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Dietary Fat Intake and Ovarian Cancer in a Cohort of US Women

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Several studies have suggested that high intake of fats and fat-rich foods may increase the risk of ovarian cancer. The authors examined these relations in the Nurses' Health Study cohort. Dietary intake was assessed in 1980, 1984, 1986, and 1990 by using a self-administered food frequency questionnaire. Food data were used to calculate intake of various fats and fatty acids. For best reflection of long-term intake, an updated, cumulative, averaged measure of fat intake was used to predict incidence of ovarian cancer. Between 1980 and 1996, 301 incident cases of invasive epithelial ovarian cancer were confirmed among the 80,258 participants who completed the baseline food frequency questionnaire. There was no evidence of a positive association between intake of any type of fat and ovarian cancer risk, even after adjustment of fat subtypes for one another. Women in the highest quintile of total fat intake were not at increased risk compared with those in the lowest quintile (multivariate relative risk = 1.03, 95 percent confidence interval: 0.72, 1.45, *p* for trend = 0.97). Intakes of fat-rich foods were also not appreciably associated with ovarian cancer risk, although an increase in risk with frequent intake of eggs was observed. Overall, results suggest no association between intake of any type of fat and ovarian cancer. *Am J Epidemiol* 2002;156:22–31.

cohort studies; fats; ovarian neoplasms; prospective studies; questionnaires

Abbreviations: CI, confidence interval; FFQ, food frequency questionnaire; NHS, Nurses' Health Study; RR, relative risk.

Ovarian cancer is the fifth most common cause of cancer deaths among women in the United States, largely due to the difficulty of early detection and the invasiveness of the disease (1, 2). Because treatment options are limited (3), primary prevention has been a major focus of research. The risk factors most consistently associated with ovarian cancer, including parity and family history, cannot be modified easily. The identification of foods and nutrients associated with ovarian cancer could provide women an opportunity for prevention. Although several studies have evaluated diet and ovarian cancer, few dietary risk factors have been consistently associated with the disease. Increases in risk associated with high intake of saturated fat, animal fat, and/or cholesterol have been reported in three large case-control studies (4–6), but others have found little or no association (7–10). Similarly, several case-control and cohort studies have found positive associations between ovarian cancer and intake of specific high-fat foods, such as red meat (11–15), eggs (10, 13), and dairy products (10), although other studies have not (6, 16). To address these associations in detail, we evaluated the relation between fat intake and ovarian cancer incidence in a large cohort of US women.

MATERIALS AND METHODS

Nurses' Health Study (NHS) cohort

The NHS is a cohort of 121,700 US female registered nurses who responded to a mailed questionnaire in 1976

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TABLE 1. Characteristics of the Nurses' Health Study cohort by quintile of energy-adjusted total fat intake in 1980*

	Quintile				
	1	2	3	4	5
Median total fat (g/day)	48.5	62.7	70.9	77.6	83.5
Age (years)	46.2	46.1	46.1	46.1	46.1
Median daily intake					
Animal fat (g/day)	34.7	45.3	52.2	58.7	65.8
Vegetable fat (g/day)	13.9	17.4	18.7	19.0	17.7
Cholesterol (mg/day)	276	313	332	351	366
Total calories (kcal/day)	1,537	1,589	1,609	1,598	1,504
Alcohol (g/day)	9.4	7.2	6.1	5.3	3.9
Lactose (g/day)	16.9	15.5	13.9	12.0	8.5
Mean parity (full-term pregnancies)	2.9	3.0	3.0	3.1	3.1
Mean age at first birth (years)†	24.5	24.6	24.5	24.4	24.2
Mean age at menarche (years)	12.5	12.6	12.5	12.5	12.5
Mean body mass index	24.1	24.2	24.2	24.2	24.4
OC‡ use					
Ever (%)	50.0	49.7	50.7	51.5	51.1
Mean duration (months)§	47.9	49.2	50.2	49.5	53.4
Tubal ligation (%)	15.8	16.1	17.0	17.2	17.3
PMH‡ use					
Premenopausal (%)	66.0	66.9	67.5	67.6	67.1
Ever (%)	30.0	30.0	29.6	29.9	30.1
Mean duration (months)¶	7.5	6.4	6.7	6.5	7.0
Smokers					
Current (%)	27.8	27.0	27.5	29.7	32.4
Past (%)	30.0	28.8	27.4	25.8	25.4
Exercise ≥4 hours/week (%)	33.4	30.5	28.9	27.8	25.2

* Age-standardized to distribution of the third quintile using direct method.
† Among parous women.
‡OC, oral contraceptive; PMH, postmenopausal hormone.
§ Among OC users.
¶ Among PMH users.

