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The risk of extra-ovarian malignancies among women with endometriosis: A systematic literature review and meta-analysis

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ABSTRACT

We conducted a meta-analysis of studies reporting on the risk of extra-ovarian malignancies among women with endometriosis. Summary relative risk (SRR) and 95% confidence intervals (CI) were calculated through random effect models. We explored causes of between-studies heterogeneity and assessed the presence of publication bias. We included 32 studies published between 1989 and 2018. We found an increased risk of endometrial (SRR 1.38, 95%CI 1.10–1.74) and thyroid cancer (SRR 1.38, 95%CI 1.17–1.63), and inverse association with cervical cancer (SRR 0.78, 95%CI 0.60–0.95). No association emerged for breast cancer (SRR 1.04, 95%CI 0.99–1.09) and melanoma (SRR 1.31, 95%CI 0.86–1.96). Between-study heterogeneity was large for breast and endometrial cancer and melanoma. Associations were generally stronger in case-control, cross-sectional, and cohort studies with internal control group, compared to cohort studies with external control group. No indication for publication bias was found. Our conclusions need to be confirmed in properly designed cohort studies with clinical confirmation of endometriosis.

1. Introduction

Endometriosis is defined as the presence of the endometrium (which normally lines the inside of the uterus) in abnormal anatomical locations outside of the uterus, most often on the ovaries, the fallopian tubes, or elsewhere in the pelvis, and more rarely in extra-pelvic locations like the bowel, rectum, and bladder (Parasar et al., 2017; Vercellini et al., 2014). Depending on its localization, endometriosis can present with a wide spectrum of symptoms including chronic pelvic pain (mostly during menstruation), menhorragia, dyspareunia, dysuria, infertility, fatigue, joint pain, and several others (Vercellini et al., 2014). Endometriosis is a common disease, whose prevalence among women of reproductive age is reported to range between 0.5%–2.5% in population-based databases (Morassutto et al., 2016; von Theobald et al., 2016; Abbas et al., 2012; Eisenberg et al., 2018). However, endometriosis often goes undiagnosed, and other reports have estimated that up to one in ten women of reproductive age may actually be affected by the disease (Buck Louis et al., 2011). Onset of endometriosis is usually in early adulthood (before 30 years), but because of the usually long time-to-diagnosis (4–7 years on average), its prevalence is highest among women aged 35–44 years (Abbas et al., 2012; von Theobald et al., 2016; Abbas et al., 2012; Eisenberg et al., 2018; Staal et al., 2016).

The pathogenesis of endometriosis remains unclear despite extensive research. According to the most convincing hypothesis, uterine hyperperistalsis and dysperistalsis activate repeated “tissue injury and repair” process and cause retrograde menstruation (i.e. backward flow of menstrual blood through the fallopian tubes), resulting in the eventual implantation of endometrial tissue fragments onto the ovaries, the peritoneum, and other abdominal organs (Vercellini et al., 2014; Leyendecker et al., 1996, 2009). Endometriosis is an estrogen-dependent disease (Wei et al., 2016; Nnoaham et al., 2012) and a role of genetic predisposition, immunity and environmental exposures is suspected as well (Burney and Giudice, 2012; Králíčková and Vetvicka, 2015), although the exact underlying mechanisms have remained elusive.

An association between endometriosis and risk of subsequent malignancy has been reported several times in the literature. Because of

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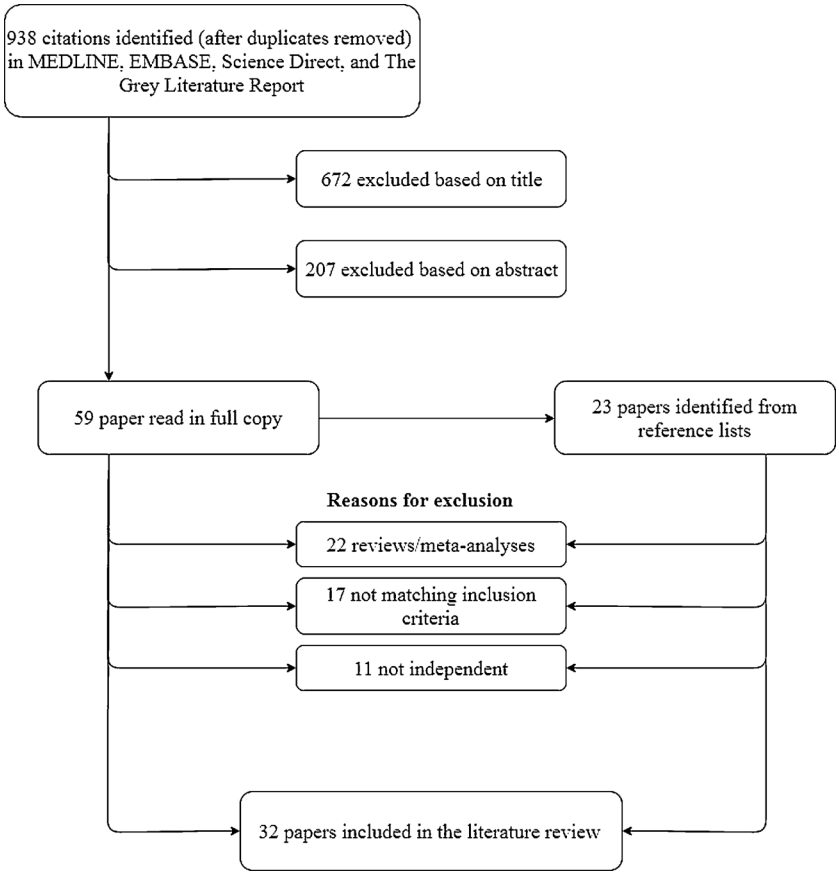

