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Dietary cholesterol intake and cancer

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Background: This study assesses the association between dietary cholesterol intake and the risk of various cancers.
Patients and methods: Mailed questionnaires were completed between 1994 and 1997 in eight Canadian provinces by 1182 incident histologically confirmed cases of the stomach, 1727 of the colon, 1447 of the rectum, 628 of the pancreas, 3341 of the lung, 2362 of the breast, 442 of the ovary, 1799 of the prostate, 686 of the testis, 1345 of the kidney, 1029 of the bladder, 1009 of the brain, 1666 non-Hodgkin's lymphomas (NHL), 1069 leukemia and 5039 population controls. Information on dietary habits and nutrition intake were obtained using a food frequency questionnaire, which provided data on eating habits 2 years before the study. Odds ratios (ORs) were derived by unconditional logistic regression to adjust for total energy intake and other potential confounding factors.
Results: Dietary cholesterol was positively associated with the risk of cancers of the stomach, colon, rectum, pancreas, lung, breast (mainly postmenopausal), kidney, bladder and NHL: the ORs for the highest versus the lowest quartile ranged from 1.4 to 1.7. In contrast, cholesterol intake was inversely associated with prostate cancer.
Conclusions: Our findings add to the evidence that high cholesterol intake is linked to increased risk of various cancers. A diet low in cholesterol may play a role in the prevention of several cancers.
Key words: Canada, cholesterol, odds ratio, logistic regression

introduction

Cholesterol accumulation in the bloodstream can cause atherosclerotic plaques to form within artery walls [1], and high serum cholesterol has been linked to the development of coronary disease [2, 3]. The association between cholesterol and cancer has also received considerable attention, but the results are inconsistent [4–12]. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention cohort study found that higher total and high-density lipoprotein cholesterol (HDL-C) concentrations were associated with decreased risk of cancer, particularly for cancers of the lung and liver (total cholesterol), and lung, liver and hematopoietic malignancies (HDL-C) [13]. Recently, the Japan Public Health Centre cohort study observed that low serum total cholesterol levels were not associated with increased risk of total cancer and of any major cancer site, except liver [14]; low HDL-C was not related to the risk of total cancer in both men and women; however, low HDL-C was associated with increased risk of liver cancer in men [15].

Considering the issue of serum cholesterol and the risk of specific cancer sites, some case–control and cohort studies showed a negative association with stomach cancer [16], a positive association with ovarian [17], high-grade prostate [18, 19], and testis cancers [20] but no association with pancreas [21], postmenopausal breast [22, 23], and prostate cancers [24]. Low HDL-C was also associated to increased the risk of cancers of the lung [25], breast for premenopausal [26] or for postmenopausal women [27], prostate cancer [28] and non-Hodgkin's lymphoma (NHL) [29]. Low serum cholesterol, however, may be a consequence, rather than a cause, of the neoplastic process (reverse causation).

With respect to dietary cholesterol intake and cancer risk, some case–control [30, 31] and cohort studies [32, 33] reported elevated risk of colorectal, pancreas and kidney cancers, but other studies found no association with cancers of the stomach [34], pancreas [35, 36], ovary [37], prostate [38] and kidney [39, 40].

Because of limited and inconsistent results of epidemiologic studies, the present study examined the association between dietary cholesterol intake and the risk of several cancers from a Canadian nationwide population-based case–control study, the National Enhanced Cancer Surveillance System (NECSS) [41].

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methods

Between 1994 and 1997, the NECSS collected individual data from a population-based sample that covered 19 types of cancer and population controls in the Canadian provinces of British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Prince Edward Island, Nova Scotia and Newfoundland. The present study did not include cases of colon, rectum and bladder cancer from the province of Ontario. Data on colon, rectum and bladder cancer cases were restricted to use by the province only. The decision was taken before the project started.

cases

Between 1994 and 1997, participating provincial cancer registries ascertained a total of 35 040 (15 872 females and 19 168 males) histologically confirmed incident cancer cases aged 20–76 years. Of these, 4934 cases (14.1%; 2026 females and 2908 males) had died by the time of physician contact, and 2753 (7.9%; 1368 females and 1385 males) were not contacted because the attending physician refused consent (generally because the patient was too ill). Of 28 305 questionnaires sent by provincial cancer registries, 19 732 were completed, yielding a response rate of 56.3% of cases ascertained or 69.7% of patients contacted. This study involved 19 732 (10 725 males and 9007 females) histologically confirmed cancer cases as defined by the second edition of the International Classification of Diseases for Oncology [42]. The cancer sites considered include stomach (803 men and 379 women), colon (959 men and 768 women), rectum (858 men and 589 women), pancreas (353 men and 275 women), lung (1736 men and 1605 women), female breast (2362), ovary (442), prostate (1799), testis (686), kidney (727 men and 618 women), bladder (670 men and 359 women), brain (617 men and 392 women), NHL (877 men and 789 women) and leukemia (640 men and 429 women).

controls

Individuals without cancer were selected from a random sample within each province, with age/sex distribution similar to that of all cancer cases in the NECSS. The strategies for selecting population controls varied by province, depending on data availability and accessibility. In Prince Edward Island, Nova Scotia, Manitoba, Saskatchewan and British Columbia, age group- and sex-stratified random samples of the population were obtained through the provincial health insurance plans. In Ontario, Ministry of Finance data were used to obtain a stratified random sample. Newfoundland and Alberta used random digit dialing to obtain population samples.

