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Selected food intake and risk of endometriosis

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BACKGROUND: To offer data on the relationship between diet and risk of pelvic endometriosis, we analysed data collected in the framework of two case–control studies. METHODS: Data from two case–control studies conducted in Northern Italy between 1984 and 1999 were combined. Cases were 504 women aged <65 years (median age 33 years, range 20–65) with a laparoscopically confirmed diagnosis of endometriosis, admitted to a network of obstetrics and gynaecology departments in Milan, Brescia and Pavia. Controls were 504 women (median age 34 years, range 20–61) admitted for acute non-gynaecological, non-hormonal, non-neoplastic conditions. RESULTS: Compared to women in the lowest tertile of intake, a significant reduction in risk emerged for higher intake of green vegetables [odds ratio (OR) = 0.3 for the highest tertile of intake] and fresh fruit (OR = 0.6), whereas an increase in risk was associated with high intake of beef and other red meat (OR = 2.0) and ham (OR = 1.8). Consumption of milk, liver, carrots, cheese, fish and whole-grain foods, as well as coffee and alcohol consumption, were not significantly related to endometriosis. CONCLUSIONS: This study suggests a link between diet and risk of endometriosis.

Key words: case–control study/diet/endometriosis/risk factors

Introduction

Endometriosis is a common gynaecological disease, but despite its relatively high prevalence (Mangtani and Booth, 1933; Houston, 1984) little is known about the aetiology.

The role of diet in the development of hormone-related diseases has become a topic of interest in recent years (Ingram *et al.*, 1987; Fentiman *et al.*, 1988). For example, diet may have some influence on ovarian and endometrial carcinogenesis and on the development of benign gynaecological conditions, such as fibroids and ovarian cysts (La Vecchia *et al.*, 1987; Mori *et al.*, 1988; Chiaffarino *et al.*, 1999; Kushi *et al.*, 1999; Britton *et al.*, 2000a,b; Bosetti *et al.*, 2001). Endometriosis is hormone-related (Olive and Schwartz, 1993), so diet may play a role in its aetiopathogenesis. A case–control study in the USA suggested that the risk of endometrioid cysts was elevated for high intake of total, vegetable, non-saturated and polyunsaturated fats (Britton *et al.*, 2000a).

In order to obtain information on the relationship between diet and risk of pelvic endometriosis, we analysed data collected in two case–control studies (Parazzini *et al.*, 1989, 1995).

Materials and methods

The present analysis combined data from two case–control studies conducted in Northern Italy between 1984 and 1999. The study designs and methods have been described (Parazzini *et al.*, 1989, 1995). The studies had the same general design and data collection forms.

The studies included 504 women aged <65 years (median age 33 years, range 20–65) with a laparoscopically confirmed diagnosis of endometriosis, admitted to a network of obstetrics and gynaecology departments in Milan and university obstetrics and gynaecology clinics in Brescia and Pavia.

Controls were women aged <65 years admitted for acute non-gynaecological, non-hormonal, non-neoplastic conditions to the Ospedale Maggiore (comprising the four major teaching and general hospitals in Milan) and several university clinics, serving a catchment area comparable to that of the hospitals where cases had been identified, and the university hospitals of Brescia and Pavia. They were recruited as controls in one of the case–control studies on endometriosis (Parazzini *et al.*, 1995) and in a case–control study of female genital neoplasms (Parazzini *et al.*, 1989, 1992). A total of 2422 controls was identified and 504 (age range 20–61 years; median 34 years) were matched with cases in a 1:1 ratio, and randomly selected within strata of 5 year age groups, centre and calendar year of interview. Of these, 31% were admitted for traumatic conditions (mostly fractures and sprains), 23% had non-traumatic orthopaedic disorders (mostly low back pain and disc disorders), 12% acute abdominal diseases requiring surgery, and 34% other miscellaneous illnesses, such as disorders of the ear, nose, throat, or teeth.

