Intake of specific carotenoids and essential fatty acids and breast cancer risk in Montreal, Canada

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ABSTRACT

Background: Evidence from previous investigations into the possible role of dietary and serum carotenoid concentrations in the etiology of breast cancer is inconsistent. No study has examined the combined effect of carotenoids and essential fatty acids on the risk of breast cancer.

Objective: The objective was to assess the possible association between specific and total carotenoids and breast cancer risk and to evaluate the effect modification by diet-related fatty acids and lifestyle factors in the development of breast cancer.

Design: A population-based case-control study involving 414 incident cases and 429 controls was conducted in French Canadians in Montreal. Dietary intake was estimated with the use of a validated food-frequency questionnaire in face-to-face interviews.

Results: No significant association was apparent between any of the individual or total carotenoids and the risk of breast cancer after adjustment for major underlying determinants of breast cancer. In premenopausal women who ever smoked, an increased risk was related to α-carotene [odds ratio (OR) for the upper relative to the lowest quartiles of intake: 2.40; 95% CI: 0.90, 6.41; \( P \) for trend = 0.046]. Conversely, a reduced risk was related to β-carotene (OR: 0.57; 95% CI: 0.26, 1.24; \( P \) for trend = 0.05) in women who never used hormone replacement therapy. In postmenopausal women, total carotenoids were positively associated with breast cancer risk in those with a high arachidonic acid intake (OR: 1.92; 95% CI: 0.93, 3.94; \( P = 0.028 \) for trend) and inversely associated in those with a high docosahexaenoic acid intake (OR: 0.52; 95% CI: 0.25, 1.07; \( P \) for trend = 0.054).

Conclusion: These findings suggest that the combined high intake of total carotenoids and docosahexaenoic acid may reduce the risk of breast cancer.

KEY WORDS Breast cancer, carotenoids, case-control study, fatty acids, food intake, prevention, French Canadians

INTRODUCTION

Breast cancer is the second leading cause of cancer-related deaths in women in most industrialized countries. The incidence of this disease in women in Western countries is 5 times that in women in developing countries and Japan (1). In Canada, breast cancer is the most common type of cancer in women, with an age-standardized incidence rate of 103 per 100,000, or 30% of all cancers in women. In 2002, 20,700 new cases and 5400 deaths were attributed to breast cancer (2).

The risk factors for breast cancer include age (3), early menarche (4), late age at menopause (5) and at first full-term pregnancy (3), nulliparity (6), and alcohol consumption (7, 8). Inverse associations with physical activity (7, 9) and breastfeeding (10) have been found.

There is compelling evidence that carotenoids play a role in the etiology of breast cancer. Although research on breast cancer prevention has focused intensively on these micronutrients, the mechanisms involved in their reported cancer-preventing activity are not fully understood (11).

Carotenoids include a large array of substances with different biological properties. Besides their overall influence on enhancement of immune function, cellular protection against DNA damage, stimulation of gap junctions intercellular communication, induction of detoxifying enzymes, and inhibition of cellular proliferation (12, 13), it has been shown that they also have specific activities. α-Carotene may decrease the activity of cytochrome P450 1AA, an activator of procarcinogens (14). β-Carotene is effective in protecting lipid membranes from damage by free radicals and reactive species. Lycopene is the most efficient quencher of singlet oxygen species, lutein and zeaxanthin are scavengers of radical oxygen species (15), and β-cryptoxanthin may stimulate the expression of RB (an antioncogene) and p73 (a p53-related gene) (16).

Many previous investigations that examined the influence of dietary intake or serum concentrations of carotenoids on the development of breast cancer have yielded mixed results (17–19). Given the inconsistency of findings and continued interest in identifying modifiable risk factors for breast cancer, we carried out a population-based case-control study of specific carotenoids and the risk of breast cancer in French Canadians. French Canadians are a relatively homogeneous population with particular food habits (20), which differentiate them from their neighbors in North America. This investigation also examined the effect modification by diet-related fatty acids, because the antioxidant in-
fluences of carotenoids and the susceptibility of these fatty acids to lipid peroxidation suggest interactive biological activities. Finally, we assessed possible associations between breast cancer risk and lifestyle factors, such as smoking, because free radicals in cigarette smoke can alter the concentrations of most carotenoids (21).

