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Background: Intervention studies have demonstrated that, in smokers, β-carotene supplements had a deleterious effect on risk of lung cancer and may have a deleterious effect on digestive cancers as well. We investigated a potential interaction between β-carotene intake and smoking on the risk of tobacco-related cancers in women. ***Methods:*** A total of 59 910 women from the French Etude Epidémiologique de Femmes de la Mutuelle Générale de l'Education Nationale (E3N) prospective investigation were studied from 1994. After a median follow-up of 7.4 years, 700 women had developed cancers known to be associated with smoking. Diet, supplement use, and smoking status at baseline were assessed by self-report. β-carotene intake was classified into four groups: first (low intake), second, and third tertiles of dietary intake, and use of supplements (high intake). Unadjusted and multivariable Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals (CIs) for cancer risk. All statistical tests were two-sided. ***Results:*** Among never smokers, multivariable hazard ratios of all smoking-related cancers were 0.72 (95% CI = 0.57 to 0.92), 0.80 (95% CI = 0.64 to 1.01), and 0.44 (95% CI = 0.18 to 1.07) for the second and third tertiles of dietary intake, and high β-carotene intake, respectively, compared with low intake (P_{trend} = .03). Among ever smokers, multivariable hazard ratios were 1.43 (95% CI = 1.05 to 1.96), 1.20 (95% CI = 0.86 to 1.67), and 2.14 (95% CI = 1.16 to 3.97) for the second and third tertiles of dietary intake, and high β-carotene intake, respectively, compared with low intake (P_{trend} = .09). Tests for interaction between β-carotene intake and smoking were statistically significant (P_{trend} =.017). In this population, the absolute rates over 10 years in those with low and high β-carotene intake were 181.8 and 81.7 cases per 10 000 women in never smokers and 174.0 and 368.3 cases per 10 000 women in ever smokers. ***Conclusions:*** β-carotene intake was inversely associated with risk of tobacco-related cancers among nonsmokers with a statistically significant dose-dependent relationship, whereas high β-carotene intake was directly associated with risk among smokers.

An inverse association between β-carotene intake and risk of neoplasms has been described largely in observational studies, thus leading researchers to design many intervention studies with this antioxidant *(1–4)*. However, its safety is debated *(5)*, as some intervention studies have suggested a positive association of high doses of supplemental β-carotene, especially in smokers, with lung cancer *(6–8)* and with digestive cancers, during the trial or the post-trial follow-up *(9,10)*. A meta-analysis of intervention studies on digestive tract cancers suggested a direct association between cancer incidence and intake of β-carotene alone or combined with retinol or tocopherol *(11)*, but a potential interaction with smoking was not investigated. In an intervention study of patients with colorectal adenomas, a precancerous lesion for colorectal cancer, an inverse association between adenoma recurrence and β-carotene intake was observed in non smokers, but a direct association was observed in those smokers who drank at least one alcoholic drink per day *(12)*. In contrast, a pooled analysis of seven cohorts *(13)* and two intervention studies *(14,15)* did not show a statistically significant interaction between β-carotene and smoking with cancer incidence. No previous study, to our knowledge, has investigated whether β-carotene intake displays a similar dual association with incidence of all tobacco-related cancers in smokers and nonsmokers, taking into account β-carotene intake from diet and supplements simultaneously. We investigated these relationships using data from the Etude Epidémiologique de Femmes de la Mutuelle Générale de l'Education Nationale (E3N) cohort study.

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Materials and Methods

The E3N Cohort Study

The E3N prospective cohort study was initiated in 1990 to study risk factors for cancer in women *(16)*. It includes 98 995 women living in France aged 40 – 65 years in 1990 and covered by the Mutuelle Générale de l'Education Nationale, the national health insurance plan for teachers and coworkers. E3N is the French component of The European Prospective Investigation into Cancer and Nutrition *(17)*. All study subjects signed an informed consent form in compliance with the rules of the French National Commission for Computed Data and Individual Freedom (Commission Nationale Informatique et Libertés) from which we obtained approval. For the present analysis, we used information from three types of self-administered questionnaires, which were provided to all participants. These questionnaires addressed medical events, dietary intake, dietary supplement intake, and smoking status.

Medical Events Data

Women reported medical events data, such as cancer incidence, in self-administered questionnaires. These questionnaires were completed approximately every 24 months, beginning in 1994 for the present study.

