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REVIEW

Diet and endometriosis risk: A literature review

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Abstract A connection between dietary factors and endometriosis onset has become a topic of interest mostly due to the observation that physiological and pathological processes of the disease can be influenced by diet. This paper systematically reviews prior publications dealing with this aspect in order to identify potentially modifiable risk factors. Comprehensive searches in the electronic databases MEDLINE, EMBASE and Science Citation Index Expanded were conducted to identify published studies evaluating the association between food intake (nutrients and food groups) and endometriosis. Eleven studies were identified: 10 case–control and one cohort study. Information on diet was collected using food frequency questionnaires in seven studies, while in one study the questionnaire focused on caffeine and alcohol intake. Women with endometriosis seem to consume fewer vegetables and omega-3 polyunsaturated fatty acids and more red meat, coffee and *trans* fats but these findings could not be consistently replicated. Most data have also been discussed herein in light of the available experimental and animal model results. At present, evidence supporting a significant association between diet and endometriosis is equivocal. Further studies are needed to clarify the role of diet on endometriosis risk and progression.

KEYWORDS: coffee, endometriosis, fat, nutrition, vegetables, vitamin

Introduction

Endometriosis is a hormone-dependent, chronic inflammatory gynaecological condition that causes pelvic pain symptoms impacting on the physical, mental and social wellbeing of reproductive-age women (Bianconi et al., 2007). Despite the high prevalence, which has been estimated to be between 6–10% (Parazzini et al., 1994) and the recognized economic burden associated with the disease (Simoens et al., 2012), its aetiology remains elusive. Various pathogenetic factors – menstrual, genetic, environmental, lifestyle – have been claimed to be implicated in the disease establishment and development (Viganò et al., 2004, 2012).

The role of nutrition in determining the establishment and progression of endometriosis has recently become a topic of interest, mostly due to the observation that some

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of the physiological and pathological processes associated with the disease, such as inflammation, oestrogen activity, menstrual cyclicity, organochlorine burden and prostaglandin metabolism, can be influenced by diet (Missmer et al., 2010). The oestrogen dependency of the disease is particularly relevant in this context. In other conditions in which hormones exert a specific role, such as breast (Colditz, 1998; Moorman and Terry, 2004; Chajès et al., 2008; Bravi et al., 2009) and endometrial carcinogenesis (Parazzini et al., 1991; Bidoli et al., 2010), scientific research has demonstrated that diet and fat excess may strongly affect the incidence. Specific habitual dietary patterns appear to have a moderate influence on some inflammatory markers shown to be increased in endometriosis (Galland, 2010). Further, organochlorines — including: (i) polychlorobiphenyls (PCBs), ubiquitary microcontaminants that tend to bioaccumulate in lipid content particularly into meat, liver and dairy products (La Rocca and Mantovani, 2006); and (ii) pesticides/insecticides that can be ingested via consumption of contaminated fruits and vegetables (Grassi et al., 2010) — have been proposed as risk factors for endometriosis since the early 1990s (Gerhard and Runnebaum, 1992). On these bases, the literature on the role of diet on endometriosis risk are herein systematically reviewed, assessing both nutrients and food groups, in order to identify potential modifiable risk factors of the disease.

Materials and methods

The electronic databases MEDLINE (1966 to 2011), EMBASE (1985 to 2011) and Science Citation Index Expanded (1945 to 2011) were searched using the Medical Subject Heading (MeSH) terms 'diet', 'nutrition', 'vitamin', 'fat', 'vegetables', 'coffee', 'caffeine', 'meat', 'fish', 'dairy' or 'fruit' combined with 'endometriosis'. All pertinent reports were retrieved and the relative reference lists were systematically searched in order to identify any potential additional studies that could be included. Only those that were published as full-length articles and in English were considered.

Data were extracted independently by two investigators (FP and PV) who also performed an initial screening of the title and abstract of all articles to exclude citations deemed irrelevant to both observers. If multiple published reports from the same study were available, only the one with the most detailed information was included. Review articles were considered only if original data were also reported. Abstracts of scientific meetings were not included. For each study, the following information was extracted: first author's last name; year of publication; country of origin; number of subjects and cases; design of the study; and category amounts of nutrient intake. Information regarding the potential role of the considered nutrients has been presented according to the mode in which findings were presented in the original papers. Given the paucity of the information reported so far, results deriving from the intake of specific food items have sometimes been described and discussed together with those reporting the main nutrients they contained (i.e. red meat and saturated fats). A pooled estimation was not considered since clinical (study populations), methodological (frequency categorization of exposure) and statistical (adjustment for confounding factors) heterogeneity is present across studies. Therefore, in order to avoid misleading conclusions, the results of this systematic review are presented using a more qualitative approach.

Results

Figure 1 shows the flow diagram of the literature search results. The database search identified 256 abstracts, 17 of which reported findings on dietary factors associated with endometriosis risk; these articles were retrieved for detailed assessment. After searching for further articles in the reference lists, another four papers were found. After the exclusion of ten articles for various reasons (**Figure 1**) a total of 11 studies were identified on the association between dietary components and endometriosis (Grodstein et al., 1993; Berube et al., 1998; Britton et al., 2000; Parazzini et al., 2004; Heilier et al., 2007; Tsuchiya et al., 2007; Matalliotakis et al., 2008; Mier-Cabrera et al., 2009; Missmer et al., 2010; Trabert et al., 2011; Savaris and do Amaral, 2011). Their main methodological characteristics are presented in **Table 1**.

