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Prospective Study of Diet and Ovarian Cancer

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Evidence on dietary risk factors for ovarian cancer is inconsistent, but some studies have suggested positive associations with dietary fat, lactose, and cholesterol and negative associations with green and yellow vegetable intake. By using information from the Iowa Women's Health Study, the authors investigated the association of epithelial ovarian cancer with dietary factors in a prospective study of 29,083 postmenopausal women. Dietary information was ascertained via a food frequency questionnaire mailed to participants in 1986. During 10 years of follow-up (1986–1995), 139 of the women developed incident epithelial ovarian cancer. Incidence of the disease was not associated with dietary fat intake. Lactose and cholesterol showed moderately elevated risks. Multivariable-adjusted relative risks for the lowest to highest quartiles of lactose intake were 1.00, 1.38, 1.25, and 1.60 (p for trend = 0.12). For cholesterol, the corresponding values were 1.00, 1.34, 1.86, and 1.55 (p for trend = 0.06). Consumption of eggs was also associated with an increased risk of ovarian cancer. Multivariable-adjusted relative risks for increasing frequency of egg consumption were 1.00 (<1/week), 1.12 (1/week), 2.04 (2–4/week), and 1.81 (>4/week) (p for trend = 0.04). Total vegetable intake was modestly and inversely associated with the risk of ovarian cancer (p for trend = 0.21). Green leafy vegetable intake was more strongly associated with a decreased risk: multivariable-adjusted relative risks for the lowest to highest intake levels were 1.00, 0.80, 0.87, and 0.44 (p = 0.01). These findings are generally in agreement with the results from previous, mostly case-control studies of diet and epithelial ovarian cancer. *Am J Epidemiol* 1999;149:21–31.

diet; nutrition; ovarian neoplasms; postmenopausal; prospective studies; risk; risk factors

Ovarian cancer has the highest mortality rate among the gynecologic cancers and is the fifth most common cause of death from cancer among women in the United States; recent estimates showed that in 1998, approximately 25,400 women would be diagnosed with ovarian cancer and that 14,500 women would die from it (1). Despite the large public health impact of this disease, relatively little is known regarding its etiology. Although the risk of ovarian cancer is elevated in women who have a family history of the disease, and parity and use of oral contraceptives are recognized as factors that reduce the risk (2), few other factors have been examined adequately. That environmental factors play a key role in the etiology of this disease is suggested by the fivefold international variation in ovarian cancer incidence and mortality rates (3) and the observation that ovarian cancer rates increase among women who emigrate from Japan, a low-incidence country, to the United States, a high-incidence country (4).

International comparisons indicate that ovarian cancer rates are associated positively with per capita dietary fat (5) and lactose (6) intake. These and other observations have formed the basis for several case-control studies of dietary factors and ovarian cancer. As reported in at least some of these studies, dietary factors related to a greater occurrence of ovarian cancer include increased intakes of lactose (7), saturated fat (8, 9), and dietary cholesterol (9) and decreased intakes of dietary fiber and beta-carotene (9–12).

To our knowledge, only two prospective studies of diet and ovarian cancer risk (13, 14) have been published. In one (13), a 13-year follow-up of 142,857 Japanese women, meat intake was associated with an increased risk of ovarian cancer. In the other (14), a 20-year follow-up of 16,190 female Seventh-day Adventists, consumption of eggs and fried foods was associated with an increased risk of fatal ovarian cancer. Neither of these prospective studies assessed diet by using methods that enabled estimation of nutrient intake. As case-control studies of diet may be ham-

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Abbreviation: RR, relative risk.

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pered by possible differential recall of dietary habits between those with and those without disease (15, 16), further prospective investigations are needed to clarify possible associations of dietary factors with ovarian cancer risk. The Iowa Women's Health Study, a large prospective study that included a comprehensive food frequency questionnaire, provided such an opportunity.

MATERIALS AND METHODS

The Iowa Women's Health Study cohort

Participants in the Iowa Women's Health Study were recruited from a random sample of 99,826 women aged 55–69 years who had valid Iowa driver's licenses in 1985. These women were mailed a 16-page questionnaire in January 1986. The 41,836 women who returned the questionnaire form the cohort under study. Nonrespondents have been characterized previously (17). The questionnaire included a food frequency assessment as well as items related to health habits (smoking and physical activity), gynecologic/menstrual history, pregnancy history, medications, personal and family medical history, and current weight and body measurements. Follow-up questionnaires were mailed in 1987, 1989, and 1992 to confirm participants' residence, vital status, and other characteristics.

