Title: Association between five lifestyle habits and cancer risk: Results from the E3N cohort
Laureen Dartois, Guy Fagherazzi, Marie-Christine Boutron-Ruault, Sylvie Mesrine, Françoise Clavel-Chapelon
Inserm (Institut National de la Santé et de la Recherche Médicale), Centre for Research in Epidemiology and Population Health (CESP), U1018, Team 9, F-94805, Villejuif, France
Univ Paris Sud, UMRS 1018, F-94805, Villejuif, France
Gustave Roussy, F-94805, Villejuif, France

Abbreviated running title: Association between lifestyle and cancer risk

Key words: Lifestyle behavior; Body Mass Index; Alcohol; Physical activity; Smoking; Fruit and vegetable; Cancer; Attributable fraction;

The authors are indebted to all participants for providing data and to practitioners for providing pathology reports. They are grateful to all members of the E3N-EPIC study group, particularly to Rafika Chait for the management of cancer databases.

Sponsoring: The E3N study was funded by the MGEN (Mutuelle Générale de l’Éducation Nationale), the Ligue contre le Cancer, Gustave Roussy Institute and the Institut National de la Santé et de la Recherche Médicale (Inserm), and received grants from the “Cohortes Santé TGIR Program”, Agence Nationale de la Recherche (ANR), Institut National du Cancer (INCa), Fondation ARC pour la recherche sur le cancer, World Cancer Research Fund (WCRF), Ligue contre le Cancer, Fondation de France, Agence Nationale de Sécurité Sanitaire (ANSES), the French Ministry of Health and the Université Paris Sud. For the
submitted work, MCBR and FCC were supported by Inserm, LD by the Fondation de France (2011-00023087), SM by the Université Paris Sud and GF by the Fondation ARC.

Correspondence to:
Françoise Clavel-Chapelon
Inserm U1018 Team 9. 114 rue Edouard Vaillant. F-94805 Villejuif Cedex, France
Phone: +33 1 42 11 41 48
Fax: +33 1 42 11 40 00
francoise.clavel@gustaveroussy.fr

Conflicts of interest: none declared

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 25th, 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

Abstract word count: 231
Text word count (excluding references): 4090
Total number of tables: 4
Total number of supplementary tables: 1
Total number of figures: 0
Total number of references: 51
Abstract

Background: 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. Methods: The study included 64,732 women from the French E3N prospective cohort, aged 43 to 68 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 (BMI), 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 hazard ratios (HRs) and their 95% confidence intervals (CIs). In addition, population-attributable fractions were used to estimate the proportion of cancer cases that could be prevented by healthier behaviors. Results: A significant decrease in all-site cancer risk was observed and was associated with a healthy lifestyle (HR=0.81 (0.73; 0.89) when comparing the highest to 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. Conclusion: Compliance with only five modifiable lifestyle behaviors could prevent a significant number of cancers, notably postmenopausal breast and lung cancers.
Acronyms used in text

ANSES (Agence Nationale de Sécurité Sanitaire)
BMI (Body Mass Index)
CI (Confidence Intervals)
E3N (Étude Épidémiologique des femmes de la Mutuelle Générale de l’Éducation Nationale)
HR (Hazard Ratio)
ICD-10 (International Classification of Diseases, 10th edition)
ICD-O-3 (International Classification of Diseases for Oncology, 3rd edition)
MET (Metabolic Equivalent Task)
MGEN (Mutuelle Générale de l’Éducation Nationale)
PAF (Population attributable fraction)
PNNS (Programme National Nutrition Santé)
UV (Ultraviolet)
WHO (World Health Organization)
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-
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 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=4705), 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=4262). Our final population for analysis consisted of 64,732 women aged 43-68 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. 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, body mass index (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)(6), the ANSES (the French food safety agency)(7) and the WHO (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 18.5-25 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
metabolic equivalents (METs)-hour per week (i.e., 300 minutes of moderate or 150 minutes of vigorous recreational physical activity per week)(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 to 20 METs-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)(8). If women did not meet any of the above criteria, they were considered non-compliant.