Of 8117 questionnaires sent to potential controls by provincial cancer registries, 573 were returned because of a wrong address; of the remainder, 5039 (2547 men and 2492 women) were completed, representing 62.1% of controls ascertained and 66.8% of controls contacted.

data collection

The cancer registries identified most cases within 1–3 months of diagnosis through pathology reports. After obtaining physician consent, questionnaires were mailed to cancer cases and controls. If the questionnaire was not completed and returned, a reminder postcard was sent out after 14 days and a second copy of the questionnaire at 4 weeks. After 6 weeks, telephone follow-up was used, if required, to complete the questionnaire. Provincial cancer registries collected information from controls using the same protocol as for the cases. Average time from diagnosis was <3 months for case and control identification and 6 months for completed questionnaire. Information was collected on socioeconomic status, height, weight, smoking history, alcohol drinking, physical activity, menstrual and reproductive history and dietary history.

For weight, we collected information on how much each subject weighed '~2 years ago'. Body mass index (BMI) was computed as weight (kilogram) divided by height (meter) squared [43]. For cigarette smoking, we defined ever smokers as people who smoked at least 100 cigarettes in their entire life and current smokers as those who were still smoking in the year preceding the interview. Information on recreational physical activity was collected for 2 years before the study. Physical activity was based on session frequency, seasons of participation and average time per session for each of 12 categories of the most common types of moderate exercise (including walking, gardening or yard work, home exercise or exercise class, golf, bowling or curling and dancing) and strenuous leisure-time physical activity (including jogging, swimming or water exercise, skiing, cycling or other strenuous exercise).

Data on cholesterol and energy intake were derived from a food frequency questionnaire (FFQ), which was based on two validated instruments, the short Block questionnaire [44] and the Willett questionnaire [45], with minor modifications to account for difference between Canadian and American diets. The same questionnaire was used to collect all information in the study. FFQ was used to ascertain usual dietary intake 2 years before the study. The FFQ included 69 specific foods and beverage grouped into eight sections: (i) breads and cereals; (ii) meat, poultry, fish, eggs and cheese; (iii) vegetables; (iv) fruits; (v) sweets; (vi) miscellaneous; (vii) water-based beverages and (viii) other beverages. For each food item, cases and controls were asked to describe how often (per day, per week, per month), on average, they ate the specified serving size. A nutrient database based on the 2005 version of the Canadian Nutrient File was used to estimate nutrient intake and total energy intake [46].

statistical analysis

Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). The following potential confounding variables were included: sex (excluding sex-specific cancers), age group (20–49, 50–59, 60–69, ≥70), province, education (≤8, 9–13, ≥14 years), BMI (<25, 25–29.99, ≥30), total alcohol drinking, pack years smoking, consumption of total vegetables and fruit, saturated fat and total energy, plus number of live births and years of menstruation for ovarian cancer, number of live births and age at menarche for premenopausal breast cancer as well as number of live births and age at first pregnancy for postmenopausal breast cancer. The analyses were also adjusted for physical activity for colon and rectal cancer. Except for age group, province, BMI and sex, confounding variables were treated as continuous in the models. Tests for trend were assessed for each study variable by substituting the variable in the model in continuous form. The cholesterol intake was categorized by quartiles based on the distribution among the controls. All analyses were made using SAS software [47].

results

Table 1 gives selected characteristics of controls and cancers by subsite. Mean age in cases of the stomach, rectum, pancreas, lung, prostate and bladder cancers was ~4–5 year older than controls. In contrast, mean age in cases of the testis and brain cancer was 20 and 7 years younger than controls, respectively. For most types of cancer, cases tended to be less educated and reported more alcohol drinking and pack years smoking than controls. There was no difference between cases and controls regarding average family income and physical activities. However, lung cancer cases had a higher proportion in low family income category and a lower proportion in high family income group compared with controls. The proportion reporting strenuous activities was lower among the lung, breast and ovarian cancer cases but higher in leukemia.