(17). The participants, who were aged 30–55 years at the time of the initial mailing, provided information on their medical history and health-related behaviors such as smoking status and use of oral contraceptives. Participants have completed questionnaires every 2 years thereafter to update information on various risk factors and to identify new diagnoses of cancer and other diseases. As of 1996, the follow-up rate was 90 percent, with vital status data available for more than 98 percent of the original cohort.

Assessment of food and nutrient intake

Dietary intake of fats and fat-rich foods was assessed in 1980, 1984, 1986, and 1990 by using a standard semiquantitative food frequency questionnaire (FFQ). A 61-item questionnaire was used for our baseline assessment of diet in 1980, whereas the FFQ used in 1984, 1986, and 1990 was expanded to include 131 foods. Women were asked to record how often they had consumed specified portion sizes of each food in the previous year (e.g., <1/month, 1–3/month,

TABLE 2. Multivariate relative risks and 95% confidence intervals for ovarian cancer according to quintile of fat and fatty acid intake (cumulative average, 1980–1996)

Nutrient	Quintile					*p* for trend*
	1	2	3	4	5	
Total fat						
No. of cases	68	59	57	56	61	
Age-adjusted RR†	1.00	0.87	0.88	0.87	0.99	
Multivariate RR*	1.00	0.91	0.90	0.90	1.03	
95% CI†		0.64, 1.30	0.63, 1.28	0.63, 1.28	0.72, 1.45	0.97
Animal fat						
No. of cases	64	56	69	59	53	
Age-adjusted RR	1.00	0.92	1.11	0.99	0.94	
Multivariate RR	1.00	0.94	1.15	1.02	0.95	
95% CI		0.66, 1.35	0.82, 1.62	0.71, 1.45	0.66, 1.38	0.97
Vegetable fat						
No. of cases	54	67	62	63	55	
Age-adjusted RR	1.00	1.10	1.08	1.07	0.94	
Multivariate RR	1.00	1.15	1.13	1.13	0.98	
95% CI		0.80, 1.64	0.78, 1.63	0.79, 1.63	0.68, 1.43	0.91
Dairy fat						
No. of cases	52	71	59	63	56	
Age-adjusted RR	1.00	1.32	1.09	1.16	1.05	
Multivariate RR	1.00	1.35	1.12	1.19	1.06	
95% CI		0.94, 1.93	0.77, 1.62	0.82, 1.72	0.73, 1.54	0.93
Saturated fat						
No. of cases	62	64	57	69	49	
Age-adjusted RR	1.00	1.02	0.94	1.18	0.87	
Multivariate RR	1.00	1.06	1.00	1.21	0.91	
95% CI		0.75, 1.50	0.70, 1.43	0.86, 1.71	0.62, 1.32	0.97
Monounsaturated fat						
No. of cases	65	63	58	53	62	
Age-adjusted RR	1.00	0.95	0.87	0.85	1.02	
Multivariate RR	1.00	0.99	0.90	0.88	1.07	
95% CI		0.70, 1.40	0.63, 1.29	0.61, 1.26	0.75, 1.52	0.99
Polyunsaturated fat						
No. of cases	56	69	54	61	61	
Age-adjusted RR	1.00	1.23	0.96	1.10	1.08	
Multivariate RR	1.00	1.27	1.00	1.15	1.14	
95% CI		0.90, 1.81	0.69, 1.45	0.80, 1.65	0.79, 1.63	0.74
Trans fat						
No. of cases	63	59	64	58	57	
Age-adjusted RR	1.00	0.98	1.03	1.00	0.98	
Multivariate RR	1.00	1.03	1.08	1.03	1.03	
95% CI		0.72, 1.46	0.76, 1.53	0.72, 1.47	0.72, 1.47	0.87
Cholesterol						
No. of cases	63	68	62	46	62	
Age-adjusted RR	1.00	1.10	1.02	0.77	1.10	
Multivariate RR	1.00	1.12	1.04	0.78	1.08	
95% CI		0.79, 1.58	0.73, 1.48	0.53, 1.13	0.76, 1.53	0.63

Table continues

TABLE 2. (Continued)