Dietary assessment

The food frequency assessment was adapted, with minor modifications, from the 126-item questionnaire used in the 1984 Nurses' Health Study survey (18). For each food, a commonly used portion size was specified, and participants chose one of nine categories ranging from "never or less than once per month" to "6+ per day" to indicate their usual frequency of consumption of that portion size. Participants were also asked to specify other foods not listed on the questionnaire that they usually ate at least once per week and to indicate their usual serving size and the number of servings they ate per week. The Harvard Nutrient Database was used to calculate the daily intake of each nutrient on the basis of portion size, frequency of consumption, and nutrient content of each food item. The ability of the food frequency questionnaire to characterize persons according to nutrient intake was examined in a subset of 44 Iowa women by comparing their questionnaire answers with the mean intake as estimated from five 24-hour dietary recalls (19). For the intake of total fat, saturated fat, and cholesterol, correlations between food frequency and dietary recall estimates, adjusted for total energy intake, were 0.62, 0.59, and 0.21, respectively.

Follow-up

Ovarian cancer cases were ascertained through linkage of cohort members with the State Health Registry of Iowa, part of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program, via an annual computer match of social security number, name, maiden name, and date of birth. Primary site, morphology, and date of diagnosis were obtained for each incident cancer case from 1986 through 1995. The analyses presented here included ovarian cancers classified as "common epithelial tumors" by the World Health Organization's *Histological Typing of Ovarian Tumors* (20).

Women were considered to be at risk from the date they filled out the baseline questionnaire (approximately January 1986) until December 31, 1995. Follow-up was terminated earlier if they were diagnosed with ovarian cancer, died, moved out of Iowa, or were otherwise lost to follow-up. Deaths in Iowa were identified through the State Health Registry. Deaths outside of Iowa were identified via follow-up questionnaires mailed in 1987, 1989, and 1992 and, for nonrespondents, via the National Death Index. Self-reported cancer diagnoses that occurred outside the reporting area covered by the Iowa Surveillance, Epidemiology, and End Results Program were not verified, and occurrence of cancer among nonrespondents who moved outside this area was not ascertained. Therefore, women known to have moved from Iowa were censored as of the date of the move (if known), at the midpoint between the date of last contact in Iowa and the first known date out of Iowa, or at the end of the follow-up period. The outmigration rate among this cohort was approximately 1 percent per year (17).

Data analysis

Women were excluded from these analyses if, on the baseline questionnaire, they reported a history of cancer other than skin cancer (n = 3,830) or a bilateral oophorectomy (n = 6,610), if their food frequency questionnaires were incomplete (i.e., 30 or more food items were left blank) (n = 2,071), or if their energy intakes were implausibly low or high (<600 or ≥5,000 kcal per day) (n = 242). After these exclusions, 29,083 women remained eligible for follow-up. Among these women, 139 incident cases of epithelial ovarian cancer were identified during the 10 years of follow-up.

The dietary factors of interest were categorized by quartiles or by other appropriate cutpoints when necessary. The relative risk of ovarian cancer for each category of intake was estimated in comparison with the lowest intake category through proportional hazards regression by using the SAS program PHREG (SAS Institute, Cary, North Carolina). Analyses were per-

formed in two ways: first by adjusting for age and energy, and second by additionally adjusting for other potential confounders. To analyze nutrients, we adjusted for total energy intake by using the residual method proposed by Willett and Stampfer (21). To analyze individual foods and food groups, total energy intake was entered into the models as a continuous variable. Additional variables in the multivariable models were included based on prior analyses of ovarian cancer risk factors in this cohort (22). These variables were the number of livebirths (none, 1–2, 3–4, or >4), age at menopause (<45 years, 45–49 years, or ≥50 years), family history of ovarian cancer in a first-degree relative, hysterectomy/unilateral oophorectomy status (neither procedure, hysterectomy only, oophorectomy only, or both procedures), waist-to-hip ratio (in quartiles), level of physical activity (low, medium, or high), cigarette smoking (number of pack-years), and level of education (<high school, high school graduate, vocational education or some college, or college graduate).

Oral contraceptive use was not considered in these analyses, as it was unrelated to ovarian cancer risk in this cohort (22). This cohort is also of limited use in investigating associations with oral contraceptives. Study participants would have been aged 28–42 years when oral contraceptives were first available in 1960 (23). Indeed, only 18 percent of the women reported ever using oral contraceptives; of those, 37 percent reported using them for less than 1 year. No information was available on tubal ligation, another possible risk factor for ovarian cancer.

RESULTS

Table 1 shows age- and multivariable-adjusted relative risks of ovarian cancer with various nutrients and associated dietary factors. This table and table 2 also provide the number of cases that occurred in each category of intake and the associated range of intake. Person-years are provided only if the cutpoints for the categories were other than quartiles (e.g., for alcohol intake), as quartile cutpoints result in equivalent numbers of person-years across categories. As shown in table 1, risk of ovarian cancer was not associated consistently with intake of energy, fat, protein, or dietary fiber. There was also no association with type of fat when examined as a percentage of total fat intake (data not shown). Relative risks were elevated for the upper three quartiles versus the lowest quartile of lactose intake (p for trend = 0.12). Relative risks were also elevated for the upper three quartiles of cholesterol intake (p for trend = 0.06). Greater intake of carbohydrates was associated with an increased risk of ovarian cancer (relative risk (RR) for highest vs. lowest quartile of intake = 1.83, 95 percent confidence interval 1.07–3.13, p for trend = 0.04). A higher intake of alcohol was associated with a decreased risk (p for trend = 0.01).

