ABSTRACT

Background: Alcohol intake is associated with increased circulating concentrations of sex hormones, which in turn may increase hormone-dependent cancer risk. This association may be modulated by dietary fiber intake, which has been shown to decrease steroid hormone bioavailability (decreased blood concentration and increased sex hormone–binding globulin concentration). However, this potential modulation has not been investigated in any prospective cohort.

Objectives: Our objectives were to study the relation between alcohol intake and the risk of hormone-dependent cancers (breast, prostate, ovarian, endometrial, and testicular) and to investigate whether dietary fiber intake modulated these associations.

Design: This prospective observational analysis included 3771 women and 2771 men who participated in the Supplément en Vitamines et Minéraux Antioxydants study (1994–2007) and completed at least 6 valid 24-h dietary records during the first 2 y of follow-up. After a median follow-up of 12.1 y, 297 incident hormone-dependent cancer cases, including 158 breast and 123 prostate cancers, were diagnosed. Associations were tested via multivariate Cox proportional hazards models.

Results: Overall, alcohol intake was directly associated with the risk of hormone-dependent cancers (tertile 3 vs. tertile 1: HR: 1.36; 95% CI: 1.00, 1.84; P-trend = 0.02) but not prostate cancer (P-trend = 0.3). In stratified analyses (by sex-specific median of dietary fiber intake), alcohol intake was directly associated with hormone-dependent cancer (tertile 3 vs. tertile 1: HR: 1.76; 95% CI: 1.10, 2.82; P-trend = 0.002), breast cancer (HR: 2.53; 95% CI: 1.30, 4.95; P-trend = 0.02), and prostate cancer (HR: 1.37; 95% CI: 0.65, 2.89; P-trend = 0.02) risk among individuals with low dietary fiber intake but not among their counterparts with higher dietary fiber intake (P-trend = 0.9, 0.8, and 0.6, respectively). The P-interaction between alcohol and dietary fiber intake was statistically significant for prostate cancer (P = 0.01) but not for overall hormone-dependent (P = 0.2) or breast (P = 0.9) cancer.

Conclusion: In line with mechanistic hypotheses and experimental data, this prospective study suggested that dietary fiber intake might modulate the association between alcohol intake and risk of hormone-dependent cancer. This trial was registered at clinicaltrials.gov as NCT00272428.

INTRODUCTION

Hormone-dependent cancers include cancer of the prostate and testis in men and breast, ovarian, and endometrial cancer in women. The sex steroid hormones, androgen, estrogen, and progesterin, are the primary modulators of both normal development and maintenance of these organs, as well as malignant growths. Increased concentrations of circulating estrogens and androgens have been related to a greater risk of hormone-dependent cancers (1–5).

Among other potentially procarcinogenic mechanisms, alcohol intake has been shown to increase circulating concentrations of steroid hormones and act on their receptors (6–13). The positive association between alcohol intake and breast cancer risk is now well established (13–15). In contrast, this association is less clear for other hormone-dependent cancers (16–21) and deserves further prospective investigation. Indeed, the level of proof regarding the association between prostate (18), ovarian (20), and endometrial (19) cancer and alcohol intake was qualified by the World Cancer Research Fund and the American Institute for Cancer Research as “limited—no conclusion.”

The simultaneous intake of nutritional bioactive compounds may modulate the association between alcohol and cancer risk. Dietary fibers represent a complex group of molecules that includes nonstarch polysaccharides (cellulose, hemicelluloses, pectins, chitins, and hydrocolloids such as gums, mucilages, and gums), oligosaccharides (inulin, α-galactosides, fructooligosaccharides, and galacto-oligosaccharides), resistant starch, resistant dextrins, and other compounds associated with dietary fiber polysaccharides such as lignin and waxes (22). Dietary fibers are good candidates for this potential modulatory role (9), because epidemiologic and experimental data showed that they may reduce concentrations of circulating estrogens and androgens through various mechanisms (9, 23–28). This is one of the

Keywords: alcohol, breast cancer, dietary fiber, hormone-dependent cancer, prospective study, prostate cancer

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mechanistic hypotheses that support the protective effect of dietary fiber intake on breast and prostate cancer risk observed in several cohorts (29–32). To our knowledge, no prospective study on alcohol consumption and hormone-dependent, breast, or prostate cancer risk has investigated a potential modulation of these relations by dietary fiber intake.