Fig. 1. Flow-chart of the selection process for the papers included in the literature review and meta-analysis on endometriosis and the risk of subsequent extra-ovarian malignancy.

the possible influence of the hormonal milieu in the pathogenesis of endometriosis, studies have mainly focused on malignancies of the female reproductive system (e.g. ovarian, endometrial and cervical cancer) and those that are more common among women (e.g. breast and thyroid cancer) or for which a role of estrogens has been suggested (e.g. melanoma and colorectal cancer) (Gandini et al., 2011; Murphy et al., 2017). Currently, convincing evidence exists that the risk of specific subtypes (i.e. clear cell and endometrioid) of ovarian cancer is increased among women with endometriosis (Pearce et al., 2012; Wang et al., 2016), while the picture is considerably less clear for other cancer sites. To help clarify this issue, we conducted a systematic literature review and meta-analysis of studies reporting on the risk of extra-ovarian malignancies among women with endometriosis.

2. Methods

This literature review and meta-analysis was planned, conducted and reported according to the MOOSE guidelines for meta-analyses and systematic reviews of observational studies (Stroup et al., 2000); the study protocol was registered in the PROSPERO register (registration number CRD42018097095) (National Institute for Health Research, 2019). We searched studies published until August 31st, 2018, in MEDLINE, EMBASE, Science Direct, and the Grey Literature Report website. The literature search was conducted using the following three strings: “endometriosis AND cancer”, “endometriosis AND malignancy”, and “endometriosis AND tumour”. We applied no time or language restrictions, as long as an abstract was available in English. After removing duplicates, all entries were independently screened by two study researchers (SC and SG) based on their title and abstract: those that were considered as potentially eligible for inclusion by at least one researcher were obtained and read in full copy (papers were translated into English when necessary). Finally, the reference list of all papers that were read in full copy, including previously published reviews and meta-analyses, was checked in order to find additional eligible papers.

We included in the present literature review and meta-analysis all papers that reported (or provided sufficient information to estimate) a measure of relative risk (RR) and a corresponding estimate of statistical uncertainty (i.e. 95% confidence intervals [CI], variance, standard errors or exact p-value) for the association between having being diagnosed with endometriosis and the risk of subsequent malignancy at an extra-ovarian site (studies that focused solely on ovarian cancer risk were not considered). Incidence rate ratio, hazard ratio, risk ratio, odds ratio, and standardized incidence ratio were all considered as equivalent RR measures based on the rare diseases assumption. If no adjusted RR estimate was provided, an unadjusted odds ratio was calculated from tabular data whenever possible. In case an RR measure for the association between endometriosis and cancer at a given body site was available from two or more papers with partially or fully overlapping study samples (e.g. subsequent follow-ups of a given cohort), we included in the review and meta-analysis the paper with the highest number of cancer cases occurring among women with endometriosis or, in case of equal sample size, that in which the RR was adjusted for the highest number of confounders. We did not consider for inclusion case reports and ecological studies; studies that focused on benign tumours (e.g. meningioma (Claus et al., 2011)); studies conducted by retrospectively reviewing gynaecological surgery specimens (e.g. from hysterectomy or salpingo-oophorectomy) for the coexistence of endometriosis foci (Nomelini et al., 2013); and the study by Kelemen et al. (2017) in which the objective was to evaluate whether the presence of endometriosis increased the risk of synchronous endometrial cancer among women with ovarian carcinoma.

Data were extracted from each article by one study researcher (SC),

Table 1
Main features of studies included in the review and meta-analysis on the risk of extra-ovarian cancer among women diagnosed with endometriosis.

First author	Publication year	Country	Inclusion criteria for endometriosis patients:[a]	Number of cancer cases among endometriosis patients:[b]				
				Breast	Endometrial	Cervical	Thyroid	Melanoma
Cohort studies								
Venn	1999	Australia	medically confirmed	25	1			
Young	2001	Australia	medically confirmed					3
Olson	2002	USA	self-reported	67	7			4
Brinton	2005	USA	medically confirmed	unknown	unknown		unknown	unknown
Melin	2006	Sweden	medically confirmed					
Melin	2007	Sweden	medically confirmed	1465	97	49	64	217
Braganza	2014	USA	self-reported				13	
Farland	2016	USA	medically confirmed	500				
Mogensen	2016	Denmark	medically confirmed	1452	118			
Farland	2017	France	medically confirmed					32
Poole	2017	USA	medically confirmed		6			
Saavalainen	2018	Finland	medically confirmed		65	28		
Saavalainen	2018	Finland	medically confirmed	1555			179	156
Saraswat	2018	Scotland	medically confirmed	251	17	18		
Surrey	2018	USA	medically confirmed	unknown	unknown			
Williams	2018	UK	medically confirmed	214	9			
Yeh	2018	Taiwan	medically confirmed	95	15	12	29	
Case-control studies								
Wyshak	1989	USA	self-reported					1
Frisch	1992	USA	self-reported					66
Moseson	1993	USA	self-reported	6				
Holly	1995	USA	self-reported					Unknown
Weiss	1999	USA	medically confirmed	53				
Glaser	2003	USA	self-reported					
Fortuny	2009	USA	self-reported		36			
Zucchetto	2009	Italy	self-reported		7			
Nichols	2011	USA	self-reported	198				
Rowlands	2011	Australia	self-reported		60			
Morales	2013	Puerto Rico	self-reported	26				
Burghaus	2015	Germany	self-reported		7			
Chuang	2015	Taiwan	medically confirmed	108				
Cross-sectional studies								
Gemmill	2010	USA	medically confirmed	16				29
Nagai	2015	Japan	self-reported	unknown	unknown	unknown		