Dietary Data

Dietary data were collected once, between June 1993 and July 1995. The dietary history questionnaire, which was sent to 95 644 women (with two reminders sent to nonresponders), consisted of two parts: 1) questions on consumption (quantity and frequency) of food groups and 2) qualitative questions that allowed us to delineate the food groups into food items. The questionnaire was sent with a booklet of photographs to facilitate estimation of portion sizes *(18)*. The questionnaire assessed dietary consumption of 208 food items and beverages. It was validated using 12 24-hour recalls as the reference, and its reproducibility was tested after 1 year *(19)* : for β-carotene intake, the correlation coefficients were 0.63 for validity and 0.66 for reproducibility.

A total of 77 613 questionnaires were collected, for an 81.1% response. Of these, 985 questionnaires were excluded because the participants did not provide consent for external health follow-up by the health insurer in the case of dropout, 2050 were excluded because of miscoded answers, 8 were excluded because all answers were missing, 46 were excluded because of double answers, and 1490 were excluded because they contained extreme values (in the bottom 1% or top 1%) of the ratio between energy intake and required energy (calculated after taking age, weight, and height into account). Thus, questionnaires for 73 034 women were available for analysis. Using a food composition table derived from the French national database *(20)*, we estimated daily dietary intakes of β-carotene and other macro- and micronutrients.

Dietary Supplement Data

In what we refer to as the 1994 questionnaire because it was mailed to the women in 1994, study participants were asked if they took a supplement for the following nutrients: β- carotene, calcium, fluoride, vitamins C, E, D, or those in the B group, retinol, folic acid, and other vitamins and minerals at least three times a week. Ninety-seven percent of the questionnaires were returned by December 1996.

Total β-Carotene Intake

β-carotene intake was categorized into four groups as: first (" low " intake), second, and third tertiles of dietary intake, and users of β-carotene supplements, whatever their dietary intake (" high " intake). Cutoff points for tertiles of dietary β-carotene intake were 3.1 mg and 4.4 mg daily.

Smoking Status

Smoking status was assessed in the 1994 questionnaire at the beginning of our study; women having smoked only occasionally (<1 cigarette per day) were considered nonsmokers. From the number of years of smoking and the number of cigarettes smoked per day by regular smokers (past or current)

reported, we calculated total lifetime smoking in pack-years. This questionnaire also assessed the number of years since quitting smoking.

Study Participants

We investigated all cancers for which any association with tobacco has been suggested for cancer itself [i.e., head-and-neck, urinary tract, digestive, lung, and cervical cancers *(21)*] or for precancerous lesions [i.e., thyroid and ovarian cancers *(22,23)*].

This analysis was performed on subjects who reported a primary tobacco-related cancer between the time they returned the 1994 questionnaire and July 2002. A total of 68 922 women completed the 1994 questionnaire and answered the dietary supplement questions. We excluded 4811 subjects who reported a cancer diagnosis before the start of the follow-up (date of return of the 1994 questionnaire) or with missing date of diagnosis, 515 subjects who were lost to follow-up from baseline in 1994, 11 subjects for whom information on smoking status was missing, and 3675 subjects with missing dietary data and who did not use β-carotene supplements, leaving 59 910 for analysis. A total of 2342 subjects reported a cancer other than tobacco-related during the study period (except basal cell skin carcinoma, not considered as cancer); these subjects were included in the analyses as noncases but were censored at the time of diagnosis. Subjects contributed person-time until the date of diagnosis of cancer, date of the last completed questionnaire, date of death, or July 2002, whichever occurred first. Complete follow-up was obtained for 95.7% of the 59 910 women.

For each self-reported cancer, a pathology report was requested. The report was obtained for 91.3% of women who declared a cancer between 1994 and 2000 and confi rmed diagnosis of cancer in 99.3%. For women whose cancer occurred between 2000 and 2002, pathology reports have been obtained to date for 68.5%. Because of the high validity of the self-reports (99.3% of self-reported cancers for which a pathology report was obtained were confirmed), we included all women who self-reported primary cancers between 1994 and July 2002 unless they were identified as non-case subjects by a pathology report. To test a potential bias due to cases not yet confirmed in the main analyses, we performed an analysis restricted to women with confirmed cancers who were diagnosed between 1994 and 2000. This restriction did not substantially modify the results, with only a broadening of confidence intervals due to loss of power. Of the 59 910 women analyzed for this study, 700 developed a tobacco-related cancer during follow-up through July 2002: 25 head-and-neck, 143 thyroid, five esophagus, 11 stomach, seven liver, 28 pancreatic, 224 colorectal, eight anal, 38 urinary tract, 96 ovarian, 58 cervical, and 57 lung cancers.

