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Endometriosis and cancer: a systematic review and meta-analysis

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BACKGROUND: Endometriosis is an often chronic, inflammatory gynaecologic condition affecting 190 million women worldwide. Studies have reported an elevated cancer risk among patients with endometriosis. However, prior research has included methodologic issues that impede valid and robust interpretation.

OBJECTIVE AND RATIONALE: We conducted a meta-analysis of studies investigating the association between endometriosis and cancer risk and analysed the results by methodologic characteristics. We discuss the implications of cancer screening in patients and management challenges faced by clinicians.

SEARCH METHODS: We searched PubMed and Embase databases for eligible studies from inception through 24 October 2019. We included cohort and case-control studies examining the association between endometriosis and cancer risk; cross-sectional studies and case reports were excluded. Publications had to present risk/rate/odds estimates with 95% CI. Random effects meta-analysis was used to estimate summary relative risks (SRR) and CIs. Heterogeneity across studies was assessed by the Q test and I^2 statistics, and publication bias using Egger's and Begg's tests. Risk of bias and quality of the included studies were assessed using the risk of bias in non-randomized studies of interventions (ROBINS-I) tool.

OUTCOMES: Forty-nine population-based case-control and cohort studies were included. Twenty-six studies were scored as having a 'serious'/'critical' risk of bias, and the remaining 23 'low'/'moderate'. Cancer-specific analyses showed a positive association between endometriosis and ovarian cancer risk (SRR = 1.93, 95% CI = 1.68–2.22; n = 24 studies) that was strongest for clear cell (SRR = 3.44, 95% CI = 2.82–4.42; n = 5 studies) and endometrioid (SRR = 2.33, 95% CI = 1.82–2.98; n = 5 studies) histotypes ($P_{heterogeneity} < 0.0001$), although with significant evidence of both heterogeneity across studies and publication bias (Egger's and Begg's *P*-values < 0.01). A robust association was observed between endometriosis and thyroid cancer (SRR = 1.39, 95% CI =1.24–1.57; n = 5 studies), a very small association with breast cancer (SRR = 1.04, 95% CI =1.00–1.09; n = 20 studies) and no association with colorectal cancer (SRR = 1.00, 95% CI =0.87–1.16; n = 5 studies). The association with endometrial cancer was not statistically significant (SRR = 1.23, 95% CI =0.97–1.57; n = 17 studies) overall and wholly null when restricted to prospective cohort studies (SRR = 0.99, 95% CI =0.72–1.37; n = 5 studies). The association with cutaneous melanoma was also non-significant (SRR = 1.17, 95% CI =0.97–1.41; n = 7 studies) but increased in magnitude and was statistically significant when restricted to studies with low/moderate risk of bias (SRR = 1.71, 95% CI = 1.24–2.36, n = 2 studies). The most robust finding both in terms of statistical significance and magnitude of effect was an inverse association with cervical cancer (SRR = 0.68, 95% CI =0.56–0.82; n = 4 studies); however, this result has a high potential to reflect heightened access to detection of dysplasia for women who reached an endometriosis diagnosis and is thus likely not causal. Several additional cancer types were explored based on <4 studies.

WIDER IMPLICATIONS: Endometriosis was associated with a higher risk of ovarian and thyroid, and minimally (only 4% greater risk) with breast cancer, and with a lower risk of cervical cancer. However, this meta-analysis confirms that: a majority of studies had severe/critical risk of bias; there is impactful heterogeneity across studies—and for ovarian cancer, publication bias; and causal inference requires temporality, which in many studies was not considered. We discuss the implications of these potential associations from the perspectives of patients with endometriosis, clinicians involved in their care, and scientists investigating their long-term health risks.

Key words: endometriosis / cancer / epidemiology / methodology / bias / endometrioma / cohort studies / case-control studies

Introduction

Endometriosis is an inflammatory disease process characterized by lesions of endometrial-like tissue outside the uterus—commonly on the pelvic peritoneum and ovaries (Johnson *et al.*, 2017). The condition can present with debilitating symptoms (dysmenorrhea, acyclic pelvic pain, dysuria, dyschezia, chronic fatigue) that have considerable adverse impacts on quality of life (Nnoaham *et al.*, 2011), including an increased risk of infertility (Prescott *et al.*, 2016). Endometriosis is estimated to affect 10% of women of reproductive age (Shafrir *et al.*, 2018; Ghiasi *et al.*, 2020), equating to 190 million women worldwide (Zondervan *et al.*, 2020), and is associated with substantial health-care costs (Simoens *et al.*, 2011a,b). Clinically informative subtypes of endometriosis have yet to be established, although macro presentation includes superficial peritoneal lesions, cysts in the ovaries (endometrioma), deep endometriosis and extra-pelvic lesions (Zondervan *et al.*, 2020). Unfortunately, little is known on the aetiology of the disease, and treatment options are ineffective long term for many women.

Although non-malignant and not marked by uncontrolled lesion growth, endometriosis shares similar features with cancer, such as development of local and distant foci, resistance to apoptosis and invasion of other tissues with subsequent damage to the target organs (Kvaskoff *et al.*, 2015). It also generates a chronic local and systemic

inflammatory milieu (Zondervan *et al.*, 2018) and has been associated with several risk factors that are also associated with risk of several cancer types (Shafrir *et al.*, 2018). These observations raised the question of whether women with endometriosis are at higher cancer risk—a topic that has had a long-lasting interest in the literature (Missmer, 2009), particularly within the last decade. Indeed, endometriosis has been reported to be associated with a higher risk of several cancer types in population research (Kvaskoff *et al.*, 2015). More recently, gene sequencing has demonstrated that about 20% of both ovarian endometriosis and deep endometriosis lesions have somatic cancer driver mutations (Anglesio *et al.*, 2015, 2017), although such mutations are also observed at high proportions in eutopic endometrium from healthy women (Lac *et al.*, 2019a).

Quantifying cancer risk in women with endometriosis is crucial for several reasons. This field has important public health implications for women in terms of cancer screening and prevention, and for clinicians in terms of the long-term management of women with endometriosis (Lippman *et al.*, 2018). Given the currently limited knowledge on endometriosis, having a clear answer as to its link with cancer, which is more deeply investigated and understood, will help enhance our understanding of endometriosis pathophysiology. Considering micro- and macro-patient characteristics will also help to identify informative biological and prognostic subgroups of the disease that will ultimately advance endometriosis treatment development.

Several studies reported a higher cancer risk among women with endometriosis. Two early meta-analyses were published on the relationships between endometriosis and ovarian cancer. Reviewing studies published in 1990–2012, Kim *et al.* (2014) estimated a summary relative risk (SRR) of 1.27 (95% CI = 1.21–1.32), based on 21 case-control or cohort studies, and of 1.80 (95% CI = 1.28–2.53) based on five studies including women with endometriosis only. Wang *et al.* (2016) then reported a summary odds ratio (OR) of 1.42 (95% CI = 1.28–1.57), based on 12 case-control studies published between 1995 and 2016. Thereafter, meta-analyses reported on the associations between endometriosis and ovarian, endometrial and cervical cancers (Li *et al.*, 2019) and between endometriosis and extra-ovarian malignancies (Gandini *et al.*, 2019), based on 25 studies published over 1997–2017, and based on 32 studies published in 1989–2018, respectively. Li *et al.* (2019) summarized a relative risk (RR) of 1.96 (95% CI = 1.69–2.29) for the relationship between endometriosis and ovarian cancer, a modest (RR = 1.18, 95% CI =0.88–1.58) and not statistically significant association with endometrial cancer, and an inverse association with cervical cancer. While Gandini *et al.* (2019) also reported an inverse association with cervical cancer, endometriosis was positively associated with endometrial cancer in their meta-analysis, with an SRR of 1.38 (CI = 1.10–1.74). They also reported a higher risk of thyroid cancer in women with endometriosis, but no apparent association with breast cancer or cutaneous melanoma.

However, the previous meta-analyses did not explore and account for the impact of methodologic characteristics among the included studies (e.g. temporality, population sampling, confounding, publication bias), which are critical to consider due to high risk of selection and diagnostic biases among studies published to date (Kvaskoff *et al.*, 2015). Another essential point to improve our understanding and identify high-risk groups is the exploration of disease heterogeneity, which continues to be limited in previous research and needs to be addressed—both in terms of cancer subtypes and of endometriosis subtypes.

In this study, we performed a systematic review and meta-analysis of published studies on the associations between endometriosis and cancer risk, and analysed the results by endometriosis and cancer subtypes and according to the methodologic characteristics of the studies. In addition, we discuss the reliability of the evidence in light of these important methodologic considerations. We also discuss the implications of the findings and offer practical and pragmatic recommendations to clinicians for the long-term management of women with endometriosis with regards to their cancer risk.

Methods

Search strategy and inclusion criteria

This systematic review was registered with PROSPERO in June 2019 and accepted for inclusion in January 2020 (Registration ID Number CRD42020139497). We searched the PubMed and Embase databases for eligible studies from inception to 24 October 2019. The search terms and algorithm that we used are detailed in Supplementary data. We followed standard criteria for reporting meta-analyses of observational studies (Stroup *et al.*, 2000). We also searched the reference lists of the selected publications to retrieve additional studies that were not identified through electronic searches.

Study selection

We included cohort and case-control studies examining the associations between endometriosis and cancer risk, overall and/or by cancer or endometriosis subtype. Cross-sectional studies and case reports or series were excluded. Risk estimates (RR, hazard ratio (HR), standardized incidence ratio (SIR) or OR) had to be reported with 95% CI in the publication. The flow chart of study selection is presented in Fig. 1. All identified studies were imported into Reference Manager for screening. Two reviewers (M.K. and Y.M.-S.) performed screening separately by reviewing titles, abstracts and keywords for relevance to endometriosis and cancer. The full text of the selected articles was then retrieved to assess their eligibility. Any discrepancies were resolved by discussion.

Data extraction

We extracted the following data from each study: first author's last name, publication year, country where the research was conducted, study design and population type (population-based or selected sample), study period, sample size (number of endometriosis and cancer cases, number of controls (where applicable), and source population), ascertainment of endometriosis and cancer cases, ability to evaluate temporality of the association (i.e. ability of the study to ensure that endometriosis occurred *prior to* cancer in a time-varying analysis and not diagnosed concurrently), risk estimate and 95% CIs (including by subgroup when available) and variables adjusted for in the analysis. Data were extracted by Y.M.-S. and extractions were checked for accuracy by M.K. Any discrepancies were resolved by discussion.

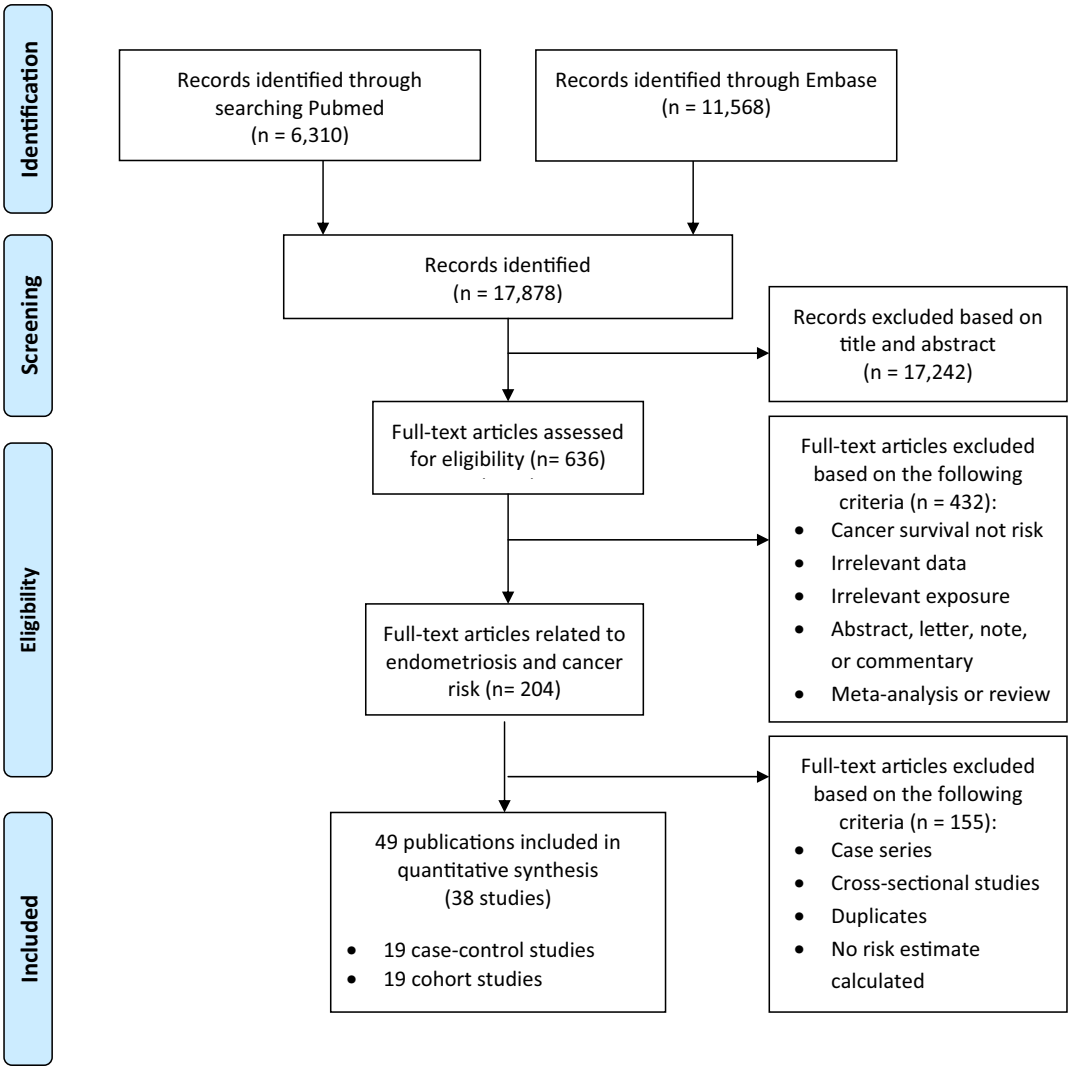

Figure 1. Flow chart of study selection for a systematic review and meta-analysis of endometriosis and cancer risk.

Quality assessment and risk of bias

We assessed the quality of the included studies and their potential risk of bias using the risk of bias in non-randomized studies of interventions (ROBINS-I) tool (Sterne *et al.*, 2016). This tool encompasses seven domains: bias due to confounding; bias in selection of study participants; bias in exposure measurement; bias due to misclassification of exposure during follow-up; bias due to missing data; bias in measurement of outcomes; and bias in selection of reported results. In this approach, a study is considered at low risk of bias if it has been rated 'low' in all domains; low-to-moderate risk of bias if it has been rated as 'probably at risk' for one domain; serious risk of bias if rated as 'high risk' for more than one domain and critical risk of bias if rated as 'critical risk' in at least one domain. If information is missing in at least two domains, the study is classified as having 'no information'. Evaluation was performed by two reviewers independently (Y.M.-S. and M.K.). Any discordance during the assessment of the quality of evidence was discussed with a third reviewer (S.A.M.) to reach consensus.

Data synthesis and meta-analysis

We calculated SRR and 95% CIs for the relation between endometriosis and cancer risk. The average of the natural logarithm of the RRs was estimated and the RR from each study was weighted using random effects weights (DerSimonian and Laird, 1986). When studies reported results only separately for specific subgroups (e.g. type I and type II ovarian cancer (Merritt *et al.*, 2013; Ruiz *et al.*, 2016), for colon and rectal cancers (Melin *et al.*, 2006; Saavalainen *et al.*, 2018a), small and large intestine cancers (Melin *et al.*, 2006; Saavalainen *et al.*, 2018a) or by endometriosis case ascertainment (self-report or medical records/registries) (Chang *et al.*, 2014; Poole *et al.*, 2017)), we combined the results using the Hamling procedure to obtain an overall estimate to be used in the meta-analysis (Hamling *et al.*, 2008). Heterogeneity between studies was quantitatively assessed by the Q test and I^2 statistics (Higgins and Thompson, 2002). Whenever possible, subgroup analyses were conducted to investigate potential sources of heterogeneity, including study characteristics such as type of

population (e.g. limited to women with infertility), study design (cohort versus case-control studies), geographic location, definition of endometriosis case ascertainment (self-report versus medical records/registries), histologic type of cancer, macro-phenotypic type of endometriosis (i.e. endometrioma, deep endometriosis, superficial peritoneal endometriosis) and requirement of temporality (yes versus no). Between-subgroup differences in summary estimates were examined using meta-regression analysis. For all analyses, the impact of study sample size was accounted for in the statistical modelling and represented by the width of 95% CI.

Several studies, for which the primary analysis did not take into account temporality, repeated their analyses after exclusion of endometriosis cases occurring within 12 months of cancer diagnosis, and thus in a sensitivity analysis, we considered these studies as meeting the temporality criteria. In additional sensitivity analyses, we also explored potential differences by quality of the study per the ROBINS-I risk of bias tool: 'low' or 'moderate' versus 'serious' or 'critical'.

Study effects, such as publication bias, were visually assessed by examining funnel plots for asymmetry, and with Egger's (Egger *et al.*, 1997) and Begg's tests (Begg and Mazumdar, 1994). Sensitivity analyses excluding one study at a time were conducted to clarify whether the results were driven by one large study or a study with an extreme result. Stata version 16 software (Stata Corp, College Station, TX, USA) was used for all statistical analyses.