Thus, our objectives were to prospectively investigate the association between alcohol intake and hormone-dependent cancer risk (overall, breast, and prostate cancers) and to explore its potential modulation by dietary fiber intake.

METHODS

Study population

The Supplémentation en Vitamines et Minéraux Antioxydants (SU.VI.MAX) study was a population-based, double-blind, placebo-controlled, randomized trial (registered at clinicaltrials.gov as NCT00272428) initially designed to assess the effect of a daily antioxidant supplementation on the incidence of cardiovascular disease and cancer (33). A total of 13,017 subjects were enrolled in 1994–1995. All participants took a single daily capsule containing a combination of 120 mg ascorbic acid, 30 mg vitamin E, 6 mg selenium, and 100 μg zinc or a placebo. The intervention study lasted 8 y, and observational follow-up of health events was maintained until September 2007. Subjects provided written informed consent, and the study was approved by the Ethics Committee for Studies with Human Subjects at the Paris-Cochin Hospital (no. 706) and the Commission Nationale de l’Informatique et des Libertés (no. 334641).

Dietary data collection

During follow-up, participants were invited to complete a dietary record every 2 mo, in which they reported all foods and beverages consumed during a period of 24 h. These dietary records were randomly distributed between week and weekend days and over all seasons to take into account intraindividual variability. Dietary records from the first 2 y of follow-up were used in the present study to comply with its prospective design. Food record completion was done through the Minitel Telematic Network, a French telephone-based terminal that was an Internet prototype. Portion sizes were assessed via a validated picture booklet (34), and the amounts consumed from composite dishes were estimated by using French recipes validated by food and nutrition professionals. The mean daily energy, alcohol, dietary fiber, and other nutrient intakes were estimated by using a published French food composition table (35). Total dietary fiber content was obtained by using the Association of Official Analytic Chemists method (36). Dietary fiber intakes in the SU.VI.MAX study have been described previously (30, 31, 37).

Data collection for covariates

At enrollment, self-administered questionnaires were filled by participants, reporting sociodemographic characteristics (sex, date of birth, and educational level); smoking status; medication use (including baseline use of hormonal treatment of menopause); number of live births; family history of overall, breast, and prostate cancer; and menopausal status. Baseline physical activity was self-reported by asking the participants if they currently practiced a physical activity on a regular basis and, if yes, if it was equivalent to 1 h of walking/d or more/less. Anthropometric measurements were taken during a baseline clinical examination. Weight was measured to the nearest 0.1 kg with an electronic scale (Seca) by study nurses and physicians. Subjects wore light clothing and no shoes. Height was measured to the nearest 1 cm with a wall-mounted stadiometer under the same conditions. A 35-mL fasting venous blood sample was collected in evacuated tubes. These plasma samples were used to determine the baseline concentrations of selenium and total prostate-specific antigen measured by immunoassay (Roche Diagnostics).

Case ascertainment

Health events occurring during the follow-up were self-reported by participants. Medical data were then requested from participants, physicians, and/or hospitals and reviewed by an independent physician expert committee. Pathologic reports were used to validate the cases and to extract cancer type characteristics. Cases were classified by using the International Chronic Disease Classification, 10th Revision, Clinical Modification (38). All incident first primary hormone-dependent cancers were considered as cases in this study: breast (in women), prostate, ovarian, endometrial, and testicular cancer.

Statistical analyses

From the 13,017 participants in the SU.VI.MAX study, 161 were excluded because they had reported a cancer diagnosis before the start of the follow-up. Among the remaining participants, 6542 provided at least 6 valid 24-h dietary records within the first 2 y of follow-up and thus were available for analysis. For all covariates, <5% of values were missing and were replaced by the respective mode value.

Baseline characteristics of participants were compared between cases and noncases by using $X^2$ tests or Student’s $t$ tests, as appropriate.