Table 2 shows the mean intake (and the corresponding standard deviation) of total cholesterol by sex and types of

Table 1. Characteristics of various types of cancer cases and controls, National Enhanced Cancer Surveillance System, Canada 1994–1997

Characteristics	Controls (n = 5039)	Types of cancer													
		Stomach (N = 1182)	Colon (N = 1727)	Rectum (N = 1447)	Pancreas (N = 628)	Lung (N = 3341)	Breast (N = 2362)	Ovarian (N = 442)	Prostate (N = 1799)	Testics (N = 686)	Kidney (N = 1345)	Bladder (N = 1029)	Brain (N = 1009)	Non-Hodgkin's lymphomas (N = 1666)	Leukemia (N = 1069)
Age (%)															
20–29	4.5	0.2	0.4	0.1		0.2	0.4	2.3		23.0	0.5	0.5	9.3	2.2	4.7
30–39	9.1	2.7	3	2.4	3.0	1.1	7.2	9.3		44.2	4.5	2.0	17.3	9.1	7.2
40–49	15.7	10.2	7.7	10.5	8.9	6.9	27.3	21.8	0.8	22.1	15.8	8.9	22.1	15.7	13.6
50–59	18.4	21.5	18.3	22.8	23.3	21.6	24.7	25.9	13.2	7.6	27.1	19.8	19.9	22.3	23.6
60–69	32.7	36.9	43.3	41.2	42.2	45.8	26.3	27.9	51.1	2.3	34.6	40.8	21.9	33.5	31.8
≥70	19.7	28.5	27.4	23	22.6	24.4	14.2	12.9	34.9	0.9	17.6	28.1	9.5	17.1	19.1
Age, mean (standard deviation)	57.1 (13.4)	61.9 (9.9)	62.6 (9.7)	61.6 (9.6)	61.6 (9.5)	62.8 (8.6)	55.7 (11.4)	55.0 (12.3)	66.3 (6.0)	36.9 (10.0)	58.7 (10.6)	62.5 (9.7)	49.9 (14.4)	57.3 (12.3)	57.1 (13.2)
Low family income[a] (%)	16.3	17.6	18.2	18.7	14.5	24.0	16.2	15.0	13.3	12.6	15.8	18.5	13.6	17.4	14.5
Lower middle family income[a] (%)	17.1	20.8	18.3	17.6	15.5	16.3		16.1	17.5	17.7	17.7	17.2	17.6	14.1	17.3
Upper middle family income[a] (%)	24.9	21.3	24	23.8	26.4	19.0	24.5	22.2	24.8	29.7	25.6	23.4	25.1	23.5	24.2
High family income[a] (%)	15.9	13.8	14.7	15.3	17.2	11.3	17.8	20.0	20.1	21.1	15.7	15.0	18.9	20.2	17.9
Family income not reported (%)	25.8	26.5	24.9	24.6	26.4	29.4	25.5	25.4	24.1	19.0	24.9	25.9	24.9	24.8	26.1
Never smoked (%)	38.2	26.3	32.6	29.9	31.7	6.0	46.5	46.9	22.7	41.8	34.0	17.2	40.9	37.4	35.3
Former smoker (%)	40.6	52.8	52.7	53.2	45.9	53.9	34.5	34.9	63.1	28.1	45.6	51.6	38.0	43.5	47.0
Current smoker (%)	19.4	12.4	10.6	12.1	14.3	18.3	15.8	15.7	11.8	24.0	15.5	24.5	15.6	14.1	12.4
Pack year smoking, mean (standard deviation)	12.2 (17.0)	18.8 (20.3)	15.2 (18.3)	15.2 (17.2)	17.0 (18.8)	35.2 (22.1)	8.7 (13.3)	8.5 (12.5)	18.5 (19.4)	36.9 (10.0)	14.5 (18.4)	21.8 (18.2)	9.2 (13.4)	12.8 (17.1)	13.2 (17.0)
Education years, mean (standard deviation)	12.2 (3.7)	11.0 (3.8)	11.5 (3.4)	11.5 (3.4)	11.8 (3.6)	10.8 (3.2)	12.5 (3.2)	12.5 (3.1)	11.6 (3.9)	13.9 (3.0)	11.6 (3.6)	11.4 (3.3)	12.9 (3.5)	12.2 (3.7)	12.1 (3.6)

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Table 1. (*Continued*)