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 one 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), non-basal 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, 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 hazard ratios (HRs) and 95% confidence intervals (CIs) 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, post-graduate), residence (North, Centre, 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, 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], [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 (PAF)**

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 non-modifiable risk factors remaining unchanged), we estimated the population-attributable fraction (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 et al(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 METs-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 4 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 five 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 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 10-20 METs-hour/week to 15-20, 15-25, 15-30, 10-25 or 10-30 METs-hour/week. We tested the potentially confounding effect of sun exposure for non-basal skin cancer analyses by adjusting the effects for the yearly mean sun ultraviolet (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 non-basal skin cancer differs, we analyzed separately the different types of non-basal skin cancer (melanoma, spinocellular or other/unspecified type). Finally, we performed a sensitivity analysis excluding non-validated cancer cases to avoid misclassification of cases. All analyses were conducted using SAS software, version 9.2 (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Population characteristics

During 840 097 person-years (median follow-up of 8 years for invasive cancer cases and 15 years for non-cases), 6938 women were diagnosed with any type of invasive cancer. Specific types (including concomitant tumors) included 3483 breast cancers (609 premenopausal and 2874 postmenopausal at diagnosis), 686 non-basal skin cancers, 481 colorectal cancers, 411...
hematopoietic malignancies (including mostly non-Hodgkin’s and Hodgkin’s lymphoma, leukemia and multiple myeloma), 274 non-colorectal 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 1. 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) \(P_{\text{trend}}<0.001\) across score categories.

The association was also observed for several specific tumor sites: lung cancer (HR = 0.19 (0.11; 0.30), \(P_{\text{trend}}<0.001\)), endometrial cancer (HR = 0.45 (0.29; 0.71), \(P_{\text{trend}}<0.001\)), digestive cancers other than colorectal (HR = 0.59 (0.36; 0.95), \(P_{\text{trend}}=0.036\)), and colorectal cancer (HR = 0.66 (0.45; 0.97), \(P_{\text{trend}}=0.013\)). A significant trend was observed for postmenopausal breast cancer (\(P_{\text{trend}}=0.016\)); 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 non-basal skin cancer (HR = 1.75 (1.17; 2.62), \( P_{\text{trend}} < 0.001 \)). 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 women had followed a healthy lifestyle an excess of 21.5% (7.5%; 34.6%) of non-basal 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% to 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/m2), 13.3% (3.7% to 22.5%) of endometrial cancer cases and 8.6% (0.2% to 16.9%) of 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 five years of follow-up (N=1897). 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 non-basal 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 non-basal skin cancer cases when adopting healthy behaviors. Associations between recreational physical activity and non-basal skin cancer remained with a PAF estimated at -9.16% (-17.00%; -1.21%). Analyses considering the subtypes of non-basal skin cancer (875 cancers in 686 women) resulted in similar results for melanomas (N=391) and other/unspecified types of non-basal skin cancers (N=257), with HR=1.44 (0.88; 2.37) and PAF=-20.8% (-38.2%; -2.0%) and HR=2.41 (1.12; 5.20) and PAF=-28.3% (-49.0%; -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%; 14.6%). When performing separate analyses according to age, results remained similar in women over 50 years old (6304 cancers diagnosed during 705 771 women-years) and those 43-50 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%; 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\(^\text{(6-8)}\), 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, metabolism) and exogenous (lifestyle, environment) causes. Therefore, the analyzed healthy behaviors, chosen to be easily modifiable lifestyle factors, are five out 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\(^\text{(17-22)}\), colorectal\(^\text{(19, 22-24)}\), breast\(^\text{(19, 22, 25)}\), endometrial\(^\text{(19, 22)}\), digestive\(^\text{(15, 19)}\) and lung\(^\text{(19)}\) cancer in women complying with public health recommendations. Compliance with recommendations was estimated to be able to prevent 11% to 31% of cancer\(^\text{(17-19)}\) and, specifically, 6% of colorectal cancer\(^\text{(23)}\). 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’s formula\(^\text{(36)}\) was demonstrated to
provide biased estimates when calculated with multivariate relative risks(37), whereas the Spiegelman’s formula(35) appears 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 meta-analysis(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 meta-analyses(42, 43). However, the association may be a reflection of reverse causation, as people with chronic 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 meta-analyses 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’s 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 five
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 non-significant 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 prior to cancer
diagnosis resulted in little risk of memory bias. Self-report bias was limited through the histological confirmation of the vast majority of cancer cases. Moreover, excluding non-validated 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 non-smoker, 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.


