diabetes (5), and have then been recognized as healthy behaviors. National public health recommendations have been established to make the general public aware of improved health expectancy and decreased cancer risk (6–8) when adopting a healthy lifestyle combining these behavioral habits.

The individual effects of these healthy lifestyle characteristics have been widely explored. Smoking has been associated with lung, laryngeal and pharyngeal, upper digestive tract and oral, bladder, kidney, pancreatic, liver, and cervical cancer risk (9). High body mass has been associated with endometrial, postmenopausal breast, renal, thyroid, pancreatic, colon, and esophageal cancer risk (10). Alcohol consumption has been associated with head and neck, esophageal, liver, colorectal, and breast cancer risk (11), whereas consumption of fruit and/or vegetables has been inversely associated with head and neck, esophageal, stomach, and colorectal cancer risk (2). Physical activity has been inversely associated with colorectal, breast, and endometrial cancer risk (2). However, as compliance with healthy behaviors is clustered (12, 13), these five healthy behaviors should be considered simultaneously to take into account their associations. However, the combined effect of these behaviors has not been well documented in the literature (14). The few studies that have investigated the combination of five (15–17) or four (18–28) such behaviors have reported a reduced all-site cancer risk (17–21) as well as a reduced risk of colorectal (23, 24), pancreatic (15), and postmenopausal breast (25) cancer and a reduced risk of cancer mortality (16, 26–28) when comparing the healthiest subjects with the less healthy ones. In addition, very few

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studies have estimated the proportion of cases that could be prevented if exposure to one or several risk factors was removed from the population (15–19, 23, 28). Taking simultaneously into account the prevalence of the studied exposures and their association with the disease permits the computation of the population-attributable fraction (PAF), which quantifies the burden of a disease and helps focus prevention strategies. The aim of the present study was to assess the proportion of all-site and site-specific cancer cases that would have been prevented if all women had followed a healthy lifestyle based on five modifiable characteristics.

Materials and Methods

Study population

The E3N [*Étude Épidémiologique auprès des femmes de la Mutuelle Générale de l'Éducation Nationale (MGEN)*] prospective cohort was launched in 1990 to investigate cancer risk factors (29). The cohort includes 98,995 French women who were regularly asked about their health status and lifestyle. Self-administered questionnaires were sent every 2 to 3 years to update the information. All women signed informed consent, in compliance with the rules of the French National Commission for Data Protection and Privacy, from which approval was obtained.

For the present study, follow-up started at the date of return of the 1993 questionnaire, which first recorded dietary habits, thereafter considered as baseline. Responders ($N = 74{,}522$) contributed person-years of follow-up until the date of any cancer diagnosis other than basal cell skin carcinoma, the date of the last completed questionnaire or the date the last available questionnaire was mailed (June 2008), whichever occurred first. We excluded women diagnosed with a cancer before inclusion ($N = 4{,}705$), those with no follow-up questionnaire ($N = 769$), cancer cases with no specified date of diagnosis ($N = 54$), and women who did not report health behaviors at baseline ($N = 4{,}262$). Our final population for analysis consisted of 64,732 women ages 43 to 68 years at baseline.

Data collection

At baseline, women were asked to fill in a dietary questionnaire using quantitative and qualitative estimates of consumed items, including alcohol consumption and fruit and vegetable consumption. Body mass index (BMI) was computed as weight/height^2 in kg/m^2, using self-reported height and weight. Validation studies, conducted to determine the accuracy of the reported anthropometric measurements and dietary data, demonstrated the reliability of the reported data (30, 31). Walking, cycling, and sports activities were combined to derive overall recreational physical activity. Durations were averaged over the summer and winter. The assigned metabolic equivalent task (MET) values were 3.0 for walking, 6.0 for cycling and other sports (32).

Construction of the health index

The five lifestyle behaviors considered in the present analysis included tobacco smoking, BMI, alcohol consumption, fruit and vegetable consumption, and recreational physical activity, all assessed at baseline. An *a priori* score was developed according to how well participants adhered to health recommendations expressed by the PNNS (the French national program for health and nutrition; ref. 6), the ANSES (the French food safety agency; ref. 7), and the World Health Organization (8). Each score ranked from 0 (not meeting the recommendation) to 1 (full compliance), with partial compliance scored as 0.5. As presented in Table 1, fully compliant women were never smokers, had a BMI within the 18.5 to 25 normal range, drank less than one alcoholic drink per day, consumed at least 5 servings of fruit and vegetables per day, and had a recreational physical activity of at least 20 MET-hour per week (i.e., 300 minutes of moderate or 150 minutes of vigorous recreational physical activity per week; ref. 8). Partial compliance was defined as former smoking, being overweight (BMI between 25 and 30), or underweight (BMI between 16 and 18.5), consuming one to two alcoholic drinks per day, 3.5 to 5 daily servings of fruit and vegetables, and having 10

