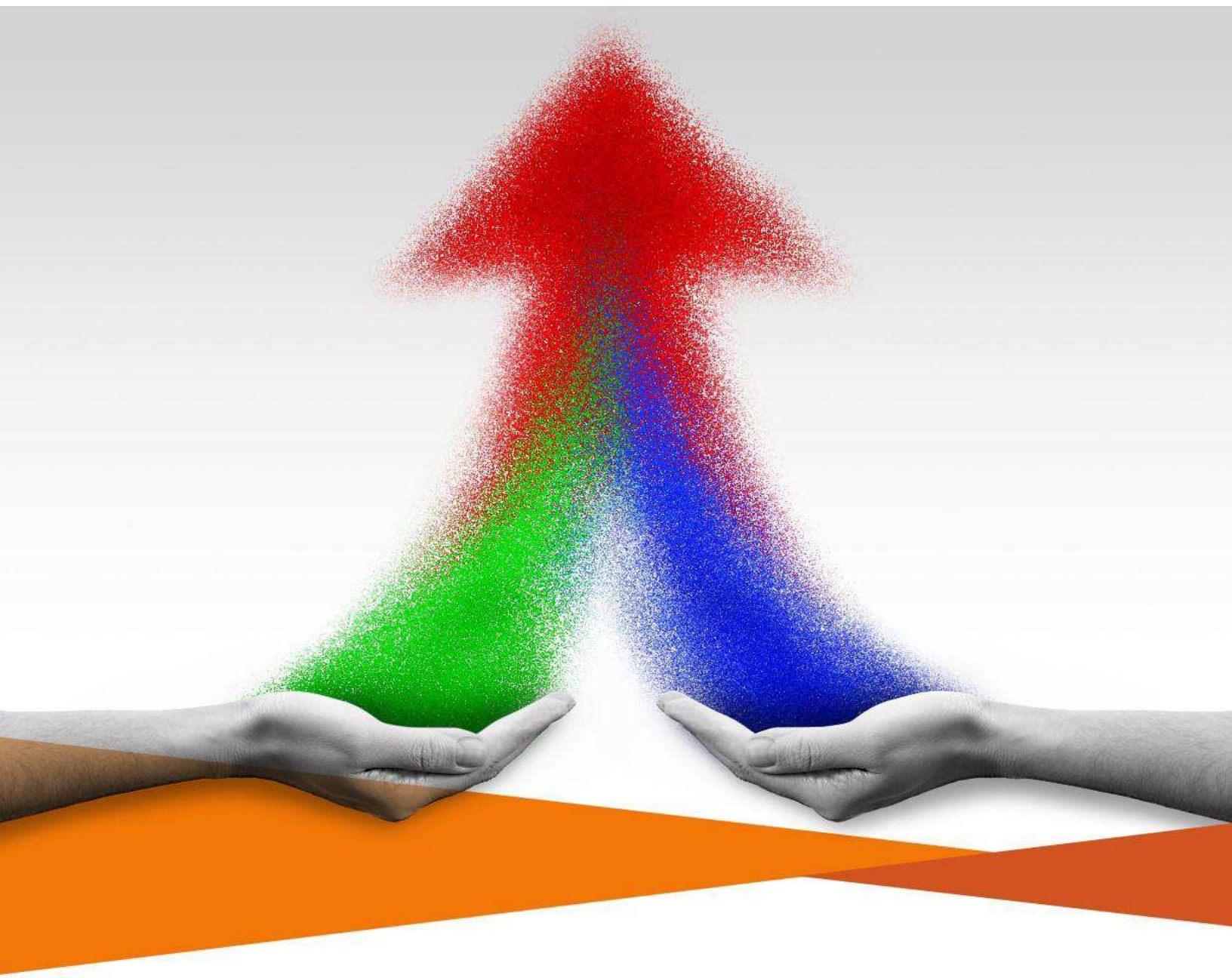

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DIETARY CAROTENOIDS AND RISK OF COLON CANCER: CASE-CONTROL STUDY

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Some epidemiological studies suggest that consumption of fruits and vegetables with a high carotenoid content may protect against colon cancer (CC). The evidence, however, is not completely consistent. Given the inconsistencies in findings in previous studies and continued interest in identifying modifiable risk factors for CC, a case-control study of French-Canadian in Montreal, Canada, was undertaken to examine the possible association between dietary carotenoids and CC risk and to investigate whether this association varies in relation to lifestyle factors such as smoking or diet, and particularly the high consumption of long-chain polyunsaturated fatty acids (LCPUFA). A total of 402 colorectal cases (200 males and 202 females) and 688 population-based controls matched for age, gender and place of residence were interviewed. Dietary intake was assessed through a validated food frequency questionnaire that collected information on over 200 food items and recipes. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in unconditional logistic regression models. After adjustment for important variables such as total energy intake, no association was found between dietary intake of carotenoids and CC risk. For women with high intakes of LCPUFA, an inverse association was found between lutein + zeaxanthin and CC risk. ORs were 0.41; 95%CI (0.19–0.91), $p=0.03$ for eicosapentaenoic acid, and OR=0.36, 95%CI (0.19–0.78), $p=0.01$ for docosahexaenoic acid, when the upper quartiles of intake were compared to the lower. Among never-smokers, a significantly reduced risk of CC was associated with intake of β-carotene [OR=0.44, 95%CI (0.21–0.92) and $p=0.02$], whereas an inverse association was found between lycopene intake and CC risk [OR=0.63, 95%CI (0.40–0.98) and $p=0.05$] among smokers. The results of our study suggest that a diet rich in both lutein + zeaxanthin and LCPUFAs may help prevent CC in French-Canadian females.