SUBJECTS AND METHODS

Study population
The procedures used to obtain cases and controls for this investigation were described elsewhere (22). Briefly, between 1989 and 1993, all patients aged 35–79 y with a histologic diagnosis of breast cancer were identified through the admission offices of 3 major teaching hospitals of the Réseau Interhospitalier de Cancérologie de l’Université de Montréal. When an eligible case was identified, the attending surgeon or physician was approached for permission to interview the patient. If permission was granted, the patient was contacted by letter and followed up with a telephone call to arrange an interview. A total of 935 breast cancer cases were identified, of which 396 (42%) were ineligible for inclusion in the study for various reasons: 62 (7%) because of age, 286 (30%) because they lived outside the study region, 37 (4%) because they had another type of primary cancer or an incorrect diagnosis, and 11 (1%) because they died before the interview. Thus, there were 539 eligible cases, which represented 58% of all cases identified. Of these eligible patients, 72 (13%) refused to participate, 45 could not obtain their doctor’s consent (8%), 6 had a change of address and were unable to be contacted (1%), and 2 had a change in diagnosis (1%) after the interview. Ultimately, 414 cases were interviewed, which represented a response rate of 77% of eligible cases.

The controls were population-based and matched for age (±5 y in each age group) and place of residence. They were selected from the telephone directory in which the corresponding case was listed and were contacted with the use of a modified, random digit-dialing method. One page from the telephone directory was randomly chosen from the sampling frame, and the names and addresses of 10 persons with the same first 3 digits of the telephone number (of the 7-digit code) were selected for each case. The occupants of these residences were then contacted by telephone to determine whether the household contained someone who matched the index case for age and who agreed to be interviewed. If the telephone was not answered, the telephone number, the date, and the time of the call were recorded, and the same number was called 7 more times during the day, evening, or weekend before the number was rejected. Eligible and willing persons were interviewed at their homes. This procedure was repeated until enough controls were enrolled. If more than one eligible control was reached at a given number, this information was kept in a database for future use. All controls were interviewed within 3 mo after the matching cases were interviewed. This study was conducted in parallel with a similar investigation of colon and prostate cancer, and a common control population was selected. A total of 2085 controls were selected, of whom only 1361 (65%) fulfilled the eligibility criteria. A total of 171 (8%) household residents never answered the telephone, 335 (16%) refused to participate before the study was explained to them, and 167 (8%) refused to participate after the study was explained to them. Thus, a total of 668 subjects were interviewed, 429 of whom were women.

Data collection
For both cases and controls, interviews were conducted in the respondent’s home with the use of structured questionnaires administered in a standardized manner. If either the case or the control was hospitalized at the time of the scheduled interview and seemed unlikely to be available for home interview within 2 wk, an in-hospital interview was arranged. If the patient was very ill, whether at home or in the hospital, the interview was carried out in the presence and with the help of any family member or other person who was available and likely to have relevant information. No proxy interviews were performed. The core questionnaire collected data on lifestyle, occupation, education, drinking and smoking habits, medical history, history of weight changes, and family history of cancer.

Food intake
Food consumption data were obtained via a food-frequency questionnaire (FFQ) developed by the National Cancer Institute of Canada. The French version of the FFQ used in this study was modified by our unit for French Canadians. The FFQ was designed to collect quantitative information based on food models and qualitative data based on food habits and dietary patterns. It includes questions about >200 different food items and recipes as well as the frequency of consumption and amounts consumed. The FFQ covered a 2-y period before the diagnosis for cases and a corresponding period for the controls. This dietary questionnaire had been assessed for both reproducibility and validity (23).

Food grouping
In total, 985 separate food items, including brand names, were retrieved from the FFQ to estimate daily intakes of specific carotenoids with the use of the US Department of Agriculture–Nutrition Coordinating Center (USDA-NCC) Carotenoid Database (release 1998; Internet: http://www.nal.usda.gov/fnic/foodcomp/Data/car98/). This online database contains data on 218 foods and 6 specific carotenoids; it provides food composition values for specific carotenoids contained in food items assessed by the FFQ. Data on other nutrients, including total carotenoids, individual fatty acids, and total energy, were obtained via the Canadian Nutrient File (release 1991 and 1997). The major food sources of individual carotenoids in the diet of this French Canadian population were carrots, tomatoes and multifood component foods containing tomatoes (α-carotene); carrots and spinach (β-carotene); orange (β-cryptoxanthin); tomatoes and tomato products (lycopene); and broccoli and green-leaf vegetables (lutein and zeaxanthin).