Nutrient	Quintile					*p* for trend*
	1	2	3	4	5	
Stearic acid (18:0)‡						
No. of cases	70	55	61	55	60	
Age-adjusted RR	1.00	0.80	0.89	0.85	0.96	
Multivariate RR	1.00	0.83	0.94	0.86	0.97	
95% CI		0.58, 1.18	0.67, 1.33	0.60, 1.23	0.68, 1.37	0.91
Oleic acid (18:1ω9)‡						
No. of cases	68	61	55	57	60	
Age-adjusted RR	1.00	0.94	0.83	0.86	0.99	
Multivariate RR	1.00	0.98	0.87	0.90	1.03	
95% CI		0.70, 1.39	0.61, 1.24	0.63, 1.28	0.73, 1.46	0.91
Linoleic acid (18:2ω6)‡						
No. of cases	61	62	60	56	62	
Age-adjusted RR	1.00	0.99	0.98	0.93	1.02	
Multivariate RR	1.00	1.04	1.02	0.96	1.07	
95% CI		0.73, 1.48	0.72, 1.46	0.66, 1.38	0.75, 1.52	0.90
CLA†,§						
No. of cases	37	32	53	42	39	
Age-adjusted RR	1.00	0.90	1.55	1.22	1.12	
Multivariate RR	1.00	0.93	1.57	1.26	1.15	
95% CI		0.61, 1.42	1.09, 2.25	0.86, 1.86	0.78, 1.72	0.23
α-Linolenic acid (18:3ω3)						
No. of cases	71	52	45	62	71	
Age-adjusted RR	1.00	0.74	0.62	0.86	0.98	
Multivariate RR	1.00	0.75	0.64	0.88	1.00	
95% CI		0.53, 1.08	0.44, 0.94	0.63, 1.24	0.72, 1.39	0.72
Arachidonic acid (20:4ω6)						
No. of cases	73	61	53	58	56	
Age-adjusted RR	1.00	0.94	0.78	0.82	0.89	
Multivariate RR	1.00	0.95	0.80	0.82	0.88	
95% CI		0.68, 1.33	0.56, 1.14	0.58, 1.15	0.62, 1.24	0.27
EPA†,§ (20:5ω3)						
No. of cases	45	40	32	43	43	
Age-adjusted RR	1.00	1.01	0.73	0.96	0.96	
Multivariate RR	1.00	1.04	0.75	1.00	0.97	
95% CI		0.68, 1.59	0.47, 1.17	0.66, 1.52	0.64, 1.48	0.80
DHA†,§ (22:6ω3)						
No. of cases	43	46	28	47	39	
Age-adjusted RR	1.00	1.06	0.67	1.05	0.88	
Multivariate RR	1.00	1.06	0.67	1.07	0.86	
95% CI		0.70, 1.61	0.42, 1.08	0.71, 1.63	0.55, 1.33	0.52

* Multivariate relative risks adjusted for age (<50, 50–54, 55–59, 60–64, and ≥65 years), parity (0, 1 – 2, 3–4, and ≥5 years), age at menarche (<12, 12, 13, 14, and ≥15 years), oral contraceptive use and duration (never use, ever use for <3, 3 – 5, and >5 years), menopausal status/postmenopausal hormone use (premenopausal/never use, current use <5 years, current use ≥5 years, past use <5 years, past use ≥5 years), tubal ligation (yes, no), and smoking status (never, past, current <15 cigarettes per day, current ≥15 cigarettes/day). Numbers of cases and person-years may not sum to totals due to missing data.

†RR, relative risk; CI, confidence interval, CLA, conjugated linoleic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

‡ Short-hand notation for identifying fatty acids. The first number refers to the number of carbon atoms in the acyl chain. The number after the colon refers to the number of unsaturated bonds between the carbon atoms. Monounsaturated and polyunsaturated fatty acids are then followed by "ω," and the location of the first unsaturated bond in terms of the number of carbon atoms is from the methyl end of the acyl chain.

§ First calculated in 1984, with follow up from 1984 to 1996.

TABLE 3. Multivariate relative risks and 95 percent confidence intervals of ovarian cancer based on fat as a percentage of total energy (cumulative average, 1980–1996)

Calories from fat (%)	No. of cases	Multivariate RR*,†	95% CI†
<25.0	9	0.83	0.42, 1.66
25.1–30.0	36	1.00	0.68, 1.48
30.1–35.0	84	1.00	
35.1–40.0	97	1.05	0.78, 1.41
40.1–45.0	50	1.00	0.70, 1.42
45.1–50.0	17	0.92	0.54, 1.55
≥50.0	8	1.07	0.52, 2.23
		p for trend = 0.85	

* Multivariate relative risks adjusted for age (<50, 50–54, 55–59, 60–64, and ≥65 years), parity (0, 1 – 2, 3–4, and ≥5 years), age at menarche (<12, 12, 13, 14, and ≥15 years), menopausal status/postmenopausal hormone use (premenopausal/never use, current use <5 years, current use ≥5 years, past use <5 years, past use ≥5 years), tubal ligation (yes, no), and smoking status (never, past, current <15 cigarettes per day, current ≥15 cigarettes/day).

† RR, relative risk; CI, confidence interval.