Table 1. Health index construction, based on five lifestyle characteristics

	Compliance with public health recommendations		
	Full (1 point)	**Partial (0.5 point)**	**Poor (0 point)**
Health recommendations			
—Smoking status	Never smoker	Former smoker	Current smoker
—BMI (kg/m^2)	[18.5–25) (normal range)	[25–30) (overweight) [16–18.5) (underweight)	≥30 (obesity) <16 (severely underweight)
—Alcohol consumption (drinks[a]/day)	<1	[1; 2)	≥2
—Fruit and vegetable consumption (servings[b]/day)	≥5	[3.5; 5)	<3.5
—Recreational physical activity level (MET-hour/week)	≥20	[10; 20)	<10

[a]One drink of alcohol corresponds to 10 g of ethanol.

[b]One serving of fruits and vegetables corresponds to 80 g of fruits and vegetables. Fruits and vegetables included raw and cooked vegetables, lettuce, and fresh fruits.

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to 20 MET-hour weekly recreational activity (i.e., between 150 and 300 minutes of moderate or between 75 and 150 minutes of vigorous recreational physical activity per week; ref. 8). If women did not meet any of the above criteria, they were considered noncompliant.

We assigned a health index to participants by summing up the individual scores of each lifestyle behavior. Consequently, the health index ranged from 0 (the least healthy) to 5 (the most healthy), with intervals of 0.5.

Ascertainment of cancer cases

All questionnaires enquired about occurrence of any cancer, type of cancer, addresses of physicians, and permission to contact them. Cancer incidence data were coded according to the 10th revision of the International Classification of diseases (ICD-10) and the 3rd edition of the International Classification of Diseases for Oncology (ICD-O-3). We considered only invasive cancers (ICD-O-3 behavior code of 3) and censored *in situ* tumors with no concomitant invasive tumor at the date of diagnosis. In addition to reported cancer cases, some cases (5.0% of all included invasive cancer cases) were identified from information on the causes of death obtained from the French National Service on Causes of Death; when the precise date of diagnosis could not be retrieved, we recorded the date of diagnosis as 1 year before the date of death, according to the median survival time after diagnosis of late-stage cancers in our cohort. Invasive cancer cases were confirmed by pathology reports or death certificates, obtained for 86.1% of our population cases. For analyses, we considered breast (ICD-10 C50), nonbasal skin (ICD-10 C43-C44, excluding ICD-O-3 M809-M811), colorectal (ICD-10 C18-C20), digestive other than colorectal (ICD-10 C15-C17 and C21-C26), endometrial (ICD-10 C54), thyroid (ICD-10 C73), ovarian (ICD-10 C56), and lung (ICD-10 C34) cancers as well as hematopoietic malignancies (ICD-10 C81-C96). Bladder, kidney, head and neck, brain, cervical cancers, other sites (such as eye and anus), and unknown sites of cancer were not included, because of the low number of cases.

Statistical methods

Cox proportional hazards regression models with age as the timescale (33) were used to estimate HRs and 95% confidence intervals (CI) of all-site and site-specific cancer risks associated with the healthiest behaviors compared with the less healthy behaviors. Multivariate models were adjusted for potential effect modifiers, i.e., level of education (undergraduate, graduate, and postgraduate), residence (North, Center, South of France), first-degree family history of any cancer (at least one, none), professional activity (active, retired/never worker), use of oral contraceptives (ever, never), menopausal status and use of menopausal hormone therapy (premenopausal, postmenopausal with current hormone therapy, and postmenopausal with no current hormone therapy), age at menarche (quartiles) and number of children and age at first full-term pregnancy (no child, one child before age 30, one child after age 30, more than one child with the first before age 30, more than one child with the first after age 30). Models for the individual effect of each of the five lifestyle characteristics scores were further adjusted for the four other characteristics. Information on menopausal status and the use of menopausal hormone therapy was updated at each questionnaire, whereas all other potential effect modifiers were assessed at baseline. Analyses were further stratified by generation (1925–1930, 1931–1935, 1936–1945, and 1946–1950) using the "strata" option in the SAS "proc phreg" command, to consider a possible cohort effect (34). We used competitive risk Cox models to assess the risk associated with specific cancer types to deal with multiple censoring types. Trends for the health index were assessed, incorporating the health index as a continuous variable in the models.