Statistical analysis
Food intakes for the cases and controls were converted to specific carotenoid intakes based on the USDA-NCC Carotenoid Database. Median intakes were computed for cases and controls separately. To determine the associations between carotenoid intakes and breast cancer risk, the study subjects were divided into 4 categories according to quartiles of calorie-adjusted carotenoid intakes in the control population. Odds ratios (ORs) and 95% CIs were calculated by using categories of residuals from the regression of carotenoids on total energy intake (24) in un-
CAROTENOIDS, EFAs, AND BREAST CANCER RISK

RESULTS

The characteristics of the study population with respect to potential confounders are summarized in Table 1. The mean (±SD) age of the subjects was 55.03 ± 11.87 y for cases and 55.73 ± 12.18 y for the controls (data not shown), with the age distribution of cases and controls being similar. Family history of breast cancer in first-degree relatives as well as family history of benign breast disease in cases and controls indicated that the cases had a significantly higher proportion of first-degree relatives (mother, sisters, and daughters) with breast cancer (P = 0.005) and relatives with benign breast disease (P = 0.001). Cases were older at the time of the first full-term pregnancy than the controls (P = 0.023), whereas more controls were ever-married than were cases (P = 0.017). A higher proportion of full-term pregnancies was observed in the control group than in the cases (P = 0.002), whereas the use of oral contraceptives and hormone replacement therapy status were not significantly different between the study groups.

The ORs and 95% CIs for breast cancer risk according to specific carotenoid intakes are shown in Table 2. After adjustment for age at first full-term pregnancy, history of breast cancer in first-degree relatives, history of benign breast disease, number of full-term pregnancies, marital status, and total energy intake, no significant association was found between the risk of breast cancer and either specific carotenoid or total carotenoid intakes. The results did not change significantly when fiber intake was included in the models or when specific carotenoid intakes were adjusted mutually.

The multivariate-adjusted ORs and 95% CIs for breast cancer risk associated with specific carotenoid intakes according to high and low intakes of AA, eicosapentaenoic acid, and DHA are shown in Table 3. Only individual carotenoid intakes with significant or nearly significant associations with breast cancer risk are presented. A positive dose-response relation was evident between total carotenoid intake and breast cancer risk (OR: 1.92; 95% CI: 0.93, 3.94; P for trend = 0.028) in postmenopausal women with high AA intakes (P for interaction = 0.04).

In the women with a high DHA intake, total carotenoid intakes were linked with a significantly reduced postmenopausal breast cancer risk (OR: 0.52; 95% CI: 0.25, 1.07; P for trend = 0.054) in postmenopausal women only (P for interaction = 0.07). No significant association was found between any specific carotenoid intake and breast cancer risk in women with low or high intakes of linoleic or α-linolenic acid (data not shown).

The multivariate-adjusted ORs and 95% CIs for breast cancer risk associated with individual carotenoid intakes according to selected lifestyle factors are shown in Table 4. In the ever-smoker, premenopausal women, a strong positive dose-response relation was noted between α-carotene intake and breast cancer risk (OR: 2.40; 95% CI: 0.90, 6.41; P for trend = 0.046). A

### Table 1
Selected characteristics of the study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤44 y</td>
<td>79 [19]</td>
<td>79 [18]</td>
</tr>
<tr>
<td>45–49 y</td>
<td>69 [17]</td>
<td>67 [16]</td>
</tr>
<tr>
<td>50–54 y</td>
<td>66 [16]</td>
<td>62 [14]</td>
</tr>
<tr>
<td><strong>Family history of breast cancer in first-degree relatives</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>295 [71.3]</td>
<td>352 [82.4]</td>
</tr>
<tr>
<td>Yes</td>
<td>119 [28.7]</td>
<td>75 [17.6]</td>
</tr>
<tr>
<td><strong>Age at first full-term pregnancy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;22 y</td>
<td>60 [14]</td>
<td>84 [20]</td>
</tr>
<tr>
<td>22–24 y</td>
<td>96 [23]</td>
<td>86 [20]</td>
</tr>
<tr>
<td>≥30 y</td>
<td>50 [12]</td>
<td>44 [10]</td>
</tr>
<tr>
<td><strong>Oral contraceptive use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>199 [48]</td>
<td>207 [48]</td>
</tr>
<tr>
<td>Ever</td>
<td>215 [52]</td>
<td>222 [52]</td>
</tr>
<tr>
<td><strong>Number of full-term pregnancies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>72 [18]</td>
<td>59 [13]</td>
</tr>
<tr>
<td>2</td>
<td>100 [24]</td>
<td>100 [23]</td>
</tr>
<tr>
<td><strong>Hormone replacement therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>145 [35]</td>
<td>165 [38]</td>
</tr>
<tr>
<td>No</td>
<td>269 [65]</td>
<td>263 [62]</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>89 [21.5]</td>
<td>65 [15.2]</td>
</tr>
<tr>
<td>Ever married</td>
<td>325 [78.5]</td>
<td>364 [84.8]</td>
</tr>
</tbody>
</table>