Characteristics	Controls (n = 5039)	Types of cancer													
		Stomach (N = 1182)	Colon (N = 1727)	Rectum (N = 1447)	Pancreas (N = 628)	Lung (N = 3341)	Breast (N = 2362)	Ovarian (N = 442)	Prostate (N = 1799)	Testics (N = 686)	Kidney (N = 1345)	Bladder (N = 1029)	Brain (N = 1009)	Non-Hodgkin's lymphomas (N = 1666)	Leukemia (N = 1069)
Alcohol intake (g/day), mean (standard deviation)	9.7 (18.1)	14.1 (24.3)	10.9 (19.8)	12.2 (20.6)	13.2 (25.4)	14.4 (25.7)	5.9 (12.3)	4.4 (8.3)	14.7 (21.9)	13.3 (19.3)	9.2 (18.1)	11.2 (19.6)	11.0 (20.8)	9.0 (17.7)	9.4 (16.90)
Body mass index (kg/m^2), mean (standard deviation)	25.7 (4.8)	26.3 (4.9)	26.9 (5.5)	26.8 (4.8)	26.4 (5.2)	25.4 (4.8)	25.6 (5.2)	26.3 (6.57)	26.6 (5.7)	25.7 (4.0)	27.6 (5.2)	26.3 (4.4)	25.7 (4.4)	26.2 (4.8)	26.5 (4.5)
Total intake of vegetables and fruits (servings/week), mean (standard deviation)[b]	26.1 (18.9)	32.8 (22.4)	32.9 (19.2)	32.8 (19.5)	32.5 (20.6)	29.9 (19.3)	33.7 (18.7)	34.1 (19.8)	31.7 (17.7)	27.0 (9.3)	30.5 (19.7)	30.6 (19.0)	31.3 (19.1)	31.9 (17.9)	31.7 (18.3)
Total energy intake (KCal/week), mean (standard deviation)	13 544.0 (6450.0)	15 071.4 (6347.8)	14 488.7 (5620.3)	14 394.4 (5644.4)	14 567.7 (6338.2)	14 153.6 (6112.0)	12 949.2 (5143.5)	13 248.5 (5151.0)	14 435.4 (6178.1)	15 553.0 (7188.7)	14 083.3 (6889.6)	14 006.8 (5637.7)	14 529.0 (5822.5)	14 295.3 (6039.1)	14 239.9 (5306.4)
Moderate activity (h/month), mean (standard deviation)	15.7 (14.1)	17.1 (16.1)	16.5 (15.0)	17.9 (16.1)	15.5 (13.9)	14.6 (14.5)	14.4 (13.2)	15.7 (13.9)	18.7 (16.5)	12.4 (12.1)	15.7 (14.6)	16.6 (15.8)	14.9 (15.2)	15.3 (15.2)	13.2 (17.0)
Strenuous activity (h/month), mean (standard deviation)	4.4 (9.4)	3.1 (7.8)	3.3 (7.6)	4.4 (9.6)	3.3 (9.0)	2.7 (7.5)	2.7 (6.7)	2.6 (6.4)	4.6 (9.4)	11.5 (16.5)	4.4 (9.7)	4.3 (9.7)	6.6 (12.2)	4.1 (9.1)	16.5 (15.3)

[a]The household income was indicated as a categorical variable with following value: low family income: <$20 000 with less than or equal to three people or $30 000 with greater than or equal to four people; lower middle family income: $20 000–$30 000 with less than or equal to three people or $30 000 to <$50 000 with greater than or equal to four people; upper middle family income: <$50 000 with less than or equal to three people or $50 000–$100 000 with greater than or equal to four people; high family income: ≥50 000 for up to three people or ≥100 000 for greater than or equal to four people.
[b]Total vegetables: tomatoes, carrots, broccoli, cabbage, cauliflower, brussel sprouts, spinach or other greens, yellow squash, green beans, corn, peas or any other vegetable; soups with vegetables, and total fruit: apples, pears, oranges, bananas, cantaloupe or other fruit, fresh or canned.

Table 2. Mean intake (stand deviation) of cholesterol (mg/week) by types of cancer and controls, National Enhanced Cancer Surveillance System, Canada, 1994–1997

Types of cancer	Cases (*N*)	Mean (standard deviation)		*P* for *t*-test (men/women)
		Men/women	Total	
Controls	5039	1682.1 (1080.3)/1397.8 (1058.5)	1541.3 (1078.8)	
Stomach	1182	1946.4 (1189.1)/15801.0 (874.6)	1829.1 (1110.9)	<0.0001
Colon	1727	1181.3 (1069.1)/1516.2 (737.9)	1680.0 (947.5)	<0.0001
Rectum	1447	1811.5 (1106.3)/1501.3 (787.8)	1685.2 (1000.4)	<0.0001
Pancreas	628	1898.1 (1231.6)/1436.7 (789.5)	1696.3 (1084.8)	<0.0001
Lung	3341	2016.3 (1517.1)/1478.8 (813.6)	1758.5 (1259.7)	<0.0001
Breast (women)	2362	1462.3 (833.6)	1462.3 (833.6)	
Premenopausal women	913	1477.4 (810.7)	1477.4 (810.7)	
Postmenopausal women	1449	1452.9 (847.9)	1452.9 (847.9)	
Ovary (women)	442	1544.7 (1312.6)	1544.7 (1312.6)	
Prostate (men)	1799	1673.0 (1382.0)	1673.0 (1382.0)	
Testis (men)	686	1841.5 (1200.6)	1841.5 (1200.6)	
Kidney	1345	1842.7 (1717.9)/1480.6 (804.3)	1676.0 (1386.5)	<0.0001
Bladder	1029	1800.9 (1091.0)/1438.7 (680.8)	1674.4 (989.1)	<0.0001
Brain	1009	1803.6 (1113.3)/1417.4 (8432.5)	1674.1 (1028.8)	<0.0001
Non-Hodgkin's lymphoma	1666	1882.0 (1328.1/1499.1 (930.7)	1700.3 (1172.1)	<0.0001
Leukemia	1069	1818.8 (1066.4)/1417.9 (626.9)	1657.2 (935.5)	<0.0001

