Dietary Fat Intake and Risk of Epithelial Ovarian Cancer

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Background: Evidence exists that dietary fat may be a contributory factor in the development of hormone-related cancers such as ovarian cancer. Previous studies have demonstrated significantly higher circulating-estrogen levels among nonvegetarian women than among vegetarian women; the increase correlated directly with consumption of saturated fat. However, the contribution that dietary fat plays in the development of hormone-related cancers remains unresolved. *Purpose:* Our purpose was to evaluate whether saturated fat intake increases the risk of ovarian cancer development. *Methods:* Population-based sampling was used to acquire cases and controls over a 3-year period from the study area, which included the highly populated region surrounding the western end of Lake Ontario, Canada. From the Ontario Cancer Registry, all histologically confirmed, primary malignant or borderline malignant epithelial ovarian tumors first diagnosed from November 1989 through October 1992 among study-area residents aged 35-79 years were determined. In total, 631 eligible case subjects were identified, of whom 450 (71.3%) were interviewed concerning reproduction and diet; 564 randomly selected population control subjects were similarly interviewed. From the quantitative diet-history information, average daily intakes of macronutrients and micronutrients were calculated. Unconditional continuous logistic regression methods were used for analysis, with adjustment for age at interview, number of full-term pregnancies, years of oral contraceptive use, and total daily caloric intake. *Results:* Saturated fat consumption was associated with increasing risk of ovarian cancer (odds ratio [OR] = 1.20 for each 10 g/day of intake; 95% confidence interval [CI] = 1.03-1.40; one-sided P = .0082). No relationship was seen with intake of unsaturated fats. Egg consumption also appeared related to increased risk (OR = 1.42 for each 100 mg of egg cholesterol per day; 95% CI = 1.18-1.72; two-sided P = .0002), though this association may have resulted from disease-related changes in the dietary practices of case subjects prior to diagnosis. Consumption of vegetable fiber (but not fruit or cereal fiber) was associated with decreased risk (OR = 0.63 for each 10 g/day; 95% CI = 0.49-0.80; two-sided P = .0001). All three nutrients (saturated fat, egg cholesterol, and vegetable fiber) remained statistically significant when included in the same regression model. *Conclusion:* Diet may contribute to risk of ovarian cancer development. *Implication:* If confirmed in further studies, this association may allow women to appreciably lower their risk of ovarian cancer through dietary modifications: reducing the intake of saturated fats and eating more vegetables. [J Natl Cancer Inst 86:1409-1415, 1994]

Ovarian cancer is a highly lethal malignancy, affecting close to 2% of the female population over their lifetimes. During the last 15 years, a number of hypotheses regarding the pathogenesis of this cancer have been suggested and explored (*1*). Although the mechanisms by which known exposure factors affect the risk of ovarian cancer development are still not well understood, there is ample evidence that pituitary and/or sex hormones play an important etiologic role (*2,3*). Perhaps the best established association with risk of ovarian cancer is the inverse relationship with parity. Women having multiple full-term pregnancies are at significantly decreased risk of developing ovarian cancer, with risk declining by about 15%-20% for each successive term pregnancy. This finding has been observed in virtually every study [12 studies summarized by Whittemore et al. (*4*); (*5-18*)]. In addition, an inverse association with risk of ovarian cancer has been seen according to duration of oral contraceptive use. For each year of oral contraceptive use, the risk seems to decrease by 5%-10%, and this finding, too, has appeared in most worl [10 of 12 studies summarized in (*4*) (*6,9,16-18*)].

Evidence exists that dietary fat may b a contributory factor in the developmen of hormone-related cancers (*19*). Studie (*20-22*) have demonstrated significantly higher circulating-estrogen levels among nonvegetarian women than among vegetarian women; the increase correlatec directly with consumption of saturated fat Also, international comparisons (*23,24*) have shown fairly sizable correlations between per-capita total fat or animal fat intake and ovarian cancer mortality. In three observational epidemiologic studies (*25-27*), case subjects scored significantly higher than control subjects on indices of animal-fat consumption.

The purpose of the present work was to evaluate whether saturated fat intake increases the risk of ovarian cancer development. Thus, we estimated past dietary intakes of subjects in a case–control study.