[a] "Medically confirmed" include the following: confirmation by laparoscopy/laparotomy, clinical diagnosis made by a medical doctor, endometriosis diagnosed during workup for infertility, and women identified through linkage with disease database (including health insurance database) or hospital discharge data.
[b] Only cancer types for which a relative risk estimate was provided in at least five independent studies. Data concerning other cancer types are summarized in Supplementary file 2.

entered into an internally piloted extraction sheet (Microsoft Excel 2010), and independently cross-checked by a second study researcher (SG). We then used the formulas proposed by Greenland (1987) to convert RR estimates and the corresponding measures of statistical uncertainty into log relative risk (logRR) and corresponding variance. In addition to main outcomes, we extracted information on factors that were considered to be relevant for the correct interpretation of the results, namely: country and years in which the study was conducted; study design; source, number and age distribution of included subjects; mean/median follow-up time (for cohort studies); type of matching (if any) and matching variables; whether the diagnosis of endometriosis was medically confirmed or self-reported; statistical methods and any variables used to adjust RR estimates.

We pooled RR estimates into a summary relative risk (SRR) using random effect models with maximum likelihood estimates (van Houwelingen et al., 2002), and obtained 95% CI assuming an underlying t distribution. An SRR was calculated only when there were RR estimates from five or more independent studies for the association between endometriosis and cancer at a given body site. We assessed the heterogeneity between studies using the I^2 statistics, which is expressed as a percentage and can be interpreted as the proportion of variation of effect that is attributable to actual heterogeneity rather than chance (Higgins and Thompson, 2002). The larger the I^2, the greater the heterogeneity, and values of I^2 lower than 50% are considered as compatible with chance alone. When the I^2 statistics was above 50%, we fitted meta-regression models to examine the impact of selected study characteristics on the effect size. We then performed an iterative leave-one-out sensitivity analysis to test whether any SRR was driven by single studies, and used the Egger and Begg test to explore whether each SRR was affected by publication bias (Begg and Mazumdar, 1994).

The methodological quality of each study was assessed using the Newcastle-Ottawa Scale (NOS) (The Newcastle-Ottawa Scale (NOS), 2019), which is a tool specifically developed for nonrandomised studies as those included in this review and meta-analysis. In particular, two separate assessment scales exist for case-control and cohort studies; the latter was slightly modified to adapt to cross-sectional studies. Assigned scores were then converted to Agency for Health Research and Quality (AHRQ) standards, and the methodological quality of each study was thus labelled as "good", "fair", or "poor" (AHRQ, 2019).

All analyses were conducted using SAS software version 9.2 (SAS Institute Inc, Cary, NC, USA). All tests were two-sided and a p-value less than 0.05 was considered as statistically significant.

3. Results

The literature search generated 938 entries, of which 672 and 207 were excluded based on title and abstract, respectively (Fig. 1). We read 59 papers in full copy, and identified 23 more papers by checking their reference lists. After removing 22 reviews and meta-analyses, 17 papers that did not match the inclusion criteria, and 11 papers that were

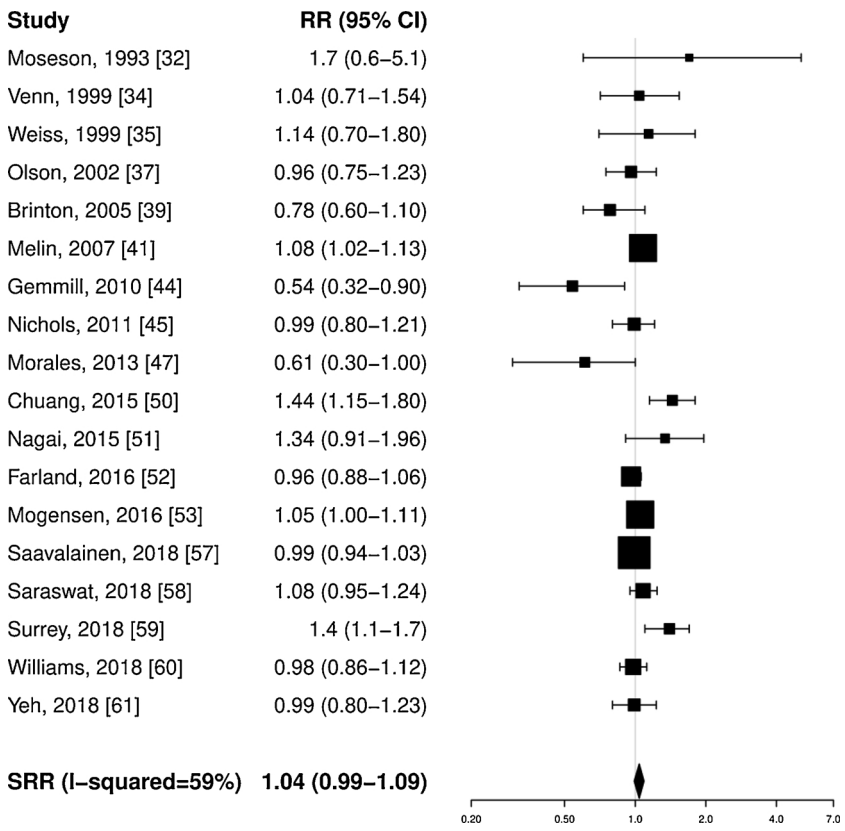

Fig. 2. Forest plot for the association between endometriosis and breast cancer risk.
RR: relative risk.
CI: confidence intervals.
SRR: summary relative risk.