(5) NICE. Preventing type 2 diabetes - risk identification and interventions for individuals at high risk (PH38). Public health guidance 38 212.


(11) Alcohol consumption and ethyl carbamate. IARC Monogr Eval Carcinog Risks Hum 2010;96:3-1383.


Table 1 Health index construction, based on five lifestyle characteristics

<table>
<thead>
<tr>
<th>Health recommendations</th>
<th>Compliance with public health recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking status</td>
<td>Full (1 point)  Partial (0.5 point)  Poor (0 point)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>Former smoker</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>[18.5-25) (normal range)</td>
</tr>
<tr>
<td></td>
<td>[16-18.5) (underweight)</td>
</tr>
<tr>
<td>Alcohol consumption (drinks/day)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Fruit and vegetable consumption (servings/day)</td>
<td>≥5</td>
</tr>
<tr>
<td>Recreational physical activity level (METs-hour/week)</td>
<td>≥20</td>
</tr>
</tbody>
</table>

a: One drink of alcohol corresponds to 10 grams of ethanol.
b: One serving of fruits and vegetables corresponds to 80 grams of fruits and vegetables. Fruits and vegetables included raw and cooked vegetables, lettuce and fresh fruits.
Table 2 Pearson correlation coefficients between the five lifestyle characteristics scores

<table>
<thead>
<tr>
<th></th>
<th>Smoking status</th>
<th>Body mass index</th>
<th>Alcohol consumption</th>
<th>Fruit and vegetable consumption</th>
<th>Physical activity level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking status</td>
<td>1</td>
<td>-0.00557</td>
<td>0.17957</td>
<td>0.05516</td>
<td>-0.00870</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td>-0.01827</td>
<td>-0.00870</td>
<td>0.01829</td>
<td>0.08793</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td>0.05885</td>
<td></td>
<td>-0.04013</td>
</tr>
<tr>
<td>Fruit and vegetable consumption</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>0.08809</td>
</tr>
<tr>
<td>Recreational physical activity level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

a: p-value<0.001
b: p-value<0.01
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)