For each potential effect modifier, missing values represented less than 5% of observations and were then all imputed to the modal category for categorical variables and the median value for quantitative variables.

Estimation of the population-attributable fractions

To quantify the proportion of cancer cases that could have been avoided if the population distribution of some risk factors was changed (all other modifiable and nonmodifiable risk factors remaining unchanged), we estimated the PAF associated with a specific modification in health behaviors with the assumption of a causal relationship. Point estimates and 95% CIs were evaluated using a method described by Spiegelman and colleagues (35). The estimation of PAFs took into account exposure prevalence and HRs of cancer risk associated with exposure and potential effect modifiers. CIs were estimated using the multivariate delta method (35). The PAF of each healthy behavior was estimated separately and expressed as the percentage of cancer cases that would have been prevented if all women had been in the healthiest category for each behavior (i.e., lifelong smoking abstinence, BMI between 18.5 and 25, drinking less than one alcohol unit per day, eating at least 5 daily servings of fruits and vegetables, or weekly exercise of at least 20 MET-hour), the four other characteristics remaining unchanged. In addition, we estimated the PAF corresponding to the combination of the five behaviors, expressing the percentage of cancer cases that would have been prevented if all women had scored 4.5 or 5 for the health index (i.e., entirely adhering to four health recommendations and partly or entirely adhering to the fifth one). A positive PAF quantified the percentage of cancer cases that would have been prevented; a negative PAF represented the percentage of cancer cases that would have additionally occurred.

Sensitivity analyses

We tested a reverse-causation hypothesis by censoring cancer cases occurring within the first 5 years of follow-up. To analyze the effect of the threshold choices, analyses were performed after modifying the categorization of each individual score, i.e., considering underweight (BMI between 16 and 18.5) as full compliance and severe underweight (BMI < 16) as full or partial compliance; alcohol abstinence as full

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compliance and consumption of less than one alcoholic drink daily as partial compliance; modifying the threshold of 3.5 servings of fruits and vegetables daily to 2.5 or 3 servings a day; and modifying the thresholds of 10 to 20 MET-hour/week to 15 to 20, 15 to 25, 15 to 30, 10 to 25, or 10 to 30 MET-hour/week. We tested the potentially confounding effect of sun exposure for nonbasal skin cancer analyses by adjusting the effects for the yearly mean sun UV dose of the residential town at baseline. In addition, we performed an analysis separating women according to their age (less than 50, more than 50) to assess effects of lifestyle according to genetic predispositions. Because the etiology of melanoma and other types of nonbasal skin cancer differs, we analyzed separately the different types of nonbasal skin cancer (melanoma, spinocellular, or other/unspecified type). Finally, we performed a sensitivity analysis excluding nonvalidated cancer cases to avoid misclassification of cases. All analyses were conducted using SAS software, version 9.2 (SAS Institute Inc.).

Results

Population characteristics

During 840,097 person-years (median follow-up of 8 years for invasive cancer cases and 15 years for noncases), 6,938 women were diagnosed with any type of invasive cancer. Specific types (including concomitant tumors) included 3,483 breast cancers (609 premenopausal and 2,874 postmenopausal at diagnosis), 686 nonbasal skin cancers, 481 colorectal cancers, 411 hematopoietic malignancies (including mostly non-Hodgkin and Hodgkin lymphoma, leukemia, and multiple myeloma), 274 noncolorectal digestive cancers (including pancreatic, stomach, liver, biliary tract, esophageal, and small bowel cancers), 270 endometrial cancers, 267 thyroid cancers, 248 ovarian cancers, and 213 lung cancers.

The main characteristics of the population according to health index categories are presented in Supplementary Table S1. Women in the highest category of the health index were more likely to live in the south of France, to be retired/never have worked, to be parous, to be postmenopausal, and to have ever used menopause hormone therapy. Table 2 presents correlations between the five lifestyle characteristics. Pearson correlation coefficients suggested a significant correlation for all pairs ($P < 0.05$), except between smoking and BMI ($P = 0.16$).

Risk of cancer

Because age-adjusted and fully adjusted estimates provided very close figures, only the latter will be addressed below.