Key words: *colon cancer; carotenoids; fatty acids; nutrition; prevention*

Colon cancer (CC) is the third most common cancer in incidence and mortality for both men and women in Canada.[1] Worldwide CC occurs with approximately equal frequency in men and women, although in high-incidence areas such as North America as much as a 20% increased incidence has been found among men as compared to women.[2] Several epidemiological studies[3] have suggested that high consumption of fruits and vegetables, especially those containing high amounts of carotenoids, may play a part in prevention of CC, particularly for individuals who are not health conscious.[4,5]

Carotenoids are plant pigments, and the mechanisms involved in their reported cancer-preventing activity are not well understood.[6] Hypotheses include antioxidant activity, stimulation of gap junction intercellular communication, induction of detoxifying enzymes and inhibition of cellular proliferation,[7] and enhancement of immune function.[8] Carotenoids include a large number of substances with different biological antioxidant activities. It has been shown that α-carotene may decrease the activity of cytochrome P450 1A1, an activator of procarcinogens.[9] β-Carotene may control growth-inhibitory and proapoptotic effects in colon adenocarcinoma cells through the redox regulation of transcription nuclear factor NF-κB activity.[10] Lycopene is the most efficient singlet oxygen quencher; lutein and zeaxanthin are scavengers of radical oxygen species,[11] while β-cryptoxantin may stimulate the expression of *RB*, an anti-oncogene and *p73*, a *p53*-related gene.[12] Given the number of possible mechanisms, it is not unreasonable to expect that intake of carotenoids may be linked with reduced CC risk. However, one intervention study[13] on the recurrence of colorectal adenomas, a pre-cancerous condition and 3 cohort studies[14–16] failed to find a relationship between consumption of fruits and vegetables, the major sources of carotenoids, and colorectal cancer. This lack of association may be the result, at least in part, of the fact that total consumption of fruits and vegetables may not be an accurate indicator of intake of carotenoids by individual study subjects, since carotenoids are not equally present in all fruits and vegetables. It is also possible that an imbalance between carotenoids and long-chain polyunsaturated fatty acids (LCPUFA) is the more important factor. Experimental studies have suggested that carotenoids inhibit lipid peroxidation in CC tissue, thereby reducing the formation of mutagenic peroxidation products.[17,18]

To provide further information on this issue, we undertook a case-control study to examine the possible association between intake of individual carotenoids and risk of CC among French-Canadians, a relatively homogeneous population whose particular food habits and nutrient intake, documented in national and international investigations,[19,20] differentiate them from their neighbors in North America. Our study also investigates the combined effect of intake of dietary carotenoids and lifestyle factors such as smoking because free radicals in cigarette smoke can alter the concentrations of most carotenoids.[21] Finally, this investigation was carried out to examine associations by intake of essential fatty acids because the antioxidant influence of carotenoids and the lipid peroxidation susceptibility of these fatty acids suggest interactive biological activities.

METHODS

Study population

Case and control ascertainment for this investigation have been described in detail elsewhere.[22] Briefly, between 1989 and 1993, a total of 1,268 patients, 35–79 years old, with a histological diagnosis of CC were identified through the admission offices of 5 major francophone teaching hospitals of the RICUM (Réseau

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inter-hospitalier de cancérologie de l'Université de Montréal). Of these, 596 cases (47%) were ineligible for the following reasons: 210 (35.2%) lived outside the study region, 178 (29.9%) were excluded because of age, 151 (25.3%) had another primary cancer or an incorrect diagnosis and 57 (9.6%) died before the interview. For 87 (12.9%) of the remaining 672 eligible cases, no consent was received from physicians in response to our request for permission to interview their patients. Physicians refused to allow interviews with 31 patients (4.6%). We were unable to contact 54 cases (8%) because of incorrect addresses, and 96 cases (14.3%) declined to be interviewed. Two cases (0.3%) were later excluded because of incorrect diagnosis. We finally interviewed 402 cases, giving an approximate response rate of 60% of eligible subjects.

The controls were population-based and frequency-matched for age (± 5 years), sex and place of residence. A modified random digit dialing method that was developed and validated by our group was used to select controls. A total of 2,085 controls were chosen, of which 1,361 (65.3%) met the study criteria. A total of 171 (8.2%) did not respond, 335 (16.1%) refused to participate before the study was explained to them, and a further 167 (8%) refused to participate after the study was explained to them. We therefore interviewed 688 subjects, 51% of eligible control subjects.