1/week, 2–4/week, 5–6/week, 1/day, 2–3/day, 4–5/day, and ≥6/day).

In 1980, participants were asked about their intake of many foods high in fat or cholesterol. These included red meat as a main dish, red meat in a sandwich or mixed dish, processed meats, hamburgers, hot dogs, bacon, chicken with and without skin, fish, eggs, butter, margarine, whole milk, hard cheese, ice cream, french fries, potato chips, a variety of baked goods, peanut butter, and nuts. Additional questions inquired about the types of fats used for frying and baking and the type of margarine used (stick vs. tub). Participants were also asked about whether their intake of each food has significantly increased or decreased in the previous 10 years. The FFQs administered in 1984, 1986, and 1990 included additional questions on usual intake of canned tuna, dark-meat fish, other fish, shrimp and lobster, oil-and-vinegar salad dressing, cream, sour cream, and mayonnaise.

We used the food intake information reported on the FFQ to calculate each participant's average total fat intake in the previous year as well as her intake of specific types of fat. These included animal, vegetable, dairy, saturated, monounsaturated, polyunsaturated, and *trans* fats and cholesterol. In addition, we measured consumption of specific fatty acids, including stearic, oleic, linoleic, α-linolenic, arachidonic, docosahexaenoic, eicosapentaenoic, and conjugated linoleic acids.

To calculate a person's total fat intake, we multiplied the portion size of a single serving of each food item by its reported frequency of intake. We then multiplied the total amount of each food consumed by the fat content of the food and added together the fat contributions from all foods (18–20). We repeated this procedure to calculate each woman's usual intake of the specific types of fat under study.

Both the 1980 and the 1986 FFQs have been validated previously for use in this population (21–24). A subset of the NHS cohort, consisting of 191 women living in the Boston, Massachusetts, area, completed two 136-item FFQs (used in 1986) 1 year apart. In the intervening year, they completed two 1-week diet records on which they recorded all foods consumed each day. Correlations between each FFQ and mean values from the two diet records were high for total, saturated, and polyunsaturated fats and cholesterol (range of coefficients, 0.48–0.73) (23). A similar validation study of the 61-item FFQ used in 1980, comparing food and nutrient intake as measured by two questionnaires, produced similar correlations (21), ranging from 0.35 for chicken with skin to 0.74 for butter (22). In addition, in a study with 185 participants, percentage of calories from fat as measured by the 1984 FFQ predicted serum triglyceride levels (24); the geometric mean triglyceride levels in women with less than 20, 20.1–25, 25.1–30, 30.1–35, 35.1–40, and more than 40 percent calories from fat were 156, 139, 129, 103, 85, and 70 mg/dl, respectively.

Information on ovarian cancer risk factors was collected by questionnaire throughout the follow-up period. Every 2 years, we updated data on most factors, including menopausal status, postmenopausal hormone use, smoking status, hysterectomy, and body mass index. Information on several factors was collected during part of the follow-up period; we updated information on these factors until the questions were no longer asked, at which point the last response was carried forward until the end of follow-up. For example, questions on oral contraceptive use were included on questionnaires until 1982, at which point fewer than 1 percent of women were still using oral contraceptives. We considered women who reported past use of oral contraceptives in 1982 to be past users for the remainder of follow-up and those who were current users in 1982 to be past users from 1984 onward. We updated parity (measured until 1984) and tubal ligation (measured until 1982) in a similar fashion. Information on age, age at menarche, age at first birth, talc use, and menstrual irregularity was collected once and then carried forward throughout the follow-up period.

Assessment of ovarian cancer

On each follow-up questionnaire, participants were asked whether they had received a physician's diagnosis of ovarian cancer during the previous 2 years. Women who reported this diagnosis were asked for permission to review their medical records. Records were reviewed by physicians blinded to the participant's exposure status to confirm the diagnosis and to identify histologic type and subtype and invasiveness. Only confirmed cases of epithelial ovarian cancer were included in the analysis. In addition, the National Death Index was searched systematically to identify women who may have died prior to reporting a diagnosis by questionnaire, and we then contacted family members to obtain medical records. A validation study of the National Death Index as a means of case ascertainment indicated that approximately 98 percent of deaths are successfully identified (25).

Statistical analysis

We excluded cohort members from the analysis at baseline if they reported a diagnosis of cancer, a bilateral oophorec-

tomy, or pelvic irradiation before the start of follow-up in 1980. We also excluded participants who did not complete the 1980 FFQ used for baseline measurement, those who left 10 or more food items blank, and those who reported an implausibly high or low total calorie intake (<500 or >3,500 kcal/day) on the 1980 FFQ. Person-years of follow-up were accrued from the date of return of the 1980 questionnaire until a diagnosis of ovarian or other cancer, the report of bilateral oophorectomy or pelvic irradiation, death, or the end of the follow-up period on June 1, 1996, whichever came first.

