Title

Endometriosis and cancer: A systematic review and meta-analysis

Running title

Endometriosis and cancer

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ABSTRACT

Background: Endometriosis is an often chronic, inflammatory gynaecologic condition affecting 190 million women worldwide. Studies have reported an elevated cancer risk among women 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 according to methodologic characteristics. We discuss the implications of cancer screening in endometriosis patients and management challenges faced by clinicians.

Search methods: We searched the PubMed and Embase databases for eligible studies through October 24th, 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 estimates with 95% confidence intervals (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 ROBINS-I tool.

Results: Forty-nine population-based case-control and cohort studies were included. Twenty-six studies were scored as having a 'serious' or 'critical' risk of bias, and the remaining 23 'low' or 'moderate'. Cancer-specific analyses showed a positive association between endometriosis and ovarian cancer risk (SRR=1.93,CI=1.68-2.22; n=24 studies) that was strongest for clear-cell (SRR=3.44,CI=2.82-4.42; n=5 studies) and endometrioid (SRR=2.33,CI=1.82-2.98; n=5 studies) histotypes ($P_{heterogeneity}$<0.0001), although there was 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, CI=1.24-1.57; n=5 studies), a very small association with breast cancer (SRR=1.04, CI=1.00-1.09; n=20 studies), and no association with colorectal cancer (SRR=1.00, CI=0.87-1.16; n=5 studies). The association with endometrial cancer was not statistically significant (SRR=1.23, CI=0.97-1.57; n=17 studies) overall and wholly null when restricted to prospective cohort studies (SRR=0.99, CI=0.72-1.37; n=5 studies). There was also a small association (17% greater risk) with cutaneous melanoma (CI=0.97-1.41; n=7 studies) that increased in magnitude (71% greater risk) and was statistically significant when restricted to studies with low/moderate risk of bias (CI=1.24-2.36, n=2 studies). The most robust finding was an inverse association with cervical cancer (SRR=0.68, CI=0.56-0.82; n=4 studies), which may reflect heightened access to detection of dysplasia for women with successful endometriosis diagnosis. Several additional cancer types were explored in <4 studies.

Conclusions: 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 (i) a majority of studies had severe/critical risk of bias, (ii) there is impactful heterogeneity across studies– and for ovarian cancer, publication bias, and (iii) causal inference requires temporality, which in many studies was not considered. We discuss the implications of these potential associations from the perspectives of the women with endometriosis, clinicians involved in their care, and scientists investigating their long-term health risks.

ABBREVIATIONS

BSO, bilateral salpingo-oophorectomy; CI, confidence intervals; HR, hazard ratio; OR, odds-ratio; SIR, standardized incidence ratio; SRR, summary relative risk; RR, relative risk

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) (Ghiasi *et al.*, 2020) (Shafrir *et al.*, 2018), equating to 190 million women worldwide (Zondervan *et al.*, 2020), and is associated with substantial healthcare costs (Simoens *et al.*, 2011a, 2011b). 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 extrapelvic 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, particularly within the last decade (Missmer, 2009). 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. estimated a summary relative risk (SRR) of 1.27 (95% confidence interval (CI)=1.21-1.32), based on 21 case-control or cohort studies, and of 1.80 (CI=1.28-2.53) based on five studies including women with endometriosis only (Kim *et al.*, 2014). Wang et al. then reported a summary odds-ratio of 1.42 (CI=1.28-1.57), based on 12 case-control studies published between 1995 and 2016 (Wang *et al.*, 2016a). Thereafter, meta-analyses reported on the associations between endometriosis and ovarian, endometrial, and cervical cancers (Li *et al.*, 2019a) 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. summarized a relative risk of 1.96 (CI=1.69-2.29) for the relationship between endometriosis and ovarian cancer, a modest (RR=1.18, CI=0.88-1.58) and not statistically significant association with endometrial cancer, and an inverse association with cervical cancer (Li *et al.*, 2019a). While Gandini et al. also reported an inverse association with cervical cancer, endometriosis was positively associated with endometrial cancer in their meta-analysis, with a SRR of 1.38 (CI=1.10-1.74) (Gandini *et al.*, 2019). 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 October 24th, 2019. The search terms and algorithm that we used are detailed in **Appendix S1**. 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 (relative risk (RR), hazard ratio (HR), standardized incidence ratio (SIR), or odds-ratio (OR)) had to be reported with 95% confidence intervals (CIs) in the publication. The flow chart of study selection is presented in **Figure 1**. All identified studies were imported into Reference Manager for screening. Two reviewers (M.K., 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.