cancer for 14 cancer sites included in the study and for controls. The average intake of cholesterol for each selected cancer in men was higher than in women, except for colon cancer.

Table 3 presents the ORs and the corresponding 95% CIs for the quartiles of total cholesterol intake. A high intake of cholesterol was significantly associated with increased risk of the cancers of stomach, colon, rectum, pancreas, postmenopausal breast cancer, kidney, bladder, NHL and leukemia; the ORs for the highest versus the lowest quartile were 1.60 (95% CI 1.21–2.13) for stomach, 1.45 (95% CI 1.12–1.87) for colon, 1.74 (95% CI 1.32–2.28) for rectum, 1.57 (95% CI 1.09–2.26) for pancreas, 1.61 (95% CI 1.28–2.03) for lung, 1.45 (95% CI 1.14–1.85) for total breast [1.48 (95% CI 1.07–2.07) for postmenopausal breast cancer], 1.41 (95% CI 1.08–1.83) for kidney, 1.54 (95% CI 1.14–2.08) for bladder cancer and 1.36 (95% CI 1.07–1.73) for NHL, respectively. An elevated risk of leukemia was also seen with third quartile, in the absence of significant trend. In contrast, a decreased risk of prostate cancer was observed for high cholesterol intake (i.e. fourth quartile). No significant association was found with premenopausal breast, ovary, testis and brain cancers.

Fat and cholesterol intakes tend to be associated with the meat, diary products and eggs. Therefore, we also examined the correlation between cholesterol and total fat, saturated fat, monounsaturated fat, polyunsaturated fat and transfat had high correlation ($r = 0.8$ for first three types of fat, 0.7 for polyunsaturated fat and 0.5 for transfat).

The risk of selected cancers with intake of cholesterol was apparently stronger in women with cancers of stomach, colon, pancreas, kidney, bladder and NHL (Table 4). However, the interaction with sex was not significant ($P > 0.05$). When analyses were stratified by age, the ORs for subjects aged ≥60 were apparently but not significantly stronger in cancers of colon, rectum, pancreas, lung, bladder and NHL among men (*P* for interaction >0.05) and cancers of stomach, rectum, lung and bladder among women (*P* for interaction >0.05). The association with intake of cholesterol was also apparently stronger in women with cancers of kidney and NHL aged <60, again in the absence of significant heterogeneity.

discussion

This is the largest nationwide population-based case–control study to assess the association between cholesterol intake and several types of cancer. Total cholesterol intake was associated with elevated risk of cancers of the stomach, colon, rectum, pancreas, lung, breast cancer (specifically postmenopausal), testis, kidney, bladder and NHL. A negative association was observed with prostate cancer. No clear association was appeared for leukemia. No association was observed for cancers of the ovary, testis and brain.

A few studies have evaluated the association between cholesterol and stomach cancer. Two cohort studies observed an inverse association between serum cholesterol levels and the incidence of gastric cancer [16, 48]. In contrast, some case–control studies, including the present one, reported a positive association between cholesterol intake and stomach cancer [49, 50], though others have found no association [7, 34].

In this study, cholesterol intake was positively associated with colon and rectal cancer. This is consistent with two cohort studies from the Finish Mobile Clinic Health Examination Survey [32] and the Shanghai Women's Health Study [51], which included both colon and rectal [32] and colon cancer only [51]. In contrast, a cross-sectional study in a Portuguese population reported that low cholesterol intake was associated to colorectal cancer [52]. Other studies, however, did not find an association between cholesterol intake and colorectal cancer, including cohort studies from the United States and Finland [53–55] and case–control studies from Japan and the United States [56, 57]. An International Collaborative study from

Table 3. Odds ratios[a] (and 95% confidence interval) of selected types according to quartiles of dietary cholesterol, National Enhanced Cancer Surveillance System, Canada, 1994–1997