Results

Study selection

The initial search identified 17 878 records, including 6310 from MEDLINE and 11 568 from Embase (Fig. 1). A total of 17 242 publications were excluded after first-stage screening by reviewing titles and abstracts; 636 full-text articles were retrieved and assessed for inclusion. Of these, 432 were excluded based on irrelevant outcome, data, exposure or publication type (abstract, letter, note, commentary, review or meta-analysis). Out of the 204 remaining publications, 155 records were further excluded because of study design (cross-sectional studies, case report or case series populations), duplicates or because no risk estimate was provided. In total, we identified 49 publications (38 studies—19 cohort and 19 case-control) on the associations between endometriosis and cancer that met all the inclusion criteria for the meta-analysis. Samples sizes varied widely among studies (Supplementary Table SI).

When more than one article was published using the same study population (Brinton *et al.*, 1997, 2004, 2005a; Melin *et al.*, 2006, 2007, 2013; Pearce *et al.*, 2012, 2013, 2015; Stewart *et al.*, 2013a,b, 2018; Chang *et al.*, 2014; Wang *et al.*, 2014; Kok *et al.*, 2015; Lee *et al.*, 2015), we selected the one that included the largest number of cases. Since both the Nurses' Health Study II (Poole *et al.*, 2017) and the Iowa Women's Health Study (Olson *et al.*, 2002) cohorts were included in the analysis from the Ovarian Cancer Cohort Consortium (Wentzensen *et al.*, 2016), we did not also include them as individual studies in the analysis for ovarian cancer. Similarly, the Australian Cancer Study (Merritt *et al.*, 2008, 2013; Nagle *et al.*, 2008) and the Diseases of the Ovary and their Evaluation Study (Rossing *et al.*, 2008) were included in an earlier pooled analysis of the Ovarian Cancer Association Consortium (Pearce *et al.*, 2012), and the study by Modugno *et al.* (2004) was included in the pooled analysis published by Ness *et al.* (2002); thus, we also did not include them as individual studies.

Characteristics of the included studies are detailed in Supplementary Table SI. Compared with previously published meta-analyses, we included an additional six studies on ovarian cancer (Bodmer *et al.*, 2011; Buis *et al.*, 2013; Stewart *et al.*, 2013b; Ruiz *et al.*, 2016; Wentzensen *et al.*, 2016; Koushik *et al.*, 2017), four on breast cancer (Baron *et al.*, 2001; Borgfeldt and Andolf, 2004; Bertelsen *et al.*, 2007; Brinton *et al.*, 2014) and three on endometrial cancer (Borgfeldt and Andolf, 2004; Brinton *et al.*, 2005a; Kok *et al.*, 2015) that were not identified in previous searches. The present meta-analysis additionally includes eight studies published after the most recent previous review (Park *et al.*, 2018; Saavalainen *et al.*, 2018a,b; Saraswat *et al.*, 2018; Surrey *et al.*, 2018; Williams *et al.*, 2018; Hsu *et al.*, 2019; Lundberg *et al.*, 2019; Vassard *et al.*, 2019). In the present work, we did not include the study by Yeh *et al.* (2018), which reported results on cancer survival rather than cancer risk.

Quality of evidence

Based on the ROBINS-I tool (Sterne *et al.*, 2016), we identified 11 studies with low risk of bias (Brinton *et al.*, 2005b; Bertelsen *et al.*, 2007; Chang *et al.*, 2014; Chuang *et al.*, 2015; Kok *et al.*, 2015; Mogensen *et al.*, 2016; Farland *et al.*, 2016a, 2017; Poole *et al.*, 2017; Guenego *et al.*, 2018; Stewart *et al.*, 2018), 12 with moderate risk of bias (Brinton *et al.*, 2005a, 2014; Buis *et al.*, 2013; Stewart *et al.*, 2013a,b; Wentzensen *et al.*, 2016; Park *et al.*, 2018; Saraswat *et al.*, 2018; Surrey *et al.*, 2018; Hsu *et al.*, 2019; Lundberg *et al.*, 2019; Vassard *et al.*, 2019), 20 with serious risk of bias (Moseson *et al.*, 1993; Holly *et al.*, 1995; Venn *et al.*, 1999; Weiss *et al.*, 1999; Baron *et al.*, 2001; Young *et al.*, 2001; Ness *et al.*, 2002; Olson *et al.*, 2002; Kobayashi *et al.*, 2007; Melin *et al.*, 2007; Fortuny *et al.*, 2009; Zucchetto *et al.*, 2009; Bodmer *et al.*, 2011; Nichols *et al.*, 2011; Rowlands *et al.*, 2011; Pearce *et al.*, 2012; Morales *et al.*, 2013; Braganza *et al.*, 2014; Ruiz *et al.*, 2016; Koushik *et al.*, 2017) and 6 with critical risk of bias (Borgfeldt and Andolf, 2004; Brinton *et al.*, 2004; Melin *et al.*, 2006; Saavalainen *et al.*, 2018a,b; Williams *et al.*, 2018) (Table I).

Overall cancer

A total of five cohort studies were included that quantified the association between endometriosis and overall cancer risk (Olson *et al.*, 2002; Melin *et al.*, 2007; Kok *et al.*, 2015; Saavalainen *et al.*, 2018a; Saraswat *et al.*, 2018). The SRR was 1.07 (95% CI = 0.98–1.16), suggesting a very small and not statistically significant positive association. However, there was substantial heterogeneity among studies (I^2 = 88%, $P < 0.0001$). Variation by geographic location was evident (North America (n = 1 study): RR = 0.90, 95% CI = 0.77–1.05; Europe (n = 3 studies): SRR = 1.03, 95% CI = 0.97–1.11; Asia (n = 1 study): HR = 1.80, 95% CI = 1.37–2.36), although the number of studies from each continent was very small and the test for heterogeneity among the continents was not statistically significant ($P_{heterogeneity}$ = 0.20). There was suggestion of heterogeneity by ROBINS-I risk of bias (low or moderate: SRR = 1.45, 95% CI = 0.98–2.13, I^2 = 86%, P = 0.008; serious or critical: SRR = 0.99, 95% CI = 0.96–1.02, I^2 = 37%, P = 0.21; $P_{heterogeneity}$ = 0.08), but interpretation is complicated by the high heterogeneity within the low/moderate group, while the studies in the serious/critical group appear to be uniformly biased towards

Table I Risk of bias for the 49 included publications (1993–2019) from 38 studies, based on the ROBINS-I tool (low, moderate, serious, critical).

Author, year, location	Type of bias							Overall rating
	Bias due to confounding	Bias due to selection of participants	Bias due to exposure assessment	Bias due to misclassification during follow-up	Bias due to missing data	Bias due to measurement of the outcome	Bias due to selective reporting of the results	
Moseson *et al.*, 1993, USA	Low	Moderate	Serious	Moderate	Low	Moderate	Moderate	Serious
Holly *et al.*, 1995, USA	Serious	Moderate	Serious	Moderate	No information	Low	Moderate	Serious
Venn *et al.*, 1999, Australia	Serious	Moderate	Low	Moderate	Moderate	Low	Moderate	Serious
Weiss *et al.*, 1999, USA	Low	Moderate	Serious	Moderate	No information	Moderate	Low	Serious
Baron *et al.*, 2001, USA	Low	Moderate	Serious	Moderate	Moderate	Moderate	Moderate	Serious
Young *et al.*, 2001, Australia	Serious	Moderate	Low	Moderate	No information	Moderate	Moderate	Serious
Ness *et al.*, 2002, Multiple locations	Low	Moderate	Serious	Moderate	Moderate	Moderate	Low	Serious
Olson *et al.*, 2002, USA	Low	Moderate	Serious	Low	Moderate	Moderate	Low	Serious
Borgfeldt and Andolf, 2004, Sweden	Critical	Moderate	Low	Moderate	Moderate	Moderate	Moderate	Critical
Brinton *et al.*, 2004, USA	Critical	Moderate	Low	Moderate	Low	Low	Moderate	Critical
Brinton *et al.*, 2005b, Denmark	Low	Low	Low	Low	Low	Low	Low	Low
Brinton *et al.*, 2005a, USA	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Melin *et al.*, 2006, Sweden	Critical	Moderate	Low	Low	No information	Low	Moderate	Critical
Bertelsen *et al.*, 2007, Denmark	Low	Low	Low	Low	No information	Low	Low	Low
Kobayashi *et al.*, 2007, Japan	Serious	Low	Low	Moderate	Low	Low	Low	Serious
Melin *et al.*, 2007, Sweden	Serious	Moderate	Low	Low	No information	Low	Low	Serious
Fortuny *et al.*, 2009, USA	Moderate	Moderate	Serious	Moderate	No information	Moderate	Low	Serious
Zucchetto *et al.*, 2009, Italy	Low	Moderate	Serious	Moderate	Moderate	Moderate	Low	Serious
Bodmer *et al.*, 2011, UK	Serious	Moderate	Low	Moderate	Moderate	Moderate	Low	Serious
Nichols *et al.*, 2011, USA	Low	Moderate	Serious	Moderate	Moderate	Moderate	Low	Serious
Rowlands *et al.*, 2011, Australia	Low	Moderate	Serious	Moderate	Moderate	Moderate	Low	Serious
	Moderate	Moderate	Serious	Moderate	Low	Moderate	Low	Serious

Continued

Table I Continued

Author, year, location	Type of bias							Overall rating
	Bias due to confounding	Bias due to selection of participants	Bias due to exposure assessment	Bias due to misclassification during follow-up	Bias due to missing data	Bias due to measurement of the outcome	Bias due to selective reporting of the results	
Pearce *et al.*, 2012 Multiple locations	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Stewart *et al.*, 2013b, Australia	Low	Moderate	Low	Low	Moderate	Low	Low	Moderate
Buis *et al.*, 2013, The Netherlands	Low	Moderate	Serious	Moderate	Moderate	Low	Moderate	Serious
Morales *et al.*, 2013, Puerto Rico	Low	Moderate	Low	Low	No information	Low	Low	Moderate
Stewart *et al.*, 2013a, Australia	Low	Low	Serious	Low	Low	Low	Low	Serious
Braganza *et al.*, 2014, USA	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Brinton et al., 2014, USA	Low	Low	Low	Low	No information	Low	Low	Low
Chang *et al.* 2014, Taiwan	Low	Low	Low	Low	No information	Low	Low	Low
Chuang *et al.*, 2015, Taiwan	Low	Low	Low	Low	No information	Low	Low	Low
Kok *et al.*, 2015, Taiwan	Low	Low	Low	Low	No information	Low	Low	Low
Farland *et al.*, 2016a, USA	Low	Low	Low	Low	No information	Low	Low	Low
Mogensen *et al.*, 2016, Denmark	No information	Moderate	Serious	Moderate	No information	Moderate	Moderate	Serious
Wentzensen *et al.*, 2016 Multiple locations	Low	Low	Moderate	Low	Low	Low	Low	Moderate
Farland *et al.*, 2017, France	Low	Low	Low	Low	Low	Low	Low	Low
Koushik *et al.*, 2017, Canada	Low	Moderate	Serious	Moderate	Low	Moderate	Low	Serious
Poole *et al.*, 2017, USA	Low	Low	Low	Low	Low	Low	Low	Low
Saavalainen *et al.*, 2018a, Finland	Critical	Low	Low	Low	No information	Low	Low	Critical
Saavalainen *et al.*, 2018b, Finland	Critical	Low	Low	Low	No information	Low	Low	Critical
	Moderate	Low	Low	Low	Low	Low	Low	Moderate

Continued

Table I Continued

Author, year, location	Type of bias							Overall rating
	Bias due to confounding	Bias due to selection of participants	Bias due to exposure assessment	Bias due to misclassification during follow-up	Bias due to missing data	Bias due to measurement of the outcome	Bias due to selective reporting of the results	
Saraswat *et al.*, 2018, Scotland								
Stewart *et al.*, 2018, Australia	Low	Low	Low	Low	No information	Low	Low	Low
Surrey *et al.*, 2018, USA	Moderate	Low	Low	Low	No information	Low	Low	Moderate
Williams *et al.*, 2018, UK	Critical	Low	Low	Low	Low	Low	Low	Critical
Guenego *et al.*, 2018, France	Low	Low	Low	Low	Low	Low	Low	Low
Park et al., 2018, USA	Low	Moderate	Low	Moderate	Low	Moderate	Low	Moderate
Vassard *et al.*, 2019, Denmark	Low	Moderate	Low	Low	Low	Low	Moderate	Moderate
Hsu *et al.*, 2019, Taiwan	Moderate	Low	Low	Low	No information	Low	Low	Moderate
Lundberg *et al.*, 2019, Sweden	Low	Moderate	Low	Low	Low	Low	Low	Moderate

ROBINS-I tool, risk of bias in non-randomized studies of interventions tool.

the null. There was no indication of heterogeneity across study designs (prospective versus retrospective cohort, $P_{heterogeneity} = 0.33$) or assessments of endometriosis (self-reported versus medical records/registry, $P_{heterogeneity} = 0.33$), nor of publication bias, with Egger's test ($P = 0.29$) or with Begg's test ($P = 0.22$).

Ovarian cancer

The meta-analysis included 24 studies evaluating the association between endometriosis and ovarian cancer (Venn *et al.*, 1999; Ness *et al.*, 2002; Borgfeldt and Andolf, 2004; Brinton *et al.*, 2004, 2005a; Kobayashi *et al.*, 2007; Melin *et al.*, 2007; Bodmer *et al.*, 2011; Pearce *et al.*, 2012; Buis *et al.*, 2013; Stewart *et al.*, 2013b; Chang *et al.*, 2014; Mogensen *et al.*, 2016; Ruiz *et al.*, 2016; Wentzensen *et al.*, 2016; Koushik *et al.*, 2017; Park *et al.*, 2018; Saavalainen *et al.*, 2018b; Saraswat *et al.*, 2018; Surrey *et al.*, 2018; Williams *et al.*, 2018; Hsu *et al.*, 2019; Lundberg *et al.*, 2019; Vassard *et al.*, 2019) (Table II). The SRR was 1.93 (95% CI = 1.68–2.22) (Fig. 2, Table II) but there was high heterogeneity among studies ($I^2 = 78\%$, $P < 0.0001$). There was a high level of heterogeneity within categories of study design (case-control studies: SRR = 1.49, 95% CI = 1.35–1.63, $I^2 = 0\%$, $P = 0.62$; retrospective cohorts: SRR = 2.03, 95% CI = 1.69–2.45, $I^2 = 77\%$, $P < 0.0001$; prospective cohorts: SRR = 2.83, 95% CI = 1.32–6.07, $I^2 = 94\%$, $P < 0.0001$) and also among the studies within the cohort designs ($P_{heterogeneity} = 0.17$ for case-control versus cohort studies). Geographic location also contributed to between- and within-continent heterogeneity (North America: SRR = 2.14, 95% CI = 1.38–3.32, $I^2 = 74\%$, $P = 0.004$; Europe: SRR = 1.81, 95% CI = 1.55–2.10, $I^2 = 75\%$, $P < 0.0001$; Asia: SRR = 4.22, 95% CI = 1.70–10.46, $I^2 = 69\%$, $P = 0.04$; Australia: SRR = 1.99, 95% CI = 1.02–3.88, $I^2 = 0\%$, $P = 0.53$; multiple locations: SRR = 1.44, 95% CI = 1.31–1.59, $I^2 = 0\%$, $P = 0.83$; $P_{heterogeneity} = 0.09$) (Table II).

The positive association between endometriosis and ovarian cancer was also stronger in studies that required temporality (i.e. endometriosis must have been diagnosed at least 12 months prior to the diagnosis of endometrial cancer) (n = 11, SRR = 2.19, 95% CI = 1.64–2.92, $I^2 = 85\%$, $P < 0.0001$) versus studies that did not (n = 13, SRR = 1.79, 95% CI = 1.55–2.05, $I^2 = 64\%$) or in studies with low or moderate risk of bias (n = 13, SRR = 2.09, 95% CI = 1.69–2.59, $I^2 = 78\%$, $P < 0.0001$) versus studies with serious or critical risk of bias (n = 11, SRR = 1.80, 95% CI = 1.49–2.17, $I^2 = 77\%$, $P < 0.0001$), albeit again with high heterogeneity within these categories and also with no statistically significant heterogeneity between these groups ($P_{heterogeneity} = 0.46$ and 0.50, respectively) (Table II). Three studies (Chang *et al.*, 2014; Mogensen *et al.*, 2016; Williams *et al.*, 2018) additionally reported estimates after excluding endometriosis cases diagnosed <12 months prior to ovarian cancer diagnosis; including these estimates within the meta-analysis instead of the primary estimates from these studies prior to exclusion did not change the overall meta-analysis SRR for ovarian cancer (SRR = 1.90, 95% CI = 1.67–2.15, $I^2 = 72\%$, $P < 0.0001$). When now including these three studies among the group restricted to those that required temporality, the results still were not substantially modified (studies requiring temporality: n = 14, SRR = 2.12, 95% CI = 1.71–2.63, $I^2 = 83\%$, $P < 0.0001$; studies not requiring temporality: n = 10, SRR = 1.75, 95% CI = 1.48–2.07, $I^2 = 62\%$, $P = 0.005$), with heterogeneity within groups remaining high.

Table II Summary relative risks and 95% CIs for the associations between endometriosis and hormone-dependent cancer risk, by cancer type for those cancer types with at least four studies published through 2019.