Most studies were case—control studies. One cohort study was identified (Missmer et al., 2010). A total of six studies were conducted in North America (Grodstein et al., 1993; Berube et al., 1998; Britton et al., 2000; Matalliotakis et al., 2008; Missmer et al., 2010; Trabert et al., 2011), two in Europe (Parazzini et al., 2004; Heilier et al., 2007), one in Japan (Tsuchiya et al., 2007), one in Mexico (Mier-Cabrera et al., 2009) and one in Brazil (Savaris and do Amaral, 2011).

Information on diet intake was collected using food frequency questionnaires in seven studies, while in one study the questionnaire focused on caffeine and alcohol intake. Simple 'no' or 'yes' questions were used in one study to evaluate coffee intake (Matalliotakis et al., 2008).

General limits of reviewed papers

Some methodological considerations should be underlined before presenting the results of this review. It should be considered that the identified studies are characterized by marked differences in exposure categorizations, analytic approaches, disease phenotypes, nutrients considered and general methodological design (**Table 1**). All these aspects should be considered in interpreting the inconsistent results deriving from the various studies.

Study design

First of all, the presented results are based on case—control studies. Only one cohort prospective study was identified (Missmer et al., 2010). Retrospective collection of diet items is difficult, particularly in long-lasting diseases. Women with endometriosis usually experience a 6—10-year delay between the onset of symptoms and definitive diagnosis and the disease can be progressive (Bianconi et al., 2007). They might have changed their dietary habits at the symptom onset or their diet might have had an effect on pain experience underlying the disease and requiring a diagnosis.

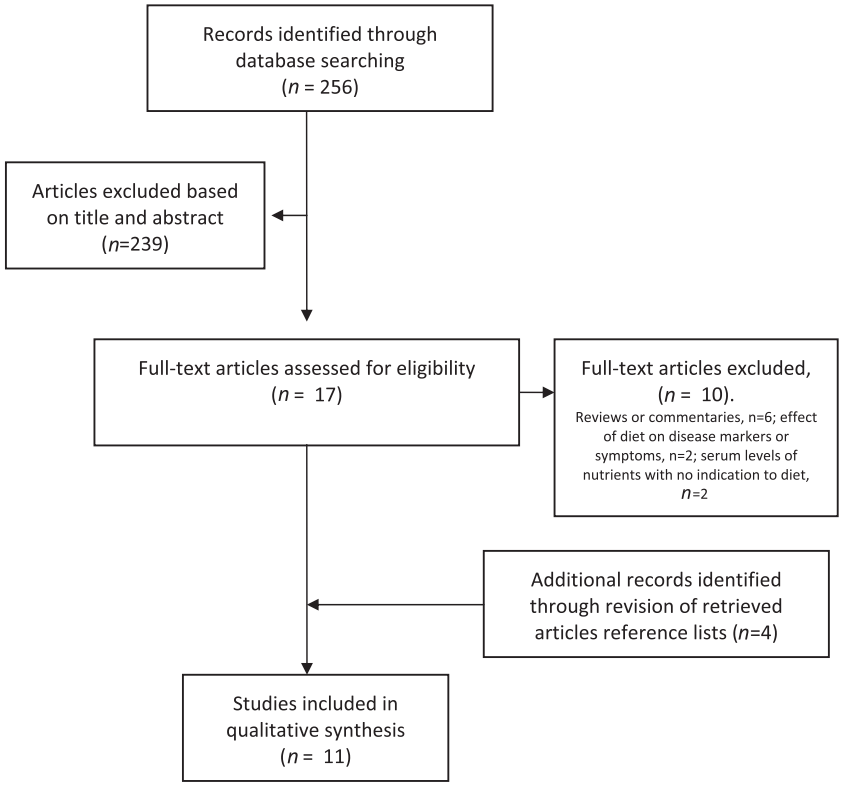

Figure 1 Flowchart of the study selection process to establish the role of diet on endometriosis risk.

Data collection

Dietary information was collected by different methods in various studies (**Table 1**), thus it is difficult to compare the results of different studies. Further, the different dietary pattern in various countries is a well-known problem of nutritional epidemiology. For instance, fruit and vegetables consumed in Italy or in the south of Europe, in general, are imported from other countries only in a small proportion, thus reducing the distance between the area of production and retail markets, the duration of storage and the extent of pesticide use (Masala et al., 2012). Similarly, dairy products consumed in the USA are different from those consumed in Europe, production methods as well as the amount of fat in the finished products vary greatly (McGee, 2004). This may in part account for the inconsistent results related to the vegetable and fruit intakes or dairy consumption when comparing the Italian study by Parazzini et al. (2004) and the American study by Trabert et al. (2011). Likewise, traditionally, the Mediterranean diet includes olive oil in higher amounts than the typical North American diet, while very high intakes in meat and sugar are common in the USA (Goulet et al., 2008). These differences may affect the comparability of the result of studies conducted in different countries. Further, it may be difficult to disentangle the separate effects of single food items (Masala et al., 2012); for example, olive oil is the main dressing fat for vegetables according to the Mediterranean tradition (Pala et al., 2006; Masala et al., 2012).

In most studies, diet was evaluated using food frequency questionnaires (**Table 1**), which are characterized by some weakness. Food frequencies measures are limited in their ability to collect complex information due to practical restrictions inherent in printed questionnaire formats. In particular, they represent an average of intakes collected in different seasons and periods with limited information on size of portions and modalities of cooking. These criticisms can be applied, for instance, to Parazzini et al. (2004). Some strategies for new epidemiological practice in large cohort studies have been proposed. These strategies include the possibility of taking advantage of modern technologies in order to improve the validity of dietary assessment or using multiple-day food records (Kristal et al., 2005). However, in the context of endometriosis in which women usually experience many years between the onset of symptoms and the definitive diagnosis, the application of these prospective strategies seems very difficult.