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: (1) bias due to confounding, (2) bias in selection of study participants, (3) bias in exposure measurement, (4) bias due to misclassification of exposure during follow-up, (5) bias due to missing data, (6) bias in measurement of outcomes, and (7) 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 summary relative risks (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). For all analyses, the impact of study sample size is accounted for in the statistical modeling and represented by the width of 95% confidence intervals.

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) 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 (**Figure 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 S1).**

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.*, 2013, 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 OCAC (Pearce *et al.*, 2012), and the study by Modugno et al (Modugno et al., 2004) was included in the pooled analysis published by Ness (Ness *et al.*, 2002), thus, we also did not included them as individual studies. Characteristics of the included studies are detailed in **Supplementary Table S1**. 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.*, 2013; 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 (b)) 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, 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). In the present work, we did not include the study by Yeh et al. (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; Farland *et al.*, 2016a, 2017; Mogensen *et al.*, 2016; 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.*, 2013; 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, 2018b; Williams *et al.*, 2018) (**Table 1**).

Overall cancer

A total of five 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) (**Table 2**). The SRR was 1.07 (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-value<0.0001). Variation by geographic location was evident (North America: RR=0.90, CI=0.77-1.05; Europe: SRR=1.03, CI=0.97-1.11; Asia: HR=1.80, 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, CI=0.98-2.13, I^2=86%, P=0.008; serious or critical: SRR=0.99,

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 with serious/critical bias appear to be uniformly biased toward the null. There was no indication of publication bias, with Egger's test (p-value=0.29) or with Begg's test (p-value=0.22).

Ovarian cancer

The meta-analysis included 28 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.*, 2013; 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). The SRR was 1.93 (CI=1.68-2.22) (**Figure 2, Table 2**) 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, CI=1.35-1.63, I^2=0%, P=0.62; retrospective cohorts: SRR=2.03, CI=1.69-2.45, I^2=77%, P<0.0001; prospective cohorts: SRR=2.83, 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, CI=1.38-3.32, I^2=74%, P=0.004; Europe: SRR=1.81, CI=1.55-2.10, I^2=75%, P<0.0001; Asia: SRR=4.22, CI=1.70-10.46, I^2=69%, P=0.04; Australia: SRR=1.99, CI=1.02-3.88, I^2=0%, P=0.53CI; multiple locations: SRR=1.44, CI=1.31-1.59, I^2=0%, P=0.83; $P_{heterogeneity}$=0.09) (**Table 2**).

389 The positive association between endometriosis and ovarian cancer was also stronger in
390 studies that required temporarily (i.e. endometriosis must have been diagnosed at least 12
391 months prior to the diagnosis of endometrial cancer) (n=11, SRR=2.19, CI=1.64-2.92,
392 I^2=85%, P<0.0001) versus studies that did not (n=13, SRR=1.79, 9% CI=1.55-2.05, I^2=64%)
393 or in studies with low or moderate risk of bias (n=13, SRR=2.09, CI=1.69-2.59, I^2=78%,
394 P<0.0001) versus studies with serious or critical risk of bias (n=11, SRR=1.80, CI=1.49-2.17,
395 I^2=77%CI, P<0.0001), albeit again with high heterogeneity within these categories and also
396 with no statistically significant heterogeneity between these groups ($P_{heterogeneity}$=0.46 and
397 0.50, respectively) (**Table 2**). Three studies (Chang *et al.*, 2014; Mogensen *et al.*, 2016;
398 Williams *et al.*, 2018) additionally reported estimates after excluding endometriosis cases
399 diagnosed less than 12 months prior to ovarian cancer diagnosis; including these estimates
400 within the meta-analysis instead of the primary estimates from these studies prior to exclusion
401 did not change the overall meta-analysis SRR for ovarian cancer (SRR=1.90, CI=1.67-2.15,
402 I^2=72%CI, P<0.0001). When now including these three studies among the group restricted to
403 those that required temporality, the results still were not substantially modified (studies
404 requiring temporality: n=14, SRR=2.12, CI=1.71-2.63, I^2=83%CI, P<0.0001; studies not
405 requiring temporality: n=10, SRR=1.75, CI=1.48-2.07, I^2=62%, P=0.005CI), with
406 heterogeneity among within group studies remaining high.
407
408 The influence analysis excluding the most influential studies suggested stable summary
409 estimates (**Supplementary Figure S1**). However, there was strong evidence of publication
410 bias towards an overestimation of the association, whether evaluated graphically
411 (**Supplementary Figure S2**) by Egger's test (P=0.01) or by Begg's test (P=0.009).
412
413 *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 2**). The strongest association was observed with the clear-cell (SRR=3.44, CI=2.82-4.20, n=5 CI 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, CI=1.82-2.98, n=5 CI 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, CI=0.74-1.29, n=5CI 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, CI=1.64-3.31; versus high-grade serous tumours: SRR=1.08, 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 histotypes (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 pelvic 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 (CI=2.25-13.00) (**Supplementary Figure 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, CI=1.98-3.27), superficial peritoneal (RR=1.32, CI=0.99-1.72), and deep endometriosis (RR=1.41, 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 neither clinically nor statistically associated with ovarian cancer risk (SIRs=0.00, 3.35, and 1.41, respectively, although confidence intervals 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; Farland *et al.*, 2016a; Mogensen *et al.*, 2016; 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 (CI=1.00-1.09) (**Supplementary Figure S4, Table 2**), 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, CI=1.14-1.75, I^2=0%, P=0.54)), endometriosis case ascertainment or ROBINS-I risk of bias (**Table 2**). The SRR for breast cancer was also similar among studies that included only populations of women with infertility (SRR=1.02, 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 Figure S8-A**).