	Number of studies	SRR (95% CI)	I^2 (%)	P^a_{within}	$P^b_{between}$
Ovarian cancer					
All studies	24	1.93 (1.68–2.22)	77.5	<0.0001	
By study design					
Case control	7	1.49 (1.35–1.63)	0.0	0.62	0.17
Cohort	17	2.14 (1.78–2.58)	82.1	<0.0001	
Retrospective cohort	14	2.03 (1.69–2.45)	77.2	<0.0001	0.42
Prospective cohort	3	2.83 (1.32–6.07)	93.7	<0.0001	
By geographic location					
North America	5	2.14 (1.38–3.32)	74.0	0.004	0.09
Europe	11	1.81 (1.55–2.10)	74.7	<0.0001	
Asia	3	4.22 (1.70–10.46)	68.7	0.04	
Australia	2	1.99 (1.02–3.88)	0.0	0.53	
Multiple locations	3	1.44 (1.31–1.59)	0.0	0.83	
By assessment of endometriosis					
Self-reported	7	1.50 (1.34–1.67)	0.0	0.61	0.35
Medical records/registry	19	2.07 (1.75–2.44)	76.8	<0.0001	
Required temporality[c]					
No	13	1.79 (1.55–2.05)	63.8	0.001	0.46
Yes	11	2.19 (1.64–2.92)	85.3	<0.0001	
ROBINS-I risk of bias					
Low/moderate	13	2.09 (1.69–2.59)	77.8	<0.0001	0.50
Serious/critical	11	1.80 (1.49–2.17)	77.3	<0.0001	
Ovarian Cancer Subtypes					
Clear cell	5	3.44 (2.82–4.20)	13.5	0.33	<0.0001
Endometrioid	5	2.33 (1.82–2.98)	54.0	0.07	
Serous	6	1.17 (1.03–1.32)	0.0	0.75	
Mucinous	5	0.98 (0.74–1.29)	0.0	0.79	
Borderline	7	1.46 (1.00–2.15)	58.3	0.04	
Grade of serous tumours					
High	3	1.08 (0.88–1.32)	24.5	0.27	0.03
Low	2	2.33 (1.64–3.31)	0.0	0.39	
Macro-phenotype of endometriosis[d]					
Endometrioma	4	5.41 (2.25–13.00)	81.5	0.001	0.03
Superficial peritoneal	1	1.32 (0.99–1.72)	–-	–-	
Deep	1	1.41 (0.29–4.10)	–-	–-	
Breast cancer					
All studies	20	1.04 (1.00–1.09)	58.7	0.001	
By study design					
Case control	6	0.96 (0.81–1.15)	60.2	0.03	0.25
Cohort	14	1.05 (1.01–1.10)	60.3	0.0002	
Retrospective cohort	10	1.06 (1.01–1.12)	62.7	0.004	0.40
Prospective cohort	4	1.03 (0.91–1.16)	60.7	0.05	
By geographic location					
North America	9	1.01 (0.89–1.15)	62.3	0.007	0.22
Europe	8	1.04 (1.00–1.08)	51.7	0.04	
Asia	2	1.41 (1.14–1.75)	0.0	0.54	
Australia	0	–-	–-	–-	

Continued

Table II Continued

	Number of studies	SRR (95% CI)	I^2 (%)	P^a_{within}	$P^b_{between}$
Multiple locations	0	–-	–-	–-	
By assessment of endometriosis					
Self-reported	7	1.01 (0.81–1.24)	70.2	0.003	0.55
Medical records/registry	13	1.04 (1.00–1.08)	45.6	0.04	
Required temporality[c]					
No	8	0.99 (0.90–1.09)	45.4	0.08	0.25
Yes	12	1.06 (1.01–1.12)	66.0	0.001	
ROBINS-I risk of bias					
Low/moderate	9	1.09 (1.01–1.17)	68.1	0.001	0.12
Serious/critical	11	1.01 (0.95–1.07)	49.5	0.03	
Endometrial cancer					
All studies	17	1.23 (0.97–1.57)	81.1	<0.0001	
By study design					
Case control	4	1.29 (0.65–2.54)	85.2	<0.0001	0.89
Cohort	13	1.25 (0.96–1.62)	79.5	<0.0001	
Retrospective cohort	8	1.40 (1.00–1.96)	86.8	<0.0001	0.49
Prospective cohort	5	0.99 (0.72–1.37)	0.0	0.70	
By geographic location					
North America	5	1.30 (0.81–2.10)	60.2	0.04	0.39
Europe	9	1.12 (0.81–1.55)	88.2	<0.0001	
Asia	1	4.05 (1.20–13.66)			
Australia	2	1.44 (0.99–2.11)	0.0	0.64	
Multiple locations	0	–-	–-	–-	
By assessment of endometriosis					
Self-reported	5	1.33 (0.93–1.90)	35.9	0.18	0.23
Medical records/registry	12	1.14 (0.85–1.53)	84.3	<0.0001	
Required temporality[c]					
No	8	1.35 (0.89–2.04)	90.0	<0.0001	0.18
Yes	9	1.11 (0.96–1.27)	0.0	0.56	
ROBINS-I risk of bias					
Low/moderate	8	1.39 (0.93–2.08)	84.6	<0.0001	0.31
Serious/critical	9	1.08 (0.83–1.39)	64.2	<0.0001	

SRR, summary relative risk.
I^2 (%) is a measure of the proportion of the heterogeneity attributed to between-study variation rather than due to chance. I^2-values of 25%, 50% and 75% indicate low, moderate and high between-study heterogeneity, respectively.
[a]*P*-value testing for heterogeneity among the studies within each cancer type.
[b]*P*-value testing for between subgroup or category heterogeneity generated from meta-regression analysis.
[c]Studies were considered to have required temporality (i.e. 'yes') if the endometriosis diagnosis had to precede the cancer diagnosis (i.e. they were not diagnosed at the same time) within the analyses.
[d]Studies quantified associations with cancers stratifying endometriosis by any documented visualization of the macro-phenotype.

The influence analysis excluding the most influential studies suggested stable summary estimates (Supplementary Fig. S1). However, there was strong evidence of publication bias towards an overestimation of the association, whether evaluated graphically (Supplementary Fig. S2) by Egger's ($P = 0.01$) or Begg's test ($P = 0.009$).

Ovarian cancer heterogeneity.

Several studies provided risk estimates by ovarian cancer histotype, and an analysis by histotype mostly eliminated the observed heterogeneity for all ovarian cancer studies (Table II). The strongest association was observed with the clear cell (SRR = 3.44, 95% CI = 2.82–4.20, n = 5 studies: Brinton *et al.*, 2005b; Pearce *et al.*, 2012; Mogensen *et al.*, 2016; Wentzensen *et al.*, 2016; Saavalainen *et al.*, 2018b) and endometrioid histotypes (SRR = 2.33, 95% CI = 1.82–2.98, n = 5 studies: Brinton *et al.*, 2005b; Pearce *et al.*, 2012; Mogensen *et al.*, 2016; Wentzensen *et al.*, 2016; Saavalainen *et al.*, 2018b), while there was no association detected with mucinous tumours (SRR = 0.98, 95% CI = 0.74–1.29, n = 5 studies: Brinton *et al.*, 2005b; Pearce *et al.*, 2012; Mogensen *et al.*, 2016; Wentzensen *et al.*, 2016; Saavalainen *et al.*, 2018b). Within serous tumours, a meta-analysis of the three studies that provided separate estimates showed that the association was restricted to low-grade serous tumours (SRR = 2.33, 95%

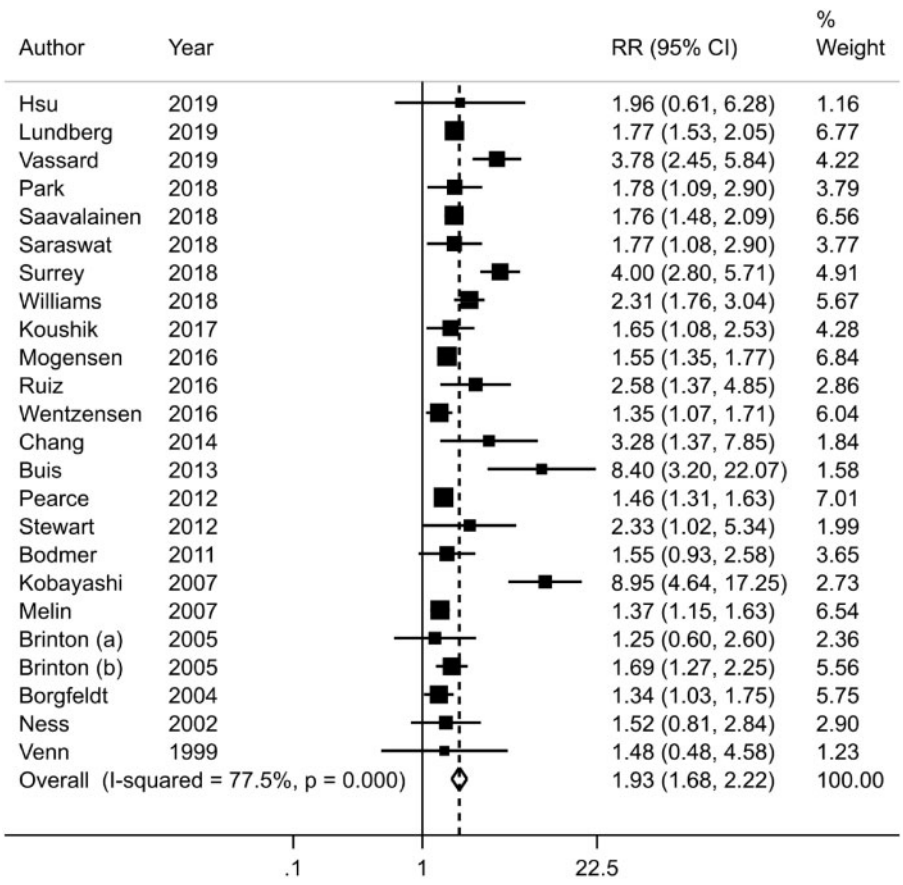

Figure 2. Association between endometriosis and ovarian cancer risk among 24 studies published through 2019. *Note: Brinton (a) conducted in the USA and Brinton (b) conducted in Denmark. Since the Nurses' Health Study II (Poole *et al.*, 2017) and the Iowa Women's Health Study (Olson *et al.*, 2002) cohorts were included in the analysis from the Ovarian Cancer Cohort Consortium (Wentzensen *et al.*, 2016), we did not also include them as individual studies in analyses for ovarian cancer. RR, relative risk, $P = P$-value, test for between-study heterogeneity.

CI = 1.64–3.31, versus high-grade serous tumours: SRR = 1.08, 95% CI = 0.88–1.32; $P_{heterogeneity} < 0.0001$). Interestingly, there was no evidence of publication bias in studies reporting endometriosis associations by ovarian cancer histotype (all Egger's or Begg's tests P-values > 0.13); however, this could be due to a lack of power given the small number of studies in each group.

Endometriosis heterogeneity.

Only four studies provided estimates of the association between endometriosis and ovarian cancer risk by endometriosis macro-phenotypic subtype (Kobayashi *et al.*, 2007; Buis *et al.*, 2013; Kok *et al.*, 2015; Saavalainen *et al.*, 2018b); three of these focused on ovarian endometrioma only, irrespectively of other subtypes (Kobayashi *et al.*, 2007; Buis *et al.*, 2013; Kok *et al.*, 2015). Based on these studies, the SRR for the association between endometrioma and ovarian cancer was 5.41 (95% CI = 2.25–13.00) (Supplementary Fig. S3), but with a very high level of heterogeneity between studies (I^2 = 82%, $P = 0.001$) albeit with no evidence of publication bias (Egger's test: $P = 0.24$; Begg's test: $P = 0.99$). This heterogeneity may exist because these studies quantified the association for endometriosis cases with any visualization of endometrioma regardless of the presence of the other macro-phenotypes (superficial peritoneal and deep endometriosis), thus prohibiting attribution of risk to endometriomas independently. Only one study reported estimates for all three macro-phenotypes: endometrioma (RR = 2.56, 95% CI = 1.98–3.27), superficial peritoneal (RR = 1.32, 95% CI = 0.99–1.72) and deep endometriosis (RR = 1.41, 95% CI = 0.29–4.10) (Saavalainen *et al.*, 2018b). The association with endometrioma was significantly stronger than that for other endometriosis subtypes ($P = 0.03$), but again, these groups were not mutually exclusive, making the estimates difficult to interpret relative to each other.

Endometriosis and ovarian cancer heterogeneity.

Only one study has produced risk estimates cross-tabulated by both histotype of ovarian cancer and macro-phenotypic type of endometriosis (Saavalainen *et al.*, 2018b). Saavalainen *et al.* found that endometrioma was positively associated with the clear cell (SIR = 10.1), endometrioid (SIR = 4.7) and serous (SIR = 1.62) histotypes; superficial peritoneal endometriosis was also associated with these ovarian cancer histotypes, but with a lower magnitude of effect (SIRs = 2.67, 2.03 and 1.32, respectively); while deep endometriosis was not associated with ovarian cancer risk (SIRs = 0.00, 3.35 and 1.41, respectively,

although CIs were very wide due to lack of power given the small number of cases with deep endometriosis). Again, a limitation of this important contribution was that the histotypes were not mutually exclusive.

Breast cancer

A total of 20 studies were included in the analysis of the association between endometriosis and breast cancer risk (Moseson *et al.*, 1993; Venn *et al.*, 1999; Weiss *et al.*, 1999; Baron *et al.*, 2001; Olson *et al.*, 2002; Borgfeldt and Andolf, 2004; Bertelsen *et al.*, 2007; Melin *et al.*, 2007; Nichols *et al.*, 2011; Morales *et al.*, 2013; Brinton *et al.*, 2014; Chuang *et al.*, 2015; Mogensen *et al.*, 2016; Farland *et al.*, 2016a; Saavalainen *et al.*, 2018a; Saraswat *et al.*, 2018; Surrey *et al.*, 2018; Williams *et al.*, 2018; Hsu *et al.*, 2019; Lundberg *et al.*, 2019), yielding a very small and borderline-statistically significant SRR of 1.04 (95% CI = 1.00–1.09) (Supplementary Fig. S4A, Table II), although with no evidence of publication bias (Egger's test: $P = 0.53$; Begg's test: $P = 0.81$). We detected a moderate level of heterogeneity among studies ($I^2 = 59\%$, $P = 0.001$), but the magnitude of difference was small when stratified by study design, geographic location (although studies from Asia were an outlier (SRR = 1.41, 95% CI = 1.14–1.75, $I^2 = 0\%$, $P = 0.54$)), endometriosis case ascertainment or ROBINS-I risk of bias (Table II). The SRR for breast cancer was also similar among studies that included only populations of women with infertility (SRR = 1.02, 95% CI = 0.97–1.07, $I^2 = 0\%$, $P = 0.72$; data not shown). The influence analysis showed no substantial influence of any of the included studies on the global estimate (Supplementary Fig. S4B).

Despite the well-established difference in risk factor profile, cancer characteristics and prognosis by breast cancer tumour subtypes (Rosner *et al.*, 2013; Farland *et al.*, 2016a), only two studies assessed associations by breast cancer subtype. Farland *et al.* reported a positive association between endometriosis and oestrogen receptor-positive (ER+)/progesterone receptor-negative (PR−) breast cancer (ER+/PR−: HR = 1.90, 95% CI = 1.44–2.50), but no association with ER+/PR+ or ER−/PR− tumours ($P_{heterogeneity} = 0.001$). Results were also similar for premenopausal (HR = 1.05, 95% CI = 0.89–1.23) and postmenopausal breast cancer (HR = 0.93, 95% CI = 0.80–1.07), and among postmenopausal women, results did not change by type of menopause (natural menopause: HR = 1.06, 95% CI = 0.80–1.36; surgical menopause: HR = 0.90, CI = 0.75–1.09) (Farland *et al.*, 2016a). Mogensen *et al.* (2016) reported no difference in association with ductal (SIR = 1.04, 95% CI = 0.97–1.10) versus lobular tumours (SIR = 1.10, 95% CI = 0.98–1.33), with both effect estimates of a magnitude similar to that observed for breast cancer risk overall. No study has evaluated the association with breast cancer by endometriosis subtypes.

Endometrial cancer

Based on 17 studies (Venn *et al.*, 1999; Olson *et al.*, 2002; Borgfeldt and Andolf, 2004; Brinton *et al.*, 2005a,b; Melin *et al.*, 2007; Fortuny *et al.*, 2009; Zucchetto *et al.*, 2009; Rowlands *et al.*, 2011; Kok *et al.*, 2015; Mogensen *et al.*, 2016; Poole *et al.*, 2017; Saavalainen *et al.*, 2018b; Saraswat *et al.*, 2018; Surrey *et al.*, 2018; Williams *et al.*, 2018; Lundberg *et al.*, 2019), the association between endometriosis and endometrial cancer yielded a non-statistically significant SRR of 1.23 (95% CI = 0.97–1.57), with a high level of heterogeneity among studies ($I^2 = 81\%$, $P < 0.0001$) (Table II, Supplementary Fig. S5A). This heterogeneity was not explained by cohort (SRR = 1.25, 95% CI = 0.96–1.62, $I^2 = 79\%$, $P < 0.0001$) versus case-control study design (SRR = 1.29, 95% CI = 0.65–2.54, $I^2 = 85\%$, $P < 0.0001$; $P_{heterogeneity} = 0.89$)—although the within-design heterogeneity was high. We indeed observed that the association was consistently null among prospective cohort studies, which rigorously required temporality (i.e. endometriosis must have been diagnosed prior to the diagnosis of endometrial cancer) and among which there was no longer any heterogeneity (n = 5 studies, SRR = 0.99, 95% CI = 0.72–1.37, $I^2 = 0\%$, $P = 0.51$) (Table II) (Olson *et al.*, 2002; Brinton *et al.*, 2005b; Poole *et al.*, 2017; Saraswat *et al.*, 2018; Williams *et al.*, 2018). This is in contrast to the retrospective cohort studies (Venn *et al.*, 1999; Brinton *et al.*, 2005a; Melin *et al.*, 2007; Kok *et al.*, 2015; Mogensen *et al.*, 2016; Saavalainen *et al.*, 2018b; Surrey *et al.*, 2018; Lundberg *et al.*, 2019) (n = 8 studies, SRR = 1.40, 95% CI = 1.00–1.96, $I^2 = 86.8\%$, $P < 0.0001$) (Table II), with a stronger attenuation than when the meta-analysis was restricted to the studies that, regardless of design, required temporality (Venn *et al.*, 1999; Olson *et al.*, 2002; Brinton *et al.*, 2005a,b; Melin *et al.*, 2007; Kok *et al.*, 2015; Poole *et al.*, 2017; Saavalainen *et al.*, 2018b; Saraswat *et al.*, 2018) (n = 9 studies, SRR = 1.11, 95% CI = 0.96–1.27, $I^2 = 0\%$, $P = 0.56$) (Fig. 3). Three studies (Rowlands *et al.*, 2011; Mogensen *et al.*, 2016; Williams *et al.*, 2018) presented sensitivity analyses that reported estimates of the endometriosis and endometrial cancer association after restricting analyses to women whose endometriosis was diagnosed more than 12 months before her endometrial cancer diagnosis. When shifting these three studies from the strata of studies that did not require temporality to the strata that required temporality and including these revised study-specific estimates in the temporality-specific meta-analysis, the SRR was almost halved—reducing from the original SRR of 1.23 to SRR = 1.16 (95% CI = 1.02–1.31, $I^2 = 6\%$, $P = 0.39$) (data not shown), similar to the original estimate among the studies requiring temporality (SRR = 1.11) (Fig. 3).