Confounding factors

Potential confounding factors should also be considered. The diagnosis of endometriosis has been shown to be more frequent among higher social class and more educated women (Parazzini et al., 1995) that could pay a greater attention to minor health problems, but as well could have a more health-oriented attitude toward diet and lifestyle habits. Closer attention to health may favour the diagnosis of endometriosis thus producing an incorrect estimation of the real association with dietary factors. Only two studies among those identified have adjusted for factors related to the social status (**Table 1**).

Table 1 Main characteristics of considered studies.

Study	Country	Study design	Cases	Controls	Sample size (cases/controls)	Age (years)	Dietary assessment	Coffee assessment	Confounding factors considered in the analysis	Adjustment for total energy
Grodstein et al. (1993)	USA, Canada	Hospital-based case–control	Women with primary infertility due to endometriosis	Fertile women	180/3833	–	–	<3.1 (reference), 3.1–5, 5.1–7, >7 g/month.	Age, centre, smoking, sexual partners, alcohol consumption, contraception, BMI, exercise.	No
Berube et al. (1998)	Canada	Case–control	Infertile women with laparoscopically diagnosed minimal or mild endometriosis	Women with unexplained infertility	329/262	20–39	Frequency questionnaire on caffeine and alcohol intake	0–99 (reference), 100–299, ≥300 mg/day	Age, BMI, age at menarche, cycle length, parity	No
Britton et al. (2000)	USA	Case hospital-based/community-matched control	Women with endometrioid ovarian cysts	Age- and hospital-matched randomly selected women	280/347	–	Validated FFQ for several micro and macronutrients	–	Age, BMI, hospital	Yes
Parazzini et al. (2004)	Italy	Hospital-based case–control (two studies)	Women with laparoscopically confirmed endometriosis	Women admitted for acute non-gynaecological, non-hormonal, non-neoplastic conditions	504/504	20–65	Validated FFQ	Low (reference), intermediate, high thresholds (based on tertiles of controls)	Age, education, parity, BMI, calendar year at interview	No
Heilier et al. (2007)	Belgium	Matched case–control	Women with peritoneal endometriosis (PE) or deep endometriotic nodules (DEN)	Women with no clinical suspicion of PE or DEN, without infertility, pelvic pain and dysmenorrhoea and with normal pelvic examination, vaginal sonography and serum CA-125 <35 U/ml.	88 (PE), 88(DEN)/88	–	FFQ	–	No	No

Table 1 (Continued)

Study	Country	Study design	Cases	Controls	Sample size (cases/controls)	Age (years)	Dietary assessment	Coffee assessment	Confounding factors considered in the analysis	Adjustment for total energy
Tsuchiya et al. (2007)	Japan	Case–control hospital-based	Infertile women with laparoscopically diagnosed endometriosis	Women with unexplained infertility	79/59	20–45	Urinary concentration	–	Age, menstrual cycle and menstrual bleeding	No
Matalliotakis et al. (2008)	USA	Case–control	Women with pelvic endometriosis	Infertile women (tubal or male factor infertility)	535/200	15–56	–	No/yes	No	No
Mier-Cabrera et al. (2009)	Mexico	Case–control	Women with surgically confirmed endometriosis	Fertile women with no evidence of endometriosis at surgery	83/80	–	FFQ	–	No	No
Missmer et al. (2010)	USA	Cohort, Nurses' Health Study II	Laparoscopically confirmed cases of endometriosis	US registered nurses	1199/586, 153 person-years	–	Semiquantitative FFQ	–	Age, age at menarche, menstrual cycle, parity, BMI, calendar year at interview	Yes
Trabert et al. (2011)	USA	Population-based case–control	Women with mild/severe endometriosis (International Classification Disease 9th Revision codes 617.0, .5, .8, .9) from the Group Health (GH) Co-operative	Women without endometriosis randomly selected from a list of the GH Co-operative during the same period	284/660	18–49	Women Health Initiative FFQ	–	Age, year of enrolment, income, BMI, smoking, alcohol consumption	Yes
Savaris and do Amaral (2011)	Brazil	Case–control	Laparoscopically confirmed cases of endometriosis	Women without endometriosis	25/20	18–35	FFQ	–	No	No

FFQ = food frequency questionnaire.

Another main methodological problem in nutritional epidemiology is the evaluation of the effect of specific dietary components with calories held constant (e.g. more red meat intake means that something else in the diet has to be decreased such as fruits or vegetables) or if calories are not held constant, it has to be established how and to what extent this may impact (e.g. more red meat means no decrease in something else but rather an additional/greater food source). All these aspects have not been consistently analysed in published papers. Several previous studies have shown an inverse relation between endometriosis risk and body mass index (Viganò et al., 2012). For this reason, the adjustment for total energy intake could be critical but very few studies have provided this correction (**Table 1**).

In general, the different methods of adjustment used in the various studies may explain some inconsistencies observed in the reported results.

Selected populations

Potential biases may also be due to the different choice of control groups in the considered studies. Some studies (Berube et al., 1998; Tsuchiya et al., 2007) have included women with uterine fibroids or unexplained infertility as controls and these conditions have been recently shown to be influenced by the intake of some nutrients (Bläuer et al., 2009; Ozkan et al., 2010; Sharan et al., 2011).

Green vegetables and fruit

The inverse association between vegetable and fruit intake and the risk of several conditions has been one of the most common reported factors in dietary epidemiology (Rieck and Fiander, 2006; Masala et al., 2012).