1,2 Significantly different from cases (Mantel extension test or Student’s t test): 1 P < 0.005, 2 P < 0.05.
with any of the carotenoid intakes in postmenopausal women (36). Intakes in premenopausal women and no significant relation with cancer risk associated with association with lycopene intake in women of all ages (38) and postmenopausal women (37). Another case-control study noted an inverse relation individual carotenoid intakes, although most of them only dressed the association between breast cancer risk and diet-addition, a large number of epidemiologic studies have addressed the combined effect of total and individual carotenoid intakes and essential fatty acids on the risk of breast cancer, as we did. We observed that total carotenoid intakes were associated with a 1.92-fold greater risk of breast cancer in postmenopausal women with a high AA intake. The biological mechanisms of these effects are unclear, but lipid peroxidation products may play a role (40).

Our results provide support for effect modification via dietary intake of long-chain fatty acids. To the best of our knowledge, no other studies have addressed the combined effect of total and individual carotenoid intakes and essential fatty acids on the risk of breast cancer, as we did. We observed that total carotenoid intakes were associated with a 1.92-fold greater risk of breast cancer in postmenopausal women with a high AA intake. The biological mechanisms of these effects are unclear, but lipid peroxidation products may play a role (40).

The involvement of AA in eicosanoid synthesis has been well-documented (41). Moreover, AA is very susceptible to lipid peroxidation, and in vitro studies have shown that the secondary products of lipid peroxidation suppress mammary tumorigenic processes by causing an increased accumulation of these cytotoxic or cytostatic products in tumor tissue (42) or by creating intermolecular linkages, intramolecular linkages, or both between amino acid sulfhydryl groups of RNA, DNA, and proteins, which leads to the inactivation or damage of these molecules (43). The addition of high amounts of antioxidants to a medium increases the amount of lipid peroxidation products and simultaneously causes a substantial increase in tumor growth (44). With these mechanistic pathways in mind, it is possible that total

**DISCUSSION**

In this population-based case-control study, we observed no remarkable association between intake of any specific or total carotenoid intake and breast cancer risk. Our results agree with those of the Canadian National Breast Screening Study (18). In addition, a large number of epidemiologic studies have addressed the association between breast cancer risk and diet-related individual carotenoid intakes, although most of them only examined β-carotene. Eight previous prospective studies reported no statistically significant associations between breast cancer risk and dietary intakes of β-carotene or carotene (27–35). In contrast, one cohort study found a significantly reduced breast cancer risk associated with β-carotene or lutein and zeaxanthin intakes in premenopausal women and no significant relation with any of the carotenoid intakes in postmenopausal women (36). One case-control study observed a decreased risk of breast cancer with β-carotene and lutein and zeaxanthin intakes in premenopausal women (37). Another case-control study noted an inverse association with lycopene intake in women of all ages (38) and another showed no relation between breast cancer risk and α- and β-carotene, β-cryptoxanthin, lycopene, and lutein intakes (39).