All-site and site-specific cancer risks are presented in Table 3. Compared with women with the lowest compliance (health index 0–2), women with the best compliance to health recommendations (health index between 4.5 and 5) exhibited a reduced all-site cancer risk: HR (95% CI) = 0.81 (0.73–0.89), $P_{trend} < 0.001$ across score categories.

The association was also observed for several specific tumor sites: lung cancer [HR = 0.19 (0.11–0.30), $P_{trend} < 0.001$], endometrial cancer [HR = 0.45 (0.29–0.71), $P_{trend} < 0.001$], digestive cancers other than colorectal [HR = 0.59 (0.36–0.95), $P_{trend} = 0.036$], and colorectal cancer [HR = 0.66 (0.45–0.97), $P_{trend} = 0.013$]. A significant trend was observed for postmenopausal breast cancer ($P_{trend} = 0.016$); however, the reduced risk for women with the best compliance compared with those with the lowest compliance was of borderline significance: HR = 0.87 (0.74–1.03). On the opposite, we observed an increased cancer risk when comparing women with the best compliance with women with lowest compliance for nonbasal skin cancer [HR = 1.75 (1.17–2.62), $P_{trend} < 0.001$]. Associations between the risk of other cancer sites (premenopausal breast, hematopoietic, thyroid, and ovarian cancers) and compliance to a healthy lifestyle did not reach significance.

Population-attributable fractions

PAFs of various tumor sites according to lifestyle characteristics, considered separately and in combination, are presented in Table 4.

Overall, if all women had followed a healthy lifestyle, i.e., had an index between 4.5 and 5, a total of 6.3% (2.2%–10.3%) of any-site cancer cases would have been prevented. The proportion of preventable cases was 6.3% (0.5%–12.1%) for postmenopausal breast cancer and 47.5% (26.8%–64.1%) for lung cancer. However, if all

Table 2. Pearson correlation coefficients between the five lifestyle characteristics scores

	Smoking status	BMI	Alcohol consumption	Fruit and vegetable consumption	Physical activity level
Smoking status	1	−0.00557	0.17957[a]	0.05515[a]	−0.00870[b]
BMI		1	−0.01827[a]	−0.01829[a]	0.08793[a]
Alcohol consumption			1	0.05885[a]	−0.04013[a]
Fruit and vegetable consumption				1	0.08809[a]
Recreational physical activity level					1

[a]*P* value < 0.001.
[b]*P* value < 0.01.

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Table 3. Association between the adherence to public health recommendations and the risk of any-site and site-specific cancer, E3N cohort ($N = 64{,}732$)

	Health index[a] categories				
	[0; 2]	[2.5; 3]	[3.5; 4]	[4.5; 5]	P_{trend}
All-site cancer ($N = 6{,}938$)					
All, number of cases (%)	450 (6.48)	1,554 (22.40)	2,974 (42.87)	1,960 (28.25)	
HR (95% CI)[b]	1.00 (reference)	**0.88 (0.79–0.98)**	**0.86 (0.78–0.95)**	**0.81 (0.73–0.89)**	**<0.001**
Breast cancer ($N = 3{,}483$)					
Premenopausal, number of cases (%)	47 (7.72)	141 (23.15)	268 (44.01)	153 (25.12)	
HR (95% CI)[c]	1.00 (reference)	0.81 (0.59–1.13)	0.90 (0.66–1.22)	0.80 (0.58–1.12)	0.288
Postmenopausal, number of cases (%)	169 (5.88)	623 (21.68)	1,284 (44.68)	798 (27.76)	
HR (95% CI)[d]	1.00 (reference)	0.95 (0.80–1.12)	0.99 (0.85–1.17)	0.87 (0.74–1.03)	**0.016**
Nonbasal skin cancer ($N = 686$)					
All, number of cases (%)	26 (3.79)	125 (18.22)	283 (41.25)	252 (36.74)	
HR (95% CI)[b]	1.00 (reference)	1.22 (0.80–1.87)	1.40 (0.94–2.09)	**1.75 (1.17–2.62)**	**<0.001**
Colorectal cancer ($N = 481$)					
All, number of cases (%)	33 (6.86)	110 (22.87)	207 (43.04)	131 (27.23)	
HR (95% CI)[b]	1.00 (reference)	0.83 (0.56–1.22)	0.76 (0.53–1.10)	**0.66 (0.45–0.97)**	**0.013**
Hematopoietic cancer ($N = 411$)					
All, number of cases (%)	18 (4.38)	97 (23.60)	160 (38.93)	136 (33.09)	
HR (95% CI)[b]	1.00 (reference)	1.33 (0.80–2.20)	1.08 (0.66–1.76)	1.27 (0.77–2.08)	0.894
Digestive cancer[e] ($N = 274$)					
All, number of cases (%)	22 (8.03)	63 (22.99)	115 (41.97)	74 (27.01)	
HR (95% CI)[b]	1.00 (reference)	0.72 (0.44–1.16)	0.65 (0.41–1.04)	**0.59 (0.36–0.95)**	**0.036**
Endometrial cancer ($N = 270$)					
All, number of cases (%)	26 (9.63)	66 (24.44)	105 (38.89)	73 (27.04)	
HR (95% CI)[b]	1.00 (reference)	**0.61 (0.39–0.97)**	**0.48 (0.31–0.73)**	**0.45 (0.29–0.71)**	**<0.001**
Thyroid cancer ($N = 267$)					
All, number of cases (%)	16 (5.99)	65 (24.34)	103 (38.58)	83 (31.09)	
HR (95% CI)[b]	1.00 (reference)	1.08 (0.62–1.87)	0.92 (0.54–1.56)	1.08 (0.63–1.86)	0.573
Ovarian cancer ($N = 248$)					
All, number of cases (%)	15 (6.05)	59 (23.79)	101 (40.73)	73 (29.43)	
HR (95% CI)[b]	1.00 (reference)	0.99 (0.56–1.75)	0.87 (0.51–1.51)	0.89 (0.51–1.55)	0.297
Lung cancer ($N = 213$)					
All, number of cases (%)	32 (15.02)	61 (28.64)	85 (39.91)	35 (16.44)	
HR (95% CI)[b]	1.00 (reference)	**0.47 (0.31–0.72)**	**0.33 (0.22–0.49)**	**0.19 (0.11–0.30)**	**<0.001**