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, 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, CI=0.89–1.23) and postmenopausal breast cancer (HR=0.93, CI=0.80–1.07), and among postmenopausal women results did not change by type of

menopause (natural menopause HR=1.06, CI=0.80–1.36; surgical menopause HR=0.90, CI=0.75–1.09) (Farland *et al.*, 2016a). Mogensen et al. reported no difference in association with ductal (SIR=1.04, CI=0.97-1.10) versus lobular tumours (SIR=1.10, CI=0.98-1.33), with both effect estimates of a magnitude similar to that observed for breast cancer risk overall (Mogensen *et al.*, 2016). 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.*, 2005b, 2005a; 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 (CI=0.97-1.57), with a high level of heterogeneity among studies (I^2=81%, P<0.0001) (**Table 2, Supplementary Figure S5**). This heterogeneity was not explained by cohort (SRR=1.25, CI=0.96-1.62, I^2=79%, P<0.0001) versus case-control study design (SRR=1.29, CI=0.65-2.54, I^2=85%, P<0.0001; $P_{heterogeneity}$=0.89) – although the within design heterogeneity was high. We observed that the association was consistently null among prospective cohort studies that rigorously required temporality (i.e. endometriosis must have been diagnosed at least 12 months prior to the diagnosis of endometrial cancer), among which there was no longer any heterogeneity (n=5 studies, SRR=0.99, CI=0.72-1.37, I^2=0%, P=0.51) (**Table 2**) (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, CI=1.00-1.96, I^2=86.8%, P<0.0001) (**Table 2**) and 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.*, 2005b, 2005a; 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, CI=0.96-1.27, I^2=0%, P=0.56) (**Figure 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 (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)(**Figure 3**).

In sensitivity analyses excluding the most influential studies, the SRR ranged from 1.15 (CI=0.93-1.41) when excluding the Mogensen et al. study (Mogensen *et al.*, 2016) to 1.31 (CI=1.05-1.65) when excluding the Borgfeldt and Andolf study (Borgfeldt and Andolf, 2004) (**Supplementary Figure S8-B**). 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. reported a stronger association for type I (SIR=1.54, CI=1.20-1.96) versus type II (SIR=1.06, CI=0.28-2.71) tumours, although confidence intervals were wide for type II tumours and included the SIR and full confidence

interval range observed for type I tumours (Mogensen *et al.*, 2016). Brinton et al. 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) (Brinton *et al.*, 2005b).

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 endometriosis was a modest borderline-significant SRR=1.17 (CI=0.97-1.41) (**Supplementary Figure S6, Table 2**) 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, CI=0.99-1.48, I^2=69%, P=0.04) versus North America (SRR=1.07, 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, CI=1.24-2.36, I^2=0%, P=0.59; serious or critical: SRR=1.08, CI=0.87-1.26, I^2=32%, P=0.21), with the statistically significant association observed among those 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

