A Case-Control Study of Diet and the Risk of Ovarian Cancer

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Abstract

Epidemiologic studies have suggested that some dietary factors may play a role in the etiology of ovarian cancer, but the findings have been inconsistent. We assessed the association of ovarian cancer with dietary factors in a population-based case-control study in Canada. Diet information was collected on 442 incident cases of ovarian cancer diagnosed in 1994 to 1997 and 2,135 population controls via a self-administered questionnaire. Compared with women in the lowest quartile of cholesterol intake, those in the second, third, and fourth quartiles had a multivariate adjusted odds ratio [OR; 95% confidence interval (95% CI)] of 1.12 (0.81–1.56), 1.20 (0.85–1.68), and 1.42 (1.03–1.97), respectively (*P* for trend = 0.031). Higher egg consumption was also associated with a nonsignificant increase in ovarian cancer risk. The ORs (95% CIs) for ovarian cancer were 0.77 (0.60–1.04) and 0.76 (0.56–0.99) among women in the highest quartile of total vegetable and cruciferous vegetable intake as compared with women in the lowest quartile. Women who took supplements of vitamin E, β-carotene, and B-complex vitamins for ≥10 years had ORs (95% CIs) of 0.49 (0.30–0.81), 0.31 (0.11–0.91), and 0.61 (0.36–1.05), respectively. However, we did not observe an association of ovarian cancer risk with dietary fat intake, including saturated, monounsaturated, and polyunsaturated fatty acids, protein, carbohydrate, dietary fiber, fruit, dairy products, meat products, fish, chicken, grain products, nut products, baked desserts, margarine, butter, mayonnaise, and supplement of multiple vitamins, vitamin A, vitamin C, calcium, iron, zinc, and selenium. Our findings suggested that ovarian cancer risk was positively associated with higher consumption of dietary cholesterol and eggs and inversely associated with higher intake of total vegetables and cruciferous vegetables and supplementation of vitamin E, β-carotene, and B-complex vitamins. (Cancer Epidemiol Biomarkers Prev 2004;13(9):1521–7)

Introduction

Ecological studies found that international rates of ovarian cancer incidence and mortality differed among countries by as much as 5-fold (1). The highest incidence areas were in Europe (especially Nordic countries and the United Kingdom) and North America (2). One study reported that ovarian cancer rates increased among women who emigrated from Japan, a country with low incidence, to the United States (3). These observations suggest that environmental factors, including diet, may play a role in the etiology of ovarian cancer and account for some of the international or ethnic variations in ovarian cancer rates.

However, the results of previous studies on the association of dietary factors with the risk of ovarian cancer at the individual level were mixed. Several case-control studies (4-10) and a meta-analysis (11) observed a positive association between dietary fat and ovarian cancer, whereas two cohort studies (12, 13) and other case-control studies (14-20) did not show similar results. Some studies also found that consumption of dairy products was related to a higher occurrence of ovarian cancer (4, 6, 8, 10, 13, 21, 22); however, others failed to replicate this association (14-16, 18, 23-27). Furthermore, some investigators reported that ovarian cancer risk was associated with other dietary factors, such as vegetable (5, 9, 10, 13, 15, 17, 23, 27) consumption (inversely associated) and dietary cholesterol (7, 13, 28, 29) and egg (7, 12, 13, 28, 30) consumption (positively associated), although these relations were not shown in other studies. Studies on the association of ovarian cancer with vitamins or minerals from foods or supplements also showed inconsistent results, for example, both protective effects for vitamin E (17, 31, 32), β-carotene (7, 17, 20, 23, 32), vitamin A (17, 33), and vitamin C (31) and no effects for vitamin E (13, 34), β-carotene (13, 16, 26, 34), vitamin A (10, 13, 26, 34), and vitamin C (13, 16, 19, 20, 32-34).