Table I. Distribution of endometriosis cases and controls[a] according to selected factors

	Endometriosis		Control		Odds ratio estimates[b]
	No.	%	No.	%	(95% CI)
Site					
Ovary	251	49.8	–	–	
Pelvis	126	25.0	–	–	
Ovary plus pelvis	127	25.2	–	–	
Age (years)					
≤25	82	16.3	82	16.3	
26–35	220	43.7	220	43.7	
36–45	151	30.0	151	30.0	
≥46	51	10.1	51	10.1	
Education (years)					
<7	84	16.7	124	24.7	1+
7–11	158	31.4	197	39.2	1.4 (1.0–2.2)
≥12	261	51.9	182	36.2	2.8 (1.9–4.3)
χ^2 trend					28.4 ($P = 0.0001$)
Parity					
0	304	60.3	204	40.5	1+
1	91	18.1	119	23.6	0.4 (0.3–0.6)
≥2	109	21.6	181	35.9	0.4 (0.3–0.6)
χ^2 trend					22.3 ($P = 0.0001$)
Body mass index (kg/m^2)					
<20	168	33.3	133	26.7	1+
20–23	199	39.5	190	38.2	0.7 (0.5–1.0)
>23	137	27.2	175	35.1	0.6 (0.4–0.9)
χ^2 trend					5.4 ($P = 0.02$)

[a]In some cases the sum does not add up to the total because of missing values.
[b]Multiple logistic regression estimates including terms for age, study, calendar year at interview.
CI = confidence interval.

Trained interviewers identified and questioned cases and controls. All interviews were conducted in hospital. Less than 3% of cases and controls refused to be interviewed.

Information was obtained using a structured questionnaire, on general socio-demographic factors, personal characteristics and habits, gynaecological and obstetric history, and lifetime oral contraceptive use. Women were also asked about their frequency of consumption per week (i.e. in 14 meals) of portions of selected dietary items including the major sources of retinoids and carotenoids in the Italian diet, and alcohol and coffee drinking in the year before interview. Subjective scores (low, intermediate and high) were used to collect information on fat intake (butter, margarine and oil) and consumption of whole-grain foods. Reproducibility of the questionnaire was satisfactory (D'Avanzo *et al.*, 1997).

The thresholds for the analysis of dietary factors were based on the best possible approximations of tertiles of control group. Specifically they were: milk (0, 0.5–6, ≥7 portions/week), meat (0–3, 4–6, ≥7 portions/week), liver (0, ≥0.5 portions/week), carrots (0, 1, ≥2 portions/week), green vegetables (0–6, 7–12, ≥13 portions/-week), fresh fruit (≤6, 7–13, ≥14 portions/week), eggs (0, 1, ≥2 per week), ham (≤1, 2, ≥3 portions/week), fish (0, 1, ≥2 portions/-week), cheese (≤2, 3–5, ≥6 portions/week). In some cases the numbers of subjects were not equally distributed in the tertiles because of the large number reporting the same frequency of consumption. The items green vegetables and fruits included all types, specifically all the main sources in the Italian diet such as spinach/-other greens, cruciferae, green and red salads, zucchini, artichokes; fruits included citrus, apple, peach, melon, strawberries/cherries, banana and pear (Franceschi *et al.*, 1993).

An estimate of the total daily average alcohol intake was derived assuming a comparable ethanol content in each type of beverage (125 ml wine = 333 ml beer = 40 ml spirits = 15 g pure alcohol). Wine accounted for >80% of the alcohol consumed.

To account simultaneously for the effects of several potential confounding factors, we performed unconditional multiple logistic regression, with maximum likelihood fitting, to obtain the odds ratios (OR) of endometriosis, their corresponding 95% confidence intervals (CI), and the test for trend when appropriate (Baker and Nelder, 1978). The variables included in the model are listed in the footnotes to the tables.

Since a total of 11 χ^2-tests for trend were done in the analysis of dietary factors, $P < 0.004$ can be considered statistically significant after taking into account the effect of multiple tests, according to the Bonferroni test (Perneger, 1998).