overlapping with more sized and/or more recent studies, a total of 32 papers were included in our review and meta-analysis (Wyshak et al., 1989; Frisch et al., 1992; Moseson et al., 1993; Holly et al., 1995; Venn et al., 1999; Weiss et al., 1999; Young et al., 2001; Olson et al., 2002; Glaser et al., 2003; Brinton et al., 2005; Melin et al., 2006, 2007; Fortuny et al., 2009; Zucchetto et al., 2009; Gemmill et al., 2010; Nichols et al., 2011; Rowlands et al., 2011; Morales et al., 2013; Braganza et al., 2014; Burghaus et al., 2015; Chuang et al., 2015; Nagai et al., 2015; Farland et al., 2016; Mogensen et al., 2016; Farland et al., 2017; Poole et al., 2017; Saavalainen et al., 2018a,b; Saraswat et al., 2018; Surrey et al., 2018; Williams et al., 2018; Yeh et al., 2018).

The main characteristics of the papers included in the review are illustrated in Table 1. Studies were conducted in thirteen different countries and published between 1989 and 2018. Seventeen studies had a cohort design, thirteen were case-control studies (of which ten were population-based and three were hospital-based), and two had a cross-sectional design (the study by Nagai et al. (2015), which was an analysis of baseline data of the Japan Nurses' Health study; and the study by Gemmill et al. (2010), which was conducted among members of the Endometriosis Association of North America). The diagnosis of endometriosis was considered as confirmed in sixteen studies: this may include surgical confirmation (laparoscopy or laparotomy) (Saraswat et al., 2018), clinical diagnosis made by a medical doctor during hospitalisation or in the outpatients setting (Mogensen et al., 2016), evidence for endometriosis based on evaluation for infertility (Brinton et al., 2005; Williams et al., 2018), or endometriosis patients identified through linkage with hospital discharge data or health insurance database (Saavalainen et al., 2018a,b). The diagnosis of endometriosis was self-reported in the remaining fifteen studies. All but three (Wyshak et al., 1989; Frisch et al., 1992; Burghaus et al., 2015) of the included studies reported RR estimates that were adjusted for some potential confounders, although only five studies adjusted for oral contraceptives use (Zucchetto et al., 2009; Nichols et al., 2011; Rowlands et al., 2011; Farland et al., 2016; Poole et al., 2017). Breast, endometrial, cervical and thyroid cancer and melanoma were the only malignancies for which RR estimates from five or more independent studies were available (Table 1).

When two or more RR estimates for the association between endometriosis and risk of a given extra-ovarian malignancy were available in the same study, only one was included in our review and meta-analysis, which was chosen as follows. In the study by Saraswat et al. (2018), cancer incidence among women with endometriosis was compared to three unexposed cohorts, which consisted of (a) women with no evidence of endometriosis at a diagnostic laparoscopy, (b) women who underwent laparoscopic sterilisation, or (c) women from the general population: RR estimates included were those obtained from the former comparison. In the study by Poole et al. (2017) we used the RR estimate that relied on medically confirmed (instead of self-reported) endometriosis, while in Rowlands et al. (2011), we considered the results based on cancers that were detected at least 1 year after the diagnosis of endometriosis.

The methodological quality of studies was judged to be fair or good for all cohort studies, for nine of thirteen case-control studies, and for one of two cross-sectional studies (Supplementary file 1). Inability to adjust for age and other confounding factors and reliance on self-reported (instead of medically confirmed) endometriosis diagnosis were the most frequent reasons to judge a study's methodological quality as "poor".

3.1. Breast cancer

There was no evidence that women with endometriosis were at

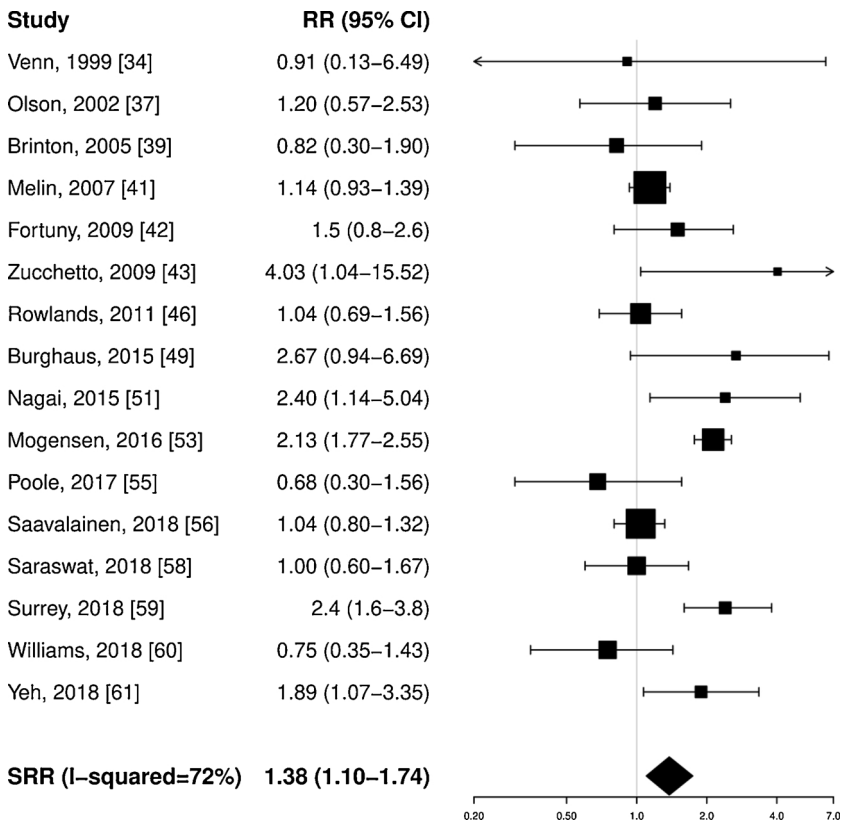

Fig. 3. Forest plot for the association between endometriosis and endometrial cancer risk.
RR: relative risk.
CI: confidence intervals.
SRR: summary relative risk.