Statistical Analysis

We estimated hazard ratios (HRs) and 95% confi dence inter-vals (CIs) associated with β-carotene or smoking exposure using the Cox proportional hazards regression models. We determined that the assumptions of proportionality were satisfi ed through examination of the log–log (survival) versus log–time plots. Global models were used to investigate associations of β-carotene and tobacco with cancer risk and their interaction. Stratified models investigated the associations between risk and β-carotene according to smoking status (ever versus never smoked). Age was used as the primary time variable. Tests for linear trend were performed using the ordinal score on categories of β-carotene intake. Analyses were duplicated after exclusion of the fi rst year of follow-up to verify the absence of biased answers in cases occurring early after the questionnaire was administered and to ensure sufficiently long duration between measurement of exposure and occurrence of cancer. Site-specific analyses were also performed. Analyses were focused on the 700 tobaccorelated cancers, but main associations were also tested in the 2342 non–tobacco-related cancers: 1779 breast, 223 skin (except basal cell skin carcinoma), 115 uterine (corpus uteri), 125 hematopoietic, and 100 other cancers. Associations were also tested considering β-carotene supplement users versus non users, with and without adjustment for dietary β- carotene. Within the ever-smokers stratum, we also investigated a potential heterogeneity of the association of cancer risk and β-carotene intake between current and past smokers using a Cox model that tested the interaction between β-carotene intake and current/ past smoking status.

For the combined sites and the site-specific analyses, we controlled for potential confounding factors by multivariable adjustment for energy intake except from alcohol (in tertiles, <1773, 1773 – 2218, and >2218 kcal/day), body mass index (continuous variable in kg/m^2), alcohol intake (continuous variable in g/day), and leisure physical activity (no leisure physical activity, <43 min per day, i.e., the median for active women, and physical activity of ≥43 min per day). In addition, all multivariable analyses stratified by smoking were adjusted for the number of cigarettes smoked per day, the number of years of smoking, and time since quitting smoking in years (continuous variables) in the ever smokers stratum. Further adjustments for family history of cancer (yes or no), use of cancer screening tests (yes or no), consumption of other nutrients by supplements (yes or no), education level (0, ≤ 5, 6 – 11, 12 – 14, 15 – 16, and ≥17 years of education, as an ordinal variable), number of children (continuous variable), dietary intake of fiber, folate, vitamins C and E, calcium and retinol, consumption of red meat, fruit, vegetables, and fats (continuous variables), and treatment with hormone replacement therapy (yes or no) at baseline were also tested for global and sitespecific analyses. Coding and cut points of all these covariates were chosen to fit the log-linearity assumption. For all potential confounders, values were missing in less than 5% of the subjects. Missing values were therefore replaced by the modal (i.e., the most common) value.
In all Cox models, two-sided tests were performed using the maximum-likelihood method; *P*<.05 was considered statistical significant. SAS version 8.2 (SAS Institute, Cary, NC) was used for all analyses.

Results

The median follow-up time was 7.4 years. The proportion of women who ever smoked represented 30.5% of our population, and the average number of pack-years smoked among smokers was 9.4. Baseline characteristics of the women according to β-carotene intake are presented in Table 1.