With both cases and controls, interviews were conducted in the respondent's home. If either the case or control was hospitalized at the time of the scheduled interview and was unlikely to be available for a home interview within 2 weeks, an in-hospital interview was arranged. If a patient was very ill, whether at home or in hospital, he or she was interviewed in the presence, and with the help, of a family member or another person who was available and likely to have relevant information. All cases were ascertained and interviewed within 1–3 months of initial diagnosis. The vast majority of controls were interviewed no longer than 3 months after the matching cases were interviewed.

Data collection

Data from both cases and controls were collected in the respondents' homes. If either the case or the control was hospitalized at the time of the scheduled interview and unlikely to be available for a home interview within 2 weeks, an in-hospital interview was arranged. If a patient was very ill, whether at home or in the hospital, he or she was interviewed in the presence and with the help of any family members or close relatives who were available and likely to have relevant information. All controls were interviewed no later than 3 months after the matching cases were interviewed. The core questionnaire asked for data on sociodemographics, body measurements, physical activity, family CC history, medical history, occupation, smoking and history of vitamin supplement use.

Food intake

Food consumption data were collected though a food frequency questionnaire (FFQ) developed by the National Cancer Institute of Canada, modified by our group for French-Canadians, and used by our group in several case-control studies of cancer of the breast, colon and prostate. The FFQ focused on the 2-year period prior to the diagnosis of the disease for cases and on a corresponding period for controls. The original (English) questionnaire was translated into French and then translated back to English and was assessed for both validity and reproducibility.[23] In face-to-face interviews, data were gathered on over 200 food items and recipes consumed over a 12-month period, using food models to help participants quantify their portions.

Food grouping

A total of 985 separate food items, including brand names of items where applicable, were retrieved from the FFQ and used to estimate daily intake of individual carotenoids, based on the US Department of Agriculture USDA-NCC Carotenoid Database (Release 1998, http://www.nal.usda.gov/fnic/foodcomp/Data/car98/). This online database contains data on 218 foods and 6 specific carotenoids and provides food composition values for specific carotenoids contained in food items identified in the study questionnaire. Information on other nutrients, including total carotenoids, individual fatty acids, fibers and total energy, was obtained through the Canadian Nutrient File (Release 1991 and 1997). The main food sources of specific carotenoids in the diet of this French-Canadian population included carrots and tomatoes (α-carotene), carrots and spinach (β-carotene), oranges (β-crypthoxanthin), tomatoes and tomato products (lycopene), and broccoli, turnips and green-leaf vegetables (lutein and zeaxanthin).

Statistical analysis

Food intake among cases and controls was analyzed according to specific carotenoid intake based on the USDA-NCC Carotenoid Database mentioned above. Median intakes were calculated separately for cases and controls. To determine any associations between carotenoids and CC risk, subjects were divided into 4 categories based on quartiles of each specific calorie-adjusted carotenoid intake. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, using the categories of residuals from the regression of carotenoids on total energy intake[24] in unconditional logistic regression models. Analyses were adjusted for age, history of CC in first-degree relatives, marital status, sex, physical activity, fibre and folate consumption and total energy intake. Body mass index 1 year prior to the diagnosis, smoking history and hormone replacement therapy did not show significant differences between cases and controls and were therefore not included in the model.

To evaluate the combined effect of intake of individual carotenoids and selected LCPUFA (arachidonic, eicosapentaenoic and docosahexaenoic acids), the p value for a multiplicative interaction term added to a fully adjusted model was examined and, when statistically significant, stratification on fatty acid intake was performed with median intake of controls as the cut-point. Subgroup analyses based on median splits of these fatty acid intakes were also assessed. Tests for linear trend were calculated by replacing the indicator carotenoid variables in each multivariate model with a single variable representing the median frequency of consumption for a given intake category and by using the Wald χ^2 value computed for the regression coefficient of this variable to test the null hypothesis of no linear trend component in CC risk across quartiles of intake.[25] This analysis focuses on individual carotenoid intake from diet rather from carotenoid supplements. At the time the study was conducted, use of carotenoid supplements was uncommon among French-Canadians and question about consumption of such supplements was not included in the FFQ. All analyses were performed for men and women separately. Results are presented for both males and females combined unless there was a significant difference between them. Such differences are indicated. Data were analyzed with SPSS statistical software (release 10.02, SPSS, Inc., 1987–1999).

RESULTS

The characteristics of the study population with respect to potential confounders are summarized in Table I. The number of CC cases increases significantly with age in both males ($p < 0.038$) and females ($p < 0.0001$). Among females, cases were more likely to have a family history of CC ($p = 0.006$), while controls were more likely to have used oral contraceptives than cases ($p < 0.0001$). The cases were more likely to be never married regardless of gender ($p < 0.05$). Women who had been much less active since reaching adulthood were more likely to be at risk ($p = 0.016$). Body mass index 1 year prior to the diagnosis of cancer, smoking history and history of hormone replacement therapy did not show statistically significant differences between cases and controls.