Types of cancer	Quartiles				*P* value for trend
	I (low)	II	III	IV (high)	
Controls (cholesterol cutpoint mg/week)	≤966.261	966.262–1412.753	1412.754–1880.265	≥1880.266	
Stomach	1.0 (ref.)	1.10 (0.87–1.39)	1.41 (1.10–1.80)	1.60 (1.21–2.13)	<0.0002
Colon	1.0 (ref.)	1.20 (0.98–1.47)	1.34 (1.08–1.68)	1.45 (1.12–1.87)	<0.005
Rectum	1.0 (ref.)	1.33 (1.08–1.65)	1.46 (1.15–1.85)	1.74 (1.32–2.28)	0.0001
Pancreas	1.0 (ref.)	1.14 (0.86–1.53)	1.52 (1.12–2.06)	1.57 (1.09–2.26)	0.01
Lung	1.0 (ref.)	1.17 (0.98–1.40)	1.30 (1.07–1.59)	1.61 (1.28–2.03)	<0.0001
Breast[b] (women)					
Breast cancer	1.0 (ref.)	1.20 (1.00–1.45)	1.32 (1.08–1.61)	1.45 (1.14–1.85)	0.002
Premenopausal women	1.0 (ref.)	1.04 (0.77–1.41)	1.10 (0.79–1.52)	1.10 (0.75–1.62)	0.58
Postmenopausal women	1.0 (ref.)	1.21 (0.93–1.56)	1.25 (0.94–1.65)	1.48 (1.07–2.07)	0.03
Ovarian	1.0 (ref.)	1.12 (0.80–1.60)	1.37 (0.95–1.97)	1.33 (0.85–2.07)	0.14
Prostate[b]	1.0 (ref.)	0.91 (0.74–1.11)	0.91 (0.73–1.15)	0.66 (0.50–0.86)	0.01
Testics[b]	1.0 (ref.)	1.01 (0.72–1.41)	1.00 (0.69–1.45)	0.94 (0.61–1.44)	0.76
Kidney	1.0 (ref.)	1.03 (0.84–1.26)	1.14 (0.91–1.42)	1.41 (1.08–1.83)	0.006
Bladder	1.0 (ref.)	1.25 (0.99–1.58)	1.26 (0.97–1.64)	1.54 (1.14–2.08)	0.01
Brain	1.0 (ref.)	0.95 (0.75–1.19)	0.83 (0.64–1.07)	0.97 (0.72–1.30)	0.69
Non-Hodgkin's lymphoma	1.0 (ref.)	1.12 (0.91–1.35)	1.25 (1.02–1.53)	1.36 (1.07–1.73)	0.009
Leukemia	1.0 (ref.)	1.16 (0.93–1.46)	1.31 (1.02–1.67)	1.20 (0.90–1.60)	0.20

[a]Adjusted for sex, age group (20–49, 50–59, 60–69, 70–76), province, education, body mass index (<25, 25–29.9, ≥30), alcohol drinking (grams/day), pack year smoking, total of vegetable and fruit intake (servings/week), saturated fat (servings/week) and total energy intake; also adjusted for strenuous and moderate activity for colon and rectum cancer; also adjusted for number of live births and years of menstruation for ovarian cancer; number of live births, age at first menstruation, number of live births for premenopausal breast cancer and number of live births and age at first pregnancy for breast for postmenopausal breast cancer.

[b]The cholesterol cutpoint for men: ≤1037.338, 1037.339–1496.258, 1496.259–2026.534, ≥2026.535, and for women: ≤886.028, 886.029–1272.655, 1272.656–1693.53, ≥1693.54.

11 population studies in eight countries considering 10-year cancer mortality also found nonsignificant association between circulating cholesterol level and colon cancer death [11].

In our study, cholesterol intake was associated with an increased risk of pancreatic cancer, as also found in some case–control studies [30, 58–60]. In contrast, total serum cholesterol (TSC) was inversely related to pancreas cancer in a cohort study [61]. No association was seen in other case–control [35, 62, 63] and cohort studies [36, 64].

The Atherosclerosis Risk in Communities cohort study indicated that lung cancer incidence was related to low plasma HDL-C, specifically among former smokers [25]. The Western Electric Study [65] and two case–control studies [66, 67] reported positive associations between cholesterol intake and lung cancer risk, in agreement with our findings. The association was more evident for cholesterol from eggs and persisted after adjustment for serum cholesterol [65]. Increased cholesterol intake was associated with lung cancer in men only and apparently restricted to current heavy smokers and squamous and small-cell types of lung cancer [67]. Our data showed that cholesterol intake was associated with lung cancer in both men and women aged ≥60. A number of cohort studies did not support the association [68–72]. However, a study based on a 10-year follow-up found that lung cancer death was inversely associated with cholesterol level in the first year only, pointing to a possible role of reverse causation [11].