There was no association of vitamin A, beta-carotene, vitamin C, or vitamin E with the incidence of ovarian cancer (table 1). Relative risks for the upper three quartiles versus the lowest quartile of retinol, vitamin D, folate, and calcium intake were all above 1.00, but there was no clear dose-response pattern for these nutrients. The positive association observed for folate intake appeared to be attributable to intake from supplements. The relative risk was 1.43 (95 percent confidence interval 0.74–2.77, p for trend = 0.13; data not provided in tables) for women who ingested more than 400 μg of folate from supplements versus those who ingested no supplemental folate. Conversely, the positive association observed for calcium appeared to be attributable to intake from food sources only. Multivariable-adjusted relative risks for four increasing quartiles of calcium intake, excluding intake from supplements, were 1.00, 1.24, 1.57, and 1.75 (p for trend = 0.02; data not provided in tables).

Age- and energy-adjusted relative risks and multivariable-adjusted relative risks for ovarian cancer, according to category of intake of various foods and food groups, are shown in table 2. There was no consistent pattern of association of meats or of breads, cereals, and starches with the incidence of ovarian cancer. However, intake of sweets was positively associated with ovarian cancer risk; relative risks from the lowest to highest categories of intake were 1.00, 2.32, 2.49, and 1.61 (p for trend = 0.17). Higher overall vegetable consumption was inversely but not significantly associated with the incidence of ovarian cancer. This pattern appeared to be attributable to intake of green leafy vegetables (multivariable-adjusted RR for highest vs. lowest category = 0.44, 95 percent confidence interval 0.25–0.79, p for trend = 0.01). Intake of beta-carotene-containing vegetables or cruciferous vegetables was not associated with the incidence of ovarian cancer (p for trend = 0.60 and 0.78, respectively; data not shown).

A positive association was found between the intake of dairy products and the incidence of ovarian cancer. In the multivariable model, relative risks were 1.25, 1.65, and 1.76 for the second, third, and fourth categories, respectively, as compared with the lowest category (p for trend = 0.03). In particular, increasing consumption of skim milk was associated with a greater risk (p for trend = 0.04). Relative risks associated with more frequent cheese intake were also elevated (p for trend = 0.14). Other individual dairy products, including whole milk, cream, ice cream, and yogurt, were not associated with ovarian cancer incidence (data not shown). There was a positive association of eggs with the incidence of ovarian

TABLE 1. Relative risks and 95% confidence intervals of ovarian cancer, according to nutrient intake as categorized by quartiles, among 29,083 postmenopausal women, Iowa Women's Health Study, 1986–1995

Quartile	Range of intake	Cases (no.)	Relative risk*	95% confidence interval*	Multivariable-adjusted relative risk†	95% confidence interval†
			Total energy (kcal)			
1	<1,384	28	1.00		1.00	
2	1,384–1,729	36	1.29	0.79–2.11	1.13	0.67–1.89
3	1,730–2,134	44	1.57	0.98–2.52	1.48	0.91–2.42
4	>2,134	31	1.10	0.66–1.84	0.91	0.53–1.57
p for trend			0.54		0.99	
			Total fat (g)			
1	<62.4	35	1.00		1.00	
2	62.4–69.2	41	1.18	0.75–1.87	1.11	0.69–1.80
3	69.3–75.9	34	0.99	0.61–1.59	0.95	0.57–1.57
4	>75.9	29	0.84	0.52–1.38	0.80	0.47–1.36
p for trend			0.38		0.34	
			Animal fat (g)			
1	<32.7	34	1.00		1.00	
2	32.7–39.0	30	0.89	0.54–1.47	0.94	0.54–1.62
3	39.1–45.7	47	1.40	0.89–2.20	1.62	1.00–2.64
4	>45.7	28	0.84	0.51–1.39	0.98	0.57–1.69
p for trend			0.94		0.56	
			Vegetable fat (g)			
1	<23.3	34	1.00		1.00	
2	23.3–28.7	41	1.22	0.76–1.94	1.14	0.70–1.84
3	28.8–34.6	33	0.98	0.60–1.59	0.93	0.56–1.54
4	>34.6	31	0.91	0.56–1.48	0.75	0.44–1.27
p for trend			0.51		0.20	
			Saturated fat (g)			
1	<21.6	33	1.00		1.00	
2	21.6–24.4	42	1.28	0.81–2.04	1.43	0.87–2.34
3	24.5–27.4	30	0.93	0.56–1.53	1.01	0.59–1.74
4	>27.4	34	1.06	0.65–1.71	1.17	0.69–1.97
p for trend			0.83		0.89	
			Monosaturated fat (g)			
1	<22.7	36	1.00		1.00	
2	22.7–25.7	37	1.04	0.65–1.65	0.93	0.57–1.52
3	25.8–28.6	41	1.16	0.74–1.82	1.18	0.74–1.90
4	>28.6	25	0.70	0.42–1.17	0.65	0.38–1.13
p for trend			0.24		0.24	
			Polyunsaturated fat (g)			
1	<10.5	43	1.00		1.00	
2	10.5–12.2	27	0.62	0.38–1.01	0.58	0.35–0.97
3	12.3–14.2	38	0.88	0.56–1.37	0.81	0.51–1.29
4	>14.2	31	0.72	0.45–1.14	0.63	0.38–1.03
p for trend			0.40		0.18	
			Total protein (g)			
1	<72.6	32	1.00		1.00	
2	72.6–81.1	35	1.10	0.68–1.79	1.04	0.61–1.77
3	81.2–89.9	38	1.21	0.75–1.94	1.19	0.71–1.98
4	>89.9	34	1.08	0.66–1.75	1.16	0.69–1.92
p for trend			0.69		0.49	