<table>
<thead>
<tr>
<th>Health index categories</th>
<th>[0; 2]</th>
<th>[2.5; 3]</th>
<th>[3.5; 4]</th>
<th>[4.5; 5]</th>
<th>( P_{\text{trend}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-site cancer (N=6938)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All, number of cases (%)</td>
<td>450 (6.48)</td>
<td>1554 (22.40)</td>
<td>2974 (42.87)</td>
<td>1960 (28.25)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)(^a)</td>
<td>1.00 (reference)</td>
<td><strong>0.88 (0.79 ; 0.98)</strong></td>
<td><strong>0.86 (0.78 ; 0.95)</strong></td>
<td><strong>0.81 (0.73 ; 0.89)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Breast cancer (N=3483)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal, number of cases (%)</td>
<td>47 (7.72)</td>
<td>141 (23.15)</td>
<td>268 (44.68)</td>
<td>153 (25.12)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)(^b)</td>
<td>1.00 (reference)</td>
<td><strong>0.81 (0.59 ; 1.12)</strong></td>
<td><strong>0.80 (0.58 ; 1.12)</strong></td>
<td><strong>&lt;0.001</strong></td>
<td></td>
</tr>
<tr>
<td>Postmenopausal, number of cases (%)</td>
<td>169 (5.88)</td>
<td>623 (21.68)</td>
<td>1284 (44.68)</td>
<td>798 (27.76)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)(^c)</td>
<td>1.00 (reference)</td>
<td><strong>0.95 (0.80 ; 1.12)</strong></td>
<td><strong>0.87 (0.74 ; 1.03)</strong></td>
<td><strong>0.016</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Non-basal skin cancer (N=686)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All, number of cases (%)</td>
<td>26 (3.79)</td>
<td>125 (18.22)</td>
<td>283 (41.25)</td>
<td>252 (36.74)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)(^d)</td>
<td>1.00 (reference)</td>
<td><strong>1.22 (0.80 ; 1.87)</strong></td>
<td><strong>1.17 (0.74 ; 1.76)</strong></td>
<td><strong>&lt;0.001</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Colorectal cancer (N=481)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All, number of cases (%)</td>
<td>33 (6.86)</td>
<td>110 (22.87)</td>
<td>207 (43.04)</td>
<td>131 (27.23)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)(^d)</td>
<td>1.00 (reference)</td>
<td><strong>0.83 (0.56 ; 1.22)</strong></td>
<td><strong>0.87 (0.53 ; 1.17)</strong></td>
<td><strong>0.013</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Hematopoietic cancer (N=411)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All, number of cases (%)</td>
<td>18 (4.38)</td>
<td>97 (23.60)</td>
<td>160 (38.93)</td>
<td>136 (33.09)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)(^d)</td>
<td>1.00 (reference)</td>
<td><strong>1.33 (0.80 ; 2.20)</strong></td>
<td><strong>1.27 (0.77 ; 2.08)</strong></td>
<td><strong>0.894</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Digestive cancer(^e) (N=274)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All, number of cases (%)</td>
<td>22 (8.03)</td>
<td>63 (22.99)</td>
<td>115 (41.97)</td>
<td>74 (27.01)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)(^d)</td>
<td>1.00 (reference)</td>
<td><strong>0.72 (0.44 ; 1.16)</strong></td>
<td><strong>0.65 (0.41 ; 1.04)</strong></td>
<td><strong>0.036</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Endometrial cancer (N=270)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All, number of cases (%)</td>
<td>26 (9.63)</td>
<td>66 (24.44)</td>
<td>105 (38.89)</td>
<td>73 (27.04)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)(^d)</td>
<td>1.00 (reference)</td>
<td><strong>0.61 (0.39 ; 0.97)</strong></td>
<td><strong>0.45 (0.29 ; 0.71)</strong></td>
<td><strong>&lt;0.001</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Thyroid cancer (N=267)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All, number of cases (%)</td>
<td>16 (5.99)</td>
<td>65 (24.34)</td>
<td>103 (38.58)</td>
<td>83 (31.09)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)(^d)</td>
<td>1.00 (reference)</td>
<td><strong>1.08 (0.62 ; 1.87)</strong></td>
<td><strong>1.08 (0.63 ; 1.86)</strong></td>
<td><strong>0.573</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Ovarian cancer (N=248)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All, number of cases (%)</td>
<td>15 (6.05)</td>
<td>59 (23.79)</td>
<td>101 (40.73)</td>
<td>73 (29.43)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)(^d)</td>
<td>1.00 (reference)</td>
<td><strong>0.99 (0.56 ; 1.75)</strong></td>
<td><strong>0.89 (0.51 ; 1.55)</strong></td>
<td><strong>0.297</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Lung cancer (N=213)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All, number of cases (%)</td>
<td>32 (15.02)</td>
<td>61 (28.64)</td>
<td>85 (39.91)</td>
<td>35 (16.44)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)(^d)</td>
<td>1.00 (reference)</td>
<td><strong>0.47 (0.31 ; 0.72)</strong></td>
<td><strong>0.33 (0.22 ; 0.49)</strong></td>
<td><strong>0.19 (0.11 ; 0.30)</strong></td>
<td><strong>&lt;0.001</strong></td>
</tr>
</tbody>
</table>

\( a. \) 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, 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 and age at first full-term pregnancy.