In sensitivity analyses excluding the most influential studies, the SRR ranged from 1.15 (95% CI = 0.93–1.41) when excluding the Mogensen *et al.* (2016) study to 1.31 (95% CI = 1.05–1.65) when excluding the Borgfeldt and Andolf (2004) study (Supplementary Fig. S5B). There was no evidence of publication bias (Egger's test: $P = 0.85$; Begg's test: $P = 0.25$).

Two studies have attempted to evaluate the relationships between endometriosis and endometrial cancer subtypes. Mogensen *et al.* (2016) reported a stronger association for type I (SIR = 1.54, 95% CI = 1.20–1.96) versus type II (SIR = 1.06, 95% CI = 0.28–2.71) tumours, although CIs were wide for type II tumours and included the SIR and the full CI range observed for type I tumours. Brinton *et al.* (2005b) reported a similar difference in association for both common indolent types (RR = 1.14) and uterine sarcomas (RR = 2.72); cases of carcinosarcoma and aggressive types of endometrial cancer were too few to quantify an association with endometriosis.

Skin cancer

Cutaneous melanoma.

A total of seven studies were included in the analysis for cutaneous melanoma (Holly *et al.*, 1995; Young *et al.*, 2001; Olson *et al.*, 2002; Brinton *et al.*, 2005a; Melin *et al.*, 2007; Farland *et al.*, 2017; Saavalainen *et al.*, 2018a), for which the summary association with

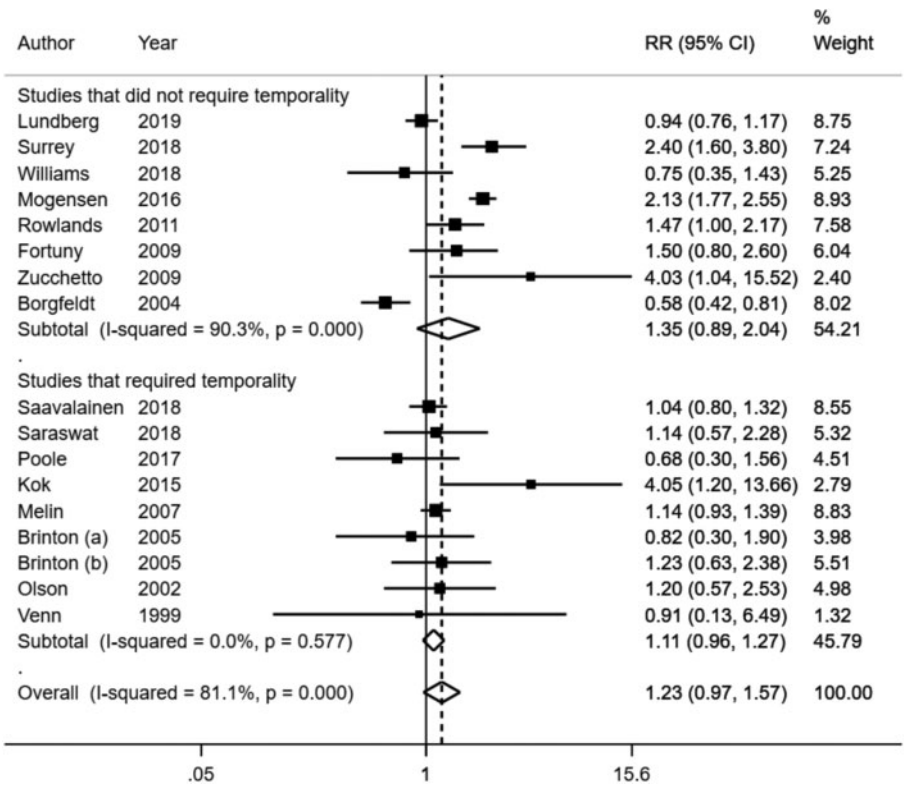

Figure 3. Evaluation of the association between endometriosis and endometrial cancer risk among 17 studies published through 2019; eight that did not require temporality in the analyses and nine that did (i.e. endometriosis diagnosis had to precede the endometrial cancer diagnosis, not diagnosed concurrently). *Note: Brinton (a) conducted in the USA and Brinton (b) conducted in Denmark. *P* = *P*-value, test for between-study heterogeneity.

endometriosis was a modest non-significant SRR = 1.17 (95% CI = 0.97–1.41) (Supplementary Fig. S6, Table III) and no evidence of publication bias was found (Egger's and Begg's tests: $P = 0.88$). There was a moderate level of heterogeneity among studies ($I^2 = 51\%$, $P = 0.05$). There were slightly higher levels of heterogeneity when comparing studies conducted in Europe (SRR = 1.21, 95% CI = 0.99–1.48, $I^2 = 69\%$, $P = 0.04$) versus North America (SRR = 1.07, 95% CI = 0.57–2.01, $I^2 = 57\%$, $P = 0.09$). However, here again, the heterogeneity appeared to be attributed to ROBINS-I risk of bias (low or moderate: SRR = 1.71, 95% CI = 1.24–2.36, $I^2 = 0\%$, $P = 0.59$; serious or critical: SRR = 1.08, 95% CI = 0.87–1.26, $I^2 = 32\%$, $P = 0.21$), with the statistically significant association observed among studies with low/moderate bias. The test for heterogeneity comparing the endometriosis to melanoma association between the two risk of bias categories was of borderline statistical significance ($P_{heterogeneity} = 0.07$). Only one study provided estimates by tumour characteristics and reported no statistically significant differences according to melanoma subtype or primary tumour body site (Farland *et al.*, 2017).

Basal-cell carcinoma.

Only two studies have assessed the association between endometriosis and the risk of basal-cell carcinoma (Farland *et al.*, 2017; Saavalainen *et al.*, 2018a). The analysis yielded an SRR of 1.18 (95% CI = 1.11–1.25), with no detected heterogeneity ($I^2 = 0\%$, $P = 0.89$) (Supplementary Table SII).

Thyroid cancer

The analysis of the association between endometriosis and thyroid cancer included five studies (Brinton *et al.*, 2005a,b; Melin *et al.*, 2007; Braganza *et al.*, 2014; Guenego *et al.*, 2018), producing an SRR of 1.39 (95% CI = 1.24–1.57) (Fig. 4, Table III). This was the most robust positive cancer association, with no evidence of heterogeneity ($I^2 = 0\%$, $P = 0.69$) or publication bias (Egger's test: $P = 0.69$; Begg's test: $P = 0.49$), and most studies considering temporality (n = 4 studies).

Colorectal cancer

Based on five studies (Olson *et al.*, 2002; Brinton *et al.*, 2005a; Melin *et al.*, 2006; Kok *et al.*, 2015; Saavalainen *et al.*, 2018a), our analysis yielded an SRR of 1.00 (95% CI = 0.87–1.16) for the association between endometriosis and colorectal cancer risk, with no evidence of publication bias (Egger's test: $P = 0.49$; Begg's test: $P = 0.21$) and low heterogeneity among studies ($I^2 = 40\%$, $P = 0.16$) (Supplementary Fig. S7). However, the association was positive (SRR = 2.29) and of borderline statistical significance, although with a wide CI (95% CI = 1.00–

Table III SRRs and 95% CIs for the associations between endometriosis and risk of non-hormone-dependent cancers, by cancer type for those cancer types with at least four studies published through 2019.

	Number of studies	SRR (95% CI)	I^2 (%)	P^a_{within}	$P^b_{between}$
Cutaneous melanoma					
All studies	7	1.17 (0.97–1.41)	51.3	0.05	
By study design					
Case control	1	0.86 (0.53–1.40)	–-	–-	0.25
Cohort	6	1.21 (0.99–1.48)	53.7	0.06	
Retrospective cohort	3	1.17 (0.96–1.44)	61.8	0.07	0.40
Prospective cohort	2	1.16 (0.52–2.16)	53.5	0.12	
By geographic location					
North America	3	1.07 (0.57–2.01)	56.7	0.09	0.59
Europe	3	1.21 (0.99–1.48)	69.3	0.04	
Asia	0	–-	–-	–-	
Australia	1	0.62 (0.16–2.41)	–-	–-	
Multiple locations	0	–-	–-	–-	
By assessment of endometriosis					
Self-reported	3	0.82 (0.53–1.27)	0.0	0.66	0.18
Medical records/registry	4	1.24 (1.01–1.52)	58.2	0.05	
Required temporality[c]					
No	3	1.11 (0.63–1.96)	63.7	0.06	0.87
Yes	4	1.15 (0.94–1.40)	53.1	0.09	
ROBINS-I risk of bias					
Low/moderate	2	1.71 (1.24–2.36)	0.0	0.59	0.07
Serious/critical	5	1.08 (0.93–1.26)	31.9	0.21	
Thyroid cancer					
All studies	5	1.39 (1.24–1.57)	0.0	0.69	
By study design					
Case control	0	–-	–-	–-	–-
Cohort	5	1.39 (1.24–1.57)	0.0	0.69	
Retrospective cohort	3	1.42 (1.25–1.60)	0.0	0.41	0.53
Prospective cohort	2	1.26 (0.91–1.74)	0.0	0.98	
By geographic location					
North America	3	1.65 (0.73–3.76)	40.6	0.19	0.86
Europe	3	1.39 (1.23–1.57)	0.0	0.77	
Asia	0	–-	–-	–-	
Australia	0	–-	–-	–-	
Multiple locations	0	–-	–-	–-	
By assessment of endometriosis					
Self-reported	2	1.26 (0.94–1.70)	0.0	0.96	0.56
Medical records/registry	4	1.40 (1.24–1.58)	0.0	0.55	
Required temporality[c]					
No	1	1.26 (0.85–1.86)	–-	–-	0.52
Yes	4	1.41 (1.25–1.59)	0.0	0.58	
ROBINS-I risk of bias					
Low/moderate	2	1.62 (0.74–3.55)	45.5	0.18	0.82
Serious/critical	3	1.40 (1.24–1.58)	0.0	0.82	
Colorectal cancer					
All studies	5	1.00 (0.87–1.16)	39.8	0.15	
By study design					

Continued

Table III Continued

	Number of studies	SRR (95% CI)	I^2 (%)	P^a_{within}	$P^b_{between}$
Case control	0	–-	–-	–-	
Cohort	5	1.00 (0.87–1.16)	39.8		
Retrospective cohort	4	1.03 (0.91–1.16)	29.1	0.24	0.28
Prospective cohort	1	0.73 (0.48–1.11)	–-	–-	
By geographic location					
North America	2	1.08 (0.41–2.83)	68.9	0.07	0.53
Europe	2	1.01 (0.93–1.10)	0.0	0.55	
Asia	1	2.99 (0.72–12.46)	–-	–-	
Australia	0	–-	–-	–-	
Multiple locations	0	–-	–-	–-	
By assessment of endometriosis					
Self-reported	4	1.03 (0.91–1.16)	29.1	0.24	0.28
Medical records/registry	1	0.73 (0.48–1.11)	–-	–-	
Required temporality[c]					
No	5	1.00 (0.87–1.16)	39.8	0.15	
Yes	0	–-	–-	–-	
ROBINS-I risk of bias					
Low/moderate	2	2.29 (1.00–5.26)	0.0	0.65	0.15
Serious/critical	3	1.00 (0.90–1.10)	24.6	0.26	
Colorectal cancer subtypes					
Colon	3	0.96 (0.86–1.07)	0.9	0.37	0.48
Small intestine	2	1.19 (0.82–1.73)	0.0	0.57	
Rectal	2	1.09 (0.96–1.25)	0.0	0.54	
Cervical cancer					
All studies	4	0.68 (0.56–0.82)	0.0	0.76	
By study design					
Case control	1	0.57 (0.37–0.89)	–-	–-	0.39
Cohort	3	0.71 (0.57–0.88)	0.0	0.80	
Retrospective cohort	2	0.73 (0.58–0.92)	0.0	0.78	0.42
Prospective cohort	1	0.60 (0.34–1.07)	–-	–-	
By geographic location					
North America	0	–-	–-	–-	–-
Europe	4	0.68 (0.56–0.82)	0.0	0.76	
Asia	0	–-	–-	–-	
Australia	0	–-	–-	–-	
Multiple locations	0	–-	–-	–-	
By assessment of endometriosis					
Self-reported	0	–-	–-	–-	–-
Medical records/registry	4	0.68 (0.56–0.82)	0.0	0.76	
Required temporality[c]					
No	1	0.57 (0.37–0.89)	–-	–-	0.39
Yes	3	0.71 (0.57–0.88)	0.0	0.80	
ROBINS-I risk of bias					
Low/moderate	1	0.60 (0.34–1.08)	–-	–-	0.69
Serious/critical	3	0.69 (0.56–0.85)	0.0	0.61	

I^2 (%) is a measure of the proportion of the heterogeneity attributed to between-study variation rather than due to chance. I^2-values of 25%, 50% and 75% indicate low, moderate and high between-study heterogeneity, respectively.

[a]*P*-value testing for heterogeneity among the studies within each cancer type.

[b]*P*-value testing for between subgroup or category heterogeneity generated from meta-regression analysis.

[c]Studies were considered to have required temporality (i.e. 'yes') if the endometriosis diagnosis had to precede the cancer diagnosis (i.e. they were not diagnosed at the same time) within the analyses.

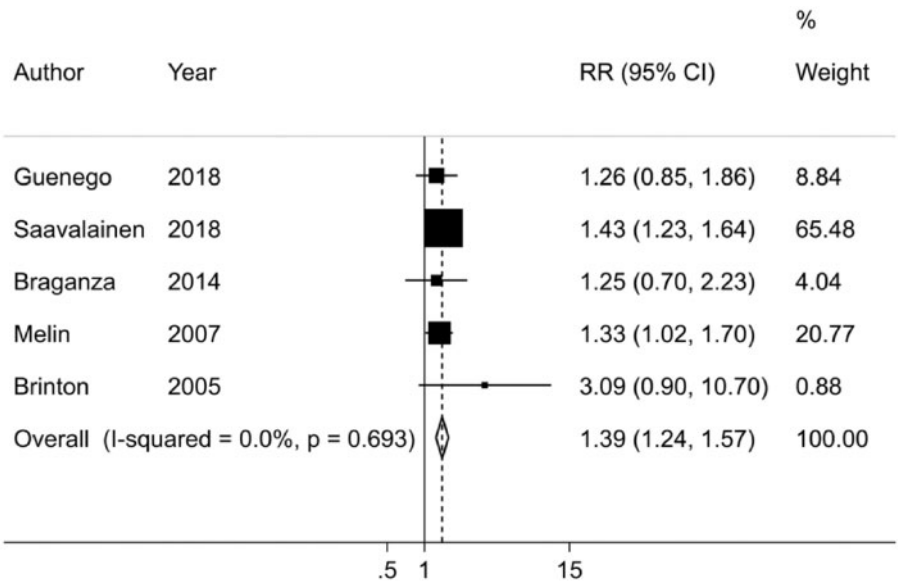

Figure 4. Evaluation of the association between endometriosis and thyroid cancer risk among five studies published through 2019. *P* = *P*-value, test for between-study heterogeneity.

5.26) when the analysis was restricted to studies with low or moderate risk of bias (Table III).

Cervical cancer

Four studies were included in the analysis of endometriosis in relation to cervical cancer (Borgfeldt and Andolf, 2004; Melin *et al.*, 2007; Saavalainen *et al.*, 2018b; Saraswat *et al.*, 2018), which yielded a robust statistically significant SRR of 0.68 (95% CI = 0.56–0.82) (Fig. 5). We detected no heterogeneity among studies (I^2 = 0%, P = 0.76) or publication bias (Egger's test: P = 0.37; Begg's test: P = 0.50). Of note, all studies were conducted in European countries and all ascertained endometriosis case definition based on self-report (Table III).

