

ORIGINAL ARTICLE

Fiber intake and endometrial cancer risk

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Abstract

Background. The epidemiological evidence on the relation between dietary fiber intake and endometrial cancer is contradictory. Consequently, a case-control study was carried out to further investigate the role of dietary fiber intake in the etiology of endometrial cancer. **Material and methods.** Cases were 454 women with incident, histologically confirmed, endometrial cancer admitted to major teaching and general hospitals. Controls were 908 women admitted for acute, non-neoplastic conditions to the same hospital network. Information on diet was elicited using a validated food frequency questionnaire. **Results.** Odds ratios (OR) and 95% confidence intervals (CI) for quintiles of various types of fiber were estimated after allowance for total energy intake and other potential confounding factors. Lignin intake was significantly inversely related to endometrial cancer (OR=0.6 for the highest versus the lowest quintile of intake; 95% CI: 0.4–0.9) with a slightly significant linear trend in risk (p-value=0.04). **Discussion.** Data suggest the potential importance of lignin in the prevention of endometrial cancer at Italian consumption levels.

Prolonged exposure to estrogens unopposed by progesterone is a strong risk factor for endometrial cancer [1]. Dietary fiber has been linked to estrogen absorption, metabolism, and hence bioavailability [2]. Thus, an inverse association of dietary fiber intake with endometrial cancer is plausible.

The epidemiological evidence on the relation between dietary fiber intake and endometrial cancer is inconsistent [3,4]. Almost all case-control studies reported a protective effect of total dietary fiber intake [5–10] with an additional study showing an inverse association separately for each type of fiber sources (vegetable, fruit, and grain) [11]. One case-control study did not find any consistent association for total fiber intake [12]. Similarly two cohort studies conducted in Canada [13] and Europe [14] showed no significant association between total or specific types of fiber and endometrial cancer after allowance for total calorie intake.

The inconsistent results observed between studies may be due to chance, bias, or confounding, to different questionnaires and nutrient assessment tools used, or differing dietary fiber characteristics considered, such as solubility or source.

As only one study looked at different types of fiber intake, we took advantage of a large multicentre case-control study conducted in Italy, based on a validated food frequency questionnaire, to provide further insight on the relation between endometrial cancer and dietary intakes of different types of fiber, in order to distinguish between their separate effects.

Material and methods

A case-control study on endometrial cancer was conducted between 1992 and 2006 in three Italian areas: the province of Milano and Pordenone in northern

Italy, and the urban area of Naples in southern Italy. Cases were 454 women (median age 60 years, range 18–79) with incident, histologically confirmed endometrial cancer, with no previous diagnosis of any cancer. Eligible women were those whose first diagnosis of endometrial cancer occurred less than one year prior to interview (median two days). Less than 10% of patients were treated before interview. Controls were 908 women (median age 61 years, range 19–79) admitted to the same network of hospitals of cases for a wide spectrum of non-neoplastic acute illnesses. Women admitted for gynecological or hormone-related conditions, or any other medical condition associated with long-term dietary changes, were not eligible as controls. Women with a history of hysterectomy were also excluded from the control group. Controls were admitted for traumatic orthopedic disorders (mainly broken harms, hands, and legs) (36%), other orthopedic disorders (32%), acute surgical conditions (mainly appendicitis and hernias) (9%) and miscellaneous other illnesses, including eye, nose, ear, skin or dental disorders (23%). Controls were frequency matched to cases with a 2:1 ratio on age and study centre. Less than 5% of cases and controls approached refused to be interviewed. Our refusal rate applied to women approached for interview only. Cases interviewed were however comparable for sociodemographic characteristics to cancer incidence cases in Pordenone and hospital registries in Milan and Naples.

All eligible patients, before the interview, agreed to participate in the study by signing an informed consent. However, because our study was strictly an observational one, gathering only data by means of a structured questionnaire without collection of biological samples, it was exempt from Institutional Review Board's approval.

The same structured questionnaire was used in all study centers. It was administered by centrally trained interviewers during the subject's hospital stay and included information on personal characteristics and lifestyle habits, anthropometric measures, a problem-oriented medical history and history of cancer in first-degree relatives, gynecologic and reproductive history, and hormone and aspirin use. An interviewer-administered food frequency questionnaire (FFQ) was adopted to assess the usual diet during the two years preceding diagnosis (for cases) or hospital admission (for controls). The FFQ included 78 foods, food groups or dishes divided into six sections: (i) bread, cereals, first courses; (ii) second courses (i.e., meat, fish and other main dishes); (iii) side dishes (i.e., vegetables); (iv) fruits; (v) sweets, desserts and soft drinks; (vi) milk, hot beverages and sweeteners. An additional section investigated lifetime history of alcoholic beverage intake. For a few