These inconsistent results indicated a need for more studies to examine the effect of these dietary factors on the risk of ovarian cancer. Therefore, we further assessed the association of certain dietary factors with

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ovarian cancer using data from the Canadian National Enhanced Cancer Surveillance System (NECSS), which collected detailed information on diet and other risk factors.

Materials and Methods

Study Population. Initiated in 1994 in Canada, the NECSS was a multicenter and multicomponent project undertaken collaboratively by Health Canada and the provincial cancer registries. The case-control component included individual data from 21,020 Canadians with 1 of 19 types of cancers and 5,039 population controls ages 20 to 76 years. The data were collected between 1994 and 1997 in 8 of 10 Canadian provinces (Alberta, British Columbia, Manitoba, Newfoundland, Nova Scotia, Ontario, Prince Edward Island, and Saskatchewan). The respective ethics review boards of each province reviewed and approved the study proposal. The current analysis was based on 442 incident cases of ovarian cancer and 2,135 female controls from all eight provinces, except Manitoba.

All ovarian cancer cases included in the NECSS were histologically confirmed as primary cancer defined as code C56 by the *International Classification of Diseases for Oncology, Second Edition*. The cases were incident cancer, newly diagnosed between 1994 and 1997 in the seven participating provinces. The cancer registries identified most cases within 1 to 3 months of diagnosis through pathology reports to decrease the loss of subjects caused by severe illness and death. The registries identified 782 women with ovarian cancer. Physicians refused consent to contact the cases for 49 (6.3%) subjects, and 89 (11.4%) cases had died before they could be sent questionnaires. Questionnaires were sent to 644 cases; 20 questionnaires were returned because of an incorrect address and no updated address could be found through publicly available sources. Of the 624 cases contacted, 442 completed and returned the questionnaires (68.6% of 644 eligible cases and 56.5% of ascertained cases).

The NECSS used frequency matching to the overall case group (19 types of cancers) to select population controls with similar age and sex distribution, so that there would be at least one control for every case within each sex and 5-year age group for any specific cancer site within each province. The sampling strategy for control selection varied by province depending on data availability, data quality (completeness and timeliness), and the confidentiality restrictions of provincial databases. Ontario used the Provincial Ministry of Finance Property Assessment databases to create a stratified random sample. Prince Edward Island, Nova Scotia, Saskatchewan, and British Columbia used databases of provincial health insurance plans to recruit a random sample of the provincial population stratified by age group and sex. Newfoundland and Alberta used random digit dialing to obtain a population sample.

The provincial cancer registries recruited 3,578 potential female controls without cancer selected in the seven provinces studied and mailed these females the same questionnaires as those sent to cases. For 286 (8.0%) of these women, the questionnaires were returned with an incorrect address and no updated one could be found. In all, 2,339 female controls completed and returned the questionnaires, representing 71.0% of those contacted and 65.4% of those ascertained. However, 204 female controls were excluded from our analysis because they had both ovaries removed at least 2 years before interview.

Data Collection. The registries used the same protocol to collect data for both cases and controls. Data were collected by a self-administered questionnaire and telephone follow-up for clarification and completeness.

Each subject was assigned a reference date defined as 2 years before interview. The questionnaires were designed to obtain detailed data on risk factors for cancers. The questionnaire collected information on education, average family income over the last 5 years, marital status, ethnic group, height, weight, recreational physical activity, alcohol consumption, diet, and vitamin and mineral supplements for the subject's reference date. Questionnaires also gathered information about smoking history, menstrual and reproductive history, employment history, residential history, and history of occupational exposure to some specific carcinogens.

Assessment of Dietary Intake. The questionnaire gathered diet information from 2 years before interview using a 69-item food frequency instrument and general changes in the diet as compared with 20 years ago. The diet component of the questionnaire was designed based on two validated instruments: the National Cancer Institute's Block Questionnaire (35) and the instrument used in the Nurses' Health Study cohort (36), with minor modification to account for the difference between the Canadian diet and the American diet. These two instruments were widely used in studies on diet and cancer.