Subjects and Methods

Population-based sampling was employed to acquire cases and controls over a 3-year period from the study area, which included the regional municipalities of York, metropolitan Toronto, Peel, Halton, Hamilton-Wentworth, Waterloo, Brant, and Niagara and the city of Guelph. These contiguous regions encompass the highly populated area surrounding the western end of Lake Ontario. To ascertain cases, we regularly reviewed all relevant hospital and laboratory pathology reports received by the Ontario Cancer Registry. All histologically confirmed, primary malignant or borderline malignant epithelial ovarian tumors first diagnosed from November 1989 through October 1992 among Ontario residents aged 35-79 years were identified from these province-wide records. Those subjects living in the study area at the time of diagnosis were eligible for the study. In total, 631 eligible case subjects were identified, of whom 450 (71.3%) were interviewed; of the remainder, 55 (8.7%) had died, 29

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See "Notes" section following "References."

(4.8%) were too ill to be interviewed, 17 (2.7%) were lost to follow-up, and 50 (7.9%) refused to participate. One interviewed case subject was able to answer only the medical/reproduction history section of the questionnaire. Eighty-three (18.4%) of the 450 interviewed case subjects had tumors of borderline malignant histologic types. Because of the relatively short time from diagnosis to interview (approximately 12-14 weeks), fewer than 10% of eligible subjects had died and thus no proxy interviews were conducted.

A sample of controls was obtained from the Enumeration Composite Record listing of individuals maintained by the Ontario Ministry of Revenue. These records contain the name, address, age, and sex of every Ontario homeowner and tenant and their family members. From this listing, the Ministry provided names and addresses of a random sample of women residing in the study area during the same 3-year period; the sample was frequency matched by age within the groupings 35-49, 50-64, and 65-79 years to the expected distribution of case subjects, based on incidence tabulations from the Ontario Cancer Registry. For each age group, a fixed number of control subjects was sampled from the entire study area. Control subjects were initially contacted by letter, with follow-up by telephone, to confirm suitability for inclusion in the study; arrangements were then made for interview. Control women found to have had ovarian cancer or to have had bilateral oophorectomy performed 1 year or more in the past (and therefore not to be at risk of ovarian cancer) were considered ineligible and were excluded from the study (n = 103). As with the case subjects, this method of control selection included only living persons. In total, 873 eligible control women were identified, of whom 564 (64.6%) were interviewed. The remainder either refused (30.2%), were too ill (1.9%), or were lost to follow-up (3.2%).

Our questionnaire interview obtained detailed information regarding menstrual characteristics, pregnancies, hormone and oral contraceptive use, and infertility factors. The complete National Cancer Institute of Canada Epidemiology Unit diet-history questionnaire (*28,29*) was used to determine usual dietary practices; quantitative portion sizes were estimated with food models. The dietary instrument included questions on usual amounts and frequencies of consumption of more than 200 food items, consisting of all those appearing in the great majority of normal diets. For cooked items, the oil or fat used in cooking was determined. Information was also obtained on use of vitamins and other dietary supplements. The questions were the same for case subjects and control subjects, except that case subjects were asked about their typical diets prior to "when they became sick," whereas control subjects were asked about their diets during the previous year or two (thereby generally matching the recall time of the case subjects). All interviews were conducted in-person in the subject's home, after the study was explained to the subject and verbal agreement was obtained from her to proceed. Using these procedures, the study was approved by the Human Subjects Review Board of the Office of Research Administration at the University of Toronto.

To analyze the dietary information, we employed food-composition tables based on the U.S. Department of Agriculture Handbook No. 8 (*30*), modified nutrients (*31-34*). For food items that were not commonly marketed or that had recipes different from the standard or "homemade" ones of the tables, the actual recipes were obtained and the ingredients were coded singly. Data on the individual food items were converted to estimated average daily intake of calories, ethanol, and 45 macronutrients and micronutrients. Medians and 90% ranges for those nutrients relevant to the evaluation of saturated fat intake are given in Appendix Table 1. Because we were interested in examining the effects of both saturated fat and cholesterol, we also calculated average daily intake of cholesterol from eggs, which supply less than 5% of dietary saturated fat (*35*). To do this calculation, we used the food-composition table values restricted to the following egg food items: eggs (e.g., raw or cooked), baby-food eggs, egg salad, quiche, French toast, and eggnog. Small concentrations of egg are found in such foods as doughnuts, cakes, and pastries; however, these foods were not included in this calculation. "Other cholesterol" was calculated as the difference between intakes of total cholesterol and egg cholesterol. One egg contains about 275 mg cholesterol.