To limit misclassification caused by differences in body size and physical activity level, we adjusted fat intake for total energy intake by using the residual method (23); residuals were calculated based on the expected nutrient intake of a woman consuming 1,600 kcal per day, the average intake at baseline. In addition, we calculated the percentage of total energy consumed as fat by multiplying each woman's total fat intake (in grams) by 9 kcal/g of fat and dividing the product by total calories consumed.

To represent overall intake during the follow-up period, we used the cumulative average of intake reported on all previous FFQs as the best estimate of exposure intensity and used this value to predict risk of disease in the subsequent interval (26). For example, for each woman, we averaged saturated fat intake reported in 1980 and 1984 and then used this average to predict ovarian cancer risk from 1984 to 1986; similarly, we used the average of saturated fat intake in 1980, 1984, and 1986 to predict risk from 1986 to 1988. To create a cumulative average of the intake of fat-rich foods, we first assigned to each of the intake categories on the FFQ a value corresponding to the average number of servings per day (e.g., 2–4 servings per week = 0.43 servings per day). Then, as described above, we used the average of all previous food intake measures to predict subsequent risk of disease.

Participants were divided into quintiles or deciles based on their intake of each type of fat and into categories based on their frequency of food intake. Person-time was allocated to each category of fat and food intake in 2-year increments, allowing each participant to change exposure status every 2 years. For years in which dietary questions were not included on the NHS questionnaire (1982, 1988, and 1992), each participant's response from the previous questionnaire was carried forward. If a participant did not complete the dietary section of the questionnaire in any given year, she was assigned a missing value for all foods included on the FFQ that year. When a participant did not provide information on a specific food item, she was assigned a missing value for that food, and that food did not contribute to the calculation of fat intake.

Incidence rates for each category of fat and food intake were calculated by dividing the number of incident cases by the follow-up time in each category. Relative risks were estimated with rate ratios comparing the incidence of ovarian cancer in each category with that of the lowest category (referent) by using pooled logistic regression (27), and 95 percent confidence intervals were calculated. We used the Mantel extension test for trend with two-sided p values to evaluate the presence of a linear trend in the relative risk across categories. For food variables, the median values for each category were included in the regression model as a continuous variable. For nutrient variables, we included quintile number as a continuous variable in the model because quintile cutpoints differed between questionnaire years.

In addition to considering the effects of each type of fat individually, we evaluated the possibility of confounding by intake of other fat subtypes. To accomplish this, we included variables for intake of saturated, monounsaturated, polyunsaturated, and *trans* fats and cholesterol in a single regression model (23). We similarly evaluated the risk associated with intake of dairy fat, nondairy animal fat, and vegetable fat.

We addressed the possible confounding effect of a wide range of other ovarian cancer risk factors, including age, body mass index, parity, age at menarche, tubal ligation, hysterectomy, oral contraceptive use, physical activity, height, smoking status, age at first birth, menstrual cycle regularity, age at menopause, postmenopausal hormone use, and talc use. We also evaluated the presence of confounding by other nutrients, including lactose, protein, carbohydrate, alcohol, caffeine, and total calories. Variables were included in multivariate regression models if their addition to the model changed the relative risks for the fat intake by 10 percent or more compared with the crude relative risk or if it was determined that they were significant predictors of ovarian cancer independent of fat intake in our population.

We performed several subanalyses to determine whether associations between diet and ovarian cancer were limited to particular subgroups of our population. First, we evaluated the effect of fat intake on specific tumor subtypes (serous, mucinous, and endometrioid). To evaluate whether remote, long-term intake of specific foods affected cancer risk, we limited the analysis to those participants who indicated on their 1980 FFQ that intake of a particular food had not substantially changed in the previous 10 years. We then used the food intake frequency reported on their 1980 FFQ to predict ovarian cancer between 1980 and 1996.

To determine whether the fat intake-ovarian cancer relation varied by levels of other risk factors, we stratified our data by age (<50 vs. ≥50 years), menopausal status, and postmenopausal hormone use (premenopausal vs. postmenopausal and never use of hormones vs. postmenopausal and ever use of hormones), body mass index (<25 vs. ≥25 kg/m^2), oral contraceptive use (ever use vs. never use), smoking status (never vs. current vs. past), and physical activity level (<4 vs. ≥4 hours/week). We then compared the association of fat intake and cancer risk across strata. Finally, we performed lagged subanalyses excluding cases diagnosed in both the first 2 and 4 years of follow-up to examine whether changes in diet preceding a diagnosis of ovarian cancer biased results.