NOTE: Bold values signify P-values < 0.05.

[a]The health index ranged from 0 (the less healthy) to 5 (the healthiest), with an interval of 0.5 and was calculated by summing the five individual scores (0, 0.5, and 1) based on recommendations on smoking, BMI, alcohol consumption, fruit and vegetable consumption, and physical activity.

[b]Adjusted for level of education, residence, first-degree family history of any cancer, professional activity, use of oral contraceptives, age at menarche and number of children, age at first full-term pregnancy, menopausal status, and use of menopausal hormone therapy.

[c]Adjusted for level of education, residence, first-degree family history of any cancer, professional activity, use of oral contraceptives, age at menarche and number of children, and age at first full-term pregnancy.

[d]Adjusted for level of education, residence, first-degree family history of any cancer, professional activity, use of oral contraceptives, age at menarche and number of children, age at first full-term pregnancy, and use of menopausal hormone.

[e]Noncolorectal digestive cancers included cancers of the pancreas, stomach, liver, biliary tract, esophagus, and small bowel.

women had followed a healthy lifestyle, an excess of 21.5% (7.5%–34.6%) of nonbasal skin cancers cases would have occurred. This proportion was not significant for the other sites of cancer.

The proportions of any-site and site-specific cancer cases that would be prevented by following one of the four other healthy behaviors varied according to cancer site. If all women had been lifelong smoking abstainers, 41.8% (24.8%–56.3%) of lung cancer cases would have been prevented; if all women had been within a healthy range of BMI (i.e., between 18.5 and 25 kg/m^2), 13.3% (3.7%–22.5%) of endometrial cancer cases and 8.6% (0.2%–16.9%) of

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Table 4. PAFs of any-site and site-specific cancer when adhering to public health recommendations, E3N cohort ($N = 64,732$)