For each food or beverage item, a commonly used portion or serving size was specified. The respondent indicated the usual frequency of consumption of that portion size for each food item by choosing one of nine categories: 0 or <1 per month, 1 to 3 per month, 1 per week, 2 to 4 per week, 5 to 6 per week, 1 per day, 2 to 3 per day, 4 to 5 per day, or ≥6 per day. The quantity of each food item consumed on a weekly basis was calculated as the product of frequency and serving size. The nutrient content of foods was determined from food composition data using the Canadian Nutrient Guide (37). We calculated the weekly intake levels of each nutrient for each item in the diet questionnaire by multiplying the quantity per week for each item with the associated nutrient value. We obtained the total intake of each nutrient as the sum of the weekly intake levels for all 69 items.

Assessment of Other Factors. Data on frequency and duration of 12 types of most common recreational physical activity in Canada were collected. The intensity of each reported activity was estimated by assigning a specific metabolic equivalent value, which was abstracted from the Compendium of Physical Activities (38, 39). The metabolic equivalent scores for 12 activities were multiplied by the midpoint of the reported frequency of the activity, converted to frequency of activity per week, and summed to create a composite index of total recreational physical activity per week.

Statistical Analysis. We evaluated risks of ovarian cancer associated with different levels of various dietary

factors. We computed the odds ratios (OR) and corresponding 95% confidence intervals (95% CI) using unconditional logistic regression modeling with the software package SAS (version 8). The dietary factors of interest were categorized by quartiles or by other appropriate cut points when necessary. The quartile cut points were based on the distribution in the control population.

We assessed the potential confounding effect of a wide range of factors, including age, province of residence, educational level, family income adequacy, marital status, ethnic group, alcohol consumption, body mass index (BMI), and total calorie intake. To analyze nutrients that are highly collinear with total energy intake, we adjusted for total energy intake by using the residual method proposed by Willett et al. (40). We assessed two models: model 1 that adjusted for only 10-year age groups and province of residence and model 2 that allowed for more potential confounders. Potential confounders included in model 2 were 10-year age groups, province of residence, alcohol consumption (servings per week, continuous), smoking pack-years (continuous), recreational physical activity (frequency per week, quartiles), education (<10, 10–12, or >12 years), BMI (<25, 25–30, or >30 kg/m^2), total caloric intake (kcal/wk, continuous), number of live births (0, 1, 2, 3, or ≥4), years of menstruation (continuous), and menopausal status (yes or no). Because the risk estimates for models 1 and 2 were similar, only the results for model 2 were presented. The tests for trend of categorized data for all models were conducted by treating different categories as a single ordinal variable.

Because Ontario also collected information on family history with cancer (first-degree relatives), oral contraceptive use, and hormone replacement therapy, and because these factors have been suggested as risk factors for ovarian cancer, we modified our analysis for this province and adjusted models for family history, oral contraceptive use, and hormone replacement therapy in addition to the above-mentioned variables.

Results

Table 1 displays selected characteristics of cases with ovarian cancer and controls. Both groups were similar in their mean age, total years of education, alcohol consumption, marital status, and years of menstruation. Compared with controls, cases were more likely to be postmenopausal, to have consumed more calories, to be obese, to have smoked slightly longer in pack-years, to have had fewer live births, and to be less physically active. In Ontario, more cases had first-degree relatives with cancer and breast cancer, slightly fewer cases used oral contraceptives, and more cases took hormone replacement therapy as compared with controls.