Other cancer types

The risk of several other cancer types was assessed in relation to endometriosis but based on three or fewer studies: lymphatic and haematopoietic cancers (SRR = 1.09, 95% CI = 1.00–1.19; I^2 = 86%, P = 0.007; n = 2 studies (Melin *et al.*, 2007; Saavalainen *et al.*, 2018a)); non-Hodgkin lymphoma (SRR = 1.18, 95% CI = 1.00–1.41; I^2 = 41%, P = 0.18; n = 3 studies (Olson *et al.*, 2002; Melin *et al.*, 2006; Saavalainen *et al.*, 2018a)); leukaemia (SRR = 1.07, 95% CI = 0.88–1.31; I^2 = 14%, P = 0.28; n = 2 studies (Melin *et al.*, 2006; Saavalainen *et al.*, 2018a)); lung cancer (SRR = 0.94, 95% CI = 0.84–1.04; I^2 = 0%, P = 0.64; n = 3 studies (Olson *et al.*, 2002; Melin *et al.*, 2006; Saavalainen *et al.*, 2018a)); gastric cancer (SRR = 0.97, 95% CI = 0.81–1.18; I^2 = 0%, P = 0.52; n = 2 studies (Melin *et al.*, 2007; Saavalainen *et al.*, 2018a)); liver cancer (SRR = 1.05, 95% CI = 0.77–1.44; I^2 = 0%, P = 0.34; n = 2 studies (Melin *et al.*, 2006; Saavalainen *et al.*, 2018a); pancreatic cancer (SRR = 0.96, 95% CI = 0.61–1.50; I^2 = 86%, P = 0.008; n = 2 studies (Melin *et al.*, 2007; Saavalainen *et al.*, 2018a)); urinary cancer (SRR = 0.99, 95% CI = 0.83–1.18; I^2 = 0%, P = 0.60; n = 2 studies (Olson *et al.*, 2002; Saavalainen *et al.*, 2018b)); bladder cancer (SRR = 0.94, 95% CI = 0.76–1.14; I^2 = 0%, P = 0.84; n = 2 studies (Melin *et al.*, 2007; Saavalainen *et al.*, 2018b)); buccal cancer (SRR = 0.83, 95% CI = 0.45–1.55; I^2 = 86%, P = 0.007; n = 2 studies (Melin *et al.*, 2007; Saavalainen *et al.*, 2018b)); brain cancer (SRR = 1.18, 95% CI = 1.02–1.36; I^2 = 49%, P = 0.16; n = 2 studies (Melin *et al.*, 2007; Saavalainen *et al.*, 2018a); and renal cancer (SRR = 1.20, 95% CI = 0.93–1.55; I^2 = 66%, P = 0.09; n = 2 studies (Melin *et al.*, 2007; Saavalainen *et al.*, 2018a)) (Supplementary Table SII).

Discussion

The present meta-analysis reviewed 49 cohort or case-control studies on endometriosis and cancer risk published through October 2019. While prior research has focused primarily on gynaecologic cancers (ovarian cancer: n = 24 studies; breast cancer: n = 20 studies; endometrial cancer: n = 17 studies), investigation of other cancer sites has been limited (n = 2–7 studies). The included studies in this meta-analysis varied by type of population and source of the unexposed group, and most were subject to bias; based on the ROBINS-I tool, only 23/49 studies had low/moderate risk of bias, while 26/49 studies had serious or critical risk of bias. Sensitivity analyses stratified by sample population and study design characteristics yielded some markedly different SRR effect estimate magnitudes; however, given the small number of papers contributing to most subgroup analyses, power to detect statistically significant heterogeneity among categories was often low.

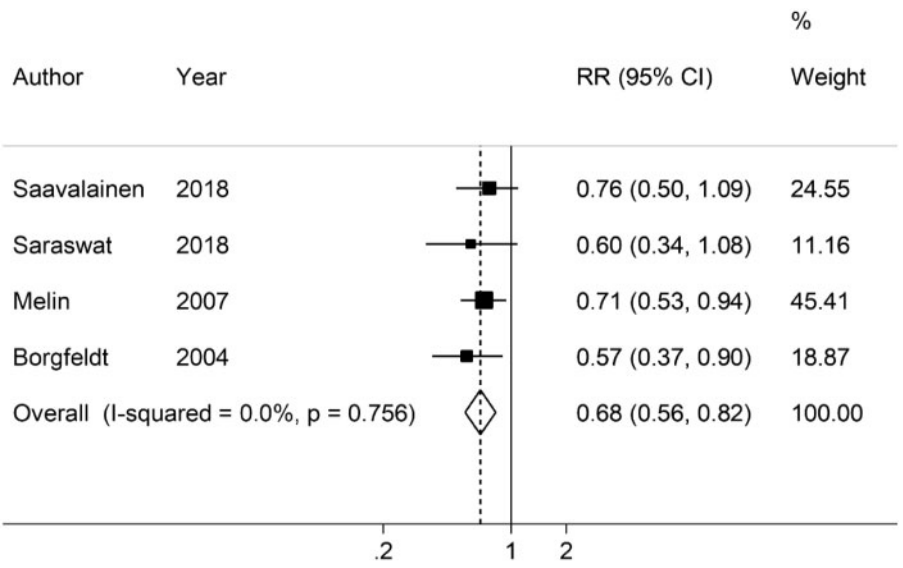

Figure 5. Evaluation of the association between endometriosis and cervical cancer risk among four studies published through 2019. *P* = *P*-value, test for between-study heterogeneity.

Associations between endometriosis and cancer

In the present meta-analysis, we confirmed that endometriosis was associated with a 1.9-fold greater risk of ovarian cancer compared with women without endometriosis, with higher magnitudes and consistency of risk for clear cell (3.4-fold) and endometrioid (2.3-fold) histotypes of ovarian cancer. Unfortunately, study heterogeneity was high and publication bias was evident. Risk was potentially driven by those with an endometrioma, although exclusion of risk for other endometriosis macro-phenotypes could not be determined.

Endometriosis was also associated with a very small (4%) but borderline-statistically significant higher risk of breast cancer. Although derived from a much smaller body of literature (n = 5 studies), endometriosis was associated with a 39% greater risk of thyroid cancer with little heterogeneity identified among studies. The relationship with endometrial cancer, although reported as statistically significantly positive in a previous meta-analysis, was strongly attenuated in this analysis and not statistically significantly associated with endometriosis when temporality was rigorously addressed to reduce the high risk of diagnostic bias. The most robust association observed was a highly significant 32% lower risk of cervical cancer for women with endometriosis compared with those without.

Ovarian cancer.

The present meta-analysis calculated a 93% greater risk of ovarian cancer among women with endometriosis compared with those without, which is a higher magnitude than those yielded in two earlier meta-analyses (Kim *et al.*, 2014: SRRs = 1.27–1.80; Wang *et al.*, 2016: OR = 1.42) (Kim *et al.*, 2014; Wang *et al.*, 2016), but similar to that in Li *et al.*'s (2019: SRR = 1.96). However, compared with our meta-analysis, these earlier works either considered some study samples twice (where we restricted to the most recent publication from the same study population), included cross-sectional studies, and/or considered a single study several times when including risk estimates presented for multiple subgroups. Of note, an analysis by geographic location showed a 4-fold increased ovarian cancer risk in women with endometriosis in Asia. However, this result is likely driven by the known higher prevalence of clear cell ovarian cancers in Asian women (Coburn *et al.*, 2017; Lee *et al.*, 2019), which unfortunately could not be verified in our analysis as estimates by ovarian cancer histotype were not available in the Asian studies.

Of critical importance to translation of these results to women with endometriosis, the clinicians who provide care, scientists considering future studies—and perhaps a warning for journal editors is that there was strong evidence for publication bias. This suggests an overestimation of the magnitude of the association between endometriosis and ovarian cancer. This may be driven by a belief by reviewers and editors that any study that does not demonstrate this positive association is incorrect, but it may also reflect that as ovarian cancer is very rare, extremely large cohort sample sizes or multi-site case-control studies are needed to yield power to quantify statistical significance that is too often the focus (Farland *et al.*, 2016b; Greenland *et al.*, 2016; Rothman, 2016; Wasserstein and Lazar, 2016; Amrhein *et al.*, 2019). Publication bias is a threat to future studies of endometriosis and other cancer types as well if assumptions about their relationship with endometriosis also become engrained, as it may have for ovarian cancer.

We also detected a high level of heterogeneity among studies that was in part driven by ovarian cancer histotype—reinforcing that the higher risk of ovarian cancer in women with endometriosis is restricted to the clear cell and endometrioid histotypes, and future studies should focus on these histotypes rather than on ovarian cancer overall. While we found no evidence of publication bias in analyses by ovarian cancer histotype, it is important to note that the tests are likely to be underpowered among the small number of publications that included

these histotypes; we thus cannot rule out publication bias in associations by subgroup also.

Some have posited that the endometrioma macro-phenotypic subtype of endometriosis is the primary pathway for neoplastic transformation (Lac et al., 2019a,b). However, only four studies quantified endometrioma-specific risk of ovarian cancer, all of which were underpowered. Furthermore, the estimates included endometrioma regardless of the co-occurrence of other endometriosis macro-phenotypes (i.e. superficial peritoneal or deep endometriosis); none of the studies were able to restrict risk estimation to presence of endometrioma exclusively. Superficial peritoneal and deep endometriosis are also associated with a peritoneal environment (e.g. hyper-inflammatory) (Zondervan et al., 2020) amenable for malignant transformation and need to be considered in light of the non-ovarian origin for many ovarian cancers (Vaughan et al., 2011). Equally importantly, since endometrioma is more likely to be visualized at diagnostic imaging than other endometriosis subtypes (Dunselman et al., 2014), a diagnostic bias specific to endometrioma is likely in this association, which may further bias the results. Moreover, endometriosis is presumably more likely to be identified and the ovary visualized in women with ovarian cancer than in those without (which also further reinforces the importance of taking temporality into account). This diagnostic bias critically needs to be explored in future research in order to determine whether the association between endometriosis and ovarian cancer is restricted to a specific endometriosis subtype.

Some pathologists have argued that endometrioma should be considered a pre-cancerous lesion. Endometrioma and ovarian cancer share common molecular alterations and somatic mutations (Ruderman and Pavone, 2017). However, the prevalence of cancer driver mutations in deep endometriosis lesions is suggested to be identical to that of endometrioma (Anglesio et al., 2017), and since deep endometriosis is not linked to ovarian cancer (Saavalainen et al., 2018b), we would have expected a significantly higher prevalence of these mutations in endometriomas to attribute causality. Furthermore, it must be considered that cancer driver mutations are also observed at high proportions in eutopic endometrium from healthy women (Lac et al., 2019a). More targeted research that focuses on both endometriosis macro-phenotypic subtypes and restricts to the ovarian cancer histotypes with evidence of association with endometriosis is needed. It is possible that all endometriosis phenotypes arise from or catalyse local and systemic changes that increase the risk of clear cell or endometrioid ovarian cancer, but endometriomas have a unique (Yland et al., 2019) additional neoplastic transformation pathway with the highest magnitude of risk.

Endometrial cancer.

In our study, the association with endometrial cancer varied greatly in sensitivity analyses, with high between-study heterogeneity and evidence of impact by methodologic considerations among the included studies. While the overall estimate suggested a 23% greater risk of endometrial cancer in women with endometriosis, the relationship was not statistically significant—similar to that reported in a recent meta-analysis (17% (Li et al., 2019)), but not in another in which the magnitude of the relation was higher and statistically significant (38% (Gandini et al., 2019)). One source of heterogeneity among the meta-analyses may be differing approaches to inclusion/exclusion of studies without adjustment for potential confounders. BMI in particular is a known risk factor for both endometriosis (higher risk for those with lean body size) (Shafrir et al., 2018) and endometrial cancer (higher risk for those with overweight or obese body size) (Renehan et al., 2008) and must be accounted for to generate valid risk estimates.

More clearly, in the present meta-analysis, the association remained of similar magnitude and borderline statistical significance when restricting to retrospective studies. However, the positive association disappeared entirely in further subgroup analyses; there was a ~10–25% decrease in the SRR estimation when carefully considering temporality, i.e. endometriosis must be diagnosed prior to the endometrial cancer diagnosis to invoke risk or causal inference. These differences suggest that, while endometriosis may be present at the time of endometrial cancer diagnosis over a woman's lifetime, heightened detection of endometriosis during the evaluation for endometrial cancer (compared with women who are not undergoing an evaluation for endometrial cancer) may be driving this association. These conflicting results remain an intriguing area for future study of both endometriosis and endometrial cancer physiology.

Cervical cancer.

Our analysis yielded a 32% lower risk of cervical cancer in women with endometriosis, which is consistent with the findings from previous meta-analyses (33% (Li et al., 2019) and 22% (Gandini et al., 2019)). However, the association between endometriosis and cervical cancer needs careful interpretation as there is an obvious sociologic mechanism. Women who reached an endometriosis diagnosis, by definition, have better than typical access to health care (Shafrir et al., 2018) and are more likely than women without endometriosis to be exposed to frequent gynaecologist visits. They therefore are also more likely to receive routine screening for, and detection and treatment of, cervical hyperplasia. Therefore, we hypothesize that this inverse association most likely does not reflect causality, but implies diagnostic and treatment bias. This shows the importance of taking into account the impact of the health-care system and access to care when assessing the associations between endometriosis and cancer. However, there are other feasible pathways that should be the target of future studies including if women with endometriosis have a lower prevalence of human papillomavirus (HPV) infection potentially due to the negative impact of dyspareunia and chronic pelvic pain on sexual relationships, or if there is altered cervical or vaginal physiology or local environmental milieu that could protect against distal neoplastic transformation.

Other cancers.

Our results suggest that endometriosis is associated with breast cancer at a very low magnitude (4% higher risk compared with women without endometriosis). This estimate is consistent with that reported by Gandini et al. (2019). However, the majority of risk factors for breast cancer have clear subtype associations with emerging physiologic patterns, and therefore breast cancer can definitively not be treated as one entity (Glynn et al., 2019; Mavaddat et al., 2019; Vallvé-Juanico et al., 2019). Unfortunately, only one study has reported on the association with endometriosis by breast cancer subtypes; Farland et al. (2017) reported a 90% higher risk of ER+/PR− tumours in women with endometriosis, but a null association with other tumour subtypes. Future studies, similar to the emerging evidence for ovarian cancer, must attempt to identify variation in risk by breast cancer subtypes. Furthermore, we found a 39% higher risk of thyroid cancer in women

with endometriosis compared with women without endometriosis. The association with endometriosis may be another example of diagnostic bias, as in the USA, there has been a large increase in diagnosis of early-stage thyroid cancer that reflects over-diagnosis among those with high access to care (Jegerlehner *et al.*, 2017).

Regarding cutaneous melanoma, although the risk estimate was close to statistical significance, our results suggest no association between endometriosis and the risk of this cancer, consistent with those from Gandini *et al.* (2019). However, more than for any other cancer, the magnitude of the SRR and statistical significance was considerably higher when the meta-analysis was restricted to studies with low/moderate risk of bias. This suggests that, compared with the other cancers explored, biases may more strongly be masking a true association between endometriosis and cutaneous melanoma, which warrants continued high-quality future study. In contrast, in the present meta-analysis, there was also no evidence of an association with colorectal cancer, which had never been reported in previous meta-analyses, in the main or any sensitivity analysis. Our results also suggest no statistically significant association with haematopoietic, lung, gastric, liver, pancreatic, urinary tract, buccal or renal cancers, and a modest increased risk of brain cancer. However, the number of studies reporting risk estimates for these associations is very low; therefore, further research needs to be undertaken before any conclusion can be made.

Critical methodologic complexities to consider in the field

Using the ROBINS-I tool, the risk of bias was severe or critical for 53% of the 49 included studies investigating the association between endometriosis and cancer risk. Therefore, determination of the true magnitude of risk and precise statistical associations, and thus causal inference, is premature. Future studies attempting to yield valid estimates must incorporate the following key methodologic issues to advance this field.

Temporality.

If endometriosis is a causal factor contributing to the aetiology of cancer, then endometriosis must occur *before* the cancer. To ensure this temporal order, the use of a prospective cohort design is recommended, allowing for time-varying covariate analysis with duration of follow-up sufficiently long to allow for post-endometriosis cancer initiation and promotion. Nevertheless, retrospective designs (case-control or retrospective cohort studies) can validly require temporality by strictly defining the exposure to include only endometriosis diagnosed at least 1 year prior to cancer diagnosis. A longer window would be more conservative with respect to a biologically sound window for causal contribution to cancer development, while this window is more conservative with respect to retaining study sample size. Our meta-analytic findings indeed illustrate that taking temporality into account can dramatically change conclusions, as shown for the purported association between endometriosis and endometrial cancer. Documentation and incorporation of dates of diagnosis are thus essential and cross-sectional diagnosis is invalid for causal inference. Nonetheless, causal inference remains complex given our lack of knowledge regarding the natural history of endometriosis initiation and progression, together with long delays to surgically or radiologically visualized diagnosis and the more well understood but imprecise timing for onset of cancer. Ideally, given the current delay from symptom onset to diagnosis for endometriosis (Nnoaham *et al.*, 2011), we would further wish to explore the impact of a latency window relative to symptom onset; however, no study has yet included analysis by symptom timing. Accounting for time-varying potential confounders and consideration of effect modifiers associated with likelihood of, and time to, diagnosis will help to better elucidate the potential true associations.

Misclassification and population sampling.

Endometriosis has a high potential to be misclassified, either by being over-reported (in hospital/clinical-based studies) or under-reported (in population-based studies) (Ghiasi *et al.*, 2020). Indeed, investigations are able to document only those women who successfully achieved evaluation and diagnosis (Shafrir *et al.*, 2018). Because of the lack of a non-invasive diagnostic tool, diagnostic biases are likely driven by the characteristics of women who are able to access surgical or imaging diagnosis, or by the clinical symptoms characteristic of different endometriosis sub-phenotypic populations (Zondervan *et al.*, 2020). In addition, the potential for diagnostic bias is likely to change over time due to the beneficial evolution of diagnostic methods and definitions, changing awareness of endometriosis in the population, and improved access to care.