<table>
<thead>
<tr>
<th>Carotenoid</th>
<th>Quartile of energy-adjusted carotenoid intake</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Carotene</td>
<td>Cases/controls (n)</td>
<td>112/107</td>
<td>108/107</td>
<td>80/108</td>
<td>114/107</td>
<td></td>
</tr>
<tr>
<td>β-Carotene</td>
<td>Median ± SD (µg/d)</td>
<td>2224 ± 1463</td>
<td>5123 ± 1476</td>
<td>8540 ± 1600</td>
<td>15309 ± 8543</td>
<td></td>
</tr>
<tr>
<td>β-Cryptoxanthin</td>
<td>Median ± SD (µg/d)</td>
<td>6.5 ± 11</td>
<td>34.7 ± 18</td>
<td>97.8 ± 29</td>
<td>223.4 ± 185</td>
<td></td>
</tr>
<tr>
<td>Lycopene</td>
<td>Median ± SD (µg/d)</td>
<td>629 ± 695</td>
<td>2614 ± 818</td>
<td>5814 ± 1314</td>
<td>12982 ± 7190</td>
<td></td>
</tr>
<tr>
<td>Lutein</td>
<td>Median ± SD (µg/d)</td>
<td>521 ± 286</td>
<td>1129 ± 292</td>
<td>2122 ± 426</td>
<td>4288 ± 2484</td>
<td></td>
</tr>
<tr>
<td>Zeaxanthin</td>
<td>Median ± SD (µg/d)</td>
<td>16 ± 16</td>
<td>63 ± 19</td>
<td>123 ± 26</td>
<td>254 ± 130</td>
<td></td>
</tr>
<tr>
<td>Total carotenoids</td>
<td>Median ± SD (RE/d)</td>
<td>257 ± 136</td>
<td>605 ± 172</td>
<td>1051 ± 172</td>
<td>2037 ± 1401</td>
<td></td>
</tr>
<tr>
<td>Cases/controls (n)</td>
<td>103/107</td>
<td>118/108</td>
<td>90/107</td>
<td>103/107</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivariate OR (95% CI)</td>
<td>1.00</td>
<td>0.94 (0.63, 1.38)</td>
<td>0.67 (0.45, 1.01)</td>
<td>0.99 (0.68, 1.46)</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Multivariate OR (95% CI)</td>
<td>1.00</td>
<td>1.38 (0.94, 2.04)</td>
<td>1.09 (0.68, 1.52)</td>
<td>0.99 (0.67, 1.48)</td>
<td>0.59</td>
<td></td>
</tr>
<tr>
<td>Multivariate OR (95% CI)</td>
<td>1.00</td>
<td>1.22 (0.81, 1.83)</td>
<td>0.98 (0.65, 1.47)</td>
<td>1.23 (0.82, 1.84)</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Multivariate OR (95% CI)</td>
<td>1.00</td>
<td>0.72 (0.48, 1.06)</td>
<td>0.75 (0.51, 1.10)</td>
<td>0.85 (0.58, 1.26)</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Multivariate OR (95% CI)</td>
<td>1.00</td>
<td>0.72 (0.48, 1.07)</td>
<td>0.88 (0.60, 1.29)</td>
<td>0.81 (0.55, 1.20)</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td>Multivariate OR (95% CI)</td>
<td>1.00</td>
<td>1.12 (0.76, 1.65)</td>
<td>0.83 (0.55, 1.24)</td>
<td>1.10 (0.74, 1.61)</td>
<td>0.92</td>
<td></td>
</tr>
<tr>
<td>Multivariate OR (95% CI)</td>
<td>1.00</td>
<td>1.22 (0.76, 1.65)</td>
<td>0.86 (0.57, 1.28)</td>
<td>0.96 (0.65, 1.43)</td>
<td>0.55</td>
<td></td>
</tr>
</tbody>
</table>

1 ORs and 95% CIs were derived from an unconditional logistic regression model adjusted for age at first full-term pregnancy, history of breast cancer in first-degree relatives, history of benign breast disease, number of full-term pregnancies, marital status, and total energy intake. RE, retinol equivalents.
TABLE 3

Odds ratios (and 95% CIs) for breast cancer risk associated with dietary carotenoids and long-chain fatty acids in premenopausal and postmenopausal women.