seasonal vegetables and fruits, consumption in season, and the corresponding duration, was elicited. At the end of each section, one or two open questions were used to include foods that were not in the questionnaire, but were eaten at least once a week. The FFQ allowed to estimate the intake of total energy as well as of selected nutrients, using Italian food composition databases integrated with other sources, when needed [15]. Dietary fiber intake was derived using the Englyst method [16,17]. A modification of the procedure permitted to measure cellulose separately from insoluble non-cellulose polysaccharides (ncp), while values for lignin were provided separately. We did not include resistant starch in the computation of total fiber, because the amount depends on how each food is processed and consumed [18], and related food composition tables were not available. Fiber intake was also divided according to the food of origin (i.e., vegetable, fruit, and grain). The FFQ was satisfactorily reproducible [19] and valid [20]. Reproducibility was evaluated by means of the Pearson product-moment correlation coefficient (r) between log-transformed intakes of fiber calculated from two questionnaires administered at intervals of 3–10 months. Pearson correlation coefficient for reproducibility for total fibers was 0.67 [19]. Validity was estimated comparing the FFQ with two 7-day diaries, by means of the Pearson product-moment correlation coefficient between intakes of fiber computed from the FFQ and the average value derived from the two 7-day diary records. After allowance for energy intake, age, sex and study centre, the Pearson correlation coefficient for validity for total fiber intake was 0.57 [20].

Statistical analysis

Odds Ratios (OR), and their corresponding 95% confidence intervals (CI), for subsequent quintiles of dietary fiber intake compared to the lowest one, were computed using conditional multiple logistic regression models [21] conditioned on study centre, and quinquennia of age, and adjusted for period of interview (3-year time periods), body mass index (BMI), physical activity, education, smoking, alcohol consumption, age at menarche, parity, menopausal status, oral contraceptive (OC) use, hormone replacement therapy (HRT) use, diabetes, and energy intake. Allowance for energy was made using the residual method [22]. When nutrients were entered in the model as quintiles of intake, these were based on the distribution of cases and controls combined. The OR for an increase equal to one standard deviation of the distribution among controls was also estimated, including fibers in the model as a continuous variable.

Results

Table I gives the distribution of endometrial cancer cases and controls according to age, study centre, education, BMI, menopausal status, parity and use of OC and HRT. By design, cases and controls had similar distribution by age and study centre. Cases had a higher BMI than controls. No consistent difference was observed for education, menopausal status, parity, and OC and HRT use.

Table II gives the mean daily intake of various types of fiber among controls and the multivariate ORs of endometrial cancer according to their subsequent quintile of intake. Most types of fiber were unrelated to endometrial cancer although ORs tended to be below unity. Fiber solubility and source (vegetable, fruit, and grain) as well as total fiber were not associated with endometrial cancer risk. Lignin intake was significantly related to a decreased risk of endometrial cancer (OR=0.6 for the highest versus the lowest quintile of intake; 95%CI: 0.4–0.9) with a slightly significant linear trend in risk (p-value for trend=0.04).

The relation between types of fiber and endometrial cancer risk was further examined in strata of BMI (<25 and ≥ 25 kg/m²), menopausal status (pre/peri and post-menopause), and HRT use (never and ever) (Table III). Although some differences in the estimated risks were observed across strata, these were compatible with the effect of random variation, since heterogeneity tests were not significant.

Discussion

Our study, one of the largest case-control investigations of dietary fiber intake and endometrial cancer to date, showed that dietary lignin intake, a cell-wall polymer, is inversely associated with endometrial cancer in this southern European population. Moreover, our study supported the existence of a different role of a specific type of fiber rather than total fiber intake itself in endometrial cancer risk. We did not confirm a protective association for any of the specific fiber sources (vegetable, fruit, and grain).

A protective effect between total dietary fiber and endometrial cancer has been observed in most case-control studies while the association is not noticeable in cohort studies. All studies but one [11] examined total fiber intake rather than specific types of fiber [5–10,13].

To our knowledge, this is the first report to investigate the effect of lignin in endometrial cancer risk. Several biologically plausible reasons may explain why lignin might be, either directly or indirectly, a protective factor for endometrial cancer. Lignin is partially converted to lignans in the gut [23]. The mammalian lignans enterolactone and enterodiol are

Table I. Distribution of 454 cases of endometrial cancer and 908 controls according to selected variables. Italy, 1992–2006.