HRs and 95% CIs obtained from Cox proportional hazards models with age as the primary time variable were used to characterize the association between tertiles of alcohol intake and risk of incident hormone-dependent (all sites), breast, and prostate cancer. Participants contributed person-time until the date of diagnosis of the studied cancer type (overall hormone-dependent, breast, or prostate), the date of the last completed questionnaire, the date of death, or September 2007, whichever occurred first. Participants who reported another cancer than the one studied during the study period were included and censored at the date of that diagnosis (except for basal cell carcinoma, which was not considered cancer). We confirmed that the assumptions of proportionality were satisfied through examination of the log-log (survival) vs. log-time plots. Tests for linear trend were performed by using the ordinal score of tertiles of alcohol intake. Multivariate models were adjusted for age (time scale in the Cox model), sex (for overall hormone-dependent cancers only), active intervention group in the SU.VI.MAX trial (yes/no), number of dietary records (continuous), height (continuous), BMI (in kg/m²; $<25$, $≥25$ to $<30$, or $≥30$), physical activity (irregular or $<1$ or $≥1$ h/d walking or equivalent), smoking status (never, former, or current), educational level (primary, secondary, or university),
mean daily dietary fiber intake (continuous), mean daily energy intake without alcohol (continuous), and first-degree family history of cancer (overall, breast, or prostate) (yes or no). For breast cancer analyses, additional adjustments were performed for baseline menopausal status (yes or no), use of hormonal treatment of menopause (yes or no), and number of live births (continuous). For prostate cancer analyses, additional adjustment was performed for baseline prostate-specific antigen concentration (continuous).

Interaction between dietary fiber intake (< vs. ≥ sex-specific population median) and alcohol intake (tertiles) was tested by introducing an interaction term into the models (product of the 2 variables). Analyses were conducted overall and then stratified by dietary fiber intake.

Models were also computed separately for premenopausal and postmenopausal breast cancer (women contributed to the premenopausal model until their age of menopause, and conversely, women contributed to the postmenopausal model from their age of menopause). Sensitivity analyses were performed by excluding heavy drinkers (>100 g alcohol/d) and cancers diagnosed during the first 2 y of follow-up. Further adjustment for a “healthy” food pattern was also tested. This dietary pattern was extracted by principal component analysis, by using the SAS “proc factor” procedure, from the mean intakes of 31 food groups across all 24-h records collected during the first 2 y of the study. Additional adjustments were also tested for dietary intake of total fat for women and for dietary intake of calcium, processed meat, tomato-based products, and vitamin E and plasma selenium concentration for men (continuous).

All tests were 2-sided, and \( P < 0.05 \) was considered statistically significant. SAS version 9.3 (SAS Institute) was used for analyses.

RESULTS

Mean follow-up time was 12.1 y. Of the subjects, 5.2% were lost to follow-up. A total of 297 incident hormone-dependent cancer cases were diagnosed during the follow-up: 158 breast (40 premenopausal and 118 postmenopausal), 123 prostate, and 16 other hormone-dependent cancers (11 ovarian and 5 endometrial). No case of testicular cancer was diagnosed. Mean age at diagnosis was 56.2 y for breast cancer and 63.1 for prostate cancer. Among breast cancer cases, 58.9% were estrogen receptor positive, and 43.0% were progesterone receptor positive. Regarding histologic type of breast cancer, 62.0% were ductal, 14.6% were lobular, and 23.4% were other types. Among prostate cancer cases, 5.1% had a Gleason score between 2 and 4, 87.2% between 5 and 7, and 7.7% between 8 and 10. The exposures of interest were as follows: 81% of alcohol intake came from wine (red, white, or rosé), 9% from beer and cider, and 10% from spirits (data not shown). Sources of dietary fibers were cereals (38.0%), vegetables (22.2%), fruit (21.2%), and legumes (6.1%). Of the dietary fibers, 20.1% were soluble and 79.8% were insoluble.

Characteristics of the subjects are presented in Table 1. Compared with noncases, subjects with hormone-dependent cancer tended to be older, were more frequently obese, had more family history of cancer, were more frequently menopausal at baseline, and took more hormonal treatment of menopause (for women).