Table 2 shows the risks of ovarian cancer associated with intakes of some food groups. Compared with women in the lowest quartile of cholesterol consumption, those with higher cholesterol intake had higher risks of ovarian cancer, with the multivariate adjusted ORs (95% CIs) of 1.12 (0.81–1.56), 1.20 (0.85–1.68), and 1.42 (1.03–1.97) corresponding to the second, third, and fourth quartiles of cholesterol intake (P for trend = 0.031). Women in the highest quartile of egg intake were at a nonsignificant increased risk of ovarian cancer as compared with those in the lowest quartile (OR, 1.30; 95% CI, 0.96–1.73). Women in the highest quartile of

Table 1. Characteristics of ovarian cancer cases and controls (n = 2,577), NECSS, Canada, 1994–1997

Characteristics	Cases (n = 442)	Controls (n = 2,135)	P
Age, y (mean ± SD)	55.1 ± 12.3	55.2 ± 12.5	0.91
Education, y (mean ± SD)	12.3 ± 3.3	12.2 ± 3.6	0.44
Alcohol consumption, drinks/wk (mean ± SD)	2.2 ± 4.3	2.6 ± 5.4	0.16
Smoking pack-years (mean ± SD)	8.4 ± 12.5	7.5 ± 12.8	0.15
BMI, kg/m^2 (mean ± SD)	26.3 ± 6.6	25.2 ± 5.2	0.0002
Total caloric intake, kcal/wk, quartiles (mean ± SD)	13,127 ± 5,201	12,769 ± 6,788	0.19
Total recreational physical activity, frequency/wk, quartiles* (mean ± SD)	22.5 ± 22.1	25.3 ± 22.8	0.016
Years of menstruation (mean ± SD)	31.8 ± 8.0	31.8 ± 7.8	0.96
Menopause status (%)			
Premenopausal	29.9	38.3	
Postmenopausal	70.1	61.7	
No. live births (%)			
0	24.1	15.1	
1	12.3	9.9	
2	28.2	29.0	
3	20.9	19.3	
≥4	14.5	26.7	
Marital status (%)			
Married	67.2	67.3	
Common law	2.7	3.2	
Divorced/separated	11.3	9.3	
Widowed	10.0	13.9	
Single	8.6	5.9	
Other	0.2	0.3	
Family income adequacy (%)			
Low	14.9	16.7	
Lower middle	17.4	16.6	
Upper middle	22.2	23.5	
High	19.9	14.8	
Missing	25.6	28.4	
Smoking status (%)			
Never smoker	46.8	50.8	
Ex-smoker	33.5	29.0	
Current smoker	19.7	20.1	
Information collected in Ontario Province only			
First relative with cancer (%)			
No	43.7	59.0	
Yes	56.3	41.0	
First relative with breast cancer (%)			
No	89.1	91.3	
Yes	10.9	8.7	
Use oral contraceptive ≥6 mo (%)			
No	55.0	53.1	
Yes	45.0	46.9	

*Composite index of total recreational physical activity.

Table 2. OR of ovarian cancer associated with intake of food groups, NECSS, Canada, 1994–1997