Table II shows the risk of CC and intake of individual carotenoids. After adjustment for age, sex, marital status, physical activity, history of CC in first-degree relatives, fibre consumption and total energy intake, there was no significant association be-

TABLE I – SOCIO-DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

Variable	Male (n = 439)				Female (n = 631)			
	Cases		Controls		Cases		Controls	
	n	%	n	%	n	%	n	%
Age								
20–29					1	0.5	4	0.9
30–39	5	2.5	4	1.7	6	3.0	31	7.2
40–49	10	5.0	12	5.0	16	7.9	111	25.9
50–59	41	20.5	37	15.5	39	19.3	114	26.6
60–69	85	42.5	85	35.6	65	32.2	98	22.8
70–79	59	29.5	101	42.2	75	37.1	71	16.6
p for trend[1]		0.038				<0.0001		
History of colon cancer in first-degree relatives								
No	179	89.5	218	91.2	173	85.6	398	92.8
Yes	21	10.5	21	8.8	29	14.4	31	7.2
p value[2]		0.63				0.006		
Marital status								
Never-married	24	12	16	6.7	44	21.8	65	15.2
Ever-married	176	88	223	93.3	158	78.2	364	84.8
p value		0.040				0.027		
BMI 1 year prior to diagnosis								
≤24.9	78	39	110	46.0	119	18.6	265	61.8
25.0–29.9	88	44	96	40.2	45	44.1	97	22.6
≥30.0	34	17	33	13.8	38	37.3	67	15.6
p for trend		0.108				0.342		
Smoking history								
No	31	15.5	30	12.6	98	48.5	201	46.8
Yes	169	84.5	209	87.4	104	51.5	228	53.1
p value		0.41				0.73		
Physical activity								
Much less active	28	14	36	15.1	31	15.3	49	11.4
Less active	97	48.5	115	48.3	118	58.4	235	54.8
More active	69	34.5	76	31.9	52	25.7	132	30.8
Much more active	6	3.0	11	4.6	1	0.5	13	3.0
p for trend		0.950				0.016		
Oral contraceptives use								
No					145	72	222	52
Yes					56	28	207	48
p value						0.0001		
Hormone replacement therapy								
No					128	64	263	61
Yes					73	36	165	39
p value						0.598		

[1]Mantel extension test for case-control difference.– [2]χ^2 test for case-control difference.

tween dietary intake of carotenoids and CC risk. The results were not significantly altered when individual carotenoids were mutually adjusted, although correlations for specific carotenoids varied substantially. The Pearson correlation coefficient between intake of total carotenoids and lycopene was 0.05; β-cryptoxanthin and β-carotene 0.21; total carotenoids and α-carotene 0.92 (data not shown).

Table III shows multivariate-adjusted ORs for CC risk associated with carotenoid intake according to smoking status. In general, carotenoid intake was somewhat higher among ever smokers than among never smokers. For never smokers, a significantly reduced risk of CC was associated with β-carotene [OR=0.44, 95%CI (0.21–0.92) and p =0.02], while a positive association was found between lutein + zeaxanthin and CC risk [OR=2.22, 95%CI (1.06–4.63) and p =0.05] when the highest intake quartile was compared to the lowest. Among ever smokers, an inverse and significant association was found between lycopene and risk of CC (OR=0.63, 95%CI=0.40–0.98 and p =0.05), when the highest and lowest quartiles were compared. Other stratified analyses were performed on oral contraceptives use or hormonal replacement therapy (data not shown). No statistically significant association was detected.

Table IV summarizes the associations between dietary carotenoids and CC risk according to intake of arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acids (DHA). Only individual carotenoids significantly associated with CC are included. Among women with high intake of LCPUFA, significant inverse associations were found between lutein + zeaxanthin and CC risk. ORs were 0.46, 95%CI (0.22–0.95) and p =0.04 for AA; OR=0.41, 95%CI (0.19–0.91) and p =0.03 for EPA and OR=0.36, 95%CI (0.19–0.78) and p =0.01 for DHA, respectively. An increased risk for CC associated with total carotenoid intake was evident among females with low intake of EPA [OR=2.18, 95%CI (1.01–4.71) and p =0.04] and DHA [OR=3.22, 95%CI (1.35–7.69) and p =0.01], respectively. A significant inverse linear association was apparent between β-carotene and CC risk among those with high intake of DHA [OR=0.36, 95%CI (0.16–0.78) and p =0.01]. There was also evidence of a strong interaction between DHA and total carotenoids (p =0.003) and β-carotene (p =0.008) (data not shown).

For male subjects, no overall association was found between intake of carotenoids and CC risk according to intake of AA, EPA or DHA.