RESULTS

Between 1980 and 1996, more than 1.1 million person-years were accrued by the 80,258 cohort members who completed the baseline FFQ (98.0 percent of total possible person-years of observation). A total of 449 cases of ovarian cancer were reported during this period. We received

TABLE 4. Multivariate relative risks and 95 percent confidence intervals of ovarian cancer based on intake of selected foods high in fat or cholesterol (cumulative average, 1980–1996)

Food	Frequency of intake						*p* for trend*
	<1/month	1–3/month	1/week	2–4/week	5–6/week	≥1/day	
Main dish of beef, pork, lamb							
No. of cases		83†	150		52		
Multivariate RR‡		1.00	1.17		1.30		
95% CI§			0.91, 1.51		0.93, 1.82		0.16
Mixed dish of beef, pork, lamb							
No. of cases	71	91	88		33		
Multivariate RR	1.00	0.89	0.67		0.87		
95% CI		0.66, 1.19	0.49, 0.90		0.58, 1.31		0.05
Hamburger							
No. of cases	61	145		79			
Multivariate RR	1.00	1.09		0.86			
95% CI		0.83, 1.44		0.63, 1.17			0.07
Chicken with skin							
No. of cases	141	75		57			
Multivariate RR	1.00	1.09		0.98			
95% CI		0.83, 1.43		0.73, 1.32			0.80
Chicken without skin							
No. of cases	89	79		107			
Multivariate RR	1.00	0.97		0.82			
95% CI		0.73, 1.30		0.62, 1.07			0.06
Eggs							
No. of cases		75	144	39	25		
Multivariate RR		1.00	0.95	1.06	1.62		
95% CI			0.73, 1.24	0.73, 1.55	1.04, 2.53		0.05
Hard cheese							
No. of cases	21	40	113	74		34	
Multivariate RR	1.00	1.29	1.02	0.89		0.76	
95% CI		0.83, 2.00	0.71, 1.46	0.60, 1.30		0.48, 1.20	0.02

Table continues

medical records from 395 (88.2 percent) cases, record receipt was still pending for two cases, 23 women denied the diagnosis when contacted, 26 women refused to release their records, one women could not be contacted, and death certificates alone were available for two women. After review of medical records, the diagnosis of ovarian cancer was confirmed for 358 participants (90.6 percent). Of the 37 cases not confirmed, nine diagnoses were rejected, 18 were changed to a more correct diagnosis, and 10 were found to be metastases from other tumors. A total of 319 (89.1 percent) of the confirmed cases were found to be invasive, of which 301 were of the epithelial subtype; only these cases were included in the analysis. This group included 174 tumors of the serous subtype, 54 mucinous tumors, 44 endometrioid tumors, and 29 other subtypes.

Characteristics of the cohort by quintile of total fat intake in 1980 are presented in table 1. Median total fat intakes for the five quintiles were 48.5, 62.7, 70.9, 77.6, and 83.5 g, respectively. By 1990, the range in total fat intake was smaller, with medians of 49.9 and 70.0 g in the first and fifth quintiles (results not shown). Women with higher total fat intakes were slightly more likely to be current smokers and less likely to participate in vigorous physical activity than were those with low intake. In addition, total fat intake was inversely associated with alcohol and lactose consumption. Other characteristics did not vary across quintiles.

TABLE 4. (Continued)

Food	Frequency of intake						*p* for trend*
	<1/month	1–3/month	1/week	2–4/week	5–6/week	≥1/day	
Butter							
No. of cases	155	14	46		9	51	
Multivariate RR	1.00	1.63	0.81		1.25	1.16	
95% CI		0.94, 2.80	0.59, 1.13		0.64, 2.44	0.85, 1.59	0.34
Margarine							
No. of cases	41	8	88		21	122	
Multivariate RR	1.00	1.36	1.11		1.32	0.98	
95% CI		0.65, 2.83	0.80, 1.54		0.80, 2.18	0.72, 1.33	0.37
Salad dressing¶							
No. of cases	30	20	66	18	19		
Multivariate RR	1.00	0.66	1.40	0.82	1.51		
95% CI		0.41, 1.06	1.02, 1.91	0.50, 1.36	0.92, 2.47		0.26
Mayonnaise¶							
No. of cases	27	52	80	24	13		
Multivariate RR	1.00	1.20	1.18	1.04	1.40		
95% CI		0.83, 1.73	0.85, 1.64	0.65, 1.67	0.77, 2.54		0.79
Nuts							
No. of cases	151	44	59		30		
Multivariate RR	1.00	1.18	0.91		0.92		
95% CI		0.85, 1.65	0.68, 1.23		0.62, 1.36		0.33
Peanut butter							
No. of cases	147	42	71		23		
Multivariate RR	1.00	1.10	1.07		0.75		
95% CI		0.79, 1.55	0.81, 1.42		0.48, 1.16		0.34

* *p* for trend, calculated using the median of each category of food intake as a continuous variable in the multivariate regression model.