Characteristic	Cases		Controls	
	No.	(%)	No.	(%)
Age (years)				
<40	19	(4.2)	38	(4.2)
40–44	12	(2.6)	24	(2.6)
45–49	36	(7.9)	72	(7.9)
50–54	59	(13.0)	118	(13.0)
55–59	81	(17.8)	162	(17.8)
60–64	84	(18.5)	167	(18.4)
65–69	82	(18.1)	165	(18.2)
≥ 70	81	(17.8)	162	(17.8)
Centre				
Pordenone	237	(52.2)	474	(52.2)
Milano	140	(30.8)	280	(30.8)
Napoli	77	(17.0)	154	(17.0)
Education (years)				
<7	263	(57.9)	553	(60.9)
7–11	119	(26.2)	225	(24.8)
≥ 12	72	(15.9)	130	(14.3)
$\chi^2_2 = 1.18$; $p = 0.56$				
Body Mass Index (kg/m ²) ^a				
<21	24	(5.3)	106	(11.7)
≥ 21 –<25	102	(22.5)	307	(34.0)
≥ 25 –<30	160	(35.2)	351	(38.8)
≥ 30	168	(37.0)	140	(15.5)
$\chi^2_3 = 85.68$; $p < 0.001$				
Menopausal status ^a				
Pre/peri	85	(19.2)	174	(19.3)
Post	358	(80.8)	726	(80.7)
$\chi^2_1 = 0.004$; $p = 0.95$				
Parity				
Nulliparous	68	(15.0)	126	(13.9)
Parous	386	(85.0)	782	(86.1)
$\chi^2_1 = 0.30$; $p = 0.58$				
Oral contraceptive use				
No	408	(89.9)	790	(87.0)
Yes	46	(10.1)	118	(13.0)
$\chi^2_1 = 2.34$; $p = 0.13$				
Hormone replacement therapy use				
No	405	(89.2)	830	(91.4)
Yes	49	(10.8)	78	(8.6)
$\chi^2_1 = 1.74$; $p = 0.19$				

^aThe sum does not add up to the total because of missing value.

phytoestrogens which may reduce the bioavailability of steroid hormones related to the risk of endometrial cancer. One study supported the protective role of dietary and circulating lignans against endometrial cancer [24] while another found no association between circulating lignans and endometrial cancer [25]. In our study population the main sources of lignin were green leafs and carrots. Protection on endometrial cancer from lignin may simply reflect the influence of other constituents of vegetables and fruits, a decreased mechanical transit time associated with a low re-absorption of bile acids, or a generally healthier lifestyle. However, the latter mechanisms are not specific for lignin and could be advocated

Table II. Odds ratios (OR)^a of endometrial cancer and corresponding 95% confidence intervals (CI) according to the intake of various types of fiber. Italy, 1992–2006.

Nutrient	Mean ^b	Standard deviation	Quintile, OR (95% CI)					χ^2 trend (p-value)	OR (continuous) ^d
			1 (lowest)	2	3	4	5 (highest)		
Total (Englyst) fiber	15.3	5.2	1	1.3 (0.9–1.9)	1.0 (0.7–1.5)	1.0 (0.7–1.4)	1.1 (0.7–1.6)	0.24 (0.62)	0.96 (0.86–1.07)
Soluble NCP	7.7	2.5	1	1.1 (0.7–1.5)	0.7 (0.5–1.0)	1.1 (0.7–1.6)	0.7 (0.5–1.1)	1.79 (0.18)	0.92 (0.83–1.03)
Total insoluble fiber	7.6	3.6	1	0.9 (0.6–1.3)	0.9 (0.6–1.3)	0.8 (0.6–1.2)	1.0 (0.7–1.5)	0.03 (0.86)	0.94 (0.85–1.05)
Cellulose	3.6	1.9	1	1.1 (0.8–1.6)	1.3 (0.9–2.0)	1.1 (0.7–1.6)	0.9 (0.6–1.3)	0.19 (0.67)	0.97 (0.87–1.08)
Insoluble NCP	4.0	1.5	1	0.9 (0.6–1.3)	0.9 (0.6–1.3)	1.2 (0.8–1.8)	0.9 (0.6–1.3)	0.01 (0.89)	1.03 (0.92–1.15)
Lignin	1.5	0.5	1	0.7 (0.5–1.1)	0.8 (0.5–1.1)	0.7 (0.5–1.0)	0.6 (0.4–0.9)	4.21 (0.04)	0.88 (0.79–0.98)
Vegetable fiber	5.7	2.2	1	1.1 (0.7–1.6)	1.0 (0.7–1.5)	1.0 (0.7–1.4)	0.9 (0.6–1.3)	0.66 (0.42)	0.98 (0.88–1.09)
Fruit fiber	5.8	3.6	1	1.0 (0.7–1.4)	1.0 (0.7–1.4)	0.9 (0.6–1.3)	0.8 (0.5–1.1)	1.53 (0.22)	0.94 (0.84–1.05)
Grain fiber	4.5	2.1	1	0.9 (0.6–1.3)	1.1 (0.7–1.6)	0.9 (0.6–1.3)	1.1 (0.7–1.6)	0.05 (0.83)	0.98 (0.88–1.11)

^aEstimates from conditional logistic regression, conditioned on centre, and age, and adjusted for period of interview, body mass index, physical activity, education, smoking, alcohol consumption, age at menarche, parity, menopausal status, oral contraceptive use, hormone replacement therapy use, diabetes, and total energy intake, according to the residual method.