DISCUSSION

Consumption of fruits and vegetables, particularly vegetables, has been associated with reduced risk of CC. This "protective effect" of consumption of certain fruits and vegetables with high carotenoid content could be due to the presence of antioxidants, which may mediate the effect of carotenoids by reducing oxidative stress *via* inhibition of lipid peroxidation and ϵ-adduct formation in

TABLE II – OR AND 95% CI FOR COLON CANCER ASSOCIATED WITH DIETARY CAROTENOIDS[1]

Individual carotenoid	Quartiles of energy-adjusted carotenoid intakes				*p* for trend[2]
	Q1	Q2	Q3	Q4	
α-Carotene					
Median ± SD (μg/d)	244 ± 201	749 ± 227	1540 ± 295	3,172 ± 2,067	
Cases/controls	108/167	89/167	113/167	92/167	
Multivariate OR (95%CI)	1.00	1.06 (0.74–1.54)	0.87 (0.61–1.24)	1.04 (0.71–1.52)	0.91
β-Carotene					
Median ± SD (μg/d)	2,314 ± 1,806	4,756 ± 1,545	8,328 ± 1,931	15,914 ± 14,314	
Cases/controls	111/167	121/167	87/167	83/167	
Multivariate OR (95%CI)	1.00	0.82 (0.58–1.18)	1.14 (0.78–1.67)	1.22 (0.83–1.81)	0.91
β-Cryptoxanthin					
Median ± SD (μg/d)	2.3 ± 6.6	25.5 ± 13.5	90.9 ± 31.5	207.3 ± 146.4	
Cases/controls	110/157	105/163	84/184	103/164	
Multivariate OR (95%CI)	1.00	0.94 (0.64–1.34)	1.38 (0.95–2.00)	0.96 (0.66–1.40)	0.14
Lycopene					
Median ± SD (μg/d)	684 ± 831	2,559 ± 980	5,776 ± 1,530	13,604 ± 12,339	
Cases/controls	95/172	102/165	96/172	109/158	
Multivariate OR (95%CI)	1.00	0.75 (0.52–1.09)	0.89 (0.62–1.30)	0.71 (0.49–1.03)	0.16
Lutein + Zeaxanthin					
Median ± SD (μg/d)	417 ± 338	1,073 ± 406	2,027 ± 495	4,330 ± 2,628	
Cases/controls	114/153	102/165	94/174	92/175	
Multivariate OR (95%CI)	1.00	0.99 (0.69–1.44)	1.20 (0.83–1.74)	1.20 (0.82–1.75)	0.22
Total carotenoids					
Median ± SD (μg/d)	247 ± 161	581 ± 155	1039 ± 185	1,952 ± 1,304	
Cases/controls	107/167	98/167	101/167	96/167	
Multivariate OR (95%CI)	1.00	0.97 (0.67–1.40)	0.95 (0.66–1.37)	1.00 (0.68–1.48)	0.98

[1]Odds ratios and 95% confidence intervals from the logistic regression model adjusted for age, sex, marital status, physical activity, history of colon cancer in first-degree relatives, fibre, folate and total energy intake.– [2]Two-sided Wald tests.

human colon epithelia, factors that predispose to a higher risk for colon cancer.[26]

In our case-control study, we found no association between dietary intake of carotenoids and risk of CC in males and females considered together. Men and women were considered separately in multivariate models and there was no evidence of association between dietary intake of carotenoids and risk of CC. Our null results are consistent with 3 previous cohort studies.[27–29] However, 2 case-control studies[30,31] reported a reduced risk of colon cancer associated with α-carotene and β-carotene30 and lutein/zeaxanthin,[30,31] which disagrees with our results. The first case-control study[30] was hospital-based and is therefore open to possible related criticism.[32] Moreover, it was carried out in an area with intermediate colorectal cancer incidence rates but comparisons are made across Europe, where incidence rates vary widely.[33] In the second investigation,[31] study participants were black, white and Hispanic but ethnicity was not taken into account. As well, several potentially intercorrelated dietary variables were included in the regression model. These methodological issues may explain in part the difference between their findings and ours.

We found a reduced risk of CC associated with intake of lutein + zeaxanthin among women with high intakes of EPA and DHA. To our knowledge no other case-control study has evaluated the combined effect of dietary intake of LCPUFA and other individual carotenoids on incidence of CC. We have previously[34] demonstrated in the same study population that EPA and DHA were provided largely by consumption of fish and shellfish. Both epidemiological and experimental studies indicate that long-chain ω-3 fatty acids have a protective effect against CC.[34,35] Multiple mechanisms involved in this chemopreventive activity may include cyclooxigenease-2 inhibition, increased apoptotic activity, angiogenesis, activation of protein kinase C, decreased ornithine decarboxylase activity and reduction of fecal bile acids as well as neutral sterol excretion.[36] In addition, lutein + zeaxanthin are provided by the cruciferae botanical group (broccoli, turnip and greens), and it has been shown experimentally that lutein and zeaxanthin are highly effective antioxidants, capable of scavenging peroxyl radicals and quenching reactive oxygen species.[11] It is possible that consumption of both vegetables in the cruciferae family and fish and seafood may reduce risk of CC more than consumption of either of these elements alone.