† Number of cases in quintile; numbers of cases and person-years may not sum to totals due to missing data

‡ Multivariate relative risks (RR) adjusted for age (<50, 50–54, 55–59, 60–64, and ≥65 years), parity (0, 1 – 2, 3–4, and ≥5 years), age at menarche (<12, 12, 13, 14, and ≥15 years), menopausal status/postmenopausal hormone use (premenopausal/never use, current use <5 years, current use ≥5 years, past use <5 years, past use ≥5 years), tubal ligation (yes, no), smoking status (never, past, current <15 cigarettes per day, current ≥15 cigarettes/day), tubal ligation, and smoking status.

§ CI, confidence interval.

¶ First queried in 1984; follow-up, 1984–1996.

Table 2 presents the relative risk of ovarian cancer associated with intake of fats and fatty acids. We observed no evidence of a positive association between intake of any type of fat and ovarian cancer risk. Women in the highest quintile of total fat intake were not at increased risk compared with those in the lowest quintile (relative risk (RR) = 1.03, 95 percent confidence interval (CI): 0.72, 1.45, *p* for trend = 0.97). Similarly, when we divided participants into deciles to compare more extreme levels of intake, we did not find evidence of an association; the relative risk comparing risk in the highest versus the lowest decile was 0.94 (95 percent CI: 0.55, 1.61, *p* for trend = 0.94).

We then assessed fat intake as a percentage of total energy intake (table 3). Although only a modest proportion of the cohort reported extremely high or low levels of intake, we found little suggestion of a positive association between intake and ovarian cancer risk (*p* for trend = 0.85). Furthermore, we did not find an association between fat intake and ovarian cancer in analyses in which fat subtypes (i.e., saturated, monounsaturated, polyunsaturated, and *trans* fats and cholesterol) and fat sources (i.e., dairy, nondairy animal, and vegetable fats) were adjusted for one another or when we used fat intake at baseline only to predict risk (results not shown).

We then evaluated risk of ovarian cancer based on intake of high-fat foods. Table 4 presents results for the foods that contributed the greatest amount to the fat intake of the cohort; these 13 foods accounted for 54.2 percent of total fat, 51.9 percent of saturated fat, and 67.9 percent of cholesterol intake. Few of these foods were associated with greater risk of ovarian cancer. Consumption of five or more eggs per week was associated with a significant 62 percent higher

cancer risk (RR = 1.62, 95 percent CI: 1.04, 2.53, p for trend = 0.05). In contrast, several foods was modestly associated with reduced risk. Participants who ate more than five servings of hard cheese per week had a relative risk of 0.76 (95 percent CI: 0.48, 1.20, p for trend = 0.02) compared with those who consumed less than one serving per month. In addition, frequent intake of several, but not all, types of red meat and poultry was associated with modestly lower risk. Results for intake of these foods at baseline only did not differ from those presented. Similarly, when we limited our analysis to women who reported that their intake of specific foods had not changed in the previous decade, the relations were essentially unchanged (results not shown).

We addressed the association between fat intake and three subtypes of ovarian cancer. Although we had limited power to evaluate the influence of fat intake on serous, mucinous, and endometrioid tumors, results did not differ substantially between subtypes (results not shown). High intake of dairy fat was associated with a marginally significant increase in the risk of serous ovarian cancer (RR for quintile 5 vs. quintile 1 = 1.66, 95 percent CI: 0.99, 2.77, p for trend = 0.16); results further adjusted for lactose intake were slightly attenuated (RR for quintile 5 vs. quintile 1 = 1.40, 95 percent CI: 0.81, 2.42, p for trend = 0.53).

To determine whether the observed fat-ovarian cancer relation was influenced by participants altering their diet preceding a diagnosis of cancer, we excluded from our analyses cases diagnosed during both the first 2 and 4 years of follow-up. Results did not differ substantially from those presented (results not shown).

Finally, we did not find that the relation between fat intake and ovarian cancer risk differed substantially by age, oral contraceptive use, menopausal status/postmenopausal hormone use, body mass index, smoking status, or physical activity level (results not shown).

DISCUSSION

We found little evidence that high intake of any type of fat or specific fatty acid increased the risk of ovarian cancer. Women who consumed more than 50 percent of their energy from fat had a risk of ovarian cancer similar to that of women who consumed less than 25 percent of energy from fat. In addition, we found little evidence that frequent consumption of fat-rich foods was associated with ovarian cancer risk.