Food group	Quartiles of intake							*P* for trend
	Q1*	Q2		Q3		Q4		
		OR†	95% CI	OR†	95% CI	OR†	95% CI	
Protein, g/wk	1.00	0.87	0.63–1.19	0.86	0.62–1.17	1.00	0.73–1.35	0.99
Carbohydrate, g/wk	1.00	0.91	0.67–1.24	0.80	0.58–1.10	0.91	0.67–1.25	0.42
Total fat, g/wk	1.00	1.11	0.81–1.52	1.02	0.74–1.41	1.21	0.88–1.65	0.34
Cholesterol, g/wk	1.00	1.12	0.81–1.56	1.20	0.85–1.68	1.42	1.03–1.97	0.031
Total dietary fiber, g/wk	1.00	1.05	0.73–1.36	0.95	0.69–1.31	0.91	0.66–1.25	0.27
All vegetables, servings/wk	1.00	1.02	0.75–1.39	0.95	0.75–1.39	0.77	0.60–1.04	0.15
All vegetables and vegetable juice, servings/wk	1.00	0.90	0.66–1.23	1.03	0.76–1.41	1.07	0.78–1.46	0.52
All fruit, servings/wk	1.00	1.01	0.73–1.39	0.98	0.71–1.36	1.12	0.80–1.57	0.37
All juice, 4 oz/wk	1.00	0.98	0.71–1.36	1.00	0.73–1.36	0.91	0.66–1.27	0.63
All dairy products, servings/wk	1.00	0.98	0.71–1.35	0.98	0.71–1.35	1.20	0.89–1.62	0.25
All meat product, servings/wk	1.00	0.76	0.55–1.04	0.82	0.59–1.12	0.91	0.67–1.24	0.73
Fish, 4 oz/wk	1.00	0.97	0.71–1.32	0.83	0.59–1.16	1.16	0.85–1.59	0.50
Chicken, 4 oz/wk	1.00	0.95	0.69–1.32	1.25	0.91–1.70	0.99	0.71–1.37	0.61
All grain products, servings/wk	1.00	0.94	0.68–1.29	1.21	0.89–1.65	0.87	0.63–1.20	0.80
All whole grain products, servings/wk	1.00	1.10	0.78–1.55	1.21	0.91–1.85	1.10	0.77–1.58	0.36
Nut products, servings/wk	1.00	1.22	0.89–1.67	1.04	0.75–1.45	1.13	0.82–1.55	0.78
Baked desserts, servings/wk	1.00	1.09	0.80–1.51	1.14	0.83–1.57	1.00	0.71–1.41	0.93
Egg, average no./wk	1.00	0.96	0.68–1.35	1.00	0.73–1.39	1.30	0.96–1.73	0.13
Margarine, butter, and mayonnaise, servings/wk	1.00	1.07	0.78–1.46	1.04	0.75–1.42	1.17	0.85–1.61	0.38

*Reference category.
†OR adjusted for 10-year age group, province of residence, education, alcohol consumption, cigarette pack-years, BMI, total caloric intake, recreational physical activity, number of live births, menstruation years, and menopause status.

total vegetable intake were at a nonsignificant decreased risk (OR, 0.77; 95% CI, 0.60–1.04). However, we did not observe a positive association between risk of ovarian cancer and total fat intake after accounting for total energy intake. Furthermore, we did not find any relation between risk of ovarian cancer and consumption of protein, carbohydrate, total dairy products, total meat products, fish, chicken, all grain products, whole grain products, baked desserts, added fat (margarine, butter, and mayonnaise), total vegetables and vegetable juice, fruit, juice, or nut products.

Table 3 gives the ORs for ovarian cancer associated with intakes of some food subgroups. We found a marginally significant trend of decreasing risk of ovarian cancer with increasing intake of cruciferous vegetables (*P* for trend = 0.048), with an OR (95% CI) of 0.76 (0.56–0.99) for the highest quartile of intake. However, we observed no association between risk of ovarian cancer and consumption of carrots and tomatoes. We saw no evidence of any pattern of association of ovarian cancer risk with any subtype of fatty acid, including saturated, monounsaturated, and polyunsaturated fatty acids; with any dairy product, including all milk, low-fat milk, low-fat and skim milk, cheese, and ice cream; or with fresh red meat and processed meat.

We assessed the risks of ovarian cancer associated with intakes of some vitamin supplements (Table 4). Compared with women who never took vitamin supplements, those with ≥10 years of vitamin supplementation had a statistically significant decrease in risk of ovarian cancer for β-carotene (OR, 0.31; 95% CI, 0.11–0.91) and vitamin E (OR, 0.49; 95% CI, 0.30–0.81), and a nonsignificant decrease for B-complex vitamins (OR, 0.61; 95% CI, 0.36–1.05). We did not observe any risk of ovarian cancer significantly related to consumption of multiple vitamins, vitamin A, vitamin C, calcium, iron, zinc, or selenium.

When we restricted our analysis to the province of Ontario and the risk estimates were further adjusted for oral contraceptive use, hormone replacement use, and family history with cancer, we did not find any substantial difference in the relation of ovarian cancer risk to the above-mentioned variables between subjects in the Ontario and all study subjects (data not shown).