Table continues

TABLE 1. Continued

Quartile	Range of intake	Cases (no.)	Relative risk*	95% confidence interval*	Multivariable-adjusted relative risk†	95% confidence interval†
			Animal protein (g)			
1	<49.6	28	1.00		1.00	
2	49.6–58.9	42	1.53	0.94–2.48	1.50	0.89–2.53
3	59.0–69.0	36	1.32	0.80–2.17	1.31	0.77–2.24
4	>69.0	33	1.20	0.73–1.99	1.32	0.77–2.24
p for trend			0.62		0.42	
			Vegetable protein (g)			
1	<19.0	29	1.00		1.00	
2	19.0–21.6	41	1.42	0.88–2.31	1.48	0.89–2.47
3	21.7–24.5	41	1.41	0.87–2.29	1.47	0.88–2.44
4	>24.5	28	0.95	0.56–1.59	0.83	0.47–1.48
p for trend			0.84		0.54	
			Total carbohydrate (g)			
1	<197.3	24	1.00		1.00	
2	197.3–217.9	38	1.56	0.93–2.62	1.54	0.89–2.66
3	218.0–238.0	35	1.42	0.84–2.40	1.43	0.81–2.51
4	>238.0	42	1.69	1.02–2.79	1.83	1.07–3.13
p for trend			0.07		0.04	
			Lactose (g)			
1	<7.7	29	1.00		1.00	
2	7.7–13.7	36	1.23	0.75–2.03	1.38	0.80–2.39
3	13.8–25.2	34	1.16	0.70–1.92	1.25	0.72–2.18
4	>25.2	40	1.36	0.84–2.20	1.60	0.95–2.70
p for trend			0.26		0.12	
			Alcohol (g)‡			
1	0	78	1.00		1.00	
2	0.9–3.9	43	1.29	0.89–1.87	1.37	0.93–2.04
3	4.0–10.0	8	0.61	0.30–1.27	0.61	0.28–1.34
4	>10.0	10	0.58	0.30–1.13	0.49	0.24–1.01
p for trend			0.03		0.01	
			Dietary fiber (g)			
1	<16.3	37	1.00		1.00	
2	16.3–19.7	31	0.82	0.50–1.33	0.95	0.57–1.59
3	19.8–23.6	33	0.86	0.54–1.39	0.88	0.52–1.48
4	>23.6	38	0.99	0.63–1.56	1.01	0.61–1.68
p for trend			0.98		0.95	
			Cholesterol (mg)			
1	<237.2	27	1.00		1.00	
2	237.2–288.4	33	1.24	0.74–2.07	1.34	0.77–2.36
3	288.5–347.7	44	1.67	1.03–2.72	1.86	1.10–3.15
4	>347.7	35	1.33	0.81–2.21	1.55	0.90–2.67
p for trend			0.15		0.06	
			Vitamin A (IU§)			
1	<8,894	33	1.00		1.00	
2	8,894–12,803	33	1.00	0.61–1.62	1.09	0.64–1.84
3	12,804–18,218	39	1.17	0.73–1.87	1.27	0.76–2.11
4	>18,218	34	1.01	0.63–1.88	1.11	0.65–1.88
p for trend			0.79		0.59	