increased risk of developing breast cancer: the SRR was 1.04 (95%CI 0.99–1.09) (Fig. 2), with between-estimates heterogeneity slightly above the range of acceptable values (I^2 = 59%). This was based on results from eighteen independent studies (Moseson et al., 1993; Venn et al., 1999; Weiss et al., 1999; Olson et al., 2002; Brinton et al., 2005; Melin et al., 2007; Gemmill et al., 2010; Nichols et al., 2011; Morales et al., 2013; Chuang et al., 2015; Nagai et al., 2015; Farland et al., 2016; Mogensen et al., 2016; Saavalainen et al., 2018b; Saraswat et al., 2018; Surrey et al., 2018; Williams et al., 2018; Yeh et al., 2018) and a total of over 6000 breast cancer cases diagnosed among women with endometriosis, of which nearly 4500 were from three countrywide prospective investigations from Scandinavian countries (Sweden (Melin et al., 2007), Denmark (Mogensen et al., 2016), and Finland (Saavalainen et al., 2018a)).

Some studies provided RR estimates stratified according to different criteria, e.g. age at endometriosis diagnosis (Nichols et al., 2011; Mogensen et al., 2016), time since endometriosis diagnosis (Weiss et al., 1999; Mogensen et al., 2016), menopausal status or age at breast cancer diagnosis (Moseson et al., 1993; Weiss et al., 1999; Chuang et al., 2015; Farland et al., 2016), and others. With few exceptions, stratified RR estimates did not substantially differ from those calculated in the whole study group.

3.2. Endometrial and cervical cancer

Sixteen independent studies reported a RR estimate for the association between endometriosis and endometrial cancer risk, including eleven prospective investigations (Venn et al., 1999; Olson et al., 2002; Brinton et al., 2005; Melin et al., 2007; Mogensen et al., 2016; Poole et al., 2017; Saavalainen et al., 2018a; Saraswat et al., 2018; Surrey et al., 2018; Williams et al., 2018; Yeh et al., 2018), five case-control studies (Fortuny et al., 2009; Zucchetto et al., 2009; Rowlands et al., 2011; Burghaus et al., 2015), and the cross-sectional study by Nagai et al. (2015) (Table 1). These studies were published over a period of two decades (1999–2018) and included a total of more than 440 endometrial cancer cases diagnosed among women with endometriosis. In meta-analysis, we found a statistically significant positive association between endometriosis and the endometrial cancer risk, although with a large between-studies heterogeneity (I^2 = 72%) (Fig. 3).

There was a statistically significant inverse association between endometriosis and cervical cancer risk (SRR 0.78, 95%CI 0.60–0.95), based on estimates from four prospective studies (Melin et al., 2007; Saavalainen et al., 2018a; Saraswat et al., 2018; Yeh et al., 2018) and the cross-sectional study by Nagai et al. (2015), with no evidence of substantial heterogeneity between studies (I^2 = 15%) (Fig. 4).

3.3. Thyroid cancer

An RR estimate for the association between endometriosis and thyroid cancer risk was reported in five independent studies, all of which had a cohort design (Brinton et al., 2005; Melin et al., 2007; Braganza et al., 2014; Saavalainen et al., 2018b; Yeh et al., 2018). All studies reported a generally moderate positive association (RR < 1.50) that achieved statistical significance in Melin et al. and (Melin et al., 2007; Saavalainen et al., 2018b). The only exception was the study by (Brinton et al., 2005), which found a more then threefold increase in thyroid cancer risk (RR 3.09), although with high statistical uncertainty as evidenced by the wide 95% confidence intervals (0.90–10.70). The SRR was 1.38 (95% CI 1.17–1.63), with no between-estimates heterogeneity (I^2 = 0%) (Fig. 5).