Two studies have analysed the relation between servings/week or day of green vegetables and fruit intake and risk of endometriosis (Parazzini et al., 2004; Trabert et al., 2011). In the Italian case–control study, green vegetable and fruit consumption were inversely associated with the risk of endometriosis (Parazzini et al., 2004). Data were analysed considering the number of servings/week. Compared with women in the lowest tertile of intake, a significant reduction in risk emerged for high intake of green vegetables (odds ratio, OR, 0.3; 95% confidence interval, CI, 0.2–0.5, $P_{trend} = 0.0001$) and fresh fruit (OR 0.6, 95% CI 0.4–0.8, $P_{trend} = 0.002$). The associations were generally consistent even after adjusting for confounding factors. In the case–control study conducted by Trabert et al. (2011), the role of a diet rich in green vegetable and fruit was analysed considering the number of servings/day similarly to the Italian case–control study. Increased number of servings/day of fruit was associated with increased disease risk (two or more versus one or less servings/day: OR 1.5, 95% CI 1.2–2.3, $P_{trend} = 0.04$), but no association emerged with vegetables (Trabert et al., 2011).

Interestingly, vegetables (in particular green vegetables) contain folate, methionine and vitamin B_6, which are involved in 'nutritional genomics' (Riscuta and Dumitrescu, 2012). Critical in this context is the group of nutrients commonly referred to as lipotropes, which includes methionine, choline, folate and vitamin B_6 that can act on the human genome to alter the expression of genes or gene products and may influence DNA methylation. (McCabe and Caudill, 2005).

All formulations of 'lipogenic methyl-deficient diets' (i.e. deficient in choline, methionine choline or methionine choline folic acid) provoke several similar molecular alterations, including altered lipid metabolism, oxidative stress and a number of epigenetic abnormalities that may result in progressive tissue injury culminating in the development of primary tumours (Pogribny et al., 2012). As a matter of fact, epigenetic abnormalities and aberrant DNA-methylation patterns have been also suggested to be involved in endometriosis (Guo, 2009).

On the other hand, vegetables but particularly fruits may contain organochlorines (Grassi et al., 2010) which in turn have been positively associated with the risk of endometriosis (Buck Louis et al., 2012). In five (Gerhard and Runnebaum, 1992; Louis et al., 2005; Porpora et al., 2006, 2009; Buck Louis et al., 2012) of 10 studies that focused on lipophilic environmental chemicals and endometriosis, significantly higher concentrations were observed in women with endometriosis than in those without the condition, but the results were not consistent (Trabert et al., 2010). Organochlorines are thought to interfere with hormonal pathways as they have been shown to exert pleiotropic effects through oestrogen and androgen receptors (Craig et al., 2011). Additional data are needed to ascertain whether endometriosis development may be influenced by nutrients such as vegetables that supply or regenerate methyl groups. Similarly, since it is not possible to draw any conclusions from the association between fruit intake and endometriosis, the impact of organochlorine exposure on endometriosis development via the ingestion of contaminated foods remains to be clarified.

Vitamins

Four studies have specifically addressed the role of selected micronutrients contained in vegetables and fruits, in particular folates, carotenoids and vitamins A, E and C, on endometriosis risk (Britton et al., 2000; Mier-Cabrera et al., 2009; Trabert et al., 2011; Savaris and do Amaral, 2011).

Folates

No association emerged between folate intake and risk of ovarian endometriotic cysts in a case–control study including 280 cases of this type of cysts (Britton et al., 2000). Similarly, no statistical association between endometriosis and total folate intake was found by Trabert et al. (2011) and in the same study, no association was found for vitamins B_6, B_{12} and niacin intake.

Vitamin A

Preformed vitamin A is present only in animal products, such as liver, kidney, fatty fish and dairy products, but may also be converted endogenously from its dietary precursor β-carotene found mostly in green leafy and yellow-coloured vegetables and orange-coloured fruits. Therefore, provitamin A carotenoids from plants are an

additional major dietary source of vitamin A for most of the world's population (Weber and Grune, 2012). In general, β-carotene or vitamin A intake were not found to be statistically associated with endometriosis risk (Britton et al., 2000; Savaris and do Amaral, 2011; Trabert et al., 2011). In the Italian study, intake of liver or carrots, two important sources of vitamin A, have been analysed in relation with endometriosis risk and no association emerged with liver consumption although the number of subjects reporting liver intake was low. With regard to carrots, reported data for a potential decreased risk were equivocal (Parazzini et al., 2004). Vitamin A intake was significantly lower in patients with endometriosis in the study by Mier-Cabrera et al. (2009). Vitamin A intake was 110 ± 23% of recommended daily intake (RDI) in patients with endometriosis compared with 163 ± 45% in controls ($P < 0.05$) (Mier-Cabrera et al., 2009).

Vitamins C and E

Data on vitamins C and E are also inconsistent. Vitamin C and vitamin E intakes were not found to be associated with endometriosis risk in three studies (Britton et al., 2000; Trabert et al., 2011; Savaris and do Amaral, 2011). In the study by Mier-Cabrera et al. (2009) in which data were reported as a percentage of the RDI, a lower intake of vitamins C and E was demonstrated in patients with endometriosis. Vitamin C intake was 308 ± 162% RDI in patients with endometriosis compared with 446 ± 142% in controls ($P < 0.05$). Vitamin E intake was 66 ± 27% RDI in patients with endometriosis compared with 112 ± 26% in controls ($P < 0.05$) (Mier-Cabrera et al., 2009).