^bg/day, among controls.

^cReference category.

^dOR relative to 1 standard deviation among controls.

Table III. Odds ratios (OR)^{a,b} of endometrial cancer and corresponding 95% confidence intervals (CI) according to the intake of various types of fiber, in strata of body mass index (BMI), menopausal status and hormone replacement therapy (HRT) use. Italy, 1992–2006.

Nutrient	BMI (kg/m ²)		Menopausal status				HRT use	
	<25	≥25	Pre-/peri-menopause		Post-menopause		Never	Ever
Total (Englyst) fiber	1.0 (0.6–1.7)	1.1 (0.7–1.7)	1.2 (0.7–2.1)		1.1 (0.6–1.5)		1.1 (0.6–1.7)	2.5 (0.5–11.3)
Soluble NCP	0.8 (0.4–1.5)	0.7 (0.4–1.2)	0.7 (0.4–1.3)		0.8 (0.5–1.5)		0.8 (0.4–1.2)	4.2 (0.4–17.2)
Total insoluble fiber	1.0 (0.6–1.8)	1.0 (0.5–1.7)	0.9 (0.6–1.3)		1.1 (0.7–1.6)		1.1 (0.6–1.6)	1.8 (0.7–6.5)
Cellulose	1.0 (0.5–1.6)	0.9 (0.5–1.4)	0.8 (0.6–1.2)		1.0 (0.8–1.3)		0.9 (0.5–1.3)	1.0 (0.2–2.7)
Insoluble NCP	0.8 (0.5–1.3)	1.2 (0.6–1.8)	1.0 (0.5–1.7)		0.9 (0.6–1.4)		1.0 (0.5–1.4)	2.5 (0.5–10.6)
Lignin	0.6 (0.3–1.0)	0.6 (0.3–1.1)	0.7 (0.4–1.1)		0.6 (0.4–1.2)		0.6 (0.3–0.9)	2.5 (0.6–8.4)
Vegetable fiber	0.9 (0.3–1.4)	1.0 (0.6–1.5)	0.9 (0.4–1.2)		1.0 (0.5–1.4)		0.9 (0.5–1.3)	2.3 (0.7–7.2)
Fruit fiber	0.8 (0.4–1.3)	0.9 (0.5–1.4)	0.9 (0.3–1.5)		0.8 (0.5–1.3)		0.9 (0.5–1.1)	3.4 (0.6–18.1)
Grain fiber	1.1 (0.7–1.9)	1.2 (0.7–1.8)	1.0 (0.7–1.6)		1.2 (0.5–2.1)		1.0 (0.6–1.5)	0.9 (0.4–2.8)

^aEstimates from conditional logistic regression, conditioned on centre, and age, and adjusted for period of interview, body mass index, physical activity, education, smoking, alcohol consumption, age at menarche, parity, menopausal status, oral contraceptive use, hormone replacement therapy use, diabetes and total energy intake, according to the residual method, when appropriate.

^bORs of highest quintile of intake vs. lowest.

for other types of fiber too. The possibility of a chance finding should be considered an alternative explanation.

Recall and selection biases were possible, given the retrospective nature of our study. However, awareness about any particular dietary hypothesis on endometrial cancer etiology had not received media attention in Italy. With reference to selection bias, the catchment areas were comparable for cases and controls. Great attention was paid to exclude all diagnoses that might have been associated to or have determined long-term modifications of diet in controls. The comparability of recall between cases and controls was improved by interviewing all subjects in a hospital setting. Moreover, allowance for total energy intake should have reduced potential bias due to differential over- or under-reporting of food intakes. Our findings were strengthened by the large dataset used, the nearly complete participation of identified cases and controls, the use of a validated FFQ [19,20], the assessment of a broad range of nutrients and the geographically heterogeneous dietary habits across Italy, which increased study power to detect any meaningful association. A large proportion of cases were detected because of clinical symptoms, thus reducing the possibility of detection bias. Allowance was made for various known potential confounding factors, and the ORs were consistent when major categories of controls were separately used. For instance, ORs in the highest versus the lowest quintile of lignin intake were 0.6, 0.7 and 0.6 considering controls from surgical, orthopedic, and other wards, respectively. Additional allowance for family history of any cancer type, smoking habits, and physical activity did not meaningfully change the results.

In conclusion, our study suggested that in the Italian population lignin intake is inversely related to the risk of endometrial cancer. Our results underline the potential importance of diet in the prevention of endometrial cancer.

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