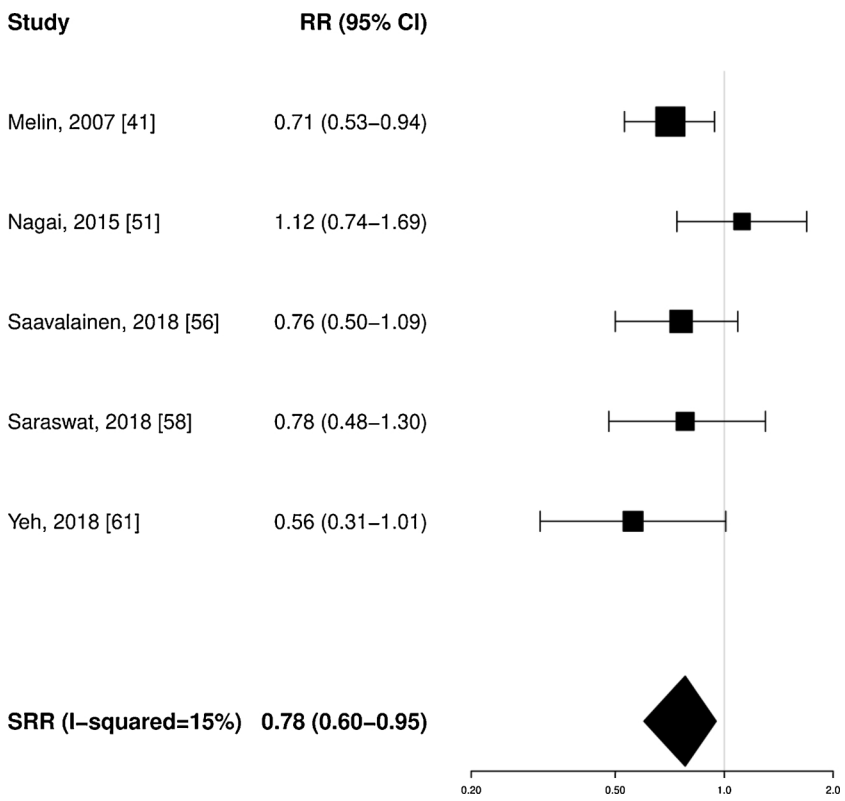

Fig. 4. Forest plot for the association between endometriosis and cervical cancer risk.
RR: relative risk.
CI: confidence intervals.
SRR: summary relative risk.

3.4. Melanoma and non-melanoma skin cancer

The SRR for the association between endometriosis and melanoma risk was 1.30 (95%CI 0.86–1.96) (Fig. 6), based on more than an overall 500 melanoma cases diagnosed among women with endometriosis in ten independent studies (Wyshak et al., 1989; Frisch et al., 1992; Holly et al., 1995; Young et al., 2001; Olson et al., 2002; Brinton et al., 2005; Melin et al., 2007; Gemmill et al., 2010; Farland et al., 2017; Saavalainen et al., 2018b). The heterogeneity was large (I^2 = 82%). In leave-one-out sensitivity analysis, the removal of the study by Gemmill et al. (2010) (i.e. the only one with a cross-sectional design) from the study pool cut down the heterogeneity within acceptable values (I^2 = 43%) and attenuated, but moved closer to statistical significance, the association between endometriosis and melanoma risk (SRR 1.15, 95%CI 0.97–1.36).

Four studies evaluated the risk of non-melanoma skin cancer or its subtypes among women with endometriosis (Supplementary file 2). Saavalainen et al. reported a statistically significant association with the risk of basal cell cancer (RR 1.18, 95%CI 1.10–1.25), based on 904 malignancies observed compared to 767.7 expected (Saavalainen et al., 2018b). The other three studies (Wyshak et al., 1989; Melin et al., 2006; Farland et al., 2017) had a much smaller study size and reported non-significant risk increases ranging between 5% and 46%.

3.5. Other malignancies

Most studies examining the risk of other malignancies among women with endometriosis reported associations that varied in direction and strength across studies and, with few exceptions, failed to achieve statistical significance (Supplementary file 2). Non-Hodgkin lymphoma (NHL) could represent a possible exception: three cohort studies reported increased risk estimates (achieving statistical significance in Melin et al. (2006)), while the only article reporting an inverse, non-significant association was the cross-sectional study by Gemmill et al. (2010), which relied on only two NHL cases. Finally, the risk of cancer at any site among women with endometriosis did not appear to diverge substantially from that of unaffected women, based on a total of over 7000 malignancies observed in two large, country-wide cohorts of endometriosis patients from Northern Europe (Sweden and Finland) (Melin et al., 2006; Saavalainen et al., 2018b) and in the Iowa Women's Health Study (Olson et al., 2002).

3.6. Between-estimates heterogeneity and publication bias

Between-study heterogeneity was large (≥50%) for breast, endometrial cancer and melanoma. Meta-regression failed to detect study characteristics able to explain a significant proportion of the observed heterogeneity when separately examining each of those malignancies, probably due to the limited number of studies. An expanded meta-regression model that included all available RR estimates and that was adjusted by type of malignancy, found suggestive, yet not statistically significant (p-value 0.17) evidence that RR estimates tended to be farther from the null value in cohort studies with an internal control group and in case-control and cross-sectional studies (i.e. studies in which the presence or absence of endometriosis was medically confirmed or self-reported for all study participants) compared to cohort studies with an external control group (i.e. in which the incidence rates of cancer among endometriosis patients were compared to reference rates from the general population, which contains an unknown, yet probably not negligible proportion of women suffering from endometriosis).

Finally, none of the studied associations was found to be significantly affected by publication bias.