	PAF for each single characteristic[a]					PAF for the five combined characteristics[b]
	Smoking	BMI	Alcohol consumption	Fruit and vegetable consumption	Physical activity	
All-type cancer ($N = 6,938$)	1.3 (−1.8 to 4.4)	1.4 (−0.5 to 3.4)	**3.2 (0.7–5.7)**	1.5 (−0.8 to 3.8)	0.0 (−2.8 to 2.8)	**6.3 (2.2–10.3)**
Breast cancer ($N = 3,483$)						
Premenopausal ($N = 609$)	2.0 (−5.2 to 9.3)	**−6.3 (−9.9 to −2.6)**	2.1 (−3.4 to 7.6)	2.5 (−3.0 to 8.0)	−1.0 (−7.4 to 5.3)	−2.3 (−12.0 to 7.5)
Postmenopausal ($N = 2,874$)	−2.6 (−7.0 to 1.8)	−0.3 (−3.2 to 2.6)	**5.2 (1.6–8.9)**	2.4 (−0.5 to 5.6)	**−0.8 (−4.8 to 3.3)**	**6.3 (0.5–12.1)**
Nonbasal skin cancer ($N = 686$)	−4.5 (−14.1 to 5.3)	−2.0 (−8.0 to 4.1)	−3.6 (−11.5 to 4.3)	−0.6 (−7.8to 6.5)	−10.6 (−19.4 to −1.7)	**−21.5 (−34.6 to −7.5)**
Colorectal cancer ($N = 481$)	7.0 (−5.0 to 18.8)	1.0 (−6.3 to 8.2)	6.6 (−2.9 to 16.0)	5.1 (−4.1 to 14.1)	−5.0 (−15.5 to 5.6)	12.8 (−2.4 to 27.4)
Hematopoietic cancer ($N = 411$)	−0.7 (−13.2 to 11.8)	**8.6 (0.2–16.9)**	−1.0 (−10.9 to 9.0)	−4.6 (−13.3 to 4.0)	−2.9 (−14.3 to 8.6)	−6.7 (−23.6 to 10.6)
Digestive[c] cancer ($N = 274$)	3.9 (−11.7 to 19.3)	6.1 (−3.8 to 15.9)	2.5 (−10.6 to 15.4)	1.7 (−9.5 to 12.8)	2.0 (−12.3 to 16.3)	12.1 (−8.4 to 31.6)
Endometrial cancer ($N = 270$)	0.7 (−15.6 to 17.0)	**13.3 (3.7–22.5)**	9.8 (−3.1 to 22.3)	1.6 (−10.3 to 13.5)	2.9 (−11.9 to 17.6)	15.0 (−5.8 to 34.6)
Thyroid cancer ($N = 267$)	−3.6 (−18.1 to 11.0)	4.6 (−6.0 to 15.1)	−7.8 (−19.7 to 4.2)	1.2 (−10.0 to 12.4)	3.0 (−11.3 to 17.1)	−7.5 (−28.7 to 14.4)
Ovarian cancer ($N = 248$)	4.5 (−11.6 to 20.3)	7.2 (−3.5 to 17.8)	−0.6 (−13.9 to 12.8)	0.5 (−11.4 to 12.3)	4.7 (−10.4 to 19.6)	2.9 (−18.8 to 24.3)
Lung cancer ($N = 213$)	**41.8 (24.8–56.3)**	−5.7 (−16.6 to 5.4)	1.2 (−14.2 to 16.5)	5.4 (−8.5 to 19.1)	**22.5 (6.3–37.5)**	**47.5 (26.8–64.1)**

NOTE: Bold values signify P-values < 0.05.

[a]Individual PAFs estimated the percentage of cancer cases that would be prevented if all women had entirely adhered to one single health recommendation (individual score of 1 for the health behavior), adjusted for level of education, residence, first-degree family history of any cancer, professional activity, use of oral contraceptives, menopausal status and use of menopausal hormone therapy, age at menarche, number of children and age at first full-term pregnancy, and the four other characteristics. Analyses on premenopausal breast cancer were not adjusted for menopausal status or use of menopausal hormone therapy. Analyses of postmenopausal breast cancers were not adjusted for menopausal status.

[b]Percentage of cancer cases that would be prevented if all women had followed a healthy lifestyle (health index between 4.5 and 5), adjusted for all above variables, except the five lifestyle characteristics.

[c]Noncolorectal digestive cancers included cancers of the pancreas, stomach, liver, biliary tract, esophagus, and small bowel.

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hematopoietic malignancies cases would have been prevented, whereas 6.3% (2.6%–9.9%) premenopausal breast cancer cases in excess would have occurred. If all women had consumed less than one alcoholic drink daily, 3.2% (0.7%–5.7%) of any-site cancer and 5.2% (1.6%–8.9%) of postmenopausal breast cancer cases would have been prevented. If all women had achieved a high level of physical activity, 22.5% (6.3%–37.5%) of lung cancer cases would have been prevented, whereas 10.6% (1.7%–19.4%) skin cancer cases in excess would have occurred; no other association with a statistically significant PAF was observed.