Table 1. **Baseline characteristics of the study population by β-carotene intake ***

Parameter‡	Intake of β-carotene†			
	1 (n = 19 570)	2 (n = 19 531)	3 (n = 19 386)	4 (n = 1423)
No. of person-years	130 469	131 156	129 660	9379
Age, y, mean (±SD)	53.6 (±6.5)	54.3 (±6.6)	55.1 (±6.7)	54.2 (±6.3)
Mean daily dietary intake of β-carotene, μg; mean (±SD)	2285.6 (±568.3)	3731.8 (±389.6)	5929.9 (±1428.1)	4207.2 (±1829.0)
Smoking, ever, § %	31.6	29.6	29.9	34.8
Current smoking, ‖ %	34.3	26.5	23.5	26.3
No. of pack-years, ‖ mean (±SD)	10.2 (±10.7)	9.0 (±9.4)	9.1 (±9.3)	9.4 (±9.7)
No. of cigarettes per day, ‖ mean (±SD)	10.7 (±7.8)	10.0 (±7.0)	10.3 (±7.4)	10.4 (±7.8)
No. of years of smoking, ‖ mean (±SD)	17.6 (±10.5)	16.7 (±10.1)	16.5 (±10.1)	16.9 (±9.7)
No. of years since quitting tobacco,¶ mean (±SD)	17.2 (±8.6)	17.6 (±8.7)	17.4 (±8.8)	17.4 (±8.3)
Leisure physical activity, min/day; mean (±SD)	39.8 (±82.5)	45.8 (±87.7)	47.5 (±91.2)	56.8 (±98.1)
Alcohol intake, g/day; mean (±SD)	12.2 (±15.2)	10.9 (±13.5)	10.0 (±13.0)	10.3 (±13.7)
Energy, kcal/day; mean (±SD)	1880.2 (±508.1)	2047.1 (±510.3)	2177.1 (±542.9)	2035.3 (±546.2)
Body mass index, kg/m^2, mean (±SD)	22.9 (±3.5)	23.2 (±4.0)	23.7 (±3.9)	22.4 (±3.1)
No. of years of schooling <12, %	11.6	10.7	11.3	7.5
Family history of cancer, # %	45.0	46.0	45.7	46.5

*The study population was composed of 59 210 cancer-free women and 700 women with tobacco-related cancers (digestive, gynecologic, thyroid, lung, head and-neck, and urinary tract cancers).
†β-carotene intake: 1 = first tertile of dietary β-carotene intake, 2 = second tertile of dietary β-carotene intake, 3 = third tertile of dietary β-carotene intake, 4 = intake of β-carotene supplements at least three times a week.
‡SD = standard deviation.
§Occasional smokers were considered as nonsmokers.
‖In ever smokers.
¶In past smokers.
#In first-degree relatives (i.e., parents, children, brothers, and sisters).

Ever smoking was associated with an increased risk of tobacco-related cancers (multivariable HR = 1.44, 95% CI = 1.23 to 1.69; *P*<.001, compared with never smoking). The absolute risks over 10 years were 158.3 cases per 10 000 women in never smokers and 212.7 cases per 10 000 women in ever smokers.

β-carotene intake was not statistically signifi cantly associated with the risk of tobacco-related cancers (multivariable HR = 0.91, 95% CI = 0.76 to 1.10, HR = 0.91, 95% CI = 0.76 to 1.10 and HR = 0.98, 95% CI = 0.60 to 1.61 in the second and third tertiles of dietary intake and in the high intake category, respectively, compared with low intake). A statistically significant interaction was observed between β-carotene intake across all groups and smoking status on cancer risk (P_{trend} = .017, multivariable model). In addition, tests for interaction with smoking status were statistically significant for the second and fourth (high) categories of β-carotene intake (P = .002 and P = .005, respectively) but not for the third category (P = .11).

In models stratified by smoking (Table 2), the risk of cancer decreased with increasing β-carotene intake among never smokers (multivariable HR = 0.72, 95% CI = 0.57 to 0.92, HR = 0.80, 95% CI = 0.64 to 1.01 and HR = 0.44, 95% CI = 0.18 to 1.07 for second and third tertiles of dietary intake, and high β-carotene intake, respectively, compared with low intake; P_{trend} = .03). Among ever smokers, multivariable hazard ratios were 1.43 (95% CI = 1.05 to 1.96), 1.20 (95% CI = 0.86 to 1.67) and 2.14 (95% CI = 1.16 to 3.97) for the second and third tertiles of dietary intake and high β-carotene intake, respectively, compared with low intake (P_{trend} = .09). The absolute rates over 10 years in low and high β-carotene consumers were 181.8, and 81.7 cases per 10 000 women in never smokers and 174.0 and 368.3 cases per 10 000 women in ever smokers.