Results

The distribution of cases and controls according to age, site and stage of endometriosis and selected characteristics are presented in Table I. Women with endometriosis were more educated, thinner and less frequently multiparous than controls.

The relationship between intake of selected foods and the risk of endometriosis is shown in Table II. Compared to women in the lowest tertile of intake, a significant reduction in risk emerged for high intake of green vegetables (OR = 0.3) and fresh fruit (OR = 0.6), and an increased risk was associated with beef and other red meat (OR = 2.0) and ham (OR = 1.8). The tests for linear trend in risk were still significant after taking multiple tests P value correction into

Table II. Risk of endometriosis and intake of selected foods

Food item	Frequency of consumption (no. of cases/ no. of controls)[a]			Odds ratio estimates[b] (95% CI)			χ^2 (trend)
	1 (low)	2 (intermediate)	3 (high)	1[b]	2	3	
Milk	80/103	186/174	236/227	1+	1.3 (0.9–2.0)	1.4 (0.9–2.0)	NS
Beef and other red meat	158/202	139/173	206/129	1+	0.9 (0.6–1.3)	2.0 (1.4–2.8)	12.7 ($P = 0.0004$)
Liver	192/242	301/260	–	1+	1.1 (0.8–1.5)		
Carrots	228/192	99/133	172/179	1+	0.7 (0.5–1.1)	0.7 (0.5–1.0)	NS
Green vegetables (all types)	185/121	220/215	99/168	1+	0.6 (0.4–0.8)	0.3 (0.2–0.5)	28.5 ($P = 0.0001$)
Fresh fruit (all types)	116/99	169/139	218/266	1+	0.8 (0.6–1.2)	0.6 (0.4–0.8)	10.0 ($P = 0.002$)
Eggs	110/140	145/111	248/251	1+	1.8 (1.2–2.8)	1.4 (1.0–2.0)	NS
Ham	150/192	109/136	244/176	1+	1.3 (0.9–1.9)	1.8 (1.3–2.5)	11.1 ($P = 0.001$)
Fish	207/167	185/211	112/126	1+	0.7 (0.5–1.0)	0.7 (0.5–1.1)	NS
Cheese	138/133	160/209	206/162	1+	0.6 (0.5–1.0)	0.8 (0.6–1.2)	NS
Whole-grain foods	355/351	82/80	67/73	1+	1.0 (0.7–1.4)	0.8 (0.6–1.3)	NS
Butter	283/332	221/172[c]	–	1+	1.5 (1.0–2.0)		
Margarine	454/453	50/50[c]	–	1+	1.2 (0.7–1.9)		
Oil	97/71	335/372	72/61	1+	0.6 (0.4–0.9)	0.7 (0.4–1.3)	NS
Coffee	204/185	123/119	177/200	1+	0.9 (0.6–1.3)	0.8 (0.5–1.1)	NS
Total alcohol intake	246/247	129/129	129/128	1+	1.0 (0.7–1.4)	0.9 (0.6–1.3)	NS

[a]For some items, the sum of strata does not add up to the total because of missing values.
[b]Multiple logistic regression estimates including terms for age, calendar year at interview, education, parity, body mass index, study.
[c]Patients with intermediate and high intake.
CI = confidence interval; NS = not significant.

Table III. Odds ratios and corresponding 95% confidence intervals (CI) for an increase in intake of one serving of selected food groups per day