Discussion

Our study found that several dietary factors were associated with ovarian cancer risk. Higher dietary cholesterol intake seemed to increase ovarian cancer risk. Egg consumption was positively, but not significantly, associated with an elevated risk. Higher intake of total vegetables and cruciferous vegetables was associated with a decreased risk of ovarian cancer. In addition, ≥10 years of β-carotene, B-complex vitamin, and vitamin E supplementation reduced the risk of ovarian cancer. However, we found little evidence that the risk of ovarian cancer was related to other dietary factors.

The positive association between ovarian cancer risk and cholesterol observed in our study agrees with one cohort study (13) and two case-control studies (7, 28). One nested case-control study of 35 cases and 67 controls in the United States also found that women with a higher serum cholesterol level had an increased risk of ovarian cancer as compared with women who had a lower cholesterol level (29). However, other studies (12, 15, 17, 19, 41) reported no such association. A case-control study of 84 cases and 629 controls in Mexico even found an inverse association between cholesterol intake and risk of ovarian cancer (16). Risch et al. (7) suggested that dietary cholesterol might influence the risk of ovarian cancer through elevated circulating estrogen (or progesterone)

Table 3. OR of ovarian cancer associated with intake of food subgroups, NECSS, Canada, 1994–1997

Food group	Quartiles of intake							*P* for trend
	Q1*	Q2		Q3		Q4		
		OR†	95% CI	OR†	95% CI	OR†	95% CI	
Fatty acid, g/wk								
Saturated	1.00	0.85	0.61–1.16	1.02	0.74–1.39	1.06	0.78–1.45	0.45
Monounsaturated	1.00	1.09	0.79–1.50	1.15	0.83–1.59	1.26	0.92–1.72	0.14
Polyunsaturated	1.00	1.13	0.83–1.55	1.09	0.79–1.49	1.28	0.94–1.76	0.16
Vegetables, 0.5 cup/wk								
Cruciferous vegetables	1.00	0.81	0.60–1.10	0.80	0.59–1.10	0.76	0.56–0.99	0.048
Tomatoes	1.00	1.24	0.90–1.71	1.20	0.88–1.63	1.23	0.86–1.75	0.30
Carrots	1.00	0.96	0.67–1.36	1.12	0.80–1.57	0.99	0.66–1.48	0.69
Dairy product								
All milk, 8 oz/wk	1.00	1.03	0.75–1.43	1.18	0.86–1.61	1.25	0.91–1.69	0.11
Low-fat milk, 8 oz/wk	1.00	0.91	0.66–1.27	1.19	0.88–1.62	0.93	0.68–1.59	0.88
Low-fat/skim milk, 8 oz/wk	1.00	1.06	0.77–1.47	1.12	0.81–1.55	1.19	0.86–1.67	0.27
Cheese, no. of 1 oz/wk	1.00	0.70	0.50–0.96	0.96	0.71–1.30	0.86	0.63–1.17	0.75
Ice cream, no. of 0.5 cup/wk	1.00	1.03	0.74–1.42	0.89	0.64–1.25	1.17	0.85–1.61	0.45
Meat product, serving/wk								
Fresh red meat	1.00	0.80	0.59–1.09	0.75	0.54–1.03	0.78	0.57–1.06	0.104
Processed meat	1.00	0.77	0.55–1.07	0.89	0.64–1.24	0.98	0.72–1.33	0.82

*Reference category.
†OR adjusted for 10-year age group, province of residence, education, alcohol consumption, cigarette pack-years, BMI, total caloric intake, recreational physical activity, number of live births, menstruation years, and menopause status.

levels due to biosynthesis from increased dietary cholesterol precursors.