Among female subjects of our study population, we observed differing effects following intake of total carotenoids and ω-3 fatty acids (EPA and DHA). Women with low intake of these fatty acids exhibit an increased risk for CC, while those with high consumption have a reduced risk. ω-3 fatty acids are very susceptible to peroxidation and it has been reported that oxidative stress enhances the development of CC.[37] Therefore, it is possible that total carotenoids are the most effective ω-3 fatty acid-based protective antioxidants since the effect of total carotenoids on these fatty acids seems greater than that of individual carotenoids. We examined the potential effect modification of dietary intake of carotenoids/CC risk association by age and menopausal status. None of these interactions were statistically significant.

The association between dietary intake of individual carotenoids, CC risk and intake of LCPUFA was statistically significant among females only. We speculate that sex-specific differences in bowel transit time or bile acid production[38] may have accounted for the sex-specific variations observed. Because smoking was much more prevalent among men than women, another explanation is that smoking-related CC among men may dilute the relative risks associated with intake of specific carotenoids and LCPUFA if these cancers develop through a causal pathway independent of carotenoids and LCPUFA intake. An alternative explanation is that women provided more accurate dietary information. Finally, if the putative mechanism of peroxidation of LCPUFA is correct, it is also possible that endogenous estrogens, which act as an antioxidant, may exert a synergistic effect with carotenoids to inhibit lipid peroxidation of these fatty acids.[39]

Among ever smokers, we found a significantly reduced risk (27%) of CC associated with lycopene, while never smokers exhibited a 56% significantly reduced risk associated with β-carotene and a 2.2-fold elevated risk associated with lutein and zeaxanthin. One case-control study,[40] after adjustment for smoking, found that intake of β-carotene was associated with a 40% greater reduced risk of colorectal adenomas than consumption of other dietary carotenoids. Another case-control study[31] reported a nonsignificant reduced risk associated with lycopene intake among

TABLE III – OR AND 95% CI FOR COLON CANCER ASSOCIATED WITH DIETARY CAROTENOIDS BY SMOKING STATUS[1]

Individual carotenoid	Smoking status	Quartiles of energy-adjusted carotenoid intakes				*p* for trend[2]
		Q1	Q2	Q3	Q4	
α-Carotene	Ever					
Median ± SD (μg/d)		249 ± 215	754 ± 226	1,573 ± 300	3,158 ± 1,646	
Cases/controls		79/118	61/107	79/108	54/104	
Multivariate OR (95%CI)		1.00	1.01 (0.65–1.57)	0.79 (0.52–1.21)	1.12 (0.70–1.78)	0.99
	Never					
Median ± SD (μg/d)		242 ± 160	735 ± 231	1478 ± 282	3,191 ± 2,587	
Cases/controls		29/49	28/60	34/59	38/63	
Multivariate OR (95%CI)		1.00	0.76 (0.39–1.51)	0.86 (0.44–1.67)	0.91 (0.47–1.77)	0.92
β-Carotene	Ever					
Median ± SD (μg/d)		2,239 ± 1,838	5,086 ± 1,556	8,605 ± 2,021	15,914 ± 16,461	
Cases/controls		81/126	78/111	61/97	53/103	
Multivariate OR (95%CI)		1.00	0.85 (0.56–1.29)	0.89 (0.57–1.39)	1.11 (0.69–1.78)	0.72
	Never					
Median ± SD (μg/d)		2,471 ± 1,710	4,246 ± 1,419	8,074 ± 1,713	15,903 ± 9,704	
Cases/controls		30/41	43/56	26/70	30/64	
Multivariate OR (95%CI)		1.00	1.10 (0.56–2.17)	0.57 (0.28–1.16)	0.44 (0.21–0.92)	0.02
β-Cryptoxanthin	Ever					
Median ± SD (μg/d)		2.32 ± 7.02	26.10 ± 13.95	91.41 ± 32.64	213.49 ± 169.34	
Cases/controls		88/125	70/100	48/114	67/98	
Multivariate OR (95%CI)		1.00	0.86 (0.56–1.32)	1.49 (0.95–2.33)	0.91 (0.59–1.41)	0.49
	Never					
Median ± SD (μg/d)		2.15 ± 3.95	25.06 ± 12.60	90.15 ± 29.63	201.65 ± 93.08	
Cases/controls		22/32	35/63	36/70	36/66	
Multivariate OR (95%CI)		1.00	0.83 (0.40–1.72)	0.74 (0.36–1.52)	0.89 (0.43–1.86)	0.98
Lycopene	Ever					
Median ± SD (μg/d)		770 ± 878	2,774 ± 959	5,941 ± 1,578	14,131 ± 14,172	
Cases/controls		67/128	65/103	65/101	76/105	
Multivariate OR (95%CI)		1.00	0.73 (0.46–1.13)	0.73 (0.47–1.15)	0.63 (0.40–0.98)	0.05
	Never					
Median ± SD (μg/d)		560 ± 664	2,386 ± 977	5,474 ± 1,418	12,674 ± 6,752	
Cases/controls		28/44	37/62	31/71	33/53	
Multivariate OR (95%CI)		1.00	0.96 (0.49–1.87)	1.50 (0.76–2.93)	1.00 (0.50–1.98)	0.65
Lutein + Zeaxanthin	Ever					
Median ± SD (μg/d)		415 ± 342	1,080 ± 445	2,072 ± 522	4,451 ± 2,924	
Cases/controls		83/115	70/104	53/113	67/105	
Multivariate OR (95%CI)		1.00	0.94 (0.61–1.45)	1.31 (0.83–2.06)	0.97 (0.62–1.51)	0.77
	Never					
Median ± SD (μg/d)		443 ± 329	1,062 ± 307	1,952 ± 432	4,084 ± 1,969	
Cases/controls		31/38	32/61	41/61	25/70	
Multivariate OR (95%CI)		1.00	1.19 (0.60–2.38)	1.15 (0.59–2.25)	2.22 (1.06–4.63)	0.05
Total carotenoids	Ever					
Median ± SD (μg/d)		255 ± 173	592 ± 154	1,038 ± 189	1,976 ± 1,110	
Cases/controls		79/125	69/111	66/102	59/99	
Multivariate OR (95%CI)		1.00	0.88 (0.57–1.36)	0.83 (0.54–1.30)	0.94 (0.59–1.49)	0.70
	Never					
Median ± SD (μg/d)		211 ± 17	544 ± 156	1,039 ± 172	1,943 ± 1,555	
Cases/controls		28/42	29/56	35/65	37/68	
Multivariate OR (95%CI)		1.00	0.69 (0.34–1.39)	0.72 (0.37–1.42)	0.71 (0.35–1.44)	0.43