To analyze the data, multivariate unconditional continuous logistic regression methods were used, allowing for simultaneous examination of multiple exposure factors, reproductive and dietary, that may act to confound each other. The GLIM computer program (*36*) was employed. Both trends in risk odds with exposure (parameter estimates of slope) as well as relative odds by categories were examined. In general, the trend effects are reported at units of 75th percentile less 25th percentile (of the combined case–control distribution), rounded to one significant digit. Tests of statistical significance were based on differences in log-likelihood, with two-sided P values given, except we used one-sided P values for "univariate" saturated fat models, since our a priori hypothesis was that intake of this nutrient conveys increased risk. Each of the models in this work includes continuous variables denoting number of full-term pregnancies and duration of oral contraceptive use, as well as indicator terms for the age categories of the frequency matching (35-49, 50-64, and 65-79 years). Age as a continuous variable has also been included in all models in order to adjust for residual age effect. Terms representing years of schooling, race, country of birth, and having regularly used cigarettes or alcohol were not statistically significant and produced no odds-ratio changes in any of the dietary (or reproduction) variables; therefore, these terms were omitted from the models.

Finally, each of the regression models incorporates variables reflecting some measure of dietary reporting. As can be seen in Table 1 and in Appendix Table 1, a general tendency was present for the case subjects to report slightly more dietary information than the control subjects. We have considered adjustment either for total calories, or for total number of reported food items, total daily food intake, and height and weight at age 21.

Results

Both case and control subjects were predominantly white (96.4% and 96.1%, respectively) and, as expected from the frequency matching, they had mean ages at diagnosis or interview that were very close, 57.2 and 57.5 years, respectively (Table 1). Moreover, the average reported height and weight at age 21 were virtually the same. The current weight of control subjects tended to be about 3.5 kg higher than that of case with invasive tumor histologies but was similar to that of case subjects with borderline malignant histologies. Slightly more control subjects than case subjects were born in Canada or the United States; however, both groups had similar mean years of schooling.

The results in Table 2 indicate trends in risk with average daily intake of a number of nutrients relevant to the examination of saturated fat. For each nutrient two odds ratios are given: the first from models containing adjustment for total number and total daily weight of reported food items and height and weight at age 21 ("reporting-adjusted") and the second from models containing adjustment for total daily caloric intake ("calorie-adjusted"). All of the results to follow regarding indices of saturated fat and cholesterol intake were appreciably stronger and more statistically significant in the reporting-adjusted models. However, because inclusion of the calorie term in the reporting-adjusted model was quite significant ($P<10^{-5}$), we will place greater emphasis on the calorie-adjusted models. With calories included in the dietary models, height and weight at age 21 showed no associations with risk, and the removal of these terms left the other variables unchanged. We have therefore omitted these terms from the calorie-adjusted models.

Table 2 shows a trend in ovarian cancer risk according to intake of saturated fat, with odds increasing by 20% for each 10 g consumed per day. There was no evidence of an association with consumption of monounsaturated or polyunsaturated fat. When consumption of saturated fat was considered in terms of its fraction of total caloric intake, the association was somewhat stronger; as a percent of total fat intake, it was stronger still. Because intakes of saturated fat and cholesterol may be correlated (r = .7 among our control subjects; r = .7 among our case subjects), we considered whether the association with saturated fa

Table 1. Descriptive and reporting factors among ovarian cancer case subjects and control subjects, southern Ontario, 1989-1992

Factor	Case subject	Control subject
Mean age at diagnosis/interview, y	57.2	57.5
Percent born in Canada or United States	59.1	64.7
Mean years of schooling	12.3	12.5
Mean parity	1.90	2.45
Percent ever used oral contraceptives	38.7	49.6
Percent ever smoked cigarettes regularly	45.1	47.9
Mean height at age 21, cm	163.2	162.9
Mean weight at age 21, kg	55.0	55.3
Mean current weight, kg	63.2*	66.7
Mean No. of reported food items	99.3	96.
Mean total daily food consumption, g	3479.	3459.
Mean daily caloric intake	2313.†	2096.