Sensitivity analyses

To test a reverse causation hypothesis, we censored cases diagnosed within the first 5 years of follow-up ($N = 1{,}897$). A decreased risk of any-site cancer was nonetheless observed when comparing women with the healthiest behaviors with those with the lowest index: HR = 0.85 (0.75–0.96). The percentage of prevented cases was 5.4% (0.6%–10.2%). In addition, when censoring non validated cancer cases ($N = 963$), associations persisted, with HR = 0.79 (0.71–0.88) and 6.2% (2.0%–10.8%) of any-site cancers prevented. Analyses of nonbasal skin cancer adjusted for sun UV dose of the baseline residential town provided similar results to the main analyses, with HR = 1.65 (1.03–2.64) and 19.50% (6.99%–31.30%) additional diagnosed nonbasal skin cancer cases when adopting healthy behaviors. Associations between recreational physical activity and nonbasal skin cancer remained with a PAF estimated at −9.16% (−17.00% to −1.21%). Analyses considering the subtypes of nonbasal skin cancer (875 cancers in 686 women) resulted in similar results for melanomas ($N = 391$) and other/unspecified types of nonbasal skin cancers ($N = 257$), with HR = 1.44 (0.88–2.37) and PAF = −20.8% (−38.2% to −2.0%) and HR = 2.41 (1.12–5.20) and PAF = −28.3% (−49.0% to −4.5%), respectively, but no association was observed for spinocellular cancers ($N = 227$), with HR = 1.25 (0.62–2.51) and PAF = −8.1% (−30.0% to 14.6%). When performing separate analyses according to age, results remained similar in women over 50 years old (6,304 cancers diagnosed during 705,771 women-years) and those 43 to 50 years old (634 cancers diagnosed during 56,326 women-years) with HR = 0.82 (0.73–0.92) and 0.72 (0.54–0.97), respectively. The PAF in the oldest women was 6.8% (2.6%–11.0%), although in the youngest women, due to the shorter follow-up duration, the PAF barely reached −1.0% (−9.9% to 7.9%). Modifying the thresholds of the lifestyle factor scores resulted in HRs of between 0.76 and 0.84 (all statistically significant at the 5% level) for any-site cancer risk associated with the highest compared with the lowest category of the modified health index, and resulted in a percentage of preventable cancer cases of between 4.9% and 7.5%.

Discussion

In this large prospective cohort of French women, we observed that adhering to one single health recommendation had a moderate impact on the proportion of prevented cancer cases. However, adhering more closely to a healthy lifestyle, by respecting recommendations for smoking, BMI, alcohol consumption, fruit and vegetable consumption, and physical activity (6–8), could reduce the number of any-site cancer cases by up to 6.3%, a percentage that varied across cancer sites, reaching 47.5% for lung cancer. Behaviors associated with the highest PAF included smoking for lung cancers, BMI for endometrial cancers and hematopoietic malignancies, alcohol consumption for postmenopausal breast cancers, and physical activity for lung and skin cancers. Cancer is a multifactorial disease that involves multiple endogenous (genetics, hormones, immunity, and metabolism) and exogenous (lifestyle and environment) causes. Therefore, the analyzed healthy behaviors, chosen to be easily modifiable lifestyle factors, are five of multiple factors related to cancer.

Literature confrontation

The few studies that quantified the impact of lifestyle on cancer risk reported a decreased risk of any-site (17–22), colorectal (19, 22–24), breast (19, 22, 25), endometrial (19, 22), digestive (15, 19), and lung (19) cancer in women complying with public health recommendations. Compliance with recommendations was estimated to be able to prevent 11% to 31% of cancer (17–19) and, specifically, 6% of colorectal cancer (23). The variation of exposure throughout the world and the use of different estimation methods could contribute to the variability of the findings. The widely used Levin formula (36) was demonstrated to provide biased estimates when calculated with multivariate relative risks (37), whereas the Spiegelman formula (35) seems to be better adapted to estimate-adjusted PAF.