Potential biological relationship between vitamins and endometriosis

Vitamins, in particular C and E, have potent antioxidant effects on lipid peroxidation (LPO). The LPO chain reaction can be initiated by many reactive oxygen species (ROS) produced by a variety of sources. LPO contributes to the development and progression of chronic diseases with an inflammatory component (Traber and Stevens, 2011). Moreover, a new role for ROS as second messenger of cellular proliferation was also described since normal cell proliferation was correlated with production of endogenous ROS through the activation of growth-related signalling pathways, including the mitogen-activated protein kinase ERK1/2 (McCubrey et al., 2006). These observations raise the question whether there is a causal relationship between oxidative stress and disease. If so, antioxidant therapy should prove beneficial in chronic inflammatory and proliferative diseases (Traber and Stevens, 2011). Markers of oxidative stress have also been found to be elevated in serum and peritoneal fluid of patients with endometriosis (Lambrinoudaki et al., 2009; Mier-Cabrera et al., 2011).

Vitamins as treatment of women with endometriosis

The known correlation between ROS and cell proliferation, along with the increased production of ROS in response to chronic inflammation in endometriosis, has suggested a possible role for ROS in the regulation of endometriotic cell proliferation. As a matter of fact, endometriotic cellular proliferation and activation of ERK1/2 are abrogated by the antioxidant molecule *N*-acetylcysteine both *in vitro* and in a mouse model of endometriosis (Ngô et al., 2009). In line with these observations, Mier-Cabrera et al. (2009) have tested the effect of a high antioxidant diet (vitamins A, C and E) in patients with endometriosis for 4 months and showed a positive effect by diminishing the oxidative stress markers and improving the antioxidant enzyme activity and the vitamin concentrations in peripheral blood. These effects were not seen in women treated with a control diet (Mier-Cabrera et al., 2009).

Finally, it is possible that the antioxidant action exerted by vitamins may reduce the clinical consequences of endometriosis. Oxidative stress has also been associated with infertility (Jackson et al., 2005). However, in a randomized placebo controlled clinical trial enrolling 44 women with endometriosis, the effect on fertility of a bar containing vitamins C and E (343 and 84 mg/day, respectively) given for 6 months was compared with placebo and no effect emerged as the pregnancy rate was 19% in the vitamin group and 12% in the placebo arm (Mier-Cabrera et al., 2008).

Dietary fat

The relationship between dietary fat intake and risk of endometriosis has been analysed in five case–control studies and in a cohort study (**Table 2**). Results obtained in relation to total fat intake are poorly defined (Britton et al., 2000; Missmer et al., 2010; Trabert et al., 2011), so the different types of fats and various fat-containing foods will be considered in order to better address this specific topic.

Red meat and saturated fat

Three studies have analysed the risk of endometriosis in relation to number of servings/week of meat or intake of butter (Parazzini et al., 2004; Heilier et al., 2007; Trabert et al., 2011) which are considered the primary sources for saturated fat. In the Italian case–control study, the risk of endometriosis was significantly higher in women reporting higher meat and ham intake (highest versus lowest tertiles: OR 2.0, 95% CI 1.4–2.8, $P_{trend} = 0.0004$; and OR 1.8, 95% CI 1.3–2.5, $P_{trend} = 0.001$, respectively). However, no association emerged with butter intake (Parazzini et al., 2004). In the Belgian clinic-based case–control study, butter consumption but not meat was marginally associated with the risk of peritoneal endometriosis in the unadjusted analysis (OR 1.87, 95% CI 1.00–3.49) (Heilier et al., 2007). In the case–control study by Trabert et al. (2011), no association emerged between endometriosis risk and number of servings/week of red meat (Trabert et al., 2011) (**Table 2**).

Saturated fat and animal fat were not significantly associated with endometriosis risk in studies addressing specific nutrients (Britton et al., 2000; Missmer et al., 2010; Savaris and do Amaral, 2011). However, this aspect needs to be further investigated considering that a diet pattern characterized by high intake of red meat is associated modestly with oestradiol and oestrone sulphate concentrations (Fung

Table 2 Association between endometriosis and fat intake/sources (literature data, 1990–2011).

Fat intake	*Britton et al. (2000)* P_{trend}	*Parazzini et al. (2004)* P_{trend}	*Heilier et al. (2007)* *OR (95% CI)*	*Trabert et al. (2011)* P_{trend}	*Missmer et al. (2010)* P_{trend}	*Savaris and do Amaral (2011)* P
Total fat	0.05↑	–	–	NS	NS	NS
Animal fat	NS	–	–	–	NS	–
Vegetable fat	0.001↑	–	–	–	NS	–
Saturated fat	NS	–	–	NS	NS	NS
Monounsaturated fat	0.05↑	–	–	NS↓[a]	NS	–
Polyunsaturated fat	0.001↑	–	–	NS	NS	–
Trans-fat	–	–	–	NS	0.001↑	–
Omega-3 fatty acids	–	–	–	NS	0.03↓	0.045↓
Omega-6 fatty acids	–	–	–	NS	NS	0.006↓
Milk	–	NS	NS	NS↓[b]	–	–
Red meat	–	0.0004↑	NS	NS	–	–
Ham	–	0.001↑	–	–	–	–
Eggs	–	NS	NS	–	–	–
Cheese	–	NS	NS	NS	–	–
Fish	–	NS	NS	NS	–	–
Oil	–	NS	–	–	–	–
Margarine	–	NS	NS	–	–	–
Butter	–	NS	1.87 (1.00–3.49) ↑	–	–	–
Bacon	–	–	NS	–	–	–

Arrows indicate risk direction.
[a]Second versus lowest quartiles: OR 0.5, 95% CI 0.3–0.9.
[b]>1–2 versus <1 servings/day: OR 0.6, 95% CI 0.4–0.9.NS = not significant.

et al., 2012) and, as a result, its consumption might directly contribute to human circulating steroid hormone concentrations (Andersson and Skakkebaek, 1999) and ultimately to the disease maintenance.