*Mean current weight for borderline malignant cases was 67.2 kg.
†Mean caloric intake for borderline malignant cases was 2366. cal/day.

might be due to an association with cholesterol. Table 2 shows an association with intake of cholesterol. If cholesterol consumption is an independent risk factor for ovarian cancer, then cholesterol from egg sources, which supply more than 30% of dietary cholesterol but less than 5% of saturated fat (*35*), should convey increased risk. In our data, cholesterol from eggs correlated to a lesser degree with saturated fat ($r = .23$ for all subjects) and indeed was more strongly associated with ovarian cancer risk than was total cholesterol (Table 2). There was no evidence, however, of an association between other-cholesterol intake and risk, despite its high correlation with saturated fat ($r = .84$).

Diets high in saturated fat may also be low in fruits and vegetables. Table 2 shows that intake of carotenes, and especially of vegetable fiber (but not fruit or cereal fiber), was associated with decreased risk of ovarian cancer. For each additional 10-g-per-day consumption of vegetable fiber, the risk odds dropped by 37%.

To permit closer examination of the trends in risk with intake of saturated fat, egg cholesterol, and vegetable fiber, Table 3 gives the relative odds by tertile of consumption (based on all subjects). For each of these nutrients, the intermediate tertile had an odds ratio falling between the odds ratios of the lowest and the highest tertile.

Finally, by using regression models incorporating multiple factors, we return to the question of the degree to which the nutrients considered above may be independently related to ovarian cancer risk. Table 4 shows calorie-adjusted results, as before, as well as "other calorie"-adjusted models. For models with indices of saturated fat, egg cholesterol, and vegetable

Table 2. Trends in ovarian cancer risk with average daily intake of saturated fat-related factors, southern Ontario, 1989-1992

Nutrient	Unit per day	Reporting-adjusted odds ratio*	Calorie-adjusted†		
			Odds ratio	95% confidence interval	P‡
Total energy	1000 cal	1.58	1.44§	1.22-1.71	‖
Total protein	40 g	1.24	0.75	0.56-1.00	.049
Total fat	40 g	1.41	1.16	0.86-1.57	.32
Total carbohydrate	100 g	1.32	0.984	0.75-1.30	.91
Saturated fat	10 g	1.27	1.20	1.03-1.40	.0082
Saturated fat/total fat	10%¶	1.47	1.45	1.16-1.82	.00056
Saturated fat calories/total calories	5%#	1.40	1.35	1.10-1.65	.0020
Monounsaturated fat	10 g	1.21	1.070	0.90-1.27	.43
Polyunsaturated fat	10 g	1.14	0.86	0.69-1.07	.19
Total cholesterol	100 mg	1.25	1.15	1.02-1.30	.021
Egg cholesterol**	100 mg	1.47	1.42	1.18-1.72	.00016
Other cholesterol**	100 mg	1.18	0.973	0.82-1.15	.75
Animal protein	10 g	1.038	0.962	0.90-1.02	.22
Vegetable protein	10 g	1.14	0.914	0.79-1.06	.24
Retinol	1000 IU	1.048	1.000	0.92-1.09	.99
Beta carotene	4000 IU	0.946	0.87	0.77-0.99	.017
Other carotenes	1000 IU	0.940	0.904	0.85-0.96	.0012
Dietary fiber	10 g	0.998	0.82	0.71-0.94	.0052
Vegetable fiber	10 g	0.76	0.63	0.49-0.80	.00011
Fruit fiber	10 g	1.23	1.032	0.75-1.43	.85
Cereal fiber	10 g	1.099	0.88	0.70-1.10	.26

*Adjusted for age at diagnosis/interview (three groups) and the continuous variables age, total number and total dietary weight of reported food items, height and weight at age 21, number of full-term pregnancies, and total duration of oral contraceptive use.
†Adjusted for age at diagnosis/interview (three groups) and the continuous variables age, total daily calorie intake, number of full-term pregnancies, and total duration of oral contraceptive use. Each line in this table represents two individual models (total: 42 models).
‡All *P* values are two-sided, except the three for saturated fat, which are one-sided.
§Odds ratio was 1.37 for borderline histology cases and 1.48 for invasive histology cases.
‖$P<10^{-5}$ in reporting-adjusted model.
¶Unit is 10% of average daily total fat intake.
#Unit is 5% of average daily total caloric intake.
**Food items included in calculating egg and other cholesterol are described in the text.