Associations between tertiles of alcohol intake and overall hormone-dependent, breast, and prostate cancer risks are presented in Table 2. Tertiles of alcohol intake were directly associated with hormone-dependent (tertile 3 vs. tertile 1: HR: 1.36; 95% CI: 1.00, 1.84; \( P_{\text{trend}} = 0.02 \)) and breast (HR: 1.70; 95% CI: 1.11, 2.61; \( P_{\text{trend}} = 0.04 \)) cancer risks, whereas no statistically significant association was observed for prostate cancer (\( P_{\text{trend}} = 0.3 \)).

Results for the associations between tertiles of alcohol intake and overall hormone-dependent, breast, and prostate cancer risks stratified by dietary fiber intake are shown in Table 3. Although the \( P \)-interaction between alcohol and dietary fiber intake was statistically significant for prostate cancer (\( P = 0.01 \)) but not for overall hormone-dependent (\( P = 0.2 \)) or breast (\( P = 0.9 \)) cancer, differential results were observed across dietary fiber strata. Indeed, alcohol intake was directly associated with hormone-dependent (\( P_{\text{trend}} = 0.002 \)), breast (\( P_{\text{trend}} = 0.02 \)), and prostate (\( P_{\text{trend}} = 0.02 \)) cancer risks among individuals with lower dietary fiber intake but not among those with higher dietary fiber consumption (\( P_{\text{trend}} = 0.9, 0.8, \) and 0.6, respectively), despite similar statistical power across fiber strata.

Similar results were observed when the stratification was performed by the median of soluble and insoluble fiber intake (data not tabulated): \( P_{\text{trend}} = 0.008 \) for hormone-dependent cancer, 0.04 for breast cancer, and 0.007 for prostate cancer in subjects with low soluble fiber intake, whereas the corresponding \( P \) values were 0.5, 0.3, and 0.4 in subjects with higher soluble fiber intake. Similarly, \( P_{\text{trend}} = 0.01 \) for hormone-dependent cancer, 0.02 for breast cancer, and 0.01 for prostate cancer in subjects with low insoluble fiber intake, whereas the corresponding \( P \) values were 0.5, 0.5, and 0.6 in subjects with higher insoluble fiber intake.

Also, similar results were observed regarding breast cancer risk when analyses were restricted to postmenopausal women: alcohol intake was directly associated with breast cancer risk among subjects with lower dietary fiber intake (tertile 3 vs. tertile 1: HR: 2.39; 95% CI: 1.10, 5.18; \( P_{\text{trend}} = 0.06 \)), whereas no association was observed among those with higher dietary fiber intake (\( P_{\text{trend}} = 0.3 \)). The statistical power was insufficient to perform such an analysis in premenopausal women.

Further adjustments for a healthy dietary pattern (all models), for fat intake (breast cancer models), or for dietary intake of calcium, processed meat, tomato products, vitamin E, and plasma selenium concentration (prostate cancer models) provided similar results (data not shown). Sensitivity analyses excluding cancer cases diagnosed within the first 2 y of follow-up (26 hormone-dependent, 21 breast, and 5 prostate cancer cases) did not modify the findings, nor did sensitivity analyses excluding subjects who consumed more than 100 g/d alcohol (heavy drinkers, \( n = 39 \)).

DISCUSSION

This prospective study confirmed the direct association between alcohol intake and breast cancer risk. It also suggested that dietary fiber intake may modulate the association between alcohol intake and hormone-dependent cancers, which, to our knowledge, had never been investigated in any epidemiologic study, despite its mechanistic plausibility. Indeed, although the \( P \)-interaction was statistically significant only for prostate cancer, alcohol intake was directly associated with overall
The direct association between alcohol intake and increased breast cancer risk is now well established (13, 15, 39). Regarding prostate cancer, a nonlinear dose-response meta-analysis of 22 cohort and 50 case-control studies showed a statistically significant increased risk of alcohol intake of 25 and 50 g/d but not of 100 g/d (17). In the recent World Cancer Research Fund/American Institute for Cancer Research meta-analysis, which included all available prospective studies (21), the summary HR for prostate cancer risk was not significant for total alcohol intake, but a weak, significantly increased risk was observed for wine and spirits. There was statistical evidence of nonlinearity in

hormone-dependent, breast, and prostate cancer in subjects with low dietary fiber intake but not in subjects with higher dietary fiber intake.