Table continues

TABLE 1. Continued

Quartile	Range of intake	Cases (no.)	Relative risk*	95% confidence interval*	Multivariable-adjusted relative risk†	95% confidence interval†
			Beta-carotene (IU)			
1	<5,503	33	1.00		1.00	
2	5,503–7,840	34	1.04	0.63–1.70	1.03	0.61–1.74
3	7,841–12,078	42	1.27	0.79–2.02	1.18	0.71–1.96
4	>12,078	30	0.90	0.55–1.48	0.91	0.53–1.55
p for trend			0.87		0.85	
			Retinol (IU)			
1	<1,707	34	1.00		1.00	
2	1,707–3,884	30	0.88	0.54–1.43	1.19	0.70–2.03
3	3,885–6,625	37	1.08	0.68–1.73	1.34	0.79–2.25
4	>6,625	38	1.11	0.70–1.77	1.42	0.85–2.37
p for trend			0.48		0.16	
			Vitamin C (mg)			
1	<129.2	33	1.00		1.00	
2	129.2–187.7	38	1.13	0.71–1.80	1.17	0.71–1.92
3	187.8–321.9	33	0.98	0.61–1.59	0.94	0.56–1.58
4	>321.9	35	1.06	0.66–1.71	1.05	0.63–1.76
p for trend			0.96		0.93	
			Vitamin D (IU)			
1	<198.5	28	1.00		1.00	
2	198.5–325.0	35	1.23	0.74–2.02	1.26	0.74–2.15
3	325.1–566.0	40	1.41	0.87–2.28	1.39	0.83–2.36
4	>566.0	36	1.27	0.77–2.08	1.37	0.81–2.32
p for trend			0.29		0.22	
			Vitamin E (mg)			
1	<6.2	41	1.00		1.00	
2	6.2–9.2	24	0.56	0.33–0.95	0.52	0.30–0.91
3	9.3–24.4	36	0.83	0.50–1.37	0.70	0.41–1.21
4	>24.4	38	0.90	0.56–1.43	0.91	0.56–1.48
p for trend			0.94		0.98	
			Folate (μg)			
1	<240.9	26	1.00		1.00	
2	240.9–305.3	37	1.41	0.85–2.33	1.37	0.80–2.35
3	305.4–488.5	33	1.25	0.75–2.09	1.21	0.70–2.11
4	>488.5	43	1.65	1.01–2.68	1.63	0.97–2.76
p for trend			0.08		0.11	
			Calcium (mg)			
1	<731	27	1.00		1.00	
2	731–1,051	41	1.51	0.93–2.46	1.79	1.05–3.05
3	1,052–1,372	31	1.14	0.68–1.91	1.41	0.80–2.48
4	>1,372	40	1.49	0.92–2.43	1.66	0.96–2.88
p for trend			0.24		0.14	

* Adjusted for age and total energy intake (total energy category adjusted for age only).

† Adjusted for age, total energy intake, number of livebirths, age at menopause, family history of ovarian cancer in a first-degree relative, hysterectomy/unilateral oophorectomy status, waist-to-hip ratio, level of physical activity, cigarette smoking (number of pack-years), and educational level.

‡ Categories of intake are based on the distribution of alcohol intake rather than on quartiles (numbers of person-years of follow-up from low to high levels of intake: 148,374, 64,274, 25,251, and 33,304).

§ IU, international units.

cancer. Multivariable-adjusted relative risks for the four categories of increasing egg intake were 1.00, 1.12, 2.04, and 1.81 (p for trend = 0.04).

DISCUSSION

In this prospective study of older women, we found that several dietary factors were associated with the risk of ovarian cancer. Among nutrients and related dietary components, greater dietary cholesterol and carbohydrate intake appeared to increase ovarian cancer risk. Lactose intake was positively but not significantly associated with an increased risk, as were folic acid and calcium intake. Alcohol intake was inversely associated with ovarian cancer risk. Otherwise, no associations with ovarian cancer risk were found for intake of fats, dietary fiber, beta-carotene, or any of several vitamins examined. Among food groups, intake of green leafy vegetables was associated with a decreased risk of ovarian cancer, while intake of eggs and dairy products, particularly skim milk and cheese, was associated with an increased risk. The associations with dairy foods and lactose suggest that lactose may play a role in the etiology of ovarian cancer. That intake of calcium, skim milk, and cheeses appeared to be associated with an increased risk, while whole milk, cream, and saturated fatty acids did not, also suggests that the fat component of dairy products is unlikely to be responsible for the observed increased risk of ovarian cancer associated with dairy foods.

The possibility that dairy foods may be related to ovarian cancer risk, in particular because of their lactose content, was first suggested by Cramer et al. (6, 7). In an ecologic study of 27 countries, Cramer (6) observed that the incidence of ovarian cancer is associated with per capita milk intake and lactase persistence; in a population-based case-control study in Massachusetts, Cramer et al. (7) concomitantly reported an association of more frequent yogurt and cottage cheese intake with an increased ovarian cancer risk. They also observed in this case-control study that galactose-1-phosphate uridyl transferase activity was decreased among the cases relative to the controls. This enzyme is required for metabolism of galactose to glucose, and a relative deficiency of this enzyme may result in an accumulation of galactose. Elevated levels of galactose may adversely influence ovarian function, as evidenced by studies indicating that excess galactose intake in rodents (23, 24) and galactosemia in women (25, 26) are associated with hypergonadotropic hypogonadism. It was therefore suggested that a plausible biologic basis exists for a positive association of dairy food and lactose intake with ovarian cancer risk (7).