Some cohort [73, 74] and case–control studies [75], including our data, reported that an elevated risk of breast cancer was associated with increased dietary cholesterol intake; however, this did not emerge in other cohort studies [76, 77] as well as in a pooled analysis of eight cohort studies [78]. There was no association between TSC and the risk of breast cancer among postmenopausal Korean women [22]. With specific reference to types of serum cholesterol, some case–control studies reported that HDL-C was inversely association with breast cancer [79], specifically among premenopausal women [23]. Cohort studies also observed an inverse association with breast cancer among postmenopausal women [27], and low HDL-C was associated to an increased breast risk in premenopausal women [26].

A cohort study including 35 cases of ovarian cancer indicated that high serum cholesterol levels were associated with an increased risk [17]. Another cohort study reported that dietary cholesterol was related to ovarian cancer [80]. Two case–control studies reported that egg cholesterol, rather than other sources of cholesterol, was positively associated with ovarian cancer [81, 82]. Our data did not show that cholesterol intake was associated with ovarian cancer. This was consistent with an Italian case–control study [37] and a pooled analysis of 12 cohort studies [83].

Our study found that cholesterol intake was inversely associated with prostate cancer. No association was seen in

Table 4. ORs[a] (95% CIs) and *P* value for trends of selected cancer sites for cholesterol intake for subjects in the highest versus the lowest quartile by sex and age, National Enhanced Cancer Surveillance System, Canada, 1994–1997

Types of cancer	ORs[a] (95% Cis) and *P* value for trends					
	Sex		Age in men		Age in women	
	Men	Women	≤59	≥60	≤59	≥60
Stomach	1.26 (0.87–1.81)	2.15 (1.34–3.45)	0.99 (0.54–1.83)	1.48 (0.94–2.33)	1.23 (0.55–2.75)	3.12 (1.73–5.63)
P	0.15	0.0002	0.59	0.14	0.39	<0.0001
Colon	1.27 (0.89–1.81)	1.58 (1.06–2.35)	0.75 (0.39–1.42)	1.65 (1.08–2.52)	1.90 (1.00–3.63)	1.42 (0.86–2.35)
P	0.25	0.01	0.30	0.02	0.07	0.06
Rectum	1.59 (1.10–2.30)	1.86 (1.22–2.85)	1.03 (0.54–1.95)	2.01 (1.27–3.18)	1.63 (0.87–3.07)	2.07 (1.16–3.70)
P	0.01	0.004	0.73	0.005	0.15	0.01
Pancreas	1.24 (0.75–2.05)	1.98 (1.14–3.45)	1.71 (0.68–4.30)	2.24 (1.12–4.50)	1.23 (0.54–2.77)	1.76 (0.94–3.28)
P	0.18	0.01	0.22	0.03	0.57	0.09
Lung	1.47 (1.07–2.02)	1.68 (1.20–2.36)	1.52 (0.79–2.93)	1.54 (1.07–2.22)	1.04 (0.61–1.77)	2.36 (1.52–3.68)
P	0.01	0.001	0.18	0.02	0.72	0.0001
Kidney	1.31 (0.95–1.81)	1.60 (1.09–2.35)	1.23 (0.70–2.14)	1.46 (0.89–2.37)	1.86 (1.07–3.23)	1.39 (0.81–2.37)
P	0.16	0.009	0.40	0.12	0.008	0.35
Bladder	1.32 (0.89–1.96)	1.92 (1.13–3.29)	0.85 (0.40–1.80)	1.77 (1.11–2.83)	1.53 (0.64–3.65)	2.20 (1.10–4.40)
P	0.29	0.01	0.74	0.01	0.30	0.03
Non-Hodgkin's lymphoma	1.16 (0.83–1.62)	1.60 (1.13–2.27)	0.90 (0.55–1.48)	1.56 (0.98–2.47)	1.77 (1.08–2.92)	1.73 (1.05–2.84)
P	0.27	0.008	0.70	0.03	0.006	0.10

[a]Adjusted for sex, age group (20–49, 50–59, 60–69, 70–76), province, education, body mass index (<25, 25–29.9, ≥30), alcohol drinking (grams/day), pack year smoking, total of vegetable and fruit intake (servings/week), saturated fat (servings/week) and total energy intake and also adjusted for strenuous and moderate activity for colon and rectum cancer.
OR, odds ratios; CI, confidence interval.

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a case–control study from Italy [38]. Several cohort studies from the United States observed that men with low plasma/or serum cholesterol were less likely to develop high-grade prostate cancer, especially organ-confined cases [18, 19, 24]. Low HDL-C was associated to increased risk of prostate cancer in a case–control study from North Dakota, the United States [28]. Another cohort study from Japan indicated that high serum cholesterol level was associated with the risk of advanced prostate cancer [14].

In our study, no significant association was observed between dietary cholesterol and testicular cancer. There are only a few other studies on cholesterol and testicular cancer. A cohort study observed that high serum cholesterol was associated with the risk of testicular cancer [20]. A case–control study also reported a positive association between dietary cholesterol intake and testicular cancer [84].