Table 3. Odds ratios by tertile of intake for dietary nutrients in a case–control study of ovarian cancer, southern Ontario, 1989-1992

Nutrient	Odds ratio*	95% confidence interval
Saturated fat, g/day		
<19.17	1.0	
≥19.17, <29.87	1.17	0.83-1.63
≥29.87	1.38	0.90-2.13
Saturated fat/total fat, %		
<31.99	1.0	
≥31.99, <36.86	1.13	0.82-1.56
≥36.86	1.55	1.13-2.14
Saturated fat calories/total calories, %		
<9.28	1.0	
≥9.28, <11.91	1.35	0.98-1.86
≥11.91	1.46	1.05-2.02
Egg cholesterol, mg/day		
<32.98	1.0	
≥32.98, <80.34	1.45	1.05-2.00
≥80.34	1.94	1.40-2.67
Vegetable fiber, g/day		
<6.82	1.0	
≥6.82, <10.44	0.88	0.64-1.20
≥10.44	0.56	0.40-0.79
Total energy, cal/day†		
<1785.	1.0	
≥1785., <2359.	1.35	0.98-1.85
≥2359.	1.65	1.20-2.27

*Each set of tertiles constitutes a separate model and was adjusted for age at diagnosis or interview (three groups) and the continuous variables age, total calories, number of full-term pregnancies, and years of oral contraceptive use.

†Adjusted as above, except for calories.

fiber, "other calories" = total calories – 9.01 g saturated fat. In models containing the three types of dietary fats, "other calories" include only non-fat sources of calories, i.e., total calories – 9.01 g saturated fat – 8.83 g unsaturated fats. Since the strongest association between saturated fat intake and ovarian cancer risk appeared for the index "saturated fat/total fat," we begin by considering saturated, monounsaturated, and polyunsaturated fat in a single model. Whether calculated as grams per day or as percent of total fat, Table 4 (models 1 and 2) shows that of the three variables, only saturated fat was associated with risk. Next, with regard to consumption of fruits and vegetables, model 3 includes indices of beta carotene and other carotenes, vegetable fiber, and other dietary fiber (i.e., total dietary fiber – vegetable fiber). In this model, only vegetable-fiber intake was related to risk. Lastly, models 4-6 contain indices for saturated fat, egg cholesterol, and vegetable fiber. In all of these models, the terms for egg cholesterol and vegetable fiber were statistically significant, and their estimated odds ratios were similar to those seen in the univariate models in Table 2. The trends for saturated fat, however, were reduced somewhat compared with the estimates given in Table 2 and were of borderline statistical significance. The reduction in odds ratio trend was due about equally to egg cholesterol and to vegetable fiber; with either one of these terms omitted from the model, the odds ratio at 10 g/day saturated fat was 1.15. With the additional inclusion of other cholesterol in models 5a and b, the index saturated fat/total fat was statistically significant (P = .0046 and .0022, respectively) (data not shown).

Discussion

The present study has certain potential limitations that should be considered before conclusions are drawn. Our overall response fraction of 71% of eligible cases suggests that the results may be slightly more representative of women with disease in the earlier stages than of all women with ovarian cancer. All of the case subjects have been analyzed together, under the assumption that the various histologic types of epithelial tumors have comparable relationships with the risk factors under consideration. For the control sample, with 65% participation of eligible subjects, it is possible that the recorded dietary practices may not be completely representative of those of the female population of southern Ontario. We have no indications, however, that the dietary habits of the noninterviewed eligible control subjects differed from those of the participating ones; the usual reason given for refusal to take part in the 2-hour interview was insufficient time. If one considers total caloric intake, the control mean in the current study, 2096 cal/day, was very close to the means observed using similar versions of the dietary instrument of the National Cancer Institute of Canada Epidemiology Unit among directly interviewed population control subjects of comparable ages in other studies in Canada, 2023 (*37*) and 2031 (*38*) cal/day, and was comparable to average or recommended daily caloric intakes for this population (*39*) and for the U.S. population (*40*).