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We observed a direct association between total alcohol intake and prostate cancer risk in men with higher alcohol intake but not in men with alcohol intake below the population median. The potential modulation of the relation between alcohol and hormone-dependent cancer risk by dietary fiber intake is in line with our initial hypothesis and with mechanistic and experimental data. Dietary fibers are metabolized by gut microbiota and may influence hormone-sensitive cancer risk through decreased bioavailability of estrogens, which probably results from the beneficial influence of dietary fibers on insulin resistance [45] [insulin resistance being associated with a decrease in sex hormone–binding globulin concentrations (26) and thus decreased bioavailability of estrogens (44), which probably results from the beneficial influence of dietary fibers on insulin resistance (45)]. Several mechanisms may be involved in this phenomenon. First, dietary fibers are thought to modify the enterohepatic circulation of estrogens by decreasing the activity of the colonic β-D-glucuronidase, an enzyme allowing estrogens to reenter the circulation (25, 27). Thus, fewer estrogens reenter the circulation and more estrogens are excreted (27). Second, dietary fiber intake has been associated with increased sex hormone–binding globulin concentrations (26) and thus decreased bioavailability of estrogens (44), which probably results from the beneficial influence of dietary fibers on insulin resistance (45) [insulin resistance being associated with a decrease in sex hormone–binding globulin concentrations (44)]. Our results suggest that although alcohol may exert its carcinogenic effect via several plausible mechanisms [including a genotoxic effect of acetaldehyde, a role as a solvent for tobacco carcinogens, and via the production of reactive oxygen species and nitrogen species (6)], its capacity to increase circulating steroid hormone concentrations (6–13) probably plays a central role in hormone-dependent cancer etiology (1–5).

Strengths of our study pertained to its prospective design with long follow-up, its originality with respect to existing literature, and precise assessment of dietary intake based on at least six 24-h dietary records. However, several limitations should be acknowledged. First,
the relatively small number of cases may have limited our ability to detect some of the hypothesized associations. The number of cancer cases was not sufficient to perform specific analyses for each breast cancer type (receptor status and histologic type) or according to the Gleason score for prostate cancer. Second, the observed relations could be affected by unmeasured or residual confounding. Some behavioral/environmental factors could not be taken into account in this study because of a lack of data (e.g., exposure to ionizing or ultraviolet radiation). However, most pertinent behavioral risk factors (i.e., other dietary factors, weight status, smoking habits, and physical activity) were taken into account in our study. Thus, it is unlikely that residual confounding entirely explains the observed associations.

Next, dietary fiber refers to a complex group of molecules, and all types of fibers may not have the same properties with regard to modulation of cancer risk. For instance, it has been suggested that oligosaccharides and resistant starch are involved in anti-inflammatory pathways through interaction with gut microflora, resulting in the production of short-chain fatty acids and reinforcement of the intestinal barrier (46–48). However, the reference method used to quantify total dietary fiber in our study did not allow the measurement of oligosaccharides and provided only a very limited measure of dietary resistant starch (no measure of native and physically inaccessible resistant starch) (36). We can hypothesize that the modulatory effect of dietary fiber on the alcohol-cancer relations suggested by our findings would be even stronger if all types of dietary fiber were better taken into account by more precise analytic methods. Besides, nutrient composition data did not allow us to distinguish the different types of fiber in the analyses (nonstarch polysaccharides, oligosaccharides, resistant starch, lignin, etc.). We observed similar results for soluble and insoluble fibers. However, beyond this aspect, information on specific types of fiber and/or their fermentation properties would have been more informative but was not available. Finally, subjects were volunteers involved in a long-term nutrition study and thus had more health-conscious behaviors than the general French population, such as lower tobacco use [13% vs. 34% current smokers (49)]. However, their dietary fiber intake (mean: 19 g/d) was similar to the one observed in a French nationally representative survey (19.0 g/d in adults aged 55–79 y) (50).