[1]Odds ratios and 95% confidence intervals from the logistic regression model adjusted for age, sex, marital status, physical activity, history of colon in first-degree relatives, fibre, folate and total energy intake.– [2]Two-sided Wald tests.

current smokers and a nonsignificant increased risk associated with β-carotene among never smokers. A cohort study[29] found a suggestion of increased risk of CC associated with lycopene and an elevated risk associated with lutein among current smokers and a reduced risk associated with β-carotene among never smokers. However, the results were not statistically significant.

Dietary carotenoid intakes correlate with their serum concentrations and it has been shown that every 10% increase in dietary lutein + zeaxanthin intake is associated with a 2.4% increase in serum lutein concentration.[41] Exposure to smoke causes extensive oxidation of β-carotene[42] and a recent study[43] reported that, independently of differences in dietary intake or other demographics factors, active and passive smoke affect plasma concentrations of provitamin A carotenoids, such as β-carotene. Moreover, it has been shown that circulating concentrations of β-carotene are, on average, decreased by more than 25% among active smokers as compared to nonsmokers, and are decreased by more than 15% among passive smokers.[44,45] Depressed plasma β-carotene concentrations have been reported in response to enhanced metabolic turnover resulting from smoking-induced oxidative stress.[46] If this mechanism can be shown to effect the relationship between β-carotene and smoking it would help explain why in this study β-carotene was associated with a reduced CC risk only among never smokers. On the other hand, it has been shown that active smoking is more weakly associated with circulating concentrations of the nonprovitamin A carotenoids such as lycopene than with serum β-carotene values.[44,47] These associations are absent among passive and nonsmoking individuals.[44,45] We speculate that the differing effects of smoking on different types of carotenoids may explain, at least in part, why associations between CC risk and pro- and nonpro-vitamin A carotenoids by smoking status do not move in same directions. However, the specific pathways responsible for this pattern of association merit further exploration.

In interpreting the results of our study, some of its limitations must be kept in mind. The retrospective design of the present study cannot preclude the possibility of recall bias. However, such a bias may not be great since information on dietary exposures was collected before the final diagnosis. Our investigation was origi-

TABLE IV – OR AND 95% CI FOR COLON CANCER ASSOCIATED WITH DIETARY CAROTENOIDS AND SELECTED LONG-CHAIN POLYUNSATURATED FATTY ACIDS[1]