We have used a quantitative diet-history method for ascertaining usual dietary practices. This method has been shown to give good correlations with 30-day food records (*41*), and the food items included cover virtually all those in most Canadian diets. As in any diet-history study, recall between case and control subjects may differ as a result of differences in perceived dietary reference frame, in subject motivation, or in interviewer probing. In the present study, the time periods for subjects' dietary practices—prior to illness for case subjects and the past year or two for control subjects—referred to similar periods before interview, with the attempt to avoid dietary changes due to case disease status. In addition, our interviewers were blinded to particular hypotheses of interest. Also, we sought to reduce general reporting differences by adjustments for various measures of reporting, e.g., number of reported food items, and total daily weight of food consumed (including beverages). Even with these adjustments, a strongly significant association between total daily caloric intake and ovarian cancer risk was present; the case subjects (both those with borderline malignant tumors and those with in-

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Table 4. Logistic regression models for dietary nutrient trends in a case–control study of ovarian cancer, southern Ontario, 1989-1992

Models	Nutrient	Unit per day	Calorie-adjusted*		Other calorie-adjusted‡	
			Odds ratio	Removal P†	Odds ratio	Removal P†
1a, 1b	Saturated fat	10 g	1.29	.026	1.31	.014
	Monounsaturated fat	10 g	0.89	.38	0.911	.46
	Polyunsaturated fat	10 g	0.910	.45	0.930	.55
2a, 2b	Saturated fat/total fat	10%§	1.60	.014	1.77	.0028
	Monounsaturated fat/total fat	10%§	1.103	.60	1.18	.36
	Polyunsaturated fat/total fat	10%§	1.15	.52	1.26	.28
3a, 3b	Beta carotene	4000 IU	0.980	.59	0.980	.59
	Other carotenes	1000 IU	0.976	.61	0.972	.55
	Vegetable fiber	10 g	0.68	.025	0.69	.030
	Other dietary fiber	10 g	0.971	.76	0.961	.68
4a, 4b	Saturated fat	10 g	1.11	.18	1.14	.051
	Egg cholesterol	100 mg	1.37	.00082	1.37	.00082
	Vegetable fiber	10 g	0.65	.00057	0.65	.00057
5a, 5b	Saturated fat/total fat	10%§	1.28	.043	1.33	.016
	Egg cholesterol	100 mg	1.37	.00077	1.38	.00063
	Vegetable fiber	10 g	0.68	.0023	0.68	.0025
6a, 6b	Saturated fat calories/total calories	5%‖	1.20	.087	1.27	.023
	Egg cholesterol	100 mg	1.36	.0012	1.36	.0012
	Vegetable fiber	10 g	0.66	.00081	0.66	.00079

*Models 1a-6a adjusted for age at diagnosis or interview (three groups) and the continuous variables age, total calories, number of full-term pregnancies, and total duration of oral contraceptive use.

†All *P* values are for removal of that term from the model and are two-sided.

‡Models 1b-6b adjusted for age at diagnosis or interview (three groups) and the continuous variables age, other calories, number of full-term pregnancies, and total duration of oral contraceptive use. In models 1b-3b, other calories = total calories – 9.01 g saturated fat – 8.83 g unsaturated fats. In models 4b-6b, other calories = total calories – 9.01 g saturated fat.

§Units for ratios to total fat are 10% of average daily total fat intake.

‖Unit is 5% of average daily total caloric intake.

vasive tumors) reported approximately 10% greater calorie consumption than the control subjects. It is unclear here whether this increased daily caloric intake reflects a reporting bias, is etiologically related to risk of ovarian cancer, or is a result of the disease process. The highest average energy intakes in this study were seen among the subjects with borderline malignant tumors; these individuals had current weights similar to those of the control subjects. This finding suggests that the risk association with calories may be due to relative overreporting of cases. On the other hand, in spite of elevated caloric intakes, case subjects with tumors of invasive histology, who were presumably sicker than those with borderline malignant tumors, had significantly lower current weights than control subjects. For these women, the apparent association with energy intake may be a result of consumption of higher calorie diets used to try to prevent weight loss from the cancer. We know of no evidence to suggest that caloric intake is an etiologic risk factor for ovarian cancer (*13*,*27*). Perhaps some combination of the three aspects may be present in our data. In any event, the results on saturated fat intake seen in this study would be appreciably stronger with calories removed from the dietary models.