\( c. \) Adjusted for all of the above + use of menopausal hormone therapy

\( d. \) Adjusted for all of the above + menopausal status and use of menopausal hormone therapy

\( e. \) Non-colorectal digestive cancers included cancers of the pancreas, stomach, liver, biliary tract, esophagus and small bowel.
Table 4 Population-attributable fractions (PAFs) of any-site and site-specific cancer when adhering to public health recommendations, E3N cohort (N=64 732)

<table>
<thead>
<tr>
<th></th>
<th>PAF for each single characteristic&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PAF for the five combined characteristics&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smoking</td>
<td>BMI</td>
</tr>
<tr>
<td>All-type cancer (N=6938)</td>
<td>1.3 (-1.8 ; 4.4)</td>
<td>1.4 (-0.5 ; 3.4)</td>
</tr>
<tr>
<td>Breast cancer (N=3483)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal (N=609)</td>
<td>2.0 (-5.2 ; 9.3)</td>
<td>-6.3 (-9.9 ; -2.6)</td>
</tr>
<tr>
<td>Postmenopausal (N=2874)</td>
<td>-2.6 (-7.0 ; 1.8)</td>
<td>-0.3 (-3.2 ; 2.6)</td>
</tr>
<tr>
<td>Non-basal skin cancer (N=686)</td>
<td>-4.5 (-14.1 ; 5.3)</td>
<td>-2.0 (-8.0 ; 4.1)</td>
</tr>
<tr>
<td>Colorectal cancer (N=481)</td>
<td>7.0 (-5.0 ; 18.8)</td>
<td>1.0 (-6.3 ; 8.2)</td>
</tr>
<tr>
<td>Hematopoietic cancer (N=411)</td>
<td>-0.7 (-13.2 ; 11.8)</td>
<td>8.6 (0.2 ; 16.9)</td>
</tr>
<tr>
<td>Digestive&lt;sup&gt;c&lt;/sup&gt; cancer (N=274)</td>
<td>3.9 (-11.7 ; 19.3)</td>
<td>6.1 (-3.8 ; 15.9)</td>
</tr>
<tr>
<td>Endometrial cancer (N=270)</td>
<td>0.7 (-15.6 ; 17.0)</td>
<td>13.3 (3.7 ; 22.5)</td>
</tr>
<tr>
<td>Thyroid cancer (N=267)</td>
<td>-3.6 (-18.1 ; 11.0)</td>
<td>4.6 (-6.0 ; 15.1)</td>
</tr>
<tr>
<td>Ovarian cancer (N=248)</td>
<td>4.5 (-11.6 ; 20.3)</td>
<td>7.2 (-3.5 ; 17.8)</td>
</tr>
<tr>
<td>Lung cancer (N=213)</td>
<td>41.8 (24.8 ; 56.3)</td>
<td>-5.7 (-16.6 ; 5.4)</td>
</tr>
</tbody>
</table>

<sup>a</sup> 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.

<sup>b</sup> 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.

<sup>c</sup> Non-colorectal digestive cancers included cancers of the pancreas, stomach, liver, biliary tract, esophagus and small bowel.
Cancer Prevention Research

Association between five lifestyle habits and cancer risk: Results from the E3N cohort
Laureen Dartois, Guy Fagherazzi, Marie-Christine Boutron-Ruault, et al.

Cancer Prev Res Published OnlineFirst February 26, 2014.

Updated version
Access the most recent version of this article at:
doi:10.1158/1940-6207.CAPR-13-0325

Author Manuscript
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.