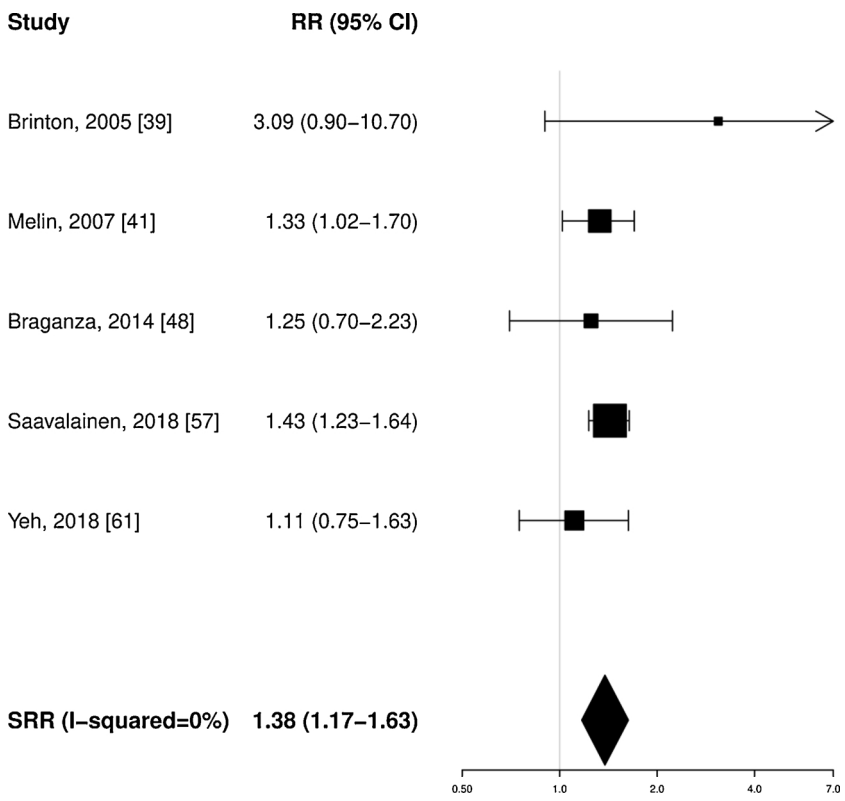

Fig. 5. Forest plot for the association between endometriosis and thyroid cancer risk.
RR: relative risk.
CI: confidence intervals.
SRR: summary relative risk.

4. Discussion

We conducted a systematic review and meta-analysis of observational studies focusing on the relationship between endometriosis and risk of extra-ovarian malignancies, and found a significantly increased risk of endometrial and thyroid cancer and an inverse association with cervical cancer risk. Our findings provide a broader and more exhaustive overview of the risk of cancer among women with endometriosis and complement the results of previous reports about ovarian cancer (Pearce et al., 2012; Wang et al., 2016).

Endometriosis is an oestrogen-dependent chronic inflammatory condition and its relationship with cancer could either be a marker of certain underlying biologic factors such as unbalanced oestrogen metabolism (Vercellini et al., 2014), or be linked to complex immune-mediated mechanisms (Symons et al., 2018). Endometriosis is a benign condition that nonetheless shares features with invasive cancer, including uncontrolled growth, inhibition of apoptosis, neo-angiogenesis, and cell invasion (Swiersz, 2002). We found a ≈40% increase in endometrial cancer risk: notably, 80–85% of these are type 1 endometrial cancers, which mostly have endometrioid histology and mainly occur in younger, obese, and perimenopausal women. Excess oestrogen is known to increase the risk of type 1 endometrial cancer, while progesterone has a protective effect against this cancer type (Kim et al., 2013). The endometriotic tissue produces biologically significant quantities of both local oestrogens and progesterone via an abnormally active steroidogenic cascade; however, there is evidence that eutopic endometrium has progesterone resistance (Kim et al., 2013), which may explain the positive association between endometriosis and endometrial cancer observed in our meta-analysis. Furthermore, type 1 endometrial cancer shares mutations in the same genes as those observed in endometriosis-associated ovarian cancers, suggesting a common genetic link for endometriosis and endometrial cancer of endometrioid histology (Pavone and Lyttle, 2015).

Unbalanced oestrogen metabolism and autoimmunity could also explain our finding of the 38% excess risk of thyroid cancer among women with endometriosis. Papillary thyroid cancer is among the most common malignancies among women with a female-to-male ratio of 3:1 (Dal Maso et al., 2011), and the peak incidence occurs at 40–49 years among women, suggesting that reproductive factors may play an important role in thyroid carcinogenesis (Sakoda and Horn-Ross, 2002). Oestrogens can enhance the proliferation, migration and invasiveness of malignant thyroid cells (Glinoer et al., 1990; Manole et al., 2001; Rajoria et al., 2010) and depurinating oestrogen-DNA adducts have been observed in women with thyroid cancer (Zahid et al., 2013). Recently, the role of female sex hormones in thyroid cancer has been further confirmed by studies focusing on the effect of continuous, unbalanced estradiol on thyroid tissues and cancer stem cells (Zane et al., 2017). Moreover, recent meta-analyses showed an inverse association between the duration of oral contraceptive use and thyroid cancer risk (Caini et al., 2015; Wu and Zhu, 2015). Interestingly, oral contraceptives represent an important therapeutic option for the treatment of endometriosis thanks to their ability to decrease retrograde menstruation, induce a pseudopregnancy state, and cause decidualization and subsequent atrophy of the eutopic and ectopic endometrium (Vercellini et al., 2014). An alternative mechanism that can be invoked to explain the association between endometriosis and thyroid cancer risk (and that may complement the retrograde menstruation theory for the aetiology of endometriosis) is autoimmunity (Giudice and Kao, 2004; Nothnick, 2001; Eisenberg et al., 2012). Thyroid peroxidase antibodies are more expressed in endometriosis patients than healthy women (Poppe et al., 2002), and Graves' disease, an autoimmune disorder causing thyrotoxicosis, was found to be associated with both endometriosis (Yuk et al., 2016) and thyroid cancer (Staniforth et al., 2016). However, the role of the immune system in the pathogenesis of endometriosis and its