Table 2. **Unadjusted and multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) of tobacco-related cancers according to β-carotene intake by smoking status ***

Smoking status	Intake of β-carotene†				P_{trend}
	1	2	3	4	
Never smokers					
No. of person-years (no. of patients)	89 666 (163)	92 853 (128)	91 206 (147)	6121 (5)	
Unadjusted HRs (95% CI)	1.00 (referent)	0.73 (0.58 to 0.92)	0.81 (0.65 to 1.02)	0.43 (0.18 to 1.05)	.03
Multivariable HRs (95% CI) ‡	1.00 (referent)	0.72 (0.57 to 0.92)	0.80 (0.64 to 1.01)	0.44 (0.18 to 1.07)	.03
Ever smokers §					
No. of person-years (no. of patients)	40 803 (71)	38 303 (93)	38 454 (81)	3258 (12)	
Unadjusted HRs (95% CI)	1.00 (referent)	1.35 (0.99 to 1.84)	1.14 (0.82 to 1.56)	2.05 (1.11 to 3.78)	.16
Multivariable HRs (95% CI) ‡	1.00 (referent)	1.43 (1.05 to 1.96)	1.20 (0.86 to 1.67)	2.14 (1.16 to 3.97)	.09

*The study population was composed of 59 210 cancer-free women and 700 women with tobacco-related cancer (digestive, gynecologic, thyroid, lung, head-and-neck, and urinary tract cancers). Cox regression with age as the primary time variable was used. *P* values (two-sided) were calculated using the maximum-likelihood method.

†β-carotene intake: 1 = first tertile of dietary β-carotene intake, 2 = second tertile of dietary β-carotene intake, 3 = third tertile of dietary β-carotene intake, 4 = intake of β-carotene supplements at least three times a week.

‡Multivariable model was adjusted for total energy intake except from alcohol (in tertiles, <1773, 1773 – 2218, and >2218 kcal/day), body mass index (continuous variable in kg/m^2), alcohol intake (continuous variable in g/day), and leisure physical activity (no leisure physical activity, leisure physical activity of <43 min/day, i.e., the median for active women, and leisure physical activity of ≥43 min/day). In the ever-smokers stratum, multivariate models were also adjusted for the number of cigarettes per day, the number of years of smoking, and time since quitting tobacco in years (continuous variables).

§Past or current.

The same unadjusted and multivariable analyses were performed for the different categories of tobacco-related cancers; no result was statistically significant. For digestive (n = 283), gynecologic (ovarian/cervical, n = 154), and thyroid (n = 143) cancers, for which numbers of patients were relatively large, associations were similar to those observed for all tobaccorelated cancers. Cancer risk decreased, albeit not statistically significantly with increasing β-carotene intake among nonsmokers, and increased, again, not statistically signifi cantly among smokers (high versus low intake, multivariable HR = 0.23, 95% CI = 0.03 to 1.67, and HR = 1.24, 95% CI = 0.29 to 5.32, for digestive cancers; HR = 0.70, 95% CI = 0.17 to 2.92, and HR = 2.49, 95% CI = 0.84 to 7.33, for gynecologic cancers; and HR = 0.76, 95% CI = 0.18 to 3.17, and HR = 1.84, 95% CI = 0.41 to 8.30, for thyroid cancers). For cancers of the lung (n = 57), head and neck (n = 25), and urinary tract (n = 38), the number of patients was too small to provide valid estimates of risk. The association between β-carotene intake and risk of head-and-neck cancers was similar to that for all tobacco-related cancers, whereas the association was similar in smokers and nonsmokers in two sites, i.e., deleterious for lung cancer and benefi cial for urinary tract cancers. Further adjustment for family history of cancer, use of cancer screening tests, consumption of other nutrients by

supplements, education level, number of children, treatment with hormone replacement therapy, and dietary variables did not substantially modify the findings for either combined site model or the site-specific models (data not shown). Associations were similar when patients with tumors that were diagnosed in the first year of follow-up were excluded, and the interaction between smoking and β-carotene intake remained statistically significant (P_{trend}=.01), thus providing evidence against biased dietary assessment in cases diagnosed soon after inclusion and ensuring sufficiently long duration between measurement of exposure and occurrence of cancer.

