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 aetopathogenesis. 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.
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, ≥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 χ²-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 I. Distribution of endometriosis cases and controls according to selected factors |
|--------------------------------------|-----------------|-----------------|-----------------|
|                                      | Endometriosis   | Control         | Odds ratio estimates |
|                                      | 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) |
| χ² 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) |
| χ² trend                             |      |         |      |         | 22.3 (P = 0.0001) |
| Body mass index (kg/m²)              |      |         |      |         |              |
| <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) |
| χ² trend                             |      |         |      |         | 5.4 (P = 0.02) |

*aIn some cases the sum does not add up to the total because of missing values.
**Multiple logistic regression estimates including terms for age, study, calendar year at interview.
CI = confidence interval.
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 simul-
taneously included in the same multiple logistic model, to 
allow for mutual confounding. The associations were gener-
ally 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 ana-
lysed 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 cata-
gories, except ham which was a single catagory, P-values 
were still significant.

Selection bias should be considered in interpreting 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 
spell the diagnosis of endometriosis, thus producing an 
underestimate of the real association. The diagnosis of endo-
metriosis 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 associ-
ation 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 repro-
ductive 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 edu-
cation, there was no significant heterogeneity.

Epidemiological data on the relationship between endo-
metriosis 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 vege-
table fats, but no reduction in risk for high intake of vege-
tables 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 associ-
ated with estrogens, and of ovarian benign and malignant epih-
thelial diseases (Risch et al., 1994). For example, endometri-
al 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 concen-
trations, which may affect ovarian function (Smith, 1986). 
Hormonal factors are a potential link between diet and endo-
metriosis, since the risk may be increased by exposure to 
onopposed estrogens, and a diet rich in fat increases circula-
ting 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 endo-
metriosis. Some studies have reported that women with endo-
metriosis 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 con-
ducted in North European or American countries, where alco-
hol 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 

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


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