<table>
<thead>
<tr>
<th>Carotenoid</th>
<th>Quartile of carotenoid intake</th>
<th>1 (referent)</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low intake of arachidonic acid</td>
<td>α-Carotene</td>
<td>Premenopausal</td>
<td>1.00</td>
<td>1.02 (0.39, 2.65)</td>
<td>2.87 (0.92, 9.02)</td>
<td>2.16 (0.78, 6.00)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>1.00</td>
<td>1.59 (0.79, 3.20)</td>
<td>0.90 (0.45, 1.83)</td>
<td>2.38 (1.18, 4.78)</td>
<td>0.070</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P for interaction = 0.69</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zeaxanthin</td>
<td>Premenopausal</td>
<td>1.00</td>
<td>1.79 (0.62, 5.19)</td>
<td>1.90 (0.69, 5.20)</td>
<td>2.94 (1.00, 8.68)</td>
<td>0.055</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>1.00</td>
<td>1.44 (0.74, 2.80)</td>
<td>0.77 (0.36, 1.64)</td>
<td>1.65 (0.83, 3.29)</td>
<td>0.371</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P for interaction = 0.34</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total carotenoids</td>
<td>Premenopausal</td>
<td>1.00</td>
<td>1.04 (0.39, 2.78)</td>
<td>1.97 (0.70, 5.54)</td>
<td>2.08 (0.73, 5.92)</td>
<td>0.108</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>1.00</td>
<td>1.19 (0.61, 2.32)</td>
<td>0.92 (0.45, 1.89)</td>
<td>2.13 (1.07, 4.24)</td>
<td>0.064</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P for interaction = 0.04</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High intake of arachidonic acid</td>
<td>α-Carotene</td>
<td>Premenopausal</td>
<td>1.00</td>
<td>0.93 (0.36, 2.45)</td>
<td>0.79 (0.28, 2.25)</td>
<td>1.01 (0.35, 2.91)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>1.00</td>
<td>1.59 (0.75, 3.35)</td>
<td>1.71 (0.80, 3.62)</td>
<td>1.83 (0.90, 3.71)</td>
<td>0.119</td>
<td></td>
</tr>
<tr>
<td>Zeaxanthin</td>
<td>Premenopausal</td>
<td>1.00</td>
<td>2.48 (0.78, 7.89)</td>
<td>2.08 (0.72, 6.01)</td>
<td>1.72 (0.58, 5.12)</td>
<td>0.473</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>1.00</td>
<td>1.14 (0.59, 2.22)</td>
<td>1.51 (0.73, 3.11)</td>
<td>0.99 (0.51, 1.95)</td>
<td>0.828</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P for interaction = 0.43</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total carotenoids</td>
<td>Premenopausal</td>
<td>1.00</td>
<td>1.15 (0.43, 3.09)</td>
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<td>0.86 (0.41, 1.78)</td>
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<td>1.00</td>
<td>0.73 (0.24, 2.25)</td>
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<td>1.17 (0.45, 3.02)</td>
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<td>1.00</td>
<td>1.17 (0.58, 2.35)</td>
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<tr>
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<td>Premenopausal</td>
<td>1.00</td>
<td>1.31 (0.40, 4.25)</td>
<td>1.44 (0.44, 4.67)</td>
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<td>0.699</td>
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<td>High intake of eicosapentaenoic acid</td>
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<td>Premenopausal</td>
<td>1.00</td>
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<td>0.28 (0.09, 0.84)</td>
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<td>Premenopausal</td>
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<td>1.18 (0.44, 3.19)</td>
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<tr>
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<td>1.36 (0.62, 3.02)</td>
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<td>Premenopausal</td>
<td>1.00</td>
<td>2.20 (0.76, 6.35)</td>
<td>1.06 (0.39, 2.89)</td>
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<td>0.65 (0.32, 1.30)</td>
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<td>Total carotenoids</td>
<td>Premenopausal</td>
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<td>1.37 (0.52, 3.63)</td>
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<td>High intake of docosahexaenoic acid</td>
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<td>Premenopausal</td>
<td>1.00</td>
<td>2.25 (0.76, 6.67)</td>
<td>1.66 (0.60, 4.66)</td>
<td>3.28 (1.15, 9.31)</td>
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<td>1.00</td>
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<td>Premenopausal</td>
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<td>0.59 (0.19, 1.84)</td>
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<td>0.706</td>
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<td>Total carotenoids</td>
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<td>0.71 (0.34, 1.50)</td>
<td>0.45 (0.21, 0.98)</td>
<td>0.52 (0.25, 1.07)</td>
<td>0.054</td>
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</table>

1 Odds ratios and 95% CIs were derived from an unconditional logistic regression model adjusted for age at first full-term pregnancy, history of breast cancer in first-degree relatives, history of benign breast disease, number of full-term pregnancies, marital status, and total energy intake. P values for the three-factor interactions were obtained from a likelihood ratio test with 3 df. None of the two-factor interactions were significant.
carotenoid intakes, rather than intakes of any specific carotenoid alone, present the most effective protection for AA against lipid peroxidation in postmenopausal women, because a significant, direct, dose-dependent gradient was found with breast cancer risk in those women with a high AA intake. A decreased risk of breast cancer associated with AA intake in postmenopausal women with a low vitamin E intake and an increased risk in those with a high vitamin E intake were reported by our group in a case-control study (45).