With inclusion of some form of caloric intake in the regression models, questions arise about the choice of nutrient index and of total calories versus "other" calories [e.g., models 3-5 in table 11-6 of (*42*); (*43*)]. The nutrients egg cholesterol and vegetable fiber are found in foods contributing little to total calorie consumption. These nutrients are strongly statistically significant and largely uncorrelated with calories in this study, so that our results are essentially identical whether crude or calorie-weighted indices are used. Saturated fat, however, contributes about 10%-15% of calories to the diet [Appendix Table 1; (*44*)] and is found in many of the foods that, together, supply the majority of dietary calories (*35*). In the present study, the three indices of saturated fat (saturated fat in grams per day, saturated fat calories/total calories, and saturated fat/total fat) had correlations with total calories of .80, .20, and .099, respectively. We therefore favor the index saturated fat/total fat, which was the most independent of caloric intake. With or without adjustment for egg cholesterol, other cholesterol, and vegetable fiber, this index was statistically significant, suggesting that saturated fat intake is associated with ovarian cancer risk and that this association is not due to a contribution to or correlation with calories or to associations with these other nutrients.

Vegetable-fiber intake was slightly inversely correlated in our data with the index saturated fat/total fat ($r = -.18$), although it remained quite statistically significant when both were included in the same regression model. For women classified in the lowest tertile of consumption, an increase in this nutrient of 6-10 g/day was associated with a 30%-40% drop in risk (Tables 2-4).

Finally, an apparent trend in risk with consumption of eggs exists in our data, and this finding also seemed to be independent of the association between saturated fat intake and ovarian cancer risk. Whether this result is actually due to the cholesterol in eggs is doubtful, because cholesterol from other sources appears unrelated to risk of ovarian cancer,

even with saturated fat omitted from models. What other component of eggs might actually convey the risk is unclear; it does not seem to be retinol or any other micronutrient in our database, and it is probably not the oil or fat used in frying (*45*), since that intake was captured in our questionnaire and was included in the calculations of saturated and unsaturated fat. Because the association with egg cholesterol (unlike that with saturated fat and with vegetable fiber) was seen only among the subjects with tumors of invasive histology—who may have been diagnosed at more symptomatic stages of disease than those with borderline malignant tumors—it is possible that the observed association might have resulted from disease-related changes in the dietary practices of case women prior to diagnosis. In our data, the correlation between daily egg consumption and caloric intake was .12 for control subjects. It was .13 for case subjects with tumors of borderline malignant histology and .25 for those with tumors of invasive histology; the latter subjects daily consumed 29% more eggs than the former subjects and 43% more than the control subjects. Thus, eggs appear to have been used as a part of the higher calorie diets of the subjects with invasive tumors, and the apparent association with eggs seen in this study may not necessarily represent an etiologic relationship to risk of ovarian cancer.

Our finding of increased ovarian cancer risk according to average daily saturated fat intake supports the results of previous studies observing this association. A large case–control study (*26*) in Milan, Italy, found an increasing trend in risk according to number of meat portions consumed per week, with relative odds = 1.7 for daily usage versus fewer than four servings per week. Animal-fat scores were computed for subjects in studies conducted in the Boston area (*25*) and in Shanghai (*27*). Both of these studies observed increasing trends in risk, with odds ratios of about 1.8 in the highest quartile of score (trend $P = .02$ and .07, respectively). A Utah study (*13*), using a detailed quantitative diet history, found a nonsignificant increase in risk (odds ratio = 1.3) for the highest tertile of saturated fat intake compared with the lowest. In Hokkaido, Japan, an ovarian cancer study (*11*), which ascertained frequency of consumption of meat, fish, and milk, found an odds ratio of 1.4 for daily consumption of meat and 1.7 for daily consumption of fish, although a slight decrease in risk was seen for daily milk drinking. Finally, a case–control study (*46*) performed in Buffalo, N.Y., computed an index of total fat intake, but it did not find an association between this index and risk.