Several other studies have examined associations of dairy, lactose, or related factors with ovarian cancer risk. In an earlier case-control study, Cramer et al. (8) reported that intake of whole milk (odds ratio = 1.51 for high vs. low intake), but not skim milk (comparable odds ratio = 0.58), was associated with an increased risk of ovarian cancer. A similar finding was reported in a case-control study in upstate New York (27), in which a whole milk intake of more than one glass per day was associated with a 3.1-fold greater risk of ovarian cancer as compared with nondrinkers, while consumption of skim and 2 percent fat milk was inversely associated with a risk of ovarian cancer. Therefore, the authors suggested that fat intake rather than lactose intake was more likely to be associated with a risk of ovarian cancer. In contrast, in our study, intake of skim milk but not whole milk was associated with an increased risk of ovarian cancer. However, skim milk consumption was much higher than whole milk consumption in this cohort, with 80 percent of the participants reporting that they drank whole milk less often than once per month. In none of the other studies that either specifically examined an association with lactose intake (12, 28, 29) or reported on milk or dairy intake (30–34) was there a positive association with ovarian cancer risk; indeed, in a study in Japan, there was the suggestion of a decreased risk with any milk intake (31, 32).

A more consistent finding in case-control studies of diet and ovarian cancer is positive associations with animal fat or meat intake. The earlier case-control study by Cramer et al. (8) noted positive associations with saturated and animal fat intake and animal fat sources, including whole milk and butter. In a case-control study in Japan (31), daily meat intake had an increased risk of 3.1 for ovarian cancer, while in a study in Milan, Italy (30), elevated risks for high versus low intake of meat (RR = 1.60), ham (RR = 1.55), and butter (RR = 1.93) were observed. A case-control study in Shanghai, China (33), reported that animal fat and red meat intake were associated with an increased risk of ovarian cancer, although these associations were somewhat attenuated after adjustment for education. Finally, in a study in Ontario, Canada, Risch et al. (9) reported that saturated fat intake was positively associated with a risk of ovarian cancer. In none of these case-control studies were measures of polyunsaturated or vegetable fat intake associated with ovarian cancer risk. Two other studies (11, 34) reported associations of saturated fat intake with ovarian cancer risk; although these associations were not statistically significant, the risks increased with increasing intake.

Results of the two previously published cohort studies are broadly consistent with the majority of the results from case-control studies. It was reported that meat intake among a large cohort in Japan (13) and intake of fried foods among a cohort of Seventh-day Adventists

TABLE 2. Relative risks and 95% confidence intervals of ovarian cancer, according to category of intake of various foods and food groups, among 29,083 postmenopausal women, Iowa Women's Health Study, 1986–1995

Category*	Range of intake (no. of servings)	Cases (no.)	Relative risk†	95% confidence interval	Multivariable-adjusted relative risk‡	95% confidence interval‡
			Meats			
1	<9/week	38	1.00		1.00	
2	9–12/week	37	1.08	0.68–1.72	1.18	0.72–1.93
3	13–17/week	18	0.58	0.32–1.04	0.68	0.37–1.24
4	>17/week	46	1.45	0.85–2.49	1.60	0.89–2.86
p for trend			0.58		0.38	
			Breads, cereals, and starches			
1	<17/week	30	1.00		1.00	
2	17–24/week	43	1.36	0.84–2.19	1.06	0.64–1.78
3	25–32/week	34	1.14	0.68–1.92	1.15	0.67–1.96
4	>32/week	32	0.99	0.55–1.77	1.05	0.58–1.91
p for trend			0.82		0.81	
			Sweets			
1	<3/week	17	1.00		1.00	
2	3–6/week	46	2.26	1.29–3.95	2.32	1.30–4.14
3	7–11/week	46	2.46	1.39–4.31	2.49	1.38–4.51
4	>11/week	30	1.67	0.88–3.17	1.61	0.81–3.18
p for trend			0.11		0.17	
			Vegetables			
1	<16/week	34	1.00		1.00	
2	16–23/week	44	1.37	0.87–2.16	1.25	0.77–2.02
3	24–31/week	33	0.95	0.58–1.56	0.87	0.51–1.48
4	>31/week	28	0.80	0.46–1.39	0.76	0.42–1.37
p for trend			0.25		0.21	
			Green leafy vegetables			
1	<2/week	48	1.00		1.00	
2	2–3/week	23	0.77	0.47–1.27	0.80	0.47–1.35
3	4–6/week	46	0.87	0.58–1.31	0.87	0.56–1.34
4	>6/week	22	0.53	0.32–0.87	0.44	0.25–0.79
p for trend			0.03		0.01	

Table continues

(14) were associated with an increased risk of ovarian cancer. In contrast, our findings do not support an association of animal fat or saturated fat intake with a risk of ovarian cancer. While there was some suggestion that a high intake of meats was positively associated with ovarian cancer risk (RR for highest vs. lowest intake category = 1.60), the overall trend was not statistically significant.