Given these detection biases, with current barriers to diagnosis, regardless of study design, there will always be undiagnosed cases of endometriosis included within the unexposed group of women, which will attenuate the quantified associations. This may be particularly impactful for studies of endometriosis and cancer as the proportion of undiagnosed cases will be larger as we move earlier in calendar time, and yet we need prospective studies of long duration to allow for the post-endometriosis window of cancer initiation, promotion and detection.

In addition, specific issues relate to the selection of the comparison/unexposed group in endometriosis studies (Missmer, 2019). While population-based studies are estimated to have a low risk of bias (Zondervan *et al.*, 2002), those basing the comparison group on a selected sample (women with infertility or who have undergone hysterectomy) have even lower levels of endometriosis misclassification. However, this selection introduces impactful biases that force comparison of endometriosis pathology to the other pathologies that brought the women into the restricted population (i.e. other causes of infertility) that also may be associated with cancer risk and thus drive the association to the null (Missmer, 2019).

Confounding and mediation.

As described in more detail below, it is important to evaluate if the associations under study are driven by common risk factors, should they precede both endometriosis and cancer (confounding) or be along the causal pathway between endometriosis and cancer (mediation).

Study robustness and study heterogeneity.

Statistically significant heterogeneity was observed among the endometriosis-associated literature for a large portion of cancer types (overall cancer risk and risk of ovarian, breast and endometrial cancers, with possible heterogeneity of borderline statistical significance for cutaneous melanoma risk). Heterogeneity was in part driven by

important limitations of many of the studies that resulted in high risk of bias (e.g. misclassification of endometriosis or cancer, temporality, confounding, missing data, population selection) and thus likely effect estimates that were at best inaccurate and at worst invalid. Heterogeneity was also contributed to by internally valid but comparatively different characteristics of the study-specific populations. From one population to another, we would expect true differences in the prevalence of endometriosis and in the incidence and distributions of different cancer types. For overall cancer risk in particular, the RR would be skewed to an inverse association if the population over-selected for cervical cancers, but skewed to a positive association if the population over-selected for ovarian cancers. Differences in other population characteristics may include confounding or mediating environmental exposures on one continent compared with another, the age distribution of the population, or access to care differences among populations that could be driven by different calendar time windows or by health-care infrastructure differences during comparable time periods. It is also important to highlight that the studies are skewed towards populations within Europe or of European descent, and thus, if risk heterogeneity by race/ethnicity or region exists, they are wholly absent or underpowered for discovery via meta-analysis of the current literature.

Endometriosis and cancer disease heterogeneity.

Very few studies were sufficiently powered to evaluate risk heterogeneity attributable to endometriosis phenotypes or to cancer subtypes. A large impediment is the lack of routine, harmonized documentation of endometriosis characteristics, whether macro-phenotype (endometrioma, superficial peritoneal or deep endometriosis) or revised American Society for Reproductive Medicine stage (Becker *et al.*, 2014) and its absence from International Classification of Diseases coding (Whitaker *et al.*, 2019). Recording (Becker *et al.*, 2014; Vitonis *et al.*, 2014) and using such data are critical, however, as identifying associations with the different forms of endometriosis may lead to new insights into the aetiology of the disease (Zondervan *et al.*, 2018, 2020). Our subgroup meta-analyses reinforced that the association between endometriosis and ovarian cancer was restricted to specific cancer subtypes (clear cell and endometrioid). However, only four studies examined the association with ovarian cancer according to endometriosis macro-phenotype, and none were able to provide estimates for any type exclusively. Beyond the association between endometriosis and cancer, very few studies overall have published estimates of the proportion of women with the different endometriosis macro-phenotypes, and existing estimates are likely biased because samples are unrepresentative of the overall population of cases. Indeed, among all women who reached an endometriosis diagnosis, only those with surgical visualization will have a valid representation of proportion with the three macro-subtypes present (i.e. for women diagnosed through imaging, superficial peritoneal endometriosis will be missed (Zondervan *et al.*, 2020)). In a recent study based on data from the Finnish Hospital Register, however, among 45 769 endometriosis cases with macro-phenotype data, 44% had superficial peritoneal endometriosis, 51% endometrioma and 5% deep endometriosis at index procedure; these subtype proportions were not exclusive of other subtypes (Saavalainen *et al.*, 2018b). This lack of data on endometriosis characterization reinforces the need to collect and report macro-phenotype data for endometriosis research globally.

Despite the well-established distinct highly informative cancer subtypes, few studies have quantified the association between endometriosis and cancer subtypes. For example, only two studies examined breast cancer subtype, one categorizing breast cancer cases by ER/PR tumour receptor status (Farland *et al.*, 2016a) and one by histologic type (Mogensen *et al.*, 2016). Two studies examined heterogeneity in the association with endometrial cancer—one by endometrial cancer histotype (Brinton *et al.*, 2005a) and one by type I/II tumour type (Mogensen *et al.*, 2016)). One study has quantified the relation between endometriosis and melanoma subtypes (Farland *et al.*, 2017). Only Kok *et al.* (2015) attempted to explore cancer risk (endometrial cancer) by endometriosis macro-phenotype. No study has evaluated cancer risk among women with extra-pelvic endometriosis.

One study produced cross-categorized risk estimates by macro-phenotype of endometriosis and ovarian cancer subtype (Saavalainen *et al.*, 2018b). An approach that includes estimates by different endometriosis and cancer types must become the seminal approach whenever possible going forward in order to fully explore disease heterogeneity. Until this specific body of literature expands, we will not have a clear understanding of the link between endometriosis and cancer risk. The difficulty is: from where will these required data come? Future research needs to focus on identifying heterogeneity that reflects informative effect modification or true endometriosis phenotypic or cancer type variation. The emerging ovarian cancer data provide early evidence of the latter, as study heterogeneity was no longer present in analyses stratified by ovarian cancer subtype.

Publication bias.

Our meta-analysis demonstrated strong evidence for publication bias in the association between endometriosis and ovarian cancer, which likely distorted the meta-analytic result by overestimating this association. This suggests that, while the body of literature focused on the relation between endometriosis and ovarian cancer is largest by far among all cancer type-specific exploration, it is skewed towards successful acceptance of studies showing a positive association. In order to obtain a true quantification of cancer risk in women with endometriosis, high-quality studies need to be published regardless of the direction or magnitude of their result (whether null, positive or inverse), so as to not mislead interpretation and mask truth.

Potential underlying mechanisms

Focusing where robust associations between endometriosis and cancers are observed that allow for generation of hypotheses regarding causal physiologic mechanisms, we first must consider if shared risk factors (e.g. genetic susceptibility or an associated patient characteristic or environmental exposure) are driving the association between endometriosis and cancer rather than a direct causal pathway. Cross-disease genetic correlation analyses, which use genome-wide association studies datasets, have reported loci common to endometriosis and ovarian cancer, again particularly with the clear cell, endometrioid and serous histotypes (Lu *et al.*, 2015; Lee *et al.*, 2016), and between endometriosis and endometrial cancer, with 13 loci identified as implicated in both diseases (Painter *et al.*, 2018). However, it is important to note that these studies did not explore variation in loci associations by method of endometriosis case ascertainment nor did they consider the potential influence of diagnostic biases.

Known shared risk factors between endometriosis and cancer include demographics, anthropometry, menstrual cycle characteristics, lifestyle and environmental toxins, which may confer classic confounding of the quantified association between the conditions if not accounted for in study design or statistical analyses. Too few studies adjusted for any potential confounders beyond age, let alone comparable confounding adjustment among the studies, to compare meta-analytic results stratified by the confounders considered in the study-specific multivariable analyses. However, when we restricted the analysis to those studies with low or moderate risk of bias, which were required by the ROBINS-I tool to consider potential confounders, the magnitude of associations was often strengthened, suggesting an overall negative confounding effect of such factors.

As noted above, the inverse association between endometriosis and cervical cancer may be unique in this footprint as it could be modified by selection bias towards a population with high access to care (women who reached an endometriosis diagnosis also have access to routine screening) or be mediated by the detrimental impact of endometriosis-specific symptoms on sexual health that may unintentionally lower risk of HPV infection (Johnson *et al.*, 2019).

It is possible that, independent of overlapping risk factors and their resulting neoplastic pathways, endometriosis has a causal effect on malignancy. Quantifying mediation between endometriosis and cancer risk would lend insight into the pathways to which these associations are attributable. Mediators—factors occurring after endometriosis but before the cancer that are along the potential causal pathways—may include infertility, depression, anxiety, chronic stress or endometriosis symptom-related lifestyle adaptations such as decreased physical activity (Sotelo *et al.*, 2014; Brinton, 2017; Tanbo and Fedorcsak, 2017; Shafrir *et al.*, 2018; McTiernan *et al.*, 2019; Brasil *et al.*, 2020), all of which are more common in women with endometriosis compared with women without and are also cancer risk factors.

Similarly, mediators may include treatment for endometriosis or endometriosis-associated symptoms (analgesics, oral contraceptives, progestins, GnRH agonists, lesion excision/ablation, hysterectomy, bilateral salpingo-oophorectomy (BSO)) that have been associated with risk of specific cancer types (Luo *et al.*, 2016; Iversen *et al.*, 2017; Barnard *et al.*, 2018; Vercellini *et al.*, 2018). Non-steroidal anti-inflammatory drug (NSAID) use is a potential mediator given that women with endometriosis more frequently use NSAIDs on a long-term basis compared with women without endometriosis, and NSAID use at high doses for durations over 10 years has been associated with ovarian cancer risk (Trabert *et al.*, 2019). These data may simply suggest that high-dose long-duration NSAID use is actually proxy for endometriosis, and thus formal mediation analyses would be beneficial. An example of the potential for quantifying mediation is the determination that, while women with endometriosis are more likely to undergo hysterectomy/oophorectomy compared with premenopausal women without endometriosis, these surgeries have also been associated with a higher risk of coronary heart disease (Howard *et al.*, 2005). Thus, a mediation analysis within the Nurses' Health Study II quantified that, while endometriosis was associated with a 1.62-fold higher risk of coronary heart disease, 42% of this association was mediated by (attributed to) hysterectomy/oophorectomy (Mu *et al.*, 2016).

Through these mediators or through other direct pathways, endometriosis may induce systemic changes that initiate or promote cancer or create a hospitable milieu, including chronic inflammation, aberrant immune response or aberrant hormonal milieu (Zondervan *et al.*, 2018). These pathways may underlie the greater risk of distal cancers, such as thyroid cancer or cutaneous melanoma, and also may underlie the greater risk of clear cell and endometrioid ovarian cancer if one exists for women with superficial peritoneal endometriosis only. Most pathology-focused discovery supports that endometriomas, particularly 'atypical' endometriomas, have the potential for neoplastic transformation to clear cell and endometrioid ovarian cancers that may be catalysed by interactive alterations in the ovarian microenvironment (Vercellini *et al.*, 2018).

The mechanisms underlying the differential associations observed between endometriosis and the risk of certain cancers (ovarian, breast, thyroid cancers) and not others need to be explored. To elucidate the pathways by which women with endometriosis appear to be at higher risk of some cancer types and not of others, cancer type-specific studies with low risk of bias must be added to the current body of literature, and emerging fundamental discoveries of -omic driven pathways must be associated with endometriosis-specific pathophysiologic patterns.

Informing women with endometriosis about their cancer risk

The reported link between endometriosis and cancer has, understandably, raised concerns in women with endometriosis. It is our responsibility to accurately inform and, where appropriate, reassure them with regards to their long-term cancer risk in context relative to women without endometriosis. For clinicians, these concerns raise practical issues for long-term management of patients endometriosis through adulthood and past the menopausal transition.

Recently, in an attempt to provide clinicians with tools to communicate accurately and effectively with patients about their risk of ovarian cancer, we argued that ovarian cancer is rare regardless of women's endometriosis status: the absolute risk to develop this neoplasm in the general population is 1.3% according to the National Cancer Institute Surveillance, Epidemiology, and End Results Program (National Cancer Institute, 2017). Translating the highest quantified RR from the meta-analyses conducted on ovarian cancer at the time of that commentary (SRR = 1.42), the absolute risk for women with endometriosis was 1.8%—just a 0.5% difference from women without endometriosis and still very low (Kvaskoff *et al.*, 2017). Updating this absolute estimate with the quantified risk estimate from the present meta-analysis (SRR = 1.93), this absolute risk increased to 2.5%, which is 1.2% higher than the absolute risk for women without endometriosis and still very low. Moreover, it is important to remind once again that the observed significant publication bias for the association between endometriosis and ovarian cancer, suggests that this risk is likely overestimated and thus the true absolute risk is likely smaller. As discussed above, data are needed to support the next critical calculations needed by women and clinicians—the endometrioma-specific absolute risk of clear cell or endometrioid ovarian cancer.

Furthermore, the absolute risk of developing breast cancer in any woman's lifetime is 12.8% (National Cancer Institute, 2017); applying the current study's meta-analytic result for endometriosis-associated risk of breast cancer (SRR = 1.04), this lifetime breast cancer risk translates to 13.3% for women with endometriosis. Finally, for thyroid cancer, the US National Cancer Institute stated lifetime absolute risk

of 1.3% translates (SRR = 1.39) to 1.8% for women with endometriosis. Therefore, while a statistically significant RR between endometriosis and these three types of cancer were confirmed in this meta-analysis, it is important to stress that based on the currently available evidence, the increase for women with endometriosis in terms of absolute cancer risk is very small.

Cancer screening and monitoring recommendations for clinicians

The report of a higher cancer risk in women with endometriosis could lead clinicians to offer more regular cancer screening to women with endometriosis. However, the results of this meta-analysis, which show 1% or smaller increases in the lifetime risks of ovarian, breast and thyroid cancers in women with endometriosis compared with those without, suggest that currently no resource utilizing cancer screening guideline should be made due to the presence of endometriosis alone. Screening guidelines are not only based on the incidence of disease but also on whether increased screening improves outcomes of patients (decreases morbidity and mortality). Therefore, even if the incidence was higher, unless there is documented benefit, we should not be screening.

The same recommendations for women in the general population apply to women with endometriosis, with heightened screening only for those with known non-endometriosis specific risk factors (e.g. family history of cancer, germline mutation predisposing to cancer risk). The American Cancer Society recommends regular screening for breast, cervical and colorectal cancers based on scientific evidence that shows these screenings save lives (American Cancer Society, 2018). Regular screening for ovarian cancer through serum CA-125 measurements or trans-vaginal ultrasound is not recommended, since randomized controlled trials have shown no benefit of these measures on early detection of ovarian cancer or mortality reduction (Buys *et al.*, 2011; Jacobs *et al.*, 2016). Significant harms have been documented for women receiving false-positive test results for ovarian cancer, such as unnecessary surgery, surgical complications, infections and cardiovascular or pulmonary complications (Buys *et al.*, 2011).

In the case of ovarian cancer, some have called for radical preventive measures to reduce risk, such as BSO. BSO is not recommended systematically to prevent ovarian cancer in women with endometriosis (Mallen *et al.*, 2018) and should be approached with caution. While BSO is recommended as an effective approach to reduce risk of ovarian cancer in high-risk women (i.e. those with a family history of ovarian or breast cancer, or with known germline mutation) (Berek *et al.*, 2010), BSO is associated with important long-term health risks (Parker *et al.*, 2009) of markedly higher incidence than the risk of ovarian cancer in women with average lifetime absolute risk. Premenopausal women undergoing BSO have a 162% increased risk of cardiovascular disease (Atsma *et al.*, 2006) and are at significantly higher risk, not just of cardiologic sequelae (hyperlipidaemia, cardiac arrhythmias, coronary heart disease), but also of depression, arthritis, asthma, chronic obstructive pulmonary disease and osteoporosis (Rocca *et al.*, 2016). In postmenopausal women, BSO is also associated with cardiovascular diseases as well as adverse effects on anxiety and sexual function (Chen *et al.*, 2013), fracture risk (Melton *et al.*, 2003), neurologic disorders and cognitive impairment (Parker, 2010). While the gynaecologic specialists caring for women with endometriosis are also on the front line for the diagnosis of—and all too often tragic care of women with—ovarian cancer, potentially obscuring its rarity, some gynaecologists might not be aware of the adverse non-reproductive health outcomes of women with endometriosis, and thus will often not be aware of the impact of BSO on the cardiovascular and other health consequences for their patients in the long term.

Furthermore, BSO does not save Quality-Adjusted Life Years (QALYs) and is not cost-effective in low-risk postmenopausal women (Manchanda *et al.*, 2015), which does not support recommending BSO in patients with endometriosis given their low lifetime absolute risk. We also cannot ignore this updated evidence that there are significant publication and diagnostic bias within the current body of endometriosis and ovarian cancer literature that may be influential. Indeed, the strong, consistent protective effect of endometriosis on cervical cancer risk—the most preventable form of cancer because of screening and early action when dysplasia is discovered—should make us pause when interpreting these associations in the context of endometriosis diagnosis that cannot yet be disentangled from access to health care.

Alternatively, if it is confirmed that subtypes of endometriomas, such as endometriomas with 'atypical' characteristics (Vercellini *et al.*, 2018), are associated with RR of clear cell or endometrioid ovarian cancer that is multiples higher than the current 'overall' endometriosis and ovarian cancer estimates, this may alter these conservative recommendations and suggest that those women with some endometriosis subtypes constitute a unique high-risk group markedly different in absolute risk from other women with and without endometriosis. Most of the studies referring to 'atypical' endometriosis come from pathologic studies of ovarian cancer cases showing 'atypical' endometrioma in the same woman. It remains untested whether these 'atypical' endometriomas are actual precursor lesions or if they are field effects of the proximal ovarian cancer tumour. Thus, care and long-term management decisions, of course, must vary according to the woman's personal and medical history, characteristics and other risk factors, and preferences after she is fully informed of the current evidence, balanced with known benefits and potential risks.