Our findings also provide support for effect modification by smoking and hormone replacement therapy. Smoking increased the breast cancer risk linked with specific carotenoid intakes, although the association was statistically significant only for α-carotene. It was shown previously that active and passive smokers are exposed to reactive free radicals present in cigarette smoke (46). Free radicals in cigarette smoke alter the concentrations of most carotenoids, and, compared with nonsmokers, active smokers have circulating concentrations of α- and β-carotene and β-cryptoxanthin (21) that are 25% lower, even after adjustment for dietary intake of carotenoids (47).

Hormone replacement therapy did not affect circulating concentrations of β-carotene, the total antioxidant capacity of plasma, or lipid peroxidation in postmenopausal women (48). We found a 43% reduction in premenopausal breast cancer risk

The table below shows the Odds ratios (and 95% CIs) for breast cancer risk associated with dietary carotenoids and selected lifestyle factors for premenopausal and postmenopausal women.

<table>
<thead>
<tr>
<th>Carotenoid</th>
<th>Quartile of carotenoid</th>
<th>1 (referent)</th>
<th>2</th>
<th>3</th>
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<th>P for trend</th>
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<tr>
<td>Smoking, ever</td>
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<td>α-Carotene</td>
<td>Premenopausal</td>
<td>1.00</td>
<td>1.27 (0.50, 3.26)</td>
<td>2.11 (0.75, 5.96)</td>
<td>2.40 (0.90, 6.41)</td>
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<td>0.75 (0.38, 1.47)</td>
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<td>1.14 (0.57, 2.28)</td>
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<tr>
<td>Smoking, never</td>
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<td>α-Carotene</td>
<td>Premenopausal</td>
<td>1.00</td>
<td>0.96 (0.38, 2.48)</td>
<td>0.62 (0.21, 1.86)</td>
<td>1.78 (0.60, 5.28)</td>
<td>0.533</td>
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<tr>
<td>Postmenopausal</td>
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<td>0.72 (0.34, 1.52)</td>
<td>0.85 (0.40, 1.80)</td>
<td>0.97 (0.49, 1.94)</td>
<td>0.810</td>
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<tr>
<td>Oral contraceptive use, yes</td>
<td>α-Carotene</td>
<td>Premenopausal</td>
<td>1.00</td>
<td>0.98 (0.46, 2.10)</td>
<td>1.73 (0.75, 3.99)</td>
<td>0.91 (0.40, 2.05)</td>
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<tr>
<td>Postmenopausal</td>
<td>1.00</td>
<td>0.61 (0.26, 1.43)</td>
<td>0.51 (0.22, 1.20)</td>
<td>1.07 (0.48, 2.38)</td>
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<tr>
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<td>α-Carotene</td>
<td>Premenopausal</td>
<td>1.00</td>
<td>0.61 (0.28, 1.33)</td>
<td>1.10 (0.49, 2.50)</td>
<td>1.13 (0.50, 2.54)</td>
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<tr>
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<td>1.00</td>
<td>1.19 (0.51, 2.74)</td>
<td>1.68 (0.70, 4.03)</td>
<td>1.95 (0.84, 4.49)</td>
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<td>Hormone replacement therapy, yes</td>
<td>β-Carotene</td>
<td>Premenopausal</td>
<td>1.00</td>
<td>0.98 (0.28, 6.35)</td>
<td>2.34 (0.33, 16.40)</td>
<td>4.74 (0.98, 22.94)</td>
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<td>1.35 (0.72, 2.53)</td>
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<td>1.11 (0.61, 2.04)</td>
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<td>1.65 (0.29, 9.30)</td>
<td>7.16 (1.01, 50.81)</td>
<td>5.32 (0.78, 36.08)</td>
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<td>1.00</td>
<td>1.55 (0.85, 2.84)</td>
<td>0.93 (0.51, 1.72)</td>
<td>0.80 (0.43, 1.48)</td>
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<td>1.36 (0.22, 8.29)</td>
<td>3.95 (0.68, 22.77)</td>
<td>12.50 (1.68, 93.20)</td>
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<td>0.26 (0.01, 5.87)</td>
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<td>0.99 (0.48, 2.06)</td>
<td>0.95 (0.45, 2.01)</td>
<td>0.90 (0.44, 1.82)</td>
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<tr>
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<td>1.30 (0.64, 2.64)</td>
<td>0.60 (0.28, 1.31)</td>
<td>0.57 (0.26, 1.24)</td>
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<td>1.32 (0.68, 2.58)</td>
<td>1.16 (0.58, 2.32)</td>
<td>0.917</td>
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</table>