Several mechanisms exist to explain how the frequent consumption of fats and animal products may be associated with ovarian cancer. The repeated rupture of the follicle associated with ovulation is believed to expose the ovarian epithelium to hormones in the surrounding fluid; high estrogen concentrations may increase the likelihood of tumor development (28). High consumption of fats may increase circulating estrogen levels, thus increasing the possibility of cell damage and proliferation (29). This theory is supported by studies indicating that vegetarian women with low-fat diets have lower urinary levels of total estrogens and estriol, higher fecal estrogen excretion, and higher levels of sex hormone-binding globulin than do nonvegetarian women with diets higher in fat (30, 31). However, differences in the diets of these groups are probably not limited to fat intake alone; it is unclear what other aspects of diet, such as fiber intake, may account for differences in hormone profiles. Other data do not support a positive association between fat intake and estrogen (23, 24). In a recent cross-sectional study of fat intake and plasma steroid hormone levels in 381 postmenopausal NHS participants, estradiol was inversely related to intake of total, vegetable, and marine omega–3 fats (24).

Several epidemiologic studies have suggested that consumption of various types of fats is positively associated with ovarian cancer. In a large, population-based case-control study, significant increases in ovarian cancer risk were noted for high intake of saturated fat and total cholesterol (4). Consumption of animal fat, in particular, was significantly associated with cancer risk in two other case-control studies (5, 6), which reported a 70–80 percent increase in risk with high intake. However, fat intake was not associated with ovarian cancer in other case-control studies (7–9). In the prospective Iowa Women's Health Study, Kushi et al. (10) found no evidence of a positive relation between intake of total, animal, vegetable, saturated, monounsaturated, or polyunsaturated fat and ovarian cancer, although nonsignificantly lower risks were observed for high intake of monounsaturated, polyunsaturated, and vegetable fats.

The absence of an association between fat intake and ovarian cancer in our data may be related to the fact that few members of our cohort reported a very low intake of dietary fat. The median values of total fat intake at baseline for our first and fifth quintiles were 48.5 and 83.5 g/day, equivalent to approximately 30 and 50 percent of calories from fat, respectively (table 1). A positive relation between fat and ovarian cancer risk may be discernible only over a greater range of intake. However, when we compared risk over deciles of total fat intake or when we evaluated fat intake as a percentage of total calories, we also did not find evidence of an association. Furthermore, the range of intake of our study does not differ substantially from those of other US studies reporting a positive association (4, 5). While it is also possible that the misclassification of fat intake as measured by the FFQ may have attenuated results to some degree, this is not a probable explanation of the absence of an association over extreme levels of intake, since it is very unlikely that participants were misclassified from one extreme category to the other (e.g., from ≤25 to ≥50 percent of calories from fat) (23).

The results of several studies are consistent with our findings concerning eggs (4, 10, 13) and cheese (5). However, given our null findings for saturated fat, animal fat, and cholesterol, which are substantial components of these foods, these results may also be due to chance. We did not find evidence of a positive association between intake of red meat and ovarian cancer. Increases in ovarian cancer risk of 60 and 170 percent with frequent intake of red meat were noted in case-control studies in Italy (11) and Japan (15), respectively. Intake of fried meats, in particular, was associated with a nonsignificant increased risk for the disease in a Finnish cohort (14). In two additional prospective studies, Seventh-day Adventist women who were lacto-ovo vegetarians had a lower risk of ovarian cancer than did nonvegetarian Adventist members (13) and non-Adventist members (12).

However, frequent meat intake was not associated with ovarian cancer in several other analyses (10, 16).

To our knowledge, ours is the largest prospective study of diet and ovarian cancer to date. It is also one of few studies of diet and ovarian cancer to use a complete FFQ to assess nutrient intake, allowing us to adjust for the effects of total energy intake. While little evidence suggests that energy intake is related to ovarian cancer (6, 9, 10), control for calorie intake can limit misclassification in nutrient intake caused by differences in body size and physical activity level (23). In addition, repeated dietary assessment over the follow-up period will minimize random within-person variation in measurement of food and nutrient intake (23). Specific types of fat intake, as measured by this FFQ, have previously been associated with coronary heart disease (32) and non-Hodgkin's lymphoma (33) in our cohort, suggesting that the observed lack of association with ovarian cancer is not likely to be the result of exposure misclassification.

In conclusion, we did not find intake of fats and high-fat foods to be associated with ovarian cancer risk. Further evaluation of this relation in large population studies may clarify the relation between intake of eggs and other fat-rich foods and ovarian cancer.

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