Four of the above studies obtained information about consumption of vegetables or related food items. In the Shanghai study (*27*), no association was seen with intake of vegetables or legumes or computed indices of crude fiber or carotene. The Milan study (*26*), however, found statistically significant inverse associations with consumption of green vegetables and of carrots (*26*). Also, slight inverse associations with ovarian cancer risk were observed in the Buffalo study (*46*) with intake of fiber and with vitamin A from fruits and vegetables. In the Utah study (*13*), decreasing trends were found for indices of dietary fiber and beta carotene, reaching odds ratios of 0.7 and 0.5, respectively, in the highest tertile of intake.

Lastly, four studies of ovarian cancer have reported specifically about consumption of eggs. In the Boston study (*25*), a nonsignificant odds ratio of 1.4 was found for intake of eggs at least once per week. No association was seen in either the Milan (*26*) or the Shanghai (*27*) study. However, a prospective study (*47*) of 16 000 Seventh-day Adventists interviewed at base line and followed for 20 years showed a statistically significant relative risk of 3.0 for eggs consumed at least 3 days per week, in comparison with less than 1 day per week.

Finally, we note that the present study is, to our knowledge, the first large ovarian cancer study to obtain complete, quantitative diet-history information. Previous studies with dietary data suffer from relatively small numbers of cases (*11,13,47*) or from limited numbers of ascertained food items (*11,25-27,46,47*). The dietary results in those studies should therefore be viewed cautiously, although the degree of consistency with the findings of the present work is notable. Given the apparent role of pituitary and/or sex hormones in the etiology of ovarian cancer, dietary influences should not be surprising. It seems possible, for example, that circulating-estrogen (or progesterone) levels could rise because of biosynthesis (*48*) from increased dietary cholesterol precursors or from estrogens present in animal meats or eggs or could fall because of competition from phytoestrogen analogues present in vegetables or because of decreased enterohepatic recirculation due to higher fecal binding and excretion from greater consumption of vegetable fiber (*22*). Dietary fat may also have an effect on prolactin secretion (*49*). Whatever the mechanism of action, the present findings, if confirmed, suggest that ovarian cancer risk may be appreciably lowered by suitable modifications of the diet: reducing the intake of saturated fat (and perhaps eggs) and eating more vegetables.

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Appendix Table 1. Medians and 90% ranges of daily intakes of food constituents examined for association with ovarian cancer risk, southern Ontario, 1989-1992

Constituent	Case percentile			Control percentile		
	5	50	95	5	50	95
Total energy, cal	1277.	2140.	3819.	1121.	2013.	3405.
Total protein, g	43.77	81.08	143.6	39.96	77.58	135.4
Total fat, g	39.22	74.78	148.3	31.37	66.29	133.5
Total carbohydrate, g	164.6	286.1	524.8	138.0	264.0	465.1
Saturated fat, g	11.86	25.61	56.10	9.650	21.93	50.10
Saturated fat/total fat, %	24.61	35.00	43.83	24.09	33.75	43.15
Saturated fat calories/total calories, %	6.397	10.74	17.14	5.868	10.42	16.00
Monounsaturated fat, g	14.35	28.51	58.88	10.62	25.73	52.13
Polyunsaturated fat, g	3.790	10.17	25.95	3.590	9.630	22.39
Total cholesterol, mg	116.6	270.6	600.3	98.63	242.3	515.1
Egg cholesterol, mg	0.000	70.31	229.6	0.000	44.35	172.5
Other cholesterol, mg	86.78	197.6	404.7	82.82	177.8	393.6
Animal protein, g	20.85	50.81	102.5	20.65	47.72	96.97
Vegetable protein, g	16.16	28.22	59.02	14.10	26.98	52.45
Retinol, IU	477.7	1286.	3730.	366.8	1126.	3730.
Beta carotene, IU	1848.	4479.	13 010.	1887.	4484.	14 440.
Other carotenes, IU	550.7	1509.	5845.	528.2	1515.	7264.
Dietary fiber, g	12.46	24.75	46.51	11.33	23.66	48.19
Vegetable fiber, g	3.380	8.450	19.91	3.400	8.625	21.73
Fruit fiber, g	0.7450	4.270	13.52	0.7500	4.465	12.18
Cereal fiber, g	3.345	9.170	21.74	2.720	8.580	21.70

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Notes

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