Carotenoids	Sex	Quartiles									
		Q1 (ref.)	Q2:OR (95%CI)	Q3:OR (95%CI)	Q4:OR (95%CI)	*p* for trend[2]	Q1 (ref.)	Q2:OR (95%CI)	Q3:OR (95%CI)	Q4:OR (95%CI)	*P* for trend[2]
		Low intake[3] of arachidonic acid					High intake[4] of arachidonic acid				
Lutein + zeaxanthin	Male	1.00	1.72 (0.76–3.93)	2.12 (0.90–4.96)	0.86 (0.39–1.87)	0.90	1.00	1.21 (0.56–2.61)	1.58 (0.69–3.60)	1.07 (0.48–2.38)	0.79
	Female	1.00	1.28 (0.58–2.81)	1.81 (0.83–3.94)	0.91 (0.34–1.92)	0.94	1.00	0.59 (0.30–1.17)	0.61 (0.32–1.18)	0.46 (0.22–0.95)	0.04
		Low intake of eicosapentaenoic acid					High intake of eicosapentaenoic acid				
Lutein + zeaxanthin	Male	1.00	2.06 (0.97–4.37)	1.68 (0.78–3.62)	1.08 (0.50–2.36)	0.90	1.00	0.86 (0.37–1.99)	1.70 (0.67–4.34)	0.76 (0.32–1.76)	0.72
	Female	1.00	0.75 (0.37–1.53)	1.19 (0.35–1.41)	0.92 (0.42–2.01)	0.84	1.00	0.81 (0.40–1.66)	0.70 (0.35–1.41)	0.41 (0.19–0.91)	0.03
Total carotenoids	Male	1.00	0.85 (0.40–1.79)	1.00 (0.47–2.12)	0.70 (0.32–1.53)	0.47	1.00	1.20 (0.53–2.75)	0.93 (0.41–2.12)	1.44 (0.56–3.66)	0.64
	Female	1.00	1.74 (0.84–3.61)	2.07 (1.00–4.29)	2.18 (1.01–4.81)	0.04	1.00	1.19 (0.57–2.48)	0.44 (0.19–1.02)	0.71 (0.32–1.59)	0.12
		Low intake of docosahexaenoic acid					High intake of docosahexaenoic acid				
α-Carotene	Male	1.00	0.99 (0.48–2.07)	0.77 (0.37–1.60)	0.96 (0.43–2.15)	0.72	1.00	0.78 (0.35–1.76)	1.00 (0.45–2.24)	0.52 (0.21–1.30)	0.28
	Female	1.00	0.75 (0.34–1.67)	1.69 (0.78–3.63)	1.98 (0.89–4.43)	0.07	1.00	0.94 (0.45–1.95)	0.65 (0.32–1.33)	0.71 (0.34–1.46)	0.24
β-Carotene	Male	1.00	0.76 (0.35–1.64)	0.46 (0.21–1.05)	1.63 (0.67–3.96)	0.66	1.00	2.06 (0.88–4.80)	1.08 (0.46–2.51)	1.44 (0.57–3.66)	0.96
	Female	1.00	1.96 (0.90–4.28)	1.46 (0.64–3.36)	2.62 (1.12–6.13)	0.06	1.00	0.62 (0.31–1.24)	0.50 (0.24–1.05)	0.36 (0.16–0.78)	0.01
		Low intake of docosahexaenoic acid					High intake of docosahexaenoic acid				
Lutein + zeaxanthin	Male	1.00	2.08 (0.97–4.48)	1.92 (0.87–4.23)	0.71 (0.32–1.56)	0.52	1.00	1.12 (0.50–2.54)	0.67 (0.28–1.60)	0.94 (0.41–2.15)	0.66
	Female	1.00	0.79 (0.37–1.70)	1.51 (0.72–3.19)	1.00 (0.44–2.28)	0.58	1.00	0.74 (0.37–1.45)	0.61 (0.32–1.18)	0.36 (0.19–0.78)	0.01
Total carotenoids	Male	1.00	1.05 (0.48–2.27)	0.83 (0.40–1.73)	0.69 (0.32–1.52)	0.31	1.00	0.98 (0.44–2.18)	0.95 (0.42–2.18)	0.72 (0.29–1.78)	0.48
	Female	1.00	1.36 (0.61–3.00)	1.96 (0.90–4.30)	3.22 (1.35–7.69)	0.01	1.00	1.30 (0.64–2.64)	0.51 (0.24–1.12)	0.57 (0.27–1.23)	0.06

[1]Odds ratios and 95% confidence intervals from the logistic regression model adjusted for age, marital status, physical activity, history of colon cancer in first-degree relatives, fibre, folate and total energy intake.– [2]Two-sided Wald tests.– [3]Intake lower than median intake in the control group.– [4]Intake higher than median intake in the control group.–

nally designed to include most of the eligible CC cases in the RICUM, which deals with approximately 90% of the French-Canadian population of the study region. Although the participation rate did not vary substantially among cases and controls, we were able to recruit only approximately 60% of CC cases. This may have led to some selection bias in our results. Moreover, although more information than shown was available on smoking history, such as number of cigarettes smoked and length of time as a smoker, it was not possible to perform subgroup analyses based on this information due to the low numbers of CC cases in each group. However, it is unlikely that smoking pattern was a confounder of the relation between carotenoids and CC since no association was found between tobacco consumption and CC risk.[22] The carotenoid content of foods is highly variable due to a number of factors, including geographical area and growing conditions, cultivar or variety, processing techniques, preparation and length and conditions of storage.[11] Although the USDA-NCC Carotenoids Database we used is the most current and comprehensive available to date, data was not available for all the Canadian food items we investigated. . As well, AA is difficult to assess with a FFQ because there are sources of intake that are not likely to be captured from a FFQ. However, EPA and DHA are measured with reasonable accuracy because food sources are mostly limited to marine foods. This may have induced nondifferential misclassifications and could have obscured some associations for both men and women.

Taken as a whole, however, results from our study support previous evidence that dietary intake of green vegetables rich in lutein + zeaxanthin and fish and seafood rich in ω-3 fatty acids may have a protective effect on CC risk.

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