Among ever smokers, the multivariable hazard ratio of all tobacco-related cancers associated with high versus low β- carotene intake was 2.02 (95% CI = 0.70 to 5.87) in women who smoked 7.5 pack-years or less (i.e., the median), and 2.21(95% CI = 1.04 to 4.70) in women who smoked more than 7.5 pack-years. After adjustment for duration and dose of smoking, there was no heterogeneity in the association between β- carotene intake and cancer risk among current and past smokers.

Multivariable hazard ratios of all tobacco-related cancers with supplement use versus nonsupplement use were 0.53 (95% CI = 0.22 to 1.27) among nonsmokers and 1.78 (95% CI = 1.00 to 3.18) among ever smokers, after adjustment for dietary β- carotene intake. The interaction between smoking and β- carotene supplement use on risk of tobacco-related cancer was statistically significant (P = .02). Associations between β- carotene sup plement use and cancer risk and interaction between smoking and β-carotene supplement use on cancer risk were similar without adjustment for dietary β-carotene.

Interaction between β-carotene and smoking on risk of cancer was not observed for non-tobacco-related cancers (breast and others; n = 2342). There was also no statistically significant association between smoking and risk of these cancers (HR = 1.08, 95% CI = 0.98 to 1.18; P = .1); β-carotene intake was not associated with risk of cancer either in smokers (high versus low β-carotene HR = 1.13, 95% CI = 0.72 to 1.77) or in nonsmokers (HR = 1.18, 95% CI = 0.87 to 1.61), and the interaction term with smoking was not statistically significant (P_{trend} = .5).

Discussion

To our knowledge, this study is the first observational survey to investigate a potential interaction between tobacco and β- carotene on all tobacco-related cancers, taking into account intake of β-carotene from both diet and supplements. Overall, β-carotene intake was not statistically signifi cantly associated with the risk of tobacco-related cancers. However, it had opposite relationships in smokers and nonsmokers. In never smokers, increasing β-carotene intake was associated with a decreased risk of cancer, whereas in women who ever smoked, high β-carotene intake was associated with an increased risk of cancer.

The study had several limitations. One is that a small number of women took supplemental β-carotene. However, the association of cancer risk with second and third tertiles of dietary β-carotene intake, involving a large number of patients, was consistent with that among women who took supplements. Another potential limitation was the restriction of the cohort to women who provided data on β-carotene intake and smoking. Although the extrapolation of the findings to the general population therefore may be debatable because these women may not be representative of the general population, many cohort studies consist of thorough responders and have an advantage of obtaining quality data from highly motivated subjects. Another possible limitation is that the 7.4-year follow-up may not have allowed us to fully demonstrate associations between β-carotene intake and tobacco-related cancer risk at earlier stages of carcinogenesis. If, for some cancers, tobacco and β-carotene exert their effects mostly on precancerous lesions, as suggested for ovarian and thyroid tumors, a longer follow-up could provide even stronger associations.

Another limitation may arise from the fact that, because β-carotene supplement doses were not recorded, we grouped all supplement users as having high β-carotene intake under the assumption that women who took supplements had higher total β-carotene intake than those who did not. Our coding of total β-carotene intake represented a compromise between several strategies for analyzing supplemental and dietary intakes of nutrients that are currently being debated *(24,25)*. Mean dietary intake in β-carotene

supplement users was 4.2 mg, which was statistically significantly higher than in nonusers ($P < .001$), and mean β-carotene supplement doses have been estimated to be 2.1 mg/day in a French survey *(26)*. Mean total β-carotene intake can thus be estimated to be about 6.3 mg per day in supplement users, which is higher than the 90th percentile of dietary intake in nonusers, i.e., 6.2 mg; therefore, the overlap between the third and fourth categories of β- carotene intake is likely to be small. Our results for the " high " β-carotene intake category (supplement users) were always in the same direction but stronger than those for second and third tertiles of dietary intake. This finding is in favor of a global mechanism involving total β-carotene intake whether from diet or from supplements. However, we also verified that when comparing only supplement users with non supplement users, whatever their dietary intake, the interaction between β- carotene and tobacco on risk of tobacco-related cancer remained statistically significant.

Because alcohol may enhance the deleterious effect of β-carotene in smokers *(8,12)*, we adjusted for alcohol intake. However, we could not test an interaction with high alcohol intake in our population of only low- to moderate-consumption drinkers. Associations between tobacco-related cancer risk, β-carotene intake, and alcohol intake should be investigated in male populations, where the association between smoking and drinking is more common than in women.