Olive oil and monounsaturated fats

Olive oil is the main source of monounsaturated fats in the Mediterranean countries. Other sources of monounsaturated fat include red meat, whole milk products, nuts, lard, sesame oil, corn oil, popcorn, wholegrain and wheat cereal.

In the Italian case–control study, no association emerged between oil intake and risk of endometriosis (Parazzini et al., 2004). Likewise no association emerged between monounsaturated fat intake or vegetable fat and risk of endometriosis in the Nurses' Health Study II study (Missmer et al., 2010). In the study by Britton et al. (2000), women in the highest quartiles of monounsaturated fat intake were at higher risk of ovarian endometrioid cysts (highest versus lowest quartiles: OR 1.7, 95% CI 1.1–2.8, $P_{trend} = 0.05$) although the risk became insignificant after the adjustment for polyunsaturated fat intake. On the other hand, an elevated risk was observed for high vegetable fat intake (highest versus lowest quartiles: OR 2.0, 95% CI 1.2–3.2, $P_{trend} = 0.001$) even after the adjustment for polyunsaturated fat intake (Britton et al., 2000).

Olive oil is an important source of micronutrients and a wide variety of valuable antioxidants that are not found in other oils (Owen et al., 2000). The high content of oleic acid makes olive oil far less susceptible to oxidation than the polyunsaturated fatty acids (PUFA), for example. Also, in olive oil, most representative phenols are thought to be potent scavengers of superoxide and other reactive species (Psaltopoulou et al., 2011). On the other hand, the immunosuppressive effects related to olive oil diet administration are not as great as those produced by long-chain omega-3 PUFA, which are considered the most immunosuppressive fatty acids (Puertollano et al., 2007). The association between monounsaturated fat intake and endometriosis remains to be determined.

Fish and omega-3 PUFA

Polyunsaturated fat can be found mostly in nuts, seeds, fish, algae, leafy greens and krill. No statistical association has been found between fish consumption and endometriosis in the Italian and Belgian studies, although a trend for a decreased risk could be observed in Parazzini et al. (2004) and Heilier et al. (2007), while a complete absence of any association was found by Trabert et al. (2011).

In the Nurses' Health Study II study (Missmer et al., 2010), although total fat consumption was not associated

with endometriosis risk, women in the highest fifth of long-chain omega-3 PUFA consumption were 22% less likely to be diagnosed with endometriosis in comparison with those in the lowest fifth of intake (multivariate rate ratio: 0.78, 95% CI 0.62–0.99, $P_{trend} = 0.03$). A higher intake of omega-3 PUFA in the control group was also observed by Savaris and do Amaral (2011) (endometriosis versus controls: mean ± SD 0.66 ± 0.47 g and 1.49 ± 1.57 g, $P = 0.045$). Omega-3 PUFA can be mostly found in salmon, tuna and halibut. Contrary to these observations, the consumption of polyunsaturated fat in general was not associated with endometriosis risk by Trabert et al. (2011) and was strongly positively associated with endometriotic cysts by Britton et al. (2000) (highest versus lowest quartiles: OR 2.0, 95% CI 1.2–3.3, $P_{trend} = 0.001$) (Britton et al., 2000; Trabert et al., 2011).

Interestingly, omega-3 PUFA play a role in the regulation of prostaglandin and cytokine physiology. Alteration of the dietary intake of omega-3 PUFA has important effects on the synthesis and biological activity of cytokines such as interleukin (IL) 1, 2 and 6 and tumour necrosis factor. Such changes in diet have also been shown to lead directly to a decrease in prostaglandin E_2 synthesis (Calder, 2003). Increased exposure to the omega-3 PUFA eicosapentaenoic acid has been shown to significantly suppress the in-vitro survival of endometrial cells compared with those cultured in media with no PUFA or low or normal omega-3:omega-6 PUFA ratios (Gazvani et al., 2001). In line with this observation, in a rabbit model of endometriosis, eicosapentaenoic acid and docosahexaenoic acid (omega-3 PUFA) were able to decrease endometrial implant diameters and reduce peritoneal fluid prostaglandin E_2 and $F_{2\alpha}$ concentrations (Covens et al., 1988).

Trans fats

Trans fats are rare in living nature, but can occur in food production processes. The most commonly known is conjugated linoleic acid. Unlike its synthetic counterparts, conjugated linoleic acid is known to have many health benefits; however, these benefits are not in any way shared with the synthetic *trans* fats produced during hydrogenation. Foods that usually contain high concentrations of *trans* fats include French fries, doughnuts, cookies/biscuits, chocolate, margarine, fried chicken and crackers. The association between *trans* fat intake and endometriosis has also been analysed in two studies (Missmer et al., 2010; Trabert et al., 2011). According to the Nurses' Health Study II (Missmer et al., 2010), the women in the highest quintile of *trans*-saturated fat intake were 48% more likely to be diagnosed with endometriosis (highest versus lowest quintiles: multivariate rate ratio 1.48, 95% CI 1.17–1.88, $P_{trend} = 0.001$). No statistical association was found by Trabert et al. (2011). Margarine was not found to be associated with endometriosis in the Italian and Belgian studies (Parazzini et al., 2004; Heilier et al., 2007). Of note, *trans* fatty acids are associated with higher circulating markers of systemic inflammation. Greater intake was associated with increased tumour necrosis factor system activity, with higher tumour necrosis factor receptor concentrations, higher concentrations of plasma IL-6 and C-reactive protein (Mozaffarian, 2006). Activation of inflammatory responses may represent important mediating steps in favouring endometriosis-mediated events (Capobianco et al., 2011) but this aspect remains to be confirmed.