	Odds ratio[a] (95% CI)			
	Beef and other red meat	Green vegetables	Fruit	Ham
Total series	2.2 (1.4–3.5)	0.5 (0.4–0.7)	0.8 (0.6–0.9)	1.8 (1.1–3.1)
Age (years)				
<36	2.1 (1.2–3.6)	0.6 (0.4–0.8)	0.8 (0.6–1.0)	1.3 (0.6–2.5)
≥36	2.9 (1.3–6.5)	0.4 (0.3–0.6)	0.8 (0.6–1.0)	3.5 (1.4–8.6)
Education (years)				
<7	8.0 (2.3–27.9)	0.4 (0.2–0.7)	0.9 (0.6–1.4)	4.7 (1.4–15.5)
7–11	1.4 (0.7–2.8)	0.8 (0.5–1.2)	0.7 (0.5–1.0)	0.9 (0.4–1.9)
≥12	2.3 (1.2–4.6)	0.4 (0.3–0.6)	0.9 (0.6–1.1)	2.3 (1.0–5.3)
Site				
Ovary	2.3 (1.4–3.9)	0.6 (0.4–0.7)	0.8 (0.7–1.0)	1.5 (0.8–2.7)
Pelvis	2.5 (1.0–6.5)	0.7 (0.4–1.2)	0.8 (0.5–1.1)	3.4 (1.3–9.1)
Ovary plus pelvis	2.2 (0.9–5.1)	0.5 (0.3–0.8)	0.6 (0.4–1.0)	3.3 (1.3–8.5)
Body mass index (kg/m^2)				
<20	1.7 (0.8–3.5)	0.7 (0.4–1.0)	0.7 (0.5–1.0)	2.1 (0.7–6.0)
20–23	2.9 (1.3–6.3)	0.5 (0.3–0.8)	0.9 (0.7–1.2)	1.8 (0.8–3.8)
>23	2.2 (0.9–5.3)	0.4 (0.3–0.7)	0.6 (0.5–0.9)	2.0 (0.7–5.6)
Parity				
0	1.8 (1.0–3.5)	0.6 (0.4–0.8)	0.7 (0.6–1.0)	1.8 (0.9–3.9)
≥1	2.6 (1.4–5.1)	0.5 (0.3–0.7)	0.8 (0.6–1.0)	2.4 (1.1–5.1)
Area of residence				
North	2.4 (1.5–3.9)	0.5 (0.4–0.7)	0.9 (0.7–1.0)	2.0 (1.1–3.5)
Central–South	2.6 (0.7–10.3)	0.8 (0.3–1.7)	0.5 (0.3–0.8)	2.3 (0.5–10.7)

[a]Derived from multiple logistic regression equation including terms for age, calendar year at interview, study, education, parity, body mass index plus, in turn, meat, green vegetables, fruit and ham intake.

account. We also computed OR using multiple logistic regression including terms for beef and other red meat, green vegetables, age, education, body mass index and parity. The OR (95% CI) were 1.0 (0.7–1.4) and 1.8 (1.3–2.5) for intermediate and high level of consumption of beef and other red meat, and 0.5 (0.3–0.9) and 0.3 (0.1–0.5) for intermediate and high consumption of vegetables (data not shown).

Consumption of milk, liver, carrots, cheese, fish and whole grain foods, or coffee and alcohol, were not significantly related to endometriosis. No association was found with butter, margarine and oil consumption.

Table III presents the OR for an increase of one serving per day for beef and other red meat, green vegetables, fruit, and ham in strata of selected variables. All food groups significantly associated with endometriosis were simultaneously included in the same multiple logistic model, to allow for mutual confounding. The associations were generally consistent in strata of age, body mass and parity; the OR for beef and ham were higher in strata of low education and high education, but no significant heterogeneity was observed. No difference emerged in the OR when we analysed the effect of diet in women living in different areas of Italy.

Discussion

The results of this study suggest that higher intake of green vegetables and fresh fruit can lower the risk of endometriosis. Conversely, intake of beef or red meat and ham can increase the risk.

Some limitations must be considered in interpreting the results. First of all, the dietary section in this study was restricted to a few selected indicator foods. Information was limited to the number of portions per week of a restricted list of dietary items, with no estimate of portion size. Thus, no estimate of total caloric intake could be obtained (Willett and Stampfer, 1986). However, a major role of information bias is unlikely, since the possible relationship between diet and endometriosis was probably not known to interviewers and to the majority of women interviewed. The diet questionnaire was satisfactorily reproducible (D'Avanzo *et al.*, 1997). We collected information on ham, but not on ground pork or pork chops; these latter, however, are rarely eaten in Italy (Turrini *et al.*, 2001).