In the Seventh-day Adventist cohort study (14), consumption of eggs was positively associated with ovarian cancer mortality, with an intake of at least three eggs versus less than one egg per week associated with a threefold increased risk. This finding was consistent with ours, in which consumption of eggs several times per week as compared with less than once per week was associated with a twofold excess risk of ovarian cancer. We also observed a nonsignificant increased risk of ovarian cancer with an increasing intake of dietary cholesterol; eggs are among the richest commonly consumed sources of cholesterol. Five case-control studies have also examined the association of eggs or dietary cholesterol with ovarian cancer risk. In one of the more recent (9), cholesterol from eggs was associated with an increased risk of about 1.4 for a 100 mg increase in intake; cholesterol from other sources was not associated with ovarian cancer risk. In two studies, one in Boston, Massachusetts (8), and the other in Greece (34), dietary cholesterol was associated with nonsignificant increased risks of ovarian cancer; associations with egg consumption were not reported in these studies. In two additional studies (30, 33) that reported findings related to egg intake, no

TABLE 2. Continued

Category*	Range of intake (no. of servings)	Cases (no.)	Relative risk†	95% confidence interval	Multivariable-adjusted relative risk‡	95% confidence interval‡
			Fruit			
1	<11/week	33	1.00		1.00	
2	11–16/week	26	0.83	0.50–1.40	0.86	0.50–1.47
3	17–23/week	40	1.22	0.76–1.95	1.05	0.63–1.76
4	>23/week	40	1.22	0.74–1.99	1.13	0.66–1.93
p for trend			0.23		0.51	
			Dairy products			
1	>9/week	28	1.00		1.00	
2	9–14/week	34	1.17	0.71–1.94	1.25	0.72–2.18
3	15–23/week	38	1.43	0.86–2.36	1.65	0.96–2.85
4	>23/week	39	1.45	0.85–2.47	1.76	0.99–3.13
p for trend			0.13		0.03	
			Skim milk			
1	<1/week	21	1.00		1.00	
2	1/month–6/week	40	1.50	0.88–2.54	1.26	0.72–2.21
3	1/day	37	1.65	0.97–2.82	1.54	0.88–2.70
4	>1/day	38	1.68	0.98–2.89	1.73	0.99–3.02
p for trend			0.05		0.04	
			Cheese			
1	<1/week	25	1.00		1.00	
2	1/week	32	1.26	0.75–2.14	1.34	0.76–2.36
3	2–4/week	55	1.39	0.86–2.25	1.52	0.90–2.55
4	>4/week	25	1.28	0.72–2.28	1.56	0.85–2.86
p for trend			0.37		0.14	
			Eggs			
1	<1/week	25	1.00		1.00	
2	1/week	28	1.08	0.63–1.86	1.12	0.62–2.02
3	2–4/week	72	1.86	1.17–2.96	2.04	1.23–3.36
4	>4/week	14	1.60	0.82–3.14	1.81	0.89–3.69
p for trend			0.07		0.04	

* As determined by quartile cutpoints, except for the following, which are based on the number of person-years of follow-up from low to high intake categories: skim milk: 60,649, 76,569, 63,733, and 64,688; cheese: 60,183, 61,773, 97,706, and 48,872; and eggs: 66,689, 70,284, 107,778, and 25,215.

† Adjusted for age and total energy intake.

‡ Adjusted for age, total energy intake, number of livebirths, age at menopause, family history of ovarian cancer in a first-degree relative, hysterectomy/unilateral oophorectomy status, waist-to-hip ratio, level of physical activity, cigarette smoking (number of pack-years), and educational level.

association with ovarian cancer risk was observed. It has been suggested that dietary cholesterol may raise the risk of ovarian cancer through its role as a precursor of steroid hormones, including estrogens (9); thus, there may be some biologic basis for the associations observed in this study.