Conclusion

This meta-analysis quantified positive associations between endometriosis and ovarian, breast and thyroid cancers, but no association with colorectal cancers. The association with endometrial cancer was null with evidence of diagnostic bias, and that with cutaneous melanoma was restricted to studies with low/moderate risk of bias, while associations with other cancer types remain too sparsely documented. Overall, we conclude that the current evidence is influenced by high risk of bias in the majority of included studies.

Given their low absolute risk of ovarian, breast and thyroid cancers and the uncertainty with regards to their risk of other cancer types, general prevention messages may be delivered to patients with endometriosis: to be aware of well-demonstrated cancer risk factors and to focus on aspects of wellness demonstrated to reduce cancer risk (https://siteman.wustl.edu/prevention/ydr/). All women will benefit from recommendations to avoid smoking, maintain a healthy weight, exercise regularly, have a balanced diet with high intakes of fruits and vegetables, low intake of alcohol and use sun protection.

There are important public health and prevalent clinical care implications of the potential link between endometriosis and cancer; thus, additional rigorous investigations are high priority to advance knowledge for women with endometriosis. Future research on the association between endometriosis and ovarian cancer must eliminate publication bias and determine whether risk is restricted to the endometrioma macrophenotype. Indeed, for all endometriosis-associated cancer discovery, future research must target endometriosis macro-phenotypic subtypes and known cancer subtypes. That the association with cutaneous melanoma was only evident when studies were restricted to those with low risk of bias suggests that the definitive association has not yet been determined and warrants additional investigation. The lack of association with endometrial cancer is an intriguing area for future study of both endometriosis and endometrial cancer physiology, given the eutopic endometrial markers found in women with endometriosis that have been hypothesized to drive retrograde menstruation-related ectopic endometrial implantation and survival. That endometriosis has multiple neoplastic hallmarks and yet is not subject to uncontrolled growth may be elucidated through better understanding of the lack of an endometriosis and endometrial cancer association. Finally, the robust 'protective' association quantified between endometriosis and cervical cancer also warrants investigation to determine if it is a consequence of bias driven by access to care or if there is a true relationship with underlying protective physiologic mechanisms within women with endometriosis.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

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Authors' roles

M.K. and S.A.M. conceived and designed the study. Y.M.S-. drafted the analysis protocol, extracted the data and performed the statistical analysis. M.K. and Y.M.-S. selected the studies and assessed their quality and risk of bias. M.K. drafted the original manuscript. M.K., Y.M.S., L.V.F., N.S., K.L.T., H.R.H., H.R., C.M.B., S.A.S., K.T.Z., A.W.H. and S.A.M. contributed to the interpretation of data discussed in the manuscript, revised the manuscript and approved its final version.

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Conflict of interest

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References

American Cancer Society. *American Cancer Society Guidelines for the Early Detection of Cancer: Cancer Screening Guidelines | Detecting Cancer Early*. 2018 www.cancer.org/healthy/find-cancer-early/cancer-screening-guidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer.html (15 September 2020, date last accessed).

Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. *Nature* 2019;**567**:305–307.

Anglesio MS, Bashashati A, Wang YK, Senz J, Ha G, Yang W, Aniba MR, Prentice LM, Farahani H, Li Chang H *et al.* Multifocal endometriotic lesions associated with cancer are clonal and carry a high mutation burden. *J Pathol* 2015;**236**:201–209.

Anglesio MS, Papadopoulos N, Ayhan A, Nazeran TM, Noë M, Horlings HM, Lum A, Jones S, Senz J, Seckin T *et al.* Cancer-associated mutations in endometriosis without cancer. *N Engl J Med* 2017;**376**:1835–1848.

Atsma F, Bartelink M-L, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. *Menopause* 2006;**13**:265–279.

Barnard ME, Poole EM, Curhan GC, Eliassen AH, Rosner BA, Terry KL, Tworoger SS. Association of analgesic use with risk of ovarian

cancer in the nurses' health studies. *JAMA Oncol* 2018;**4**: 1675–1682.

Baron JA, Weiderpass E, Newcomb PA, Stampfer M, Titus-Ernstoff L, Egan KM, Greenberg ER. Metabolic disorders and breast cancer risk (United States). *Cancer Causes Control* 2001;**12**:875–880.

Becker CM, Laufer MR, Stratton P, Hummelshoj L, Missmer SA, Zondervan KT, Adamson GD, Adamson GD, Allaire C, Anchan R *et al*. World endometriosis research foundation endometriosis phenome and biobanking harmonisation project: I. Surgical phenotype data collection in endometriosis research. *Fertil Steril* 2014; **102**:1213–1222.

Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;**50**:1088–1101.

Berek JS, Chalas E, Edelson M, Moore DH, Burke WM, Cliby WA, Berchuck A; Society of Gynecologic Oncologists Clinical Practice Committee. Prophylactic and risk-reducing bilateral salpingo-oophorectomy: recommendations based on risk of ovarian cancer. *Obstet Gynecol* 2010;**116**:733–743.

Bertelsen L, Mellemkjær L, Frederiksen K, Kjær SK, Brinton LA, Sakoda LC, van Valkengoed I, Olsen JH. Risk for breast cancer among women with endometriosis. *Int J Cancer* 2007;**120**: 1372–1375.

Bodmer M, Becker C, Meier C, Jick SS, Meier CR. Use of metformin and the risk of ovarian cancer: a case–control analysis. *Gynecol Oncol* 2011;**123**:200–204.

Borgfeldt C, Andolf E. Cancer risk after hospital discharge diagnosis of benign ovarian cysts and endometriosis. *Acta Obstet Gynecol Scand* 2004;**83**:395–400.

Braganza MZ, González A. D, Schonfeld SJ, Wentzensen N, Brenner AV, Kitahara CM. Benign breast and gynecologic conditions, reproductive and hormonal factors, and risk of thyroid cancer. *Cancer Prev Res* 2014;**7**:418–425.

Brasil DL, Montagna E, Trevisan CM, La Rosa VL, Laganà AS, Barbosa CP, Bianco B, Zaia V. Psychological stress levels in women with endometriosis: systematic review and meta-analysis of observational studies. *Minerva Med* 2020;**111**: 90–102.

Brinton L, Westhoff C, Scoccia B, Lamb E, Althuis M, Mabie J, Moghissi K. Causes of infertility as predictors of subsequent cancer risk. *Epidemiology* 2005a;**16**:500–507.

Brinton LA. Fertility status and cancer. *Semin Reprod Med* 2017;**35**: 291–297.

Brinton LA, Gridley G, Persson I, Baron J, Bergqvist A. Cancer risk after a hospital discharge diagnosis of endometriosis. *Am J Obstet Gynecol* 1997;**176**:572–579.

Brinton LA, Lamb EJ, Moghissi KS, Scoccia B, Althuis MD, Mabie JE, Westhoff CL. Ovarian cancer risk associated with varying causes of infertility. *Fertil Steril* 2004;**82**:405–414.

Brinton LA, Sakoda LC, Sherman ME, Frederiksen K, Kjaer SK, Graubard BI, Olsen JH, Mellemkjaer L. Relationship of Benign Gynecologic Diseases to Subsequent Risk of ovarian and uterine tumors. *Cancer Epidemiol Biomarkers Prev* 2005b;**14**:2929–2935.

Brinton LA, Scoccia B, Moghissi KS, Westhoff CL, Niwa S, Ruggieri D, Trabert B, Lamb EJ. Long-term relationship of ovulation-stimulating drugs to breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 2014;**23**:584–593.

Buis CCM, Leeuwen F. V, Mooij TM, Burger CW; on behalf of the OMEGA Project Group. Increased risk for ovarian cancer and borderline ovarian tumours in subfertile women with endometriosis. *Hum Reprod* 2013;**28**:3358–3369.

Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, Reding DJ, Greenlee RT, Yokochi LA, Kessel B. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. *JAMA* 2011;**305**:2295–2303.

Chang W-H, Wang K-C, Lee W-L, Huang N, Chou Y-J, Feng R-C, Yen M-S, Huang B-S, Guo C-Y, Wang P-H. Endometriosis and the subsequent risk of epithelial ovarian cancer. *Taiwan J Obstet Gynecol* 2014;**53**:530–535.

Chen X, Guo T, Li B. Influence of prophylactic oophorectomy on mood and sexual function in women of menopausal transition or postmenopausal period. *Arch Gynecol Obstet* 2013;**288**:1101–1106.

Chuang S-C, Wu G-J, Lu Y-S, Lin C-H, Hsiung CA. Associations between medical conditions and breast cancer risk in Asians: a nationwide population-based study in Taiwan. *PLoS One* 2015;**10**: e0143410.

Coburn SB, Bray F, Sherman ME, Trabert B. International patterns and trends in ovarian cancer incidence, overall and by histologic subtype. *Int J Cancer* 2017;**140**:2451–2460.

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–188.

Dunselman GAJ, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, Heikinheimo O, Horne AW, Kiesel L, Nap A *et al*. ESHRE guideline: management of women with endometriosis. *Hum Reprod* 2014;**29**:400–412.

Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**:629–634.

Farland L, Tamimi R, Eliassen A, Spiegelman D, Hankinson S, Chen W, Missmer S. Laparoscopically confirmed endometriosis and breast cancer in the nurses' health study II. *Obstet Gynecol* 2016a; **128**:1025–1031.

Farland LV, Correia KF, Wise LA, Williams PL, Ginsburg ES, Missmer SA. P-values and reproductive health: what can clinical researchers learn from the American Statistical Association? *Hum Reprod* 2016b;**31**:2406–2410.

Farland LV, Lorrain S, Missmer SA, Dartois L, Cervenka I, Savoye I, Mesrine S, Boutron-Ruault M-C, Kvaskoff M. Endometriosis and the risk of skin cancer: a prospective cohort study. *Cancer Causes Control* 2017;**28**:1011–1019.

Fortuny J, Sima C, Bayuga S, Wilcox H, Pulick K, Faulkner S, Zauber AG, Olson SH. Risk of endometrial cancer in relation to medical conditions and medication use. *Cancer Epidemiol Biomarkers Prev* 2009;**18**:1448–1456.

Gandini S, Lazzeroni M, Peccatori FA, Bendinelli B, Saieva C, Palli D, Masala G, Caini S. The risk of extra-ovarian malignancies among women with endometriosis: a systematic literature review and meta-analysis. *Crit Rev Oncol Hematol* 2019;**134**:72–81.

Ghiasi M, Kulkarni MT, Missmer SA. Is endometriosis more common and more severe than it was 30 years ago? *J Minim Invasive Gynecol* 2020;**27**:452–461.

Glynn RJ, Colditz GA, Tamimi RM, Chen WY, Hankinson SE, Willett WW, Rosner B. Comparison of questionnaire-based breast cancer prediction models in the nurses' health study. *Cancer Epidemiol Biomarkers Prev* 2019;**28**:1187–1194.

Greenland S, Senn SJ, Rothman KJ, Carlin JB, Poole C, Goodman SN, Altman DG. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. *Eur J Epidemiol* 2016;**31**: 337–350.

Guenego A, Mesrine S, Dartois L, Leenhardt L, Clavel-Chapelon F, Kvaskoff M, Boutron-Ruault M-C, Bonnet F. *Relation between Hysterectomy, Oophorectomy and the Risk of Incident Differentiated Thyroid Cancer: The E3N Cohort*. 2018. https://hal-univ-rennes1.archives-ouvertes.fr/hal-01952338 (15 September 2020, date last accessed).

Hamling J, Lee P, Weitkunat R, Ambühl M. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. *Statist Med* 2008;**27**:954–970.

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statist Med* 2002;**21**:1539–1558.

Holly EA, Cress RD, Ahn DK. Cutaneous melanoma in women III. Reproductive factors and oral contraceptive use. *Am J Epidemiol* 1995;**141**:943–950.

Howard BV, Kuller L, Langer R, Manson JE, Allen C, Assaf A, Cochrane BB, Larson JC, Lasser N, Rainford M *et al*. Risk of cardiovascular disease by hysterectomy status, with and without oophorectomy: the Women's Health Initiative Observational Study. *Circulation* 2005;**111**:1462–1470.

Hsu H-C, Tseng K-Y, Wang H-C, Sung F-C, Ma W-F. Risk of endometriosis and subsequent ovary and breast cancers in nurses: a population-based cohort study in Taiwan. *Int J Environ Res Public Health* 2019;**16**:3469.

Iversen L, Sivasubramaniam S, Lee AJ, Fielding S, Hannaford PC. Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study. *Am J Obstet Gynecol* 2017;**216**:580.e1–580-e9.

Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, Amso NN, Apostolidou S, Benjamin E, Cruickshank D *et al*. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. *Lancet* 2016;**387**:945–956.

Jegerlehner S, Bulliard J-L, Aujesky D, Rodondi N, Germann S, Konzelmann I, Chiolero A, NICER Working Group. Overdiagnosis and overtreatment of thyroid cancer: A population-based temporal trend study. *PLoS One* 2017;**12**:e0179387.

Johnson CA, James D, Marzan A, Armaos M. Cervical cancer: an overview of pathophysiology and management. *Semin Oncol Nurs* 2019;**35**:166–174.

Johnson NP, Hummelshoj L, Adamson GD, Keckstein J, Taylor HS, Abrao MS, Bush D, Kiesel L, Tamimi R, Sharpe-Timms KL *et al*. World Endometriosis Society consensus on the classification of endometriosis. *Hum Reprod* 2017;**32**:315–324.

Kim HS, Kim TH, Chung HH, Song YS. Risk and prognosis of ovarian cancer in women with endometriosis: a meta-analysis. *Br J Cancer* 2014;**110**:1878–1890.

Kobayashi H, Sumimoto K, Moniwa N, Imai M, Takakura K, Kuromaki T, Morioka E, Arisawa K, Terao T. Risk of developing ovarian cancer among women with ovarian endometrioma: a cohort study in Shizuoka. *Int J Gynecol Cancer* 2007;**17**:37–43.

Kok VC, Tsai H-J, Su C-F, Lee C-K. The risks for ovarian, endometrial, breast, colorectal, and other cancers in women with newly diagnosed endometriosis or adenomyosis: a population-based study. *Int J Gynecol Cancer* 2015;**25**:968–976.

Koushik A, Grundy A, Abrahamowicz M, Arseneau J, Gilbert L, Gotlieb WH, Lacaille J, Mes-Masson A-M, Parent M-É, Provencher DM *et al*. *Hormonal and Reproductive Factors and the Risk of Ovarian Cancer*. 2017. https://hal-riip.archives-ouvertes.fr/pasteur-01534637 (14 November 2019, date last accessed).

Kvaskoff M, Horne AW, Missmer SA. Informing women with endometriosis about ovarian cancer risk. *Lancet* 2017;**390**:2433–2434.

Kvaskoff M, Mu F, Terry KL, Harris HR, Poole EM, Farland L, Missmer SA. Endometriosis: a high-risk population for major chronic diseases? *Hum Reprod Update* 2015;**21**:500–516.

Lac V, Nazeran TM, Tessier-Cloutier B, Aguirre-Hernandez R, Albert A, Lum A, Khattra J, Praetorius T, Mason M, Chiu D *et al*. Oncogenic mutations in histologically normal endometrium: the new normal? *J Pathol* 2019a;**249**:173–181.

Lac V, Verhoef L, Aguirre-Hernandez R, Nazeran TM, Tessier-Cloutier B, Praetorius T, Orr NL, Noga H, Lum A, Khattra J *et al*. Iatrogenic endometriosis harbors somatic cancer-driver mutations. *Hum Reprod* 2019b;**34**:69–78.

Lee AW, Navajas EE, Liu L. Clear differences in ovarian cancer incidence and trends by ethnicity among Asian Americans. *Cancer Epidemiol* 2019;**61**:142–149.

Lee AW, Templeman C, Stram DA, Beesley J, Tyrer J, Berchuck A, Pharoah PP, Chenevix-Trench G, Pearce CL, Ness RB *et al*. Evidence of a genetic link between endometriosis and ovarian cancer. *Fertil Steril* 2016;**105**:35–43.e1–10.

Lee W-L, Chang W-H, Wang K-C, Guo C-Y, Chou Y-J, Huang N, Huang H-Y, Yen M-S, Wang P-H. The risk of epithelial ovarian cancer of women with endometriosis may be varied greatly if diagnostic criteria are different: a nationwide population-based cohort study. *Medicine* 2015;**94**:e1633.

Li J, Liu R, Tang S, Feng F, Liu C, Wang L, Zhao W, Zhang T, Yao Y, Wang X *et al*. Impact of endometriosis on risk of ovarian, endometrial and cervical cancers: a meta-analysis. *Arch Gynecol Obstet* 2019;**299**:35–46.

Lippman SM, Abate-Shen C, Colbert Maresso KL, Colditz GA, Dannenberg AJ, Davidson NE, Disis ML, DuBois RN, Szabo E, Giuliano AR *et al*. AACR white paper: shaping the future of cancer prevention—a roadmap for advancing science and public health. *Cancer Prev Res* 2018;**11**:735–778.

Lu Y, Cuellar-Partida G, Painter JN, Nyholt DR, Morris AP, Fasching PA, Hein A, Burghaus S, Beckmann MW, Lambrechts D, Australian Ovarian Cancer Study *et al*. Shared genetics underlying epidemiological association between endometriosis and ovarian cancer. *Hum Mol Genet* 2015;**24**:5955–5964.

Lundberg FE, Iliadou AN, Rodriguez-Wallberg K, Gemzell-Danielsson K, Johansson ALV. The risk of breast and gynecological cancer in women with a diagnosis of infertility: a nationwide population-based study. *Eur J Epidemiol* 2019;**34**:499–507.