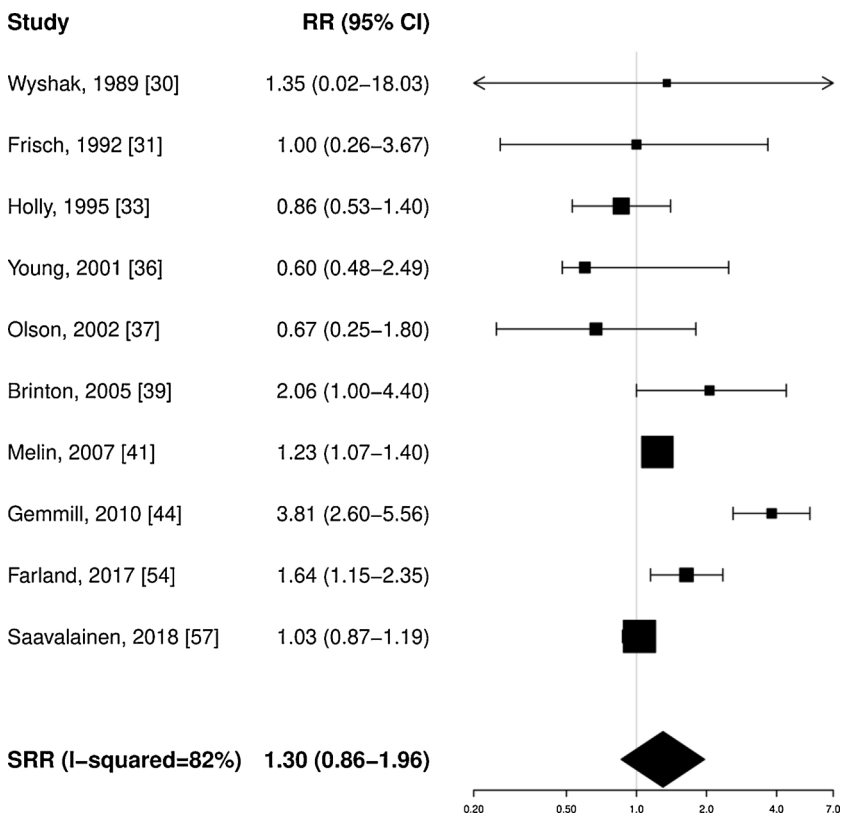

Fig. 6. Forest plot for the association between endometriosis and melanoma risk.
RR: relative risk.
CI: confidence intervals.
SRR: summary relative risk.

co-morbidities (including cancer) and the biological mechanisms underlying these associations remain to be elucidated (Králíčková and Vetvicka, 2015).

Our meta-analysis showed no association between endometriosis and the risk of breast cancer despite the frequent hormonal imbalance with excess oestrogen production (a known risk factor for breast cancer) in these patients. Likewise, there was no significant association between endometriosis and melanoma risk, but we observed a statistically significant risk reduction for cervical cancer. Notably, Melin et al. and Saavalainen et al. also found a lower risk of precancerous cervical lesions among endometriosis patients (which allows to discard intensified cervical screening as an explanatory hypothesis) (Melin et al., 2006; Saavalainen et al., 2018a), and the latter also reported a 40% reduced risk of developing buccal and pharynx carcinomas in the same cohort (Saavalainen et al., 2018b). As all of these conditions are strongly related to human papillomavirus (HPV) infections, authors speculated that endometriosis patients might be less exposed to HPV infections than healthy women. The concept of the infectious origin of endometriosis has developed recently and there have not been many studies in this field. In fact, only a few studies so far have measured the prevalence of HPV in ovaries of women with endometriosis, with conflicting results (Oppelt et al., 2010; Vestergaard et al., 2010; Heidarpour et al., 2017), while no study to date has aimed to determine the prevalence of HPV infection in the cervix of women with endometriosis. This knowledge gap leaves open alternative explanations for our finding, including a lower exposure to HPV infections or more complex alterations in the immune response associated with both endometriosis and HPV-related diseases (Saavalainen et al., 2018a).

The main strengths of our work were the comprehensiveness of the literature search and the large number of studies that were included, which allowed calculating a summary risk estimates for five cancer sites (breast, endometrium, cervix, thyroid, and skin melanoma). Quality was good for most studies and results were robust to changes in model assumptions: this strengthens the reliability and validity of our findings and argues against a major effect of confounding and bias affecting our conclusions. Our meta-analysis also has important limitations that need to be acknowledged. Despite the methodological quality was good for most included studies, there was a large variability in terms of study design, methods for exposure definition, statistical methods, and other important characteristics potentially affecting the study results, including the ability to control for potential confounders (e.g. oral contraceptives use). This translated into substantial between-estimates heterogeneity, thus emphasizing the need to standardize methods in order to obtain comparable risk estimates and draw more reliable conclusions. In particular, endometriosis is a common disease and the use of general population reference rates to calculate standardized incidence ratios may not be the best choice, as it may cause the underestimation of risk and eventually the inability to observe true associations. Moreover, endometriosis can go undiagnosed for years, which may also represent an important source of bias in prospective studies. In general, we recommend that attention should be paid in future studies to the correct classification of participants as affected/unaffected by endometriosis in order to minimize as much as possible the problem of exposure misclassification and the consequent dilution of associations.

In conclusion, our meta-analysis suggests that women with endometriosis may be at increased risk of developing endometrial and thyroid cancer, while having a reduced cervical cancer risk. Endometriosis was not associated with altered breast cancer or melanoma risk, and the epidemiological evidence was not sufficient to draw reliable conclusions on malignancies at other extra-ovarian sites. Research priorities in this field are to elucidate the biological mechanisms underlying the observed associations and to fully clarify the

potential of oral contraceptives (a common treatment for endometriosis) to modulate the risk of endometrial and thyroid cancer among women with endometriosis.

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Declaration of interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2018.12.009.

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