Our other principal finding that is consistent with observations from other studies is the inverse association between intake of green leafy vegetables and ovarian cancer. Most other studies that have examined associations of some measure of vegetable intake have observed inverse associations with ovarian cancer risk. It has been reported that the risk is inversely associated with intake of total dietary fiber and fiber from vegetables (9), crude fiber (34), provitamin A carotenoids (10–12), green vegetables (12, 30), and carrots (12). Although the specific dietary factors shown to be inversely associated have varied, these results are consistent with an association of a dietary pattern of high vegetable intake with a decreased risk of ovarian cancer. These inverse associations may be attributable to some or several phytochemicals present in vegetable foods (34), and differences in study populations and dietary assessment methods may result in different aspects of vegetable intake being associated with a decreased risk of ovarian cancer.

Although intake of green leafy vegetables was inversely associated with ovarian cancer risk in our study, intake of carbohydrates was positively associated. This finding was not attributable to intake of breads, cereals, and other high-starch foods, as they were not associated with ovarian cancer risk. On the other hand, intake of sweets was positively associated with a risk of ovarian cancer. Three other studies (9, 33, 35) provided information on whether carbohydrate intake may be associated with a risk of ovarian cancer; in none was there evidence of an association. One of these studies (35) suggested that sucrose intake may increase the risk of ovarian cancer, but no information pertaining to complex carbohydrate intake was provided. In another study (33), intake of complex carbohydrate foods was inversely but weakly associated with ovarian cancer risk; no information was provided regarding intake of sucrose or high-sugar foods.

An unexpected finding in our study was the inverse association of alcohol intake with ovarian cancer risk. Women who consumed at least 10 g of alcohol per day had a reduced risk of ovarian cancer of about 0.5 as compared with nondrinkers. Two case-control studies (10, 36) also reported inverse associations of alcoholic beverages with ovarian cancer risk, but in neither did this association approach statistical significance. At least 10 other case-control studies (8, 12, 30–32, 37–41) have examined associations of alcohol or alcoholic beverages with ovarian cancer risk. In only one (37) was a significant positive association reported, although possible positive associations were suggested in three other studies (30, 31, 39). In the context of these inconsistent observations from case-control studies, our findings of an inverse association may be due to chance or may be a result of unexplained confounding variables.

Ours is one of the first prospective cohort studies to examine associations of dietary factors with ovarian cancer risk and to our knowledge the first cohort study to assess diet in a manner that enabled nutrient intake to be estimated. Thus, discrepancies in results between our study and the case-control studies may relate to differences in study design and in the ages of participants. In particular, case-control studies of dietary exposures may be compromised by differential recall bias; that is, because of their disease status, cases may report past dietary habits differently from controls. For example, a study of breast cancer (15) has suggested that cases are more likely to overreport fat intake than are noncases. If a similar bias occurs with ovarian cancer cases, this may in part explain the discrepancy in findings between our study and some of the case-control studies that have reported positive associations between fat intake and ovarian cancer.

Although differences in study design may be one factor contributing to discrepancies in results, some of our observations may simply be chance findings. For example, although there was an increasing risk of ovarian cancer with an increasing carbohydrate intake, this finding was unexpected. While intake of sweets was also associated with an increased ovarian cancer risk, only three other studies (9, 33, 35) have presented information regarding associations of carbohydrates or carbohydrate foods with the risk of ovarian cancer. Similarly, the inverse association with alcohol intake was unexpected, and none of the case-control studies that examined associations of alcohol and ovarian cancer reported a significant inverse association. Related to this issue of chance findings, many of the associations examined were not based on prior hypotheses.

It has also been recognized that for some dietary variables such as fat intake, there is relatively little variation in intake within a cohort such as our study population compared with the variation that may exist internationally (42). In addition, dietary assessment methods are compromised by measurement error, which will tend to further decrease the apparent variation in intake (43). This has the potential effect of decreasing power to detect associations of interest (44) and may have also contributed to our failure to observe associations of ovarian cancer risk with dietary fat and related variables. With 139 cases of ovarian cancer, there was relatively little power to detect moderate associations between dietary factors and ovarian cancer risk. Several of the associations of interest were also characterized by relative risk estimates that did not increase or decrease monotonically, and individual confidence intervals were broad. Given these caveats, these associations of dietary factors with ovarian cancer risk may be of a larger magnitude than we observed, and associations that have been observed in other studies may have been equivocal in our study because of a lack of power. Overall, these associations require confirmation from other prospective studies before they can be considered established risk factors for ovarian cancer.

In summary, in this prospective study of older women we observed associations of several dietary factors with ovarian cancer risk. Some of these associations have been observed in other studies and thus have a prior epidemiologic basis for inferring causality. These include positive associations of ovarian cancer risk with intake of eggs and dietary cholesterol and an inverse association with intake of green leafy vegetables. Although we observed a positive association of dairy, lactose, and calcium intake with ovarian cancer risk, only one (7) of several case-control studies to examine this association supported this finding. A positive association with intake of carbohydrates, apparently attributable to intake of sweets, and an inverse association with alcohol intake were unexpected.

Overall, these findings suggest that dietary factors may play an important role in the etiology of ovarian cancer.

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