Odds ratios and 95% CIs were derived from an unconditional logistic regression model adjusted for age at first full-term pregnancy, history of breast cancer in first-degree relatives, history of benign breast disease, number of full-term pregnancies, marital status, and total energy intake. P values for the three-factor interactions were obtained from a likelihood ratio test with 3 df. None of the two-factor interactions were significant.
associated with β-carotene in women who did not receive hormone replacement therapy. Although chance could have played a role, further evaluation is needed to clarify the underlying mechanisms of this association. Our results, however, differ from those of Terry et al (18) and Cho et al (35). Terry et al (18) reported no remarkable association between intakes of any specific carotenoids and breast cancer risk in the total group or in subgroups defined by smoking status, BMI, menopausal status, family history of breast cancer, and intakes of total fat, energy, alcohol, or folic acid. Cho et al (35) found that intakes of α-carotene and total carotenoids were related to a significant reduction in premenopausal breast cancer risk in smokers but not in nonsmokers.

The major strengths of our investigation are that it focused on French Canadians, a relatively stable and homogeneous North American population with similar lifestyle, food habits and food patterns that distinguish them from their neighbors (20). Its population-based design minimized the potential for biased selection of cases and controls. The participation rates in cases and controls were somewhat similar, and we have no reason to believe, however, that they were influenced differently by past diet. In addition, the cases were interviewed before the final diagnosis and major treatment of cancer.

However, our investigation had some limitations. The 2-y time interval between the interview and the retrospective assessment of diet may have been too long for the study subjects to accurately recall past dietary intakes; therefore, the influence of current diet on the memory of past intakes may have increases the potential for recall bias. However, because this method was used to collect information from both cases and controls, such a bias would not be great. Moreover, because a considerable number of tests was performed, the likelihood that some associations were found by chance could not be excluded completely. In addition to the incompleteness of the USDA-NCC Carotenoid Database, although the FFQ used in this study had been tested for validity and reproducibility for most macronutrients and some essential fatty acids, specific carotenoid intakes determined by the questionnaire had not been validated. However, any bias from these sources may have induced nondifferential misclassification regarding case-control status and reduced the potential to detect some relations. Furthermore, by stratifying for menopausal status, some associations may have been missed because of less-than-optimal sample sizes. These issues may have influenced the results of our study.

In conclusion, we found that a high intake of total carotenoids in combination with a high intake of DHA is associated with a reduced risk of breast cancer in postmenopausal women. As a whole, our data suggest that a diet with a high content of fruit, carotenoid-rich vegetables, and DHA-rich fish may reduce the whole, our data suggest that a diet with a high content of fruit, family history of breast cancer, and intakes of total fat, energy, alcohol, or folic acid. Cho et al (35) found that intakes of α-carotene and total carotenoids were related to a significant reduction in premenopausal breast cancer risk in smokers but not in nonsmokers.

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In conclusion, we found that a high intake of total carotenoids in combination with a high intake of DHA is associated with a reduced risk of breast cancer in postmenopausal women. As a whole, our data suggest that a diet with a high content of fruit, carotenoid-rich vegetables, and DHA-rich fish may reduce the risk of breast cancer. Additional studies are warranted to examine this finding and to identify the biological mechanisms involved.

We gratefully acknowledge the editorial assistance of Ovid Da Silva. AN helped with the data entry, analyzed the data, interpreted the analyses, and wrote the manuscript. PG planned and designed the study and helped edit the manuscript. None of the authors had any personal or financial conflicts of interest.

REFERENCES