The healthy lifestyle characteristics analyzed in the present study seemed to play a minor role in the etiology of thyroid cancer, for which radiation exposure is the only well-established risk factor (38). The strong association observed between tobacco smoking and lung cancer is in line with a recent metaanalysis (39) and emphasizes the causal nature of the relationship. Surprisingly, we did not observe that physical activity can prevent colorectal or postmenopausal breast cancer cases, despite convincing evidence of the association between physical activity and these cancer sites (2). The increased number of skin cancer cases that would have occurred if all women had been highly physically active suggests residual confounding by individual sun exposure habits through outdoors activities, which has been associated with an increased risk of skin cancer (40), and underlines the importance of recommending that patients avoid sunburn and excessive sun exposure without protection (41). We observed that approximately 22% of lung cancer cases would have been prevented if all women had achieved a high physical activity, in agreement with the inverse relationship between risk of lung cancer and physical activity found in metaanalyses (42, 43). However, the association may be a reflection of reverse causation, as people with chronic

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lung disease who are at an increased risk of lung cancer may be less prone to practicing physical activity (2). In agreement with the individual effects of the analyzed healthy behaviors on cancer risk observed in this study, previously published metaanalyses concluded that women should limit alcohol consumption to prevent an increased risk of breast cancer (44, 45), that BMI was inversely associated with the risk of premenopausal breast cancer (46), and that lower BMI was associated with a decreased risk of endometrial cancer (47). Low BMI was also associated with lower risk of non-Hodgkin lymphoma (48), leukemia (49), and multiple myeloma (50), three hematopoietic malignancies with very few established risk factors (51). Finally, consistent with our results, other studies observed that weight management, physical activity, alcohol consumption, and smoking likely explained most of the observed association between healthy lifestyle scores and cancer risk (17, 19, 21, 22). The results remained unchanged when excluding cases diagnosed within the first 5 years of follow-up and when excluding women younger than 50 years. These results suggest that reverse causation was unlikely and that lifestyle may play a role in the etiology of cancer in older women, which is less related to genetic factors.

Strengths and limits

The study has some limitations. The choice of a threshold for creating a health index may be disputable, although our approach was chosen to be as close as possible to public health recommendations (6–8). However, our results are strengthened by the sensitivity analyses, in which the health dimension categories were modified but produced similar results. In addition, the E3N cohort, like most cohorts of volunteers, is prone to a "healthy cohort effect." As the impact of lifestyle varies according to the prevalence of exposure, higher PAFs can be expected in the general population. The nonsignificant associations observed for several site-specific cancer sites might be a reflection of a lack of statistical power due to a small number of cases. As the values of the five characteristics taken into account in the construction of the health index were not updated at each questionnaire, this approach cannot capture the effect of adopting healthy behaviors over time. The estimation of PAFs was based on the assumption of a causal relationship between exposure and cancer and should therefore be interpreted with caution.

The study has also several strengths. A major strength is that it was based on a large prospective cohort with an extended follow-up. The design permitted adjustment for many potential confounders and provided high statistical power and the ability to examine the impact of lifestyle on various cancer sites. Information on exposure collected before cancer diagnosis resulted in little risk of memory bias. Self-report bias was limited through the histologic confirmation of the vast majority of cancer cases. Moreover, excluding nonvalidated cases of cancer produced similar results. In addition, dietary and anthropometric data were validated (30, 31), limiting declaration bias.

An even larger cohort with longer follow-up and information on lifestyle changes would nicely complete our study and enable the identification of a key period during which changes in lifestyle may modify cancer incidence.

Conclusion

Several studies have been published using similar evaluation of lifestyle exposure and cancer outcomes, though few have quantified the impact of lifestyle on overall cancer risk using adequate methodology. While adhering to one specific recommendation has a moderate impact on the proportion of prevented cancer cases, combining healthy behaviors—being a nonsmoker, drinking moderately, consuming the recommended amounts of fruits and vegetables, being physically active, and having a BMI within the recommended range—may substantially decrease the incidence of some specific cancers, especially lung and postmenopausal breast cancers. These results should encourage research into ways of enforcing these five simple health behaviors in the general population to improve cancer prevention.

Ethical Approval

The E3N study received approval from the national commission overseeing ethical data collection in France ("Commission Nationale de l'Informatique et des Libertés"), classification AG662, 12489 (September 25, 1988). All women signed an informed consent.

Data Sharing

The dataset can be requested from the principal investigator of the E3N study at francoise.clavel@gustaveroussy.fr.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: L. Dartois, G. Fagherazzi, S. Mesrine
Development of methodology: L. Dartois, G. Fagherazzi
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): F. Clavel-Chapelon
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Dartois, G. Fagherazzi, S. Mesrine
Writing, review, and/or revision of the manuscript: L. Dartois, G. Fagherazzi, M.-C. Boutron-Ruault, S. Mesrine, F. Clavel-Chapelon
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L. Dartois
Study supervision: M.-C. Boutron-Ruault, F. Clavel-Chapelon

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Cancer Prevention Research

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