Dairy products, calcium and vitamin D

Trabert et al. (2011) found an inverse correlation between dairy intake and endometriosis. Odds ratio for endometriosis was, in comparison with women reporting ≤1 serving/day of dairy products, 0.6 (95% CI 0.4–0.9) in women reporting 1–2 servings/day and 0.7 (95% CI 0.4–1.2) in women reporting >2 servings/day (Trabert et al., 2011). Interestingly, the authors explained this potential association in terms of the effect of vitamin D and calcium on the mechanisms promoting the disease. Along this line, the same study reported a decreased, but not significant, risk of endometriosis associated with increased vitamin D and calcium intake. An intriguing explanation for the association between endometriosis and vitamin D may derive from the observation that vitamin D stimulates T-regulatory cells and secretion of IL-10, reduces concentrations of the proinflammatory cytokine IL-17 and dampens T-helper 1 immune function (Correale et al., 2009; Hewison, 2010; Chambers and Hawrylowicz, 2011). Therefore, a deficiency of vitamin D may be revealed as a biologically plausible pathway to an increase in the risk of inflammatory diseases (Kriegel et al., 2011) and this explanation may also apply to endometriosis. However, two studies, including one from this study group, failed to observe lower vitamin D concentrations in women with endometriosis (Hartwell et al., 1990; Somigliana et al., 2007). Along this line, no relationship between milk and cheese intake and endometriosis risk has been reported in the Italian and Belgian studies (Parazzini et al., 2004; Heilier et al., 2007).

Coffee

Table 3 shows the main findings from four studies evaluating the relationship between coffee intake and endometriosis risk. In three studies, an increased risk was reported in women reporting any versus no or infrequent coffee consumption (Grodstein et al., 1993; Berube et al., 1998; Matalliotakis et al., 2008). The association was statistically significant in two (Grodstein et al., 1993; Matalliotakis et al., 2008).

The intake of caffeine and caffeine-containing beverages has been positively associated with sex hormone-binding globulin concentrations and inversely with bioavailable testosterone (Homan et al., 2007). However, concentrations of early follicular phase oestrogens and concentrations of oestrone were found to be higher in women with high caffeine intake (Ferrini and Barrett-Connor, 1996; Lucero et al., 2001). These hormonal changes may influence hormone-dependent diseases. The limited data, however, do not provide the opportunity of drawing any conclusion on the association between coffee drinking and risk of endometriosis.

Table 3 Coffee intake and risk of endometriosis.

Study	Coffee intake				
	No/infrequent	*Moderate*	*Regular*	*Heavier*	*Any*[a]
Grodstein et al. (1993)	1 (<3.1 g/month)	1.1 (0.6–1.9) (3.1–5 g/month)	1.9 (1.2–2.9) (5.1–7 g/month)	1.6 (1.1–2.4) (>7 g/month)	1.7 (1.2–2.3)
Berube et al. (1998)	1 (0–99 mg/day)	1.0 (0.7–1.6) (100–299 mg/day)[b]	–	1.3 (0.9–1.9) (≥300 mg/day)	1.2 (0.9–1.7)
Parazzini et al. (2004)[c]	1	0.9 (06–1.3)	0.8 (0.5–1.1)		0.9 (0.7–1.1)
Matalliotakis et al. (2008)	1[d]	–	–	–	1.6 (0.95–2.6)

Values are odds ratio (95% confidence interval).
[a]Not adjusted: OR not reported, calculated from table frequencies.
[b]Prevalence OR.
[c]Tertile of intake; reference category = low intake.
[d]No coffee intake.

Fibres, whole and refined cereals

Three studies have specifically addressed the association between fibre intake with endometriosis risk (Britton et al., 2000; Trabert et al., 2011; Savaris and do Amaral, 2011). In the study by Trabert et al. (2011), the median daily intake of fibre was 13.9 g in cases and 14.7 g in controls and the difference was not significant (Trabert et al., 2011). Crude fibre intake was not associated with the risk of endometriosis in the study by Britton et al. (2000). On the other hand, Savaris and do Amaral (2011) found a statistically higher intake of fibres in endo-

Table 4 Main findings for effects of specific foods on endometriosis-associated pathological processes