Luo G, Zhang Y, Wang L, Huang Y, Yu Q, Guo P, Li K. Risk of colorectal cancer with hysterectomy and oophorectomy: a systematic review and meta-analysis. *Int J Surg* 2016;**34**:88–95.

Mallen A, Soong TR, Townsend MK, Wenham RM, Crum CP, Tworoger SS. Surgical prevention strategies in ovarian cancer. *Gynecol Oncol* 2018;**151**:166–175.

Manchanda R, Legood R, Pearce L, Menon U. Defining the risk threshold for risk reducing salpingo-oophorectomy for ovarian cancer prevention in low risk postmenopausal women. *Gynecol Oncol* 2015;**139**:487–494.

Mavaddat N, Michailidou K, Dennis J, Lush M, Fachal L, Lee A, Tyrer JP, Chen T-H, Wang Q, Bolla MK *et al*. Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. *Am J Hum Genet* 2019;**104**:21–34.

McTiernan A, Friedenreich CM, Katzmarzyk PT, Powell KE, Macko R, Buchner D, Pescatello LS, Bloodgood B, Tennant B, Vaux-Bjerke A *et al*. Physical activity in cancer prevention and survival: a systematic review. *Med Sci Sports Exerc* 2019;**51**:1252–1261.

Melin A, Sparén P, Bergqvist A. The risk of cancer and the role of parity among women with endometriosis. *Hum Reprod* 2007;**22**:3021–3026.

Melin A, Sparén P, Persson I, Bergqvist A. Endometriosis and the risk of cancer with special emphasis on ovarian cancer. *Hum Reprod* 2006;**21**:1237–1242.

Melin A-S, Lundholm C, Malki N, Swahn M-L, Sparèn P, Bergqvist A. Hormonal and surgical treatments for endometriosis and risk of epithelial ovarian cancer. *Acta Obstet Gynecol Scand* 2013;**92**:546–554.

Melton LJ, Khosla S, Malkasian GD, Achenbach SJ, Oberg AL, Riggs BL. Fracture risk after bilateral oophorectomy in elderly women. *J Bone Miner Res* 2003;**18**:900–905.

Merritt MA, Green AC, Nagle CM, Webb PM, Australian Cancer Study (Ovarian Cancer) and Australian Ovarian Cancer Study Group. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *Int J Cancer* 2008;**122**:170–176.

Merritt MA, Pari MD, Vitonis AF, Titus LJ, Cramer DW, Terry KL. Reproductive characteristics in relation to ovarian cancer risk by histologic pathways. *Hum Reprod* 2013;**28**:1406–1417.

Missmer SA. Commentary: endometriosis–epidemiologic considerations for a potentially "high-risk" population. *Int J Epidemiol* 2009;**38**:1154–1155.

Missmer SA. Why so null? Methodologic necessities to advance endometriosis discovery. *Paediatr Perinat Epidemiol* 2019;**33**:26–27.

Modugno F, Ness RB, Allen GO, Schildkraut JM, Davis FG, Goodman MT. Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. *Am J Obstet Gynecol* 2004;**191**:733–740.

Mogensen JB, Kjær SK, Mellemkjær L, Jensen A. Endometriosis and risks for ovarian, endometrial and breast cancers: a nationwide cohort study. *Gynecol Oncol* 2016;**143**:87–92.

Morales L, Alvarez-Garriga C, Matta J, Ortiz C, Vergne Y, Vargas W, Acosta H, Ramírez J, Perez-Mayoral J, Bayona M. Factors associated with breast cancer in Puerto Rican women. *J Epidemiol Glob Health* 2013;**3**:205–215.

Moseson M, Koenig KL, Shore RE, Pasternack BS. The influence of medical conditions associated with hormones on the risk of breast cancer. *Int J Epidemiol* 1993;**22**:1000–1009.

Mu F, Rich-Edwards J, Rimm EB, Spiegelman D, Missmer SA. Endometriosis and risk of coronary heart disease. *Circ Cardiovasc Qual Outcomes* 2016;**9**:257–264.

Nagle CM, Olsen CM, Webb PM, Jordan SJ, Whiteman DC, Green AC. Endometrioid and clear cell ovarian cancers—a comparative analysis of risk factors. *Eur J Cancer* 2008;**44**:2477–2484.

National Cancer Institute. *SEER Cancer Statistics Review (CSR) 1975–2014*. 2017. https://seer.cancer.gov/csr/1975_2014 (26 June 2017, date last accessed).

Ness RB, Cramer DW, Goodman MT, Kjaer SK, Mallin K, Mosgaard BJ, Purdie DM, Risch HA, Vergona R, Wu AH. Infertility, fertility drugs, and ovarian cancer: a pooled analysis of case-control studies. *Am J Epidemiol* 2002;**155**:217–224.

Nichols HB, Visvanathan K, Newcomb PA, Hampton JM, Egan KM, Titus-Ernstoff L, Trentham-Dietz A. Bilateral oophorectomy in relation to risk of postmenopausal breast cancer: confounding by nonmalignant indications for surgery? *Am J Epidemiol* 2011;**173**:1111–1120.

Nnoaham KE, Hummelshoj L, Webster P, d'Hooghe T, de Cicco Nardone F, de Cicco Nardone C, Jenkinson C, Kennedy SH, Zondervan KT. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. *Fertil Steril* 2011;**96**:366–373.e8.

Olson JE, Cerhan JR, Janney CA, Anderson KE, Vachon CM, Sellers TA. Postmenopausal cancer risk after self-reported endometriosis diagnosis in the Iowa Women's Health Study. *Cancer* 2002;**94**:1612–1618.

Painter JN, O'Mara TA, Morris AP, Cheng THT, Gorman M, Martin L, Hodson S, Jones A, Martin NG, Gordon S *et al*. Genetic overlap between endometriosis and endometrial cancer: evidence from cross-disease genetic correlation and GWAS meta-analyses. *Cancer Med* 2018;**7**:1978–1987.

Park HK, Schildkraut JM, Alberg AJ, Bandera EV, Barnholtz-Sloan JS, Bondy M, Crankshaw S, Funkhouser E, Moorman PG, Peters ES *et al*. Benign gynecologic conditions are associated with ovarian cancer risk in African-American women: a case-control study. *Cancer Causes Control* 2018;**29**:1081–1091.

Parker WH. Bilateral oophorectomy versus ovarian conservation: effects on long-term women's health. *J Minim Invasive Gynecol* 2010;**17**:161–166.

Parker WH, Jacoby V, Shoupe D, Rocca W. Effect of bilateral oophorectomy on women's long-term health. *Womens Health (Lond)* 2009;**5**:565–576.

Pearce CL, Rossing MA, Lee AW, Ness RB, Webb PM, Chenevix-Trench G, Jordan SM, Stram DA, Chang-Claude J, Hein R, for Australian Cancer Study (Ovarian Cancer) *et al*. Combined and interactive effects of environmental and GWAS-identified risk factors in ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 2013;**22**:880–890.

Pearce CL, Stram DO, Ness RB, Stram DA, Roman LD, Templeman C, Lee AW, Menon U, Fasching PA, McAlpine JN *et al*. Population distribution of lifetime risk of ovarian cancer in the United States. *Cancer Epidemiol Biomarkers Prev* 2015;**24**:671–676.

Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, Nagle CM, Doherty JA, Cushing-Haugen KL, Wicklund KG *et al*. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case–control studies. *Lancet Oncol* 2012;**13**:385–394.

Poole EM, Lin WT, Kvaskoff M, De Vivo I, Terry KL, Missmer SA. Endometriosis and risk of ovarian and endometrial cancers in a large prospective cohort of U.S. nurses. *Cancer Causes Control* 2017;**28**:437–445.

Prescott J, Farland LV, Tobias DK, Gaskins AJ, Spiegelman D, Chavarro JE, Rich-Edwards JW, Barbieri RL, Missmer SA. A prospective cohort study of endometriosis and subsequent risk of infertility. *Hum Reprod* 2016;**31**:1475–1482.

Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;**371**: 569–578.

Rocca WA, Gazzuola-Rocca L, Smith CY, Grossardt BR, Faubion SS, Shuster LT, Kirkland JL, Stewart EA, Miller VM. Accelerated accumulation of multimorbidity after bilateral oophorectomy: a population-based cohort study. *Mayo Clin Proc* 2016;**91**: 1577–1589.

Rosner B, Glynn RJ, Tamimi RM, Chen WY, Colditz GA, Willett WC, Hankinson SE. Breast cancer risk prediction with heterogeneous risk profiles according to breast cancer tumor markers. *Am J Epidemiol* 2013;**178**:296–308.

Rossing MA, Cushing-Haugen KL, Wicklund KG, Doherty JA, Weiss NS. Risk of epithelial ovarian cancer in relation to benign ovarian conditions and ovarian surgery. *Cancer Causes Control* 2008;**19**: 1357–1364.

Rothman KJ. Disengaging from statistical significance. *Eur J Epidemiol* 2016;**31**:443–444.

Rowlands IJ, Nagle CM, Spurdle AB, Webb PM. Gynecological conditions and the risk of endometrial cancer. *Gynecol Oncol* 2011;**123**: 537–541.

Ruderman R, Pavone ME. Ovarian cancer in endometriosis: an update on the clinical and molecular aspects. *Minerva Ginecol* 2017; **69**:286–294.

Ruiz MP, Morales-Ramirez PB, Dziadek OL, Algren SD. Epithelial ovarian cancer and type of peritoneal insult: a case-control study. *Eur J Obstet Gynecol Reprod Biol* 2016;**205**:170–173.

Saavalainen L, Lassus H, But A, Tiitinen A, Härkki P, Gissler M, Heikinheimo O, Pukkala E. A Nationwide Cohort Study on the risk of non-gynecological cancers in women with surgically verified endometriosis. *Int J Cancer* 2018a;**143**:2725–2731.

Saavalainen L, Lassus H, But A, Tiitinen A, Härkki P, Gissler M, Pukkala E, Heikinheimo O. Risk of gynecologic cancer according to the type of endometriosis. *Obstet Gynecol* 2018b;**131**:1095–1102.

Saraswat L, Ayansina D, Cooper KG, Bhattacharya S, Horne AW, Bhattacharya S. Impact of endometriosis on risk of further gynaecological surgery and cancer: a national cohort study. *BJOG* 2018; **125**:64–72.

Shafrir AL, Farland LV, Shah DK, Harris HR, Kvaskoff M, Zondervan K, Missmer SA. Risk for and consequences of endometriosis: a critical epidemiologic review. *Best Pract Res Clin Obstet Gynaecol* 2018;**51**:1–15.

Simoens S, Hummelshoj L, Dunselman G, Brandes I, Dirksen C, D'Hooghe T, Consortium E. Endometriosis cost assessment (the EndoCost study): a cost-of-illness study protocol. *Gynecol Obstet Invest* 2011a;**71**:170–176.

Simoens S, Meuleman C, D'Hooghe T. Non-health-care costs associated with endometriosis. *Hum Reprod* 2011b;**26**:2363–2367.

Sotelo JL, Musselman D, Nemeroff C. The biology of depression in cancer and the relationship between depression and cancer progression. *Int Rev Psychiatry* 2014;**26**:16–30.

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;**355**:i4919.

Stewart L, Holman D, Finn J, Preen D, Hart R. In vitro fertilization is associated with an increased risk of borderline ovarian tumours. *Gynecol Oncol* 2013a;**129**:372–376.

Stewart LM, Holman CDJ, Aboagye-Sarfo P, Finn JC, Preen DB, Hart R. In vitro fertilization, endometriosis, nulliparity and ovarian cancer risk. *Gynecol Oncol* 2013b;**128**:260–264.

Stewart LM, Spilsbury K, Jordan S, Stewart C, Holman CDJ, Powell A, Reekie J, Cohen P. Risk of high-grade serous ovarian cancer associated with pelvic inflammatory disease, parity and breast cancer. *Cancer Epidemiol* 2018;**55**:110–116.

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA* 2000;**283**:2008–2012.

Surrey ES, Soliman AM, Johnson SJ, Davis M, Castelli-Haley J, Snabes MC. Risk of developing comorbidities among women with endometriosis: a retrospective matched cohort study. *J Womens Health* 2018;**27**:1114–1123.

Tanbo T, Fedorcsak P. Endometriosis-associated infertility: aspects of pathophysiological mechanisms and treatment options. *Acta Obstet Gynecol Scand* 2017;**96**:659–667.

Trabert B, Poole EM, White E, Visvanathan K, Adami H-O, Anderson GL, Brasky TM, Brinton LA, Fortner RT, Gaudet M, Ovarian Cancer Cohort Consortium (OC3) *et al.* Analgesic use and ovarian cancer risk: an analysis in the ovarian cancer cohort consortium. *J Natl Cancer Inst* 2019;**111**:137–145.

Vallvé-Juanico J, Santamaria X, Vo KC, Houshdaran S, Giudice LC. Macrophages display proinflammatory phenotypes in the eutopic endometrium of women with endometriosis with relevance to an infectious etiology of the disease. *Fertil Steril* 2019;**112**:1118–1128.

Vassard D, Schmidt L, Glazer CH, Lyng Forman J, Kamper-Jørgensen M, Pinborg A. Assisted reproductive technology treatment and risk of ovarian cancer—a nationwide population-based cohort study. *Hum Reprod* 2019;**34**:2290–2296.

Vaughan S, Coward JI, Bast RC, Berchuck A, Berek JS, Brenton JD, Coukos G, Crum CC, Drapkin R, Etemadmoghadam D *et al.* Rethinking ovarian cancer: recommendations for improving outcomes. *Nat Rev Cancer* 2011;**11**:719–725.

Venn A, Watson L, Bruinsma F, Giles G, Healy D. Risk of cancer after use of fertility drugs with in-vitro fertilisation. *Lancet* 1999;**354**: 1586–1590.

Vercellini P, Viganò P, Buggio L, Makieva S, Scarfone G, Cribiù FM, Parazzini F, Somigliana E. Perimenopausal management of ovarian endometriosis and associated cancer risk: when is medical or surgical treatment indicated?. *Best Pract Res Clin Obstet Gynaecol* 2018; **51**:151–168.

Vitonis AF, Vincent K, Rahmioglu N, Fassbender A, Buck Louis GM, Hummelshoj L, Giudice LC, Stratton P, Adamson GD, Becker CM *et al.* World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project: II. Clinical and covariate phenotype data collection in endometriosis research. *Fertil Steril* 2014;**102**:1223–1232.

Wang C, Liang Z, Liu X, Zhang Q, Li S. The association between endometriosis, tubal ligation, hysterectomy and epithelial ovarian cancer: meta-analyses. *Int J Environ Res Public Health* 2016;**13**:1138.

Wang K-C, Chang W-H, Lee W-L, Huang N, Huang H-Y, Yen M-S, Guo C-Y, Wang P-H. An increased risk of epithelial ovarian cancer in Taiwanese women with a new surgico-pathological diagnosis of endometriosis. *BMC Cancer* 2014;**14**:831.

Wasserstein RL, Lazar NA. The ASA statement on p-values: context, process, and purpose. *Am Statistician* 2016;**70**:129–133.

Weiss HA, Brinton LA, Potischman NA, Brogan D, Coates RJ, Gammon MD, Malone KE, Schoenberg JB. Breast cancer risk in young women and history of selected medical conditions. *Int J Epidemiol* 1999;**28**:816–823.

Wentzensen N, Poole EM, Trabert B, White E, Arslan AA, Patel AV, Setiawan VW, Visvanathan K, Weiderpass E, Adami H-O *et al.* Ovarian cancer risk factors by histologic subtype: an analysis from the ovarian cancer cohort consortium. *J Clin Oncol* 2016;**34**: 2888–2898.

Whitaker LHR, Byrne D, Hummelshoj L, Missmer SA, Saraswat L, Saridogan E, Tomassetti C, Horne AW. Proposal for a new ICD-11 coding classification system for endometriosis. *Eur J Obstet Gynecol Reprod Biol* 2019;**241**:134–135.

Williams CL, Jones ME, Swerdlow AJ, Botting BJ, Davies MC, Jacobs I, Bunch KJ, Murphy MFG, Sutcliffe AG. Risks of ovarian, breast, and corpus uteri cancer in women treated with assisted reproductive technology in Great Britain, 1991-2010: data linkage study including 2.2 million person years of observation. *BMJ* 2018;**362**:k2644.

Yeh C-C, Su F-H, Tzeng C-R, Muo C-H, Wang W-C. Women with adenomyosis are at higher risks of endometrial and thyroid cancers: A population-based historical cohort study. *PLoS One* 2018; **13**:e0194011.

Yland J, Carvalho LFP, Beste M, Bailey A, Thomas C, Abrão MS, Racowsky C, Griffith L, Missmer SA. Endometrioma, the follicular fluid inflammatory network and its association with oocyte and embryo characteristics. *Reprod Biomed Online* 2019;**40**:399–408.

Young P, Purdie D, Jackman L, Molloy D, Green A. A study of infertility treatment and melanoma. *Melanoma Res* 2001;**11**:535–541.

Zondervan K, Becker C, Missmer SA. Endometriosis. *N Engl J Med* 2020;**382**:1244–1256.

Zondervan KT, Becker CM, Koga K, Missmer SA, Taylor RN, Viganò P. Endometriosis. *Nat Rev Dis Primers* 2018;**4**:1–25.

Zondervan KT, Cardon LR, Kennedy SH. What makes a good case–control study? Design issues for complex traits such as endometriosis. *Hum Reprod* 2002;**17**:1415–1423.

Zucchetto A, Serraino D, Polesel J, Negri E, Paoli AD, Maso LD, Montella M, Vecchia CL, Franceschi S, Talamini R. Hormone-related factors and gynecological conditions in relation to endometrial cancer risk. *Eur J Cancer Prev* 2009;**18**:316–321.