There are several published studies on the relation between egg consumption and risk of ovarian cancer. Our finding of an increased risk with higher egg consumption is consistent with three cohort studies (12, 13, 30) and two case-control studies (7, 28), although other studies did not have similar findings (5, 10). The studies by Risch et al. (7) and Pirozzo et al. (28) reported that cholesterol from eggs was associated with an increased risk of ovarian cancer, whereas cholesterol from other sources was not. Although the small nonsignificant increase in ovarian cancer risk among women with higher egg consumption observed in our study could be attributed to chance, it could also be related to the fact that eggs are among the richest sources of cholesterol commonly consumed by humans. However, Pirozzo et al. (28) suggested that the association was not due to the cholesterol in eggs and speculated that it could be the role of highly lipophilic organochlorine residues.

We did not find a relation between total fat intake and ovarian cancer risk, which concurs with two cohort studies (12, 13) and several case-control studies (14-20). However, our result is contrary to the findings of several

Table 4. OR of ovarian cancer associated with vitamin supplement, NECSS, Canada, 1994–1997

Vitamin supplement	Total years of vitamin supplement									*P* for trend
	0*	<1		1–5		6–9		≥10		
	OR	OR†	95% CI	OR†	95% CI	OR†	95% CI	OR†	95% CI	
Multiple vitamins	1.00	1.09	0.78–1.54	1.14	0.86–1.53	1.08	0.69–1.69	0.91	0.64–1.27	0.81
Vitamin A	1.00	1.31	0.84–2.06	1.05	0.66–1.68	1.06	0.47–2.42	0.58	0.30–1.14	0.38
β-carotene	1.00	1.14	0.73–1.76	1.18	0.75–1.80	0.76	0.25–2.29	0.31	0.11–0.91	0.031
B-complex vitamins	1.00	1.19	0.74–1.70	0.85	0.59–1.21	1.08	0.62–1.89	0.61	0.36–1.05	0.14
Vitamin C	1.00	1.36	0.98–1.87	1.08	0.80–1.45	0.93	0.57–1.51	0.80	0.56–1.16	0.30
Vitamin E	1.00	1.11	0.77–1.60	1.08	0.74–1.53	1.15	0.73–2.07	0.49	0.30–0.81	0.04
Calcium	1.00	1.19	0.85–1.67	1.10	0.82–1.52	0.93	0.54–1.59	0.82	0.53–1.28	0.56
Iron	1.00	1.05	0.58–1.73	1.18	0.86–1.63	1.21	0.62–2.38	1.04	0.60–1.80	0.53
Zinc	1.00	1.12	0.69–1.82	0.98	0.58–1.65	0.65	0.19–2.28	0.63	0.28–1.37	0.29
Selenium	1.00	1.41	0.76–2.61	1.24	0.65–2.69	0.91	0.25–3.32	0.55	0.18–1.68	0.73

*Reference category.
†OR adjusted for 10-year age group, province of residence, education, alcohol consumption, cigarette pack-years, BMI, total caloric intake, recreational physical activity, number of live births, menstruation years, and menopause status.

case-control studies (4-10) and a meta-analysis (11), which suggested a positive association. One possible explanation is the difference in methods used to adjust for total energy intake. We found a positive association between ovarian cancer and total fat intake when we used the standard method for adjusting total energy intake, but the positive association disappeared after we applied the residual method. All the studies with positive findings (4-10) did not adjust for total energy intake by the residual method or other methods. Five of eight studies included in the meta-analysis (11) were these same positive studies (4, 5, 7, 8, 10). Two other studies included (13, 19) used the residual method to adjust for total energy intake and reported no association. The other study (20) in the meta-analysis did not adjust for total energy intake by any method.

We also observed no association of ovarian cancer risk with consumption of various types of fat, including saturated, monounsaturated, and polyunsaturated fats. Several cohort (12, 13) and case-control studies (14, 15, 17, 19, 20) did not find any association either. An Italian case-control study even reported an inverse association between risk of ovarian cancer and consumption of total fat, monounsaturated, and polyunsaturated fatty acids (41).