**TABLE 3**

Associations between tertiles of alcohol intake and overall hormone-dependent, breast, and prostate cancer risk, stratified by median of dietary fiber intake, SU.VI.MAX cohort, France, 1994–2007

<table>
<thead>
<tr>
<th>Cases/noncases, n</th>
<th>HR (95% CI)</th>
<th>P-trend</th>
<th>P-interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone-dependent cancers (n = 297)(^1)</td>
<td></td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>Dietary fiber intake &lt; median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 28/1020</td>
<td>1</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>T2 58/984</td>
<td>2.27 (1.43, 3.59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 59/1121</td>
<td>1.76 (1.10, 2.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dietary fiber intake ≥ median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 47/1085</td>
<td>1</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>T2 54/1085</td>
<td>1.09 (0.74, 1.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 51/950</td>
<td>1.12 (0.74, 1.70)</td>
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</tr>
<tr>
<td>Breast cancer (n = 158)(^4)</td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>Dietary fiber intake &lt; median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 13/634</td>
<td>1</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>T2 24/550</td>
<td>2.25 (1.13, 4.47)</td>
<td></td>
<td></td>
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<tr>
<td>T3 35/629</td>
<td>2.53 (1.30, 4.95)</td>
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<tr>
<td>Dietary fiber intake ≥ median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 23/587</td>
<td>1</td>
<td>0.8</td>
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</tr>
<tr>
<td>T2 31/652</td>
<td>1.13 (0.65, 1.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 32/561</td>
<td>1.24 (0.70, 2.19)</td>
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<tr>
<td>Prostate cancer (n = 123)(^5)</td>
<td></td>
<td></td>
<td>0.01</td>
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<tr>
<td>Dietary fiber intake &lt; median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 13/388</td>
<td>1</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>T2 30/438</td>
<td>2.45 (1.23, 4.87)</td>
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<tr>
<td>T3 23/493</td>
<td>1.37 (0.65, 2.89)</td>
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<tr>
<td>Dietary fiber intake ≥ median</td>
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<tr>
<td>T1 22/500</td>
<td>1</td>
<td>0.6</td>
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<tr>
<td>T2 17/439</td>
<td>0.71 (0.37, 1.37)</td>
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</tr>
<tr>
<td>T3 18/390</td>
<td>0.76 (0.38, 1.51)</td>
<td></td>
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</tr>
</tbody>
</table>

\(^1\)From multivariate Cox proportional hazards models. Cutoffs for tertiles of alcohol intake were 3.0 and 12.1 g/d for women and 15.3 and 35.4 g/d for men. Median of mean daily dietary fiber intake was 16.8 g/d for women and 20.5 g/d for men. SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants; T, tertile.

\(^2\)Between alcohol and dietary fiber intakes.

\(^3\)Adjusted for age, sex, active intervention group during SU.VI.MAX trial, number of dietary records, smoking status, educational level, physical activity, height, BMI, family history of cancer, energy intake without alcohol, and dietary fiber intake.

\(^4\)Same adjustment + menopausal status at baseline, use of hormonal treatment of menopause at baseline, number of live births, and family history of breast (instead of overall) cancer.

\(^5\)Same adjustment + baseline prostate specific antigen concentration and family history of prostate (instead of overall) cancer.
In conclusion, this prospective study suggested that dietary fiber intake may modulate the associations between alcohol intake and hormone-dependent, breast, and prostate cancer risks, with a statistically significant interaction for prostate cancer. Mechanistic data support this epidemiologic result: dietary fibers may contribute to counteract the procarcinogenic increase in circulating sex hormones induced by alcohol intake. These results provide useful insights to better understand the etiologic involvement of alcohol in carcinogenesis and may contribute to explain the contrasted findings of some prior prospective studies investigating alcohol intake and cancer risk. From a public health standpoint, these findings also suggest that several risk factors (such as alcohol consumption and low dietary fiber intake) may cumulate and act in synergy to increase cancer risk. Further experimental data and large prospective cohorts are needed to confirm these results.

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The authors were responsible for the final content; and all authors: read and interpreted and revised each draft for important intellectual content; MT: PF, PL-M, ND-P, LZ, LD, SH, PG, MD, and MT: contributed to the data collection and analysis; and Rachida Mehroug (logistics assistant) for their technical contribution to the SU.VI.MAX study.

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