A major effect of selection bias is unlikely because the control group included only women with acute conditions and we excluded women with digestive tract diseases or any condition potentially related to long-term dietary changes. Controls were not examined by laparoscopy, so we cannot exclude that some may have had undiagnosed endometriosis. This can be considered a limitation of this study, but the potential misclassification should only underestimate any difference between cases and controls.

We analysed several dietary items, so the association between endometriosis risk and green vegetable, fruit and meat intake might be due to chance. However, after taking into account multiple tests for all dietary items in the catagories, except ham which was a single catagory, *P*-values were still significant.

Selection bias should be considered in interpretating of the findings. Green vegetables, fruit and fish may be general indicators of a more health-oriented attitude toward diet and other lifestyle habits. Closer attention to health may also favour the diagnosis of endometriosis, thus producing an underestimate of the real association. The diagnosis of endometriosis was more frequent among more educated women of higher social class (Mangtani and Booth, 1933; Cramer *et al.*, 1986; Parazzini *et al.*, 1995; Signorello *et al.*, 1997) and could to some extent reflect the greater attention such women pay to relatively minor health problems. The association between socio-economic status and endometriosis risk may also involve the inverse association between parity and socio-economic status, since more educated women are more likely to be nulliparous in Italy.

Socio-economic status, body weight, and potential reproductive and hormonal risk factors for endometriosis did not explain the results. The estimated OR were not markedly affected by the inclusion of terms for education and parity in the multivariate models (data not shown). Although the OR estimates for beef and ham were different in strata of education, there was no significant heterogeneity.

Epidemiological data on the relationship between endometriosis and diet are scanty. A study conducted in the USA on ovarian endometrioid cysts reported elevated risks of endometriosis for higher intakes of polyunsaturated and vegetable fats, but no reduction in risk for high intake of vegetables and fruits (Britton *et al.*, 2000a).

There are, however, some indications that a diet poor in vegetables and fruits and rich in fat increases the risk of endometrial cancer (Armstrong, 1979) and fibroids (Chiaffarino *et al.*, 1999), two diseases known to be associated with estrogens, and of ovarian benign and malignant epithelial diseases (Risch *et al.*, 1994). For example, for endometrial and ovarian cancer and fibroids, there was a direct association with the frequency of consumption of meat and ham in this Italian population, whereas high intake of vegetables and fruits conferred some protection (Levi *et al.*, 1993; Chiaffarino *et al.*, 1999; Bosetti *et al.*, 2001). In biological terms, fats may influence prostaglandin concentrations, which may affect ovarian function (Smith, 1986). Hormonal factors are a potential link between diet and endometriosis, since the risk may be increased by exposure to unopposed estrogens, and a diet rich in fat increases circulating unopposed estrogens (Armstrong *et al.*, 1981; Goldin *et al.*, 1982; Gorbach and Goldin, 1987). More difficult to explain in biological terms is the protective effect of a diet rich in green vegetables and fruits. However, similar findings emerge for the risk of breast and endometrial cancer, two estrogen-related diseases. A diet rich in green vegetables and fruits includes high levels of vitamin C, carotenoids, folic acid and lycopene, micronutrients which may help to protect against cell proliferation (Bosetti *et al.*, 2002). We did not find any association between alcohol intake and risk of endometriosis. Some studies have reported that women with endometriosis tend to drink more alcohol than those without the disease (Grodstein *et al.*, 1994; Missmer and Cramer, 2003), also after taking into account the potential effect of alcohol on fertility. Most of these studies, however, have been conducted in North European or American countries, where alcohol intake is likely to be higher than in Italy. This may partly explain the lack of association found in the present study.

In accordance with previous studies, we found an inverse association between body mass and risk of endometriosis (Darrow *et al.*, 1993; Signorello *et al.*, 1997; Missmer and Cramer, 2003).

In conclusion, despite its limitations, this study suggests that there is some link between diet and risk of endometriosis. These findings suggest the need for a proper prospective interventional investigation designed to study these factors.

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