Food	Effect on the disease	Processes potentially involved
Vegetables	Debated ↓	Supply or regenerating DNA methyl groups in critical genes (Riscuta and Dumitrescu, 2012)
Fruits	Debated	Polychlorinated biphenyl containers interfering with hormonal pathways (Grassi et al., 2010; Craig et al., 2011; Buck Louis et al., 2012)
Carrots, β-carotene and vitamin A	Debated	Production of ROS and cell proliferation (Mier-Cabrera et al., 2009; Traber and Stevens, 2011)
Vitamins C and E	Debated	Production of ROS and cell proliferation (Ngô et al., 2009; Traber and Stevens, 2011)
Folates	No effect reported	–
Total fat	Debated	Increased plasma concentration of oestradiol and oestrogen-mediated disease maintenance (Bulun et al., 2012; Fung et al., 2012)
Red meat: ham, saturated fat	Debated ↑	Increased plasma concentration of oestradiol and oestrogen-mediated disease maintenance (Bulun et al., 2012; Fung et al., 2012)
Butter	Debated	Oestrogen-mediated disease maintenance (Pape-Zambito et al., 2010; Bulun et al., 2012)
Olive oil, monounsaturated fats	Debated	ROS scavengers (Psaltopoulou et al., 2011)
Fish, omega-3 polyunsaturated fatty acids	Debated ↓	Production of prostaglandin E_2 and cytokines (Calder, 2003)
Trans fat	Debated ↑	Increased concentrations of inflammatory markers (Mozaffarian, 2006)
Milk, vitamin D	Debated	Effect on the immune system (Correale et al., 2009; Chambers and Hawrylowicz, 2011; Kriegel et al., 2011)
Fibres	Debated	Decrease bioavailable oestrogens (Kaneda et al., 1997)
Refined and whole cereal carbohydrates	Debated	Endometrial cell proliferation through insulin and insulin-like growth factor-1 receptors (Friberg et al., 2011)
Soy phyto-oestrogens	Debated	Anti-oestrogenic effect (Yavuz et al., 2007; Chen et al., 2011)
Coffee	Debated ↑	Changes in availability of various hormones (Ferrini and Barrett-Connor, 1996; Lucero et al., 2001; Homan et al., 2007)

Arrows indicate risk direction.
ROS = reactive oxygen species.

metriosis patients (endometriosis versus controls: mean ± SD 20.89 ± 8.36 g and 15.69 ± 5.75 g, $P = 0.023$) but the study is too numerically limited to draw any conclusions.

Analysis of the number servings/week of whole grains did not show any association with endometriosis risk in the study by Trabert et al. (2011). Likewise, no association emerged in the Italian case–control study between wholegrain foods intake and risk of endometriosis (Parazzini et al., 2004). Diets rich in fibre increase oestrogen excretion and lower bioavailable oestrogens (Kaneda et al., 1997), while refined and wholegrain cereals influence glycaemic index and glycaemic load, variables which measure the rate of absorption of carbohydrates and consequently insulin demand. Insulin has been shown to be able to stimulate endometrial stromal cell proliferation by binding to its receptors in the endometrium. Moreover, hyperinsulinaemia may increase concentrations of oestrogens through decreasing concentrations of sex hormone-binding globulin and may increase concentrations of insulin-like growth factor 1 through decreasing concentrations of insulin-like growth factor-binding protein 1. Both oestrogens and insulin-like growth factor 1 stimulate endometrial cell proliferation (Friberg et al., 2011).

Based on these observations, fibre and cereal consumption could be associated with the risk of endometriosis. However, the published data do not convincingly support this association.

Soy and phyto-oestrogens

Soy intake is common in Japan and in south-east Asia in general. In consideration of the link between endometriosis and oestrogens, it is conceivable that soy or, in general, phyto-oestrogen intake may be related with the risk of the disease. One single study in Japan has investigated this relationship. Higher concentrations of urinary genistein and daidzein were associated with a decreased risk of advanced but not minimal-mild stage endometriosis among infertile women (Tsuchiya et al., 2007). The adjusted OR for the highest quartile group was 0.21 (95% CI 0.06–0.76, $P_{trend} = 0.01$) for genistein and 0.29 (95% CI 0.08–1.03, $P_{trend} = 0.06$) for daidzein when compared with the lowest group. Soy is rich in phyto-oestrogens, which for their weak oestrogenic and anti-oestrogenic effect have been associated with the risk of oestrogen-related diseases (Andres et al., 2011). Both genistein and puerarin have been tested in animal models of endometriosis where they have been shown to reduce weight and surface area of endometriotic lesions through inhibition of aromatase and oestrogen receptor-α expression and reduction of oestrogen concentrations (Yavuz et al., 2007; Chen et al., 2011). However, these findings require confirmation in humans.

Discussion

Table 4 summarizes the main findings emerging from this overview of the literature regarding the association between intake of selected dietary factors and endometriosis risk. Several books and websites have recently focused on the protective or conversely deleterious effect of dietary factors on endometriosis risk (Missmer et al., 2010). However, from the findings presented herein, it is evident that this topic is characterized by an extreme paucity of scientific data and by an extreme variability of the results obtained.

The findings emerging on the role of vegetables, fruits, red meat, vitamins in general, dairy products, coffee and nonsaturated fats are inconsistent. Some biological mechanisms have been suggested to support a role of all these dietary factors in affecting endometriosis risk, but epidemiological data do not consistently support these hypotheses. Based on the paucity of scientific data, this study describes the results of the few studies in detail in order to underline even small effects, but given the evident inconsistencies in reported findings, strong or convincing information could not be provided.

This overview would like to represent an initial platform for further investigations designed to study these factors. This review has underlined the critical aspects of the studies performed so far in order to strengthen the idea that additional studies need to be conducted. As a first-line attempt, based on the data provided, a re-analysis of existing case–control studies with a pooled approach may be more warranted than an intervention study.

This review has also underlined the idea that endometriosis is a multistep phenomenon in which a phase of disease establishment is followed by proliferation, vascularization and peritoneal invasion of the endometriotic lesions with the concomitant manifestation of an inflammatory response. Different nutrients may exert different effects on the different stages of disease development. Further research may analyse separately the role of diet in the development or in the clinical consequences of endometriosis.

In conclusion, despite the conflicting results reported by the few epidemiological studies, the public health implications and the biological plausibility of a beneficial effect of some nutrients on endometriosis suggest that further research should be conducted in this area.

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