Some studies reported an association of ovarian cancer risk with consumption of various dairy products, both a positive association with per capita milk consumption (22), all dairy products (13), whole milk (4, 6, 8), skim milk (13), cheese (21), and ice cream (8) and an inverse association with all dairy products (14), all kinds of milk (14, 24), skim or low-fat milk (4, 6, 8, 14, 26), and cheese (27). However, other investigations, including ours, failed to find an association with any dairy products (9, 15, 18, 23, 25).

The protective effect of consumption of total vegetables and cruciferous vegetables on ovarian cancer risk found in our study agrees with several others (5, 9, 10, 13, 15, 17, 23, 27). Similarly, the protective effect of vitamin E (17, 31, 32) and β-carotene (7, 17, 20, 23, 32) consumption (from supplements or diet) on the risk of ovarian cancer was also shown in other studies. On the other hand, some researchers reported no decrease in risk related to vitamin E (13, 34) and β-carotene (13, 16, 26, 34). The nonsignificant decrease in ovarian cancer risk for B-complex vitamins observed in our study could not be confirmed in other studies. Two studies were published on the association of ovarian cancer risk with vitamin B, with no association with vitamin B6 reported in one study (32), and an inverse association with vitamin B12 and no association with vitamin B6 observed in another study with only 84 cases (16).

Vegetables are rich in a variety of nutrients, including vitamins, trace minerals, and many other classes of biologically active compounds. Lampe (42) suggested that these phytochemicals may have complementary and overlapping mechanisms of action, including antioxidant activity, decreased platelet aggregation, modulation of detoxification enzymes, stimulation of the immune system, adjustment of steroid hormone concentrations, and hormone metabolism. Compounds in vegetables such as flavonoids have been shown to have potent antioxidant and anticarcinogenic properties (42-45). Other phytochemicals contained in vegetables could affect endogenous hormone levels through the change in bile acid metabolism and estrogen reabsorption or through competition with cholesterol as a substrate for steroid hormone synthesis (42, 46). A constituent of cruciferous vegetables may exert effects on estrogen metabolism by increasing estrone 2 hydroxylation (47, 48) or increasing urinary excretion of 2-hydroxylated estrogen (49). Vitamin E is an important lipid-soluble antioxidant, and animal and human studies have shown that vitamin E can prevent the formation of lipid peroxides, which have been observed to induce oxidant damage of DNA or lipid or protein (42, 50-54). β-carotene is also a potent antioxidant (42, 52, 55). In addition, vitamin E and β-carotene can improve immune function (56-60).

Some potential limitations of this study should be considered when interpreting the results. A major limitation is that 20.2% of the cases could not be included in this analysis because they died before they could be sent questionnaires or their physicians denied contact or could not be located and 23.3% of the cases did not return questionnaires. This low response rate among cases was largely due to the poor prognosis of ovarian cancer and could affect the generalization of our result. Specifically, our results might be generalizable only to less aggressive ovarian tumors or to subjects who were able to be diagnosed at the earlier stages or who responded better to treatment. Recall bias could be possible; however, awareness of any specific dietary hypothesis about the etiology of ovarian cancer was very limited in the public. Although we used a widely validated questionnaire, measurement error of dietary intakes could introduce misclassification in exposure status, but it is likely to be nondifferential. Our food frequency questionnaire inquired about only 69 items; therefore, our study did not capture all kinds of food consumed and underestimated total dietary intake. Because our questionnaire asked the diet information 2 years before recruitment into the study, the possibility could arise that the dietary exposure captured might have occurred after initiation of ovarian tumor development. The risk estimates in our study were not allowed for oral contraceptive use, hormone replacement therapy, and family history of cancer; however, when the analyses for subgroup from the province of Ontario were further allowed for these variables, the results did not materially differ.

In summary, our population-based case-control study found that women with higher consumption of dietary cholesterol and eggs were at increased risk of ovarian cancer. It also supported the findings that higher intakes of total vegetables and cruciferous vegetables as well as vitamin E and β-carotene supplementation were associated with reduced ovarian cancer risk. The protective effect of B-complex vitamin supplementation needs further study to confirm.

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