A USA case–control study reported that dietary cholesterol intake was associated with an elevated risk of renal cell carcinoma (RCC) [31], in agreement with our data. However, no association emerged either in another case–control study [40] or in the European Prospective Investigation into Cancer and Nutrition [39]. A pooled analysis of 13 cohort studies also did not found that cholesterol intake was related to RCC [85].

Studies on cholesterol and cancers of the bladder, brain, NHL and leukemia are sparse. A case–control study reported that dietary cholesterol was inversely associated with adult glioma [86], but no association was observed in another one [87]. A cohort study observed that high HDL-C was inversely related to NHL during the first 10 years but not with diagnoses during later follow-up [29]. Our study showed that high dietary cholesterol was positively associated with bladder cancer and NHL, but there was no significant association with brain cancer.

Ecological studies form China showed that low dietary cholesterol were correlated to cancers of the liver [88], colon [88], rectum, lung, female breast, childhood leukemia, adult leukemia, childhood brain, adult brain, stomach and esophagus [89]. This, however, may reflect the correlation between poor nutrition and cancer in several areas of China in the past.

An Austrian 19-year follow-up study on TSC and cancer incidence found that the overall cancer risk in men and women was significantly decreased for subjects in the highest TSC for malignancies diagnosed shortly after baseline TSC measurement, while after 5, 12 or 24 months, overall cancer risk was not significantly associated with TSC [90]. The short-term inverse association of TSC with cancer was restricted to digestive sites and lymphoid and hematopoietic tissue. Another study found that subjects dying in the first year after diagnosis had markedly lower cholesterol levels, but no significant difference was seen in the later years [11]. A strong time-dependent association of cholesterol and cancer could be explained by the preclinical cancer effect [11, 90].

Several mechanisms have been proposed to explain the possible role of cholesterol in cancer development. Alterations in lipid and apolipoprotein levels could contribute to cellular inflammation [91]. Decreased levels of HDL-C and increased low-density lipoprotein cholesterol (LDL-C) and total cholesterol levels have been related to increased levels of proinflammatory cytokines, including tumor necrosis factor-α and interleukin-6 [92]. The Framingham Offspring Cohort study suggested that elevated serum iron levels coupled with either high very low density lipoprotein cholesterol or low HDL-C appeared to interact to increase cancer risk [93]. Another cohort study indicated that independent elevations of either iron or total cholesterol were not significantly related to the development of cancer, but a combination of iron and total cholesterol above the 75th percentile was associated with significant increases in the risk of all cancers and supported the theory that the iron-induced oxidation of serum lipids is important in the pathogenesis of cancer [94].

We had an estimate of dietary intake of total cholesterol but no information on various serum lipoproteins. Thus, the findings of this study should essentially be viewed as an indication that diet rich in meat, dairy products, eggs (and hence animal fat) is an unfavorable indicator of the risk of several common cancers in the Canadian general population. The data have been collected between 1994 and 1997. Dietary cholesterol intake may have changed over recent years, but this cannot substantially influence the patterns of risk observed. We were unable, however, to investigate cholesterol intake over time. The present findings showed an association between cholesterol intake and cancer in the short term before the cancer occurrence. Cancer incidence for various Canadian Provinces registration has long been considered reliable.

This is a large population-based study from 8 of 10 Canadian provinces, based on a widely used and validated FFQ [44]. Information was collected on dietary habits 2 years before the study. Still, the possibility of misclassification of diet (recall bias) cannot be excluded. Nondifferential misclassification between cases and controls would likely bias the ORs towards unity in most instances [95]: consequently, the actual risks may be stronger than observed. Cases might report their food intake differently than controls. However, in general, knowledge on a possible link between cholesterol intake and cancer risk is not widespread, as compared with knowledge on cardiovascular diseases. The project was presented to subjects as a 'Canadian Study of Health and the Environment', thus reducing the scope for differential reporting. Furthermore, it has been shown that recall of FFQ data by controls is satisfactorily reproducible [96].

About 14% of the cancer cases were not included in this study (either were too ill or had died). However, the response rate for cases and controls was satisfactory, with about two-third of cases and controls participating. The present results are, therefore, unlikely to be substantially influenced by selection bias. In addition, we were able to allow in the analyses for a large number of potential confounding factors, including education, BMI, alcohol, tobacco, vegetable and fruit consumption and total energy intake.

Our findings add evidence that a diet low in cholesterol may not only prevent cardiovascular diseases [2, 3] but also may reduce the risk of several cancers. Limitation of dietary (animal) fat and cholesterol intake is therefore a favorable public health measure for cancer prevention [97].

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disclosure

The authors declare no conflict of interest.

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