Strengths of our study included careful adjustment for a large range of suspected confounders and the consistent results across all models. The intensity of tobacco consumption (in terms of quantity or duration of smoking) was slightly weaker among the second and third tertiles of dietary intake and among high β-carotene consumers than among low consumers, so that any residual confounding of tobacco is likely to have weakened rather than strengthened our findings. Analyses for broad sites were consistently homogeneous, which suggests that the observed interaction represents a general mechanism rather than a site-specific one.

Our results were consistent with the findings of previous studies that have reported a positive association between β- carotene intake and risk of some neoplasms in smokers *(6,7,9,10)* and with those that observed an interaction between β- carotene intake and smoking on the risk of some cancers or precancerous lesions *(12,27)*. In contrast, a pooled analysis of seven cohorts *(13)* and two intervention studies *(14,15)* did not observe a statistically significant interaction between β-carotene and smoking on cancer incidence. Reasons for these discrepancies may include higher intakes of β-carotene in the reference groups of studies with statistically nonsignificant fi ndings, lack of power for site-specific analyses, absence of simultaneous stratification by smoking and tobacco-related cancers, and differences in susceptibility by sex. Indeed, long-term follow-up of the Beta-Carotene and Retinol Efficacy Trial suggests a stronger association between β-carotene intake and risk of tobacco-related cancer in women than in men *(28)*, which, added to a higher supplement use *(29)*, may therefore represent a problem in view of the increasing exposure of women to tobacco. Our definition of high β-carotene intake was lower than that in intervention studies, in which participants took pharmacologic doses of supplements of approximately 20 mg per day. To date, it has been considered that only such pharmacologic doses of β-carotene are deleterious in association with tobacco *(30,31)*. However, doses of 20 mg can be achieved by the dietary intake of two or three carrots a day. Because our results are consistent with a recent case–control study of colorectal cancer suggesting an interaction between smoking and dietary β-carotene *(27)*, an interaction between tobacco and β-carotene may also occur at moderate levels of intake and not only at pharmacological doses.

Our results are consistent with the combined action of tobacco and β-carotene that has been described in experimental models. In a supplementation study, high β-carotene intake was associated with a decrease in DNA adduct levels in nonsmokers but with an increase in such adducts in smokers *(32)*. Suggested mechanisms for this effect are complex and debated *(33)*. In in vitro models, β-carotene may serve as an antioxidant or as a prooxidant, depending on the redox potential of the biologic environment in which it acts, as reviewed previously *(34)*. Although β-carotene exerts a growth inhibitory and proapopto - tic effect on malignant colonic cell lines *(35)*, it also enhances DNA oxidative damage and modifies p53-related pathways of cell proliferation and apoptosis when cells are exposed to tobacco smoke condensate *(36)*.

Although β-carotene may act as a cocarcinogen *(37)*, there is no evidence that smokers should

avoid consuming β- carotenerich foods such as fruit and vegetables, in which other components, such as vitamins C and E *(34)*, may counteract a potentially deleterious interaction of β-carotene with smoking. In our study, former smokers were more likely to take supplements than current or never smokers, as reported elsewhere *(29)*. This behavior, which may have been part of a healthier lifestyle for women who decided to stop smoking, may have unexpected adverse effects when supplements include β-carotene. In our study, not smoking and consuming relatively high doses of β-carotene were associated with the lowest level of risk of tobacco-related cancer, in agreement with ongoing public health advice.

In conclusion, the interaction between tobacco and β-carotene, which was initially described for lung cancer *(6–8)*, may extend to other tobacco-related cancers. In our cohort, tobacco-related cancers represented 23.0% of all cancers observed during the study period. This rate is slightly lower than the 30% reported in the literature *(21)* but consistent with the study population's relatively low exposure to tobacco. This proportion emphasizes the public health importance of our results. Because the observed interaction between β-carotene and smoking on tobacco-related cancer risk could strongly influence a global effect of β-carotene on risk of neoplasms, future studies on the effect of this nutri ent should include stratification by smoking status. In general, studies should systematically investigate potential interactions between nutrients and environmental or genetic factors *(38–40)*. Large-scale studies should further explore the effect of dose, du-ration, temporality, and sex on the interaction between smoking and β-carotene.

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Notes

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