563 Only two studies have assessed the association between endometriosis and the risk of basal-
564 cell carcinoma (Farland *et al.*, 2017; Saavalainen *et al.*, 2018a). The analysis yielded a SRR of
565 1.18 (CI=1.11-1.25), with no detected heterogeneity (I^2=0%, P=0.89; data not shown)
566 (**Supplementary Table S2**).
567
568 **Thyroid cancer**
569 The analysis of the association between endometriosis and thyroid cancer included five
570 studies (Brinton *et al.*, 2005b, 2005a; Melin *et al.*, 2007; Braganza *et al.*, 2014; Guenego *et*
571 *al.*, 2018), producing a SRR of 1.39 (CI=1.24-1.57) (**Figure 4, Table 2**). This was the most
572 robust positive cancer association, with no evidence of heterogeneity (I^2=0%, P=0.69) or
573 publication bias (Egger's test: P=0.69; Begg's test: P=0.49), and most studies considering
574 temporality (n=4 studies).
575
576 **Colorectal cancer**
577 Based on five studies (Olson *et al.*, 2002; Brinton *et al.*, 2005a; Melin *et al.*, 2006; Kok *et al.*,
578 2015; Saavalainen *et al.*, 2018a), our analysis yielded a SRR of 1.00 (CI=0.87-1.16) for the
579 association between endometriosis and colorectal cancer risk, with no evidence of publication
580 bias (Egger's test: P=0.49; Begg's test: P=0.21) and low heterogeneity among studies
581 (I^2=40%, P=0.16) (**Supplementary Figure S7**). However, the association was positive
582 (SRR=2.29) and of borderline statistical significance (CI=1.00-5.26) when the analysis was
583 restricted to studies with low or moderate risk of bias (**Table 2**).
584
585 **Cervical cancer**
586 Four studies were included in the analysis of endometriosis in relation to cervical cancer
587 (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 (CI=0.56-0.82) (**Figure 5**). We detected no heterogeneity among studies (I^2=0%, P=0.76) nor 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 2**).

Other cancer types

The risk of several other cancer types was assessed in relation to endometriosis but in three or fewer studies: lymphatic and haematopoietic cancers (SRR=1.09, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, 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, CI=0.93-1.55; I^2=66%, P=0.09; n=2 studies (Melin *et al.*, 2007; Saavalainen *et al.*, 2018a)) (**Supplementary Table S2**).

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 summary relative risk 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.

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 greater magnitudes and consistency of risk for clear-cell (3.4-fold) and endometrioid (2.3-fold) subtypes 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 greater 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 previous meta-analyses, 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 30% lower risk of cervical cancer for women with endometriosis compared with those without.

Ovarian cancer

The present meta-analysis calculated an 93% greater risk of ovarian cancer among women with endometriosis compared to those without, which is a higher magnitude than those yielded in two earlier meta-analyses (Kim *et al.*, 2014: SRRs=1.27 to 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 (Li *et al.*, 2019: SRR=1.96) (Li *et al.*, 2019b). However, compared to our meta-analysis, these earlier works either considered some study samples twice (where we restricted 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

663 overestimation of the magnitude of the association between endometriosis and ovarian cancer.
664 This may be driven by a belief by reviewers and editors that any study that does not
665 demonstrate this positive association is incorrect, but it may also reflect that as ovarian cancer
666 is very rare, extremely large cohort sample sizes or multi-site case-control studies are needed
667 to yield power to quantify statistical significance that is too often the focus (Farland *et al.*,
668 2016b; Greenland *et al.*, 2016; Rothman, 2016; Wasserstein and Lazar, 2016; Amrhein *et al.*,
669 2019). Publication bias is a threat to future studies of endometriosis and other cancer types as
670 well if assumptions about their relationship with endometriosis also becomes engrained as it
671 may have for ovarian cancer.
672
673 We also detected a high level of heterogeneity among studies that was in part driven by
674 ovarian cancer histotype – reinforcing that the higher risk of ovarian cancer in women with
675 endometriosis is restricted to the clear-cell and endometrioid histotypes, and future studies
676 should focus on these histotypes rather than on ovarian cancer overall. While we found no
677 evidence of publication bias in analyses by ovarian cancer histotype, it is important to note
678 that the tests are likely to be underpowered among the small number of publications that
679 included these histotypes; we thus cannot rule out publication bias in associations by
680 subgroup also.
681
682 Some have posited that the endometrioma macro-phenotypic subtype of endometriosis is the
683 primary pathway for neoplastic transformation (Lac *et al.*, 2019a, 2019b). However, only four
684 studies quantified endometrioma-specific risk of ovarian cancer, all of which were
685 underpowered. Furthermore, the estimates included endometrioma regardless of the co-
686 occurrence of other endometriosis macro-phenotypes (i.e. superficial peritoneal or deep
687 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 needs 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. Further, 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.*, 2019a)), 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. Body mass index 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% to ~25% decrease in the summary relative risk 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 to 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.*, 2019a) 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 successfully diagnosed with endometriosis 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 healthcare 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 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% greater risk compared to women without endometriosis). This estimate is

consistent with that reported by Gandini et al. (Gandini *et al.*, 2019). However, the majority of risk factors of 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. reported a 90% greater risk of ER+/PR- tumours in women with endometriosis (Farland *et al.*, 2017), 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. Further, we found a 39% greater risk of thyroid cancer in women with endometriosis compared to women without endometriosis. The association with endometriosis may be another example of diagnostic bias as in the US, there has been a large increase in diagnosis of early stage thyroid cancer that reflects overdiagnosis 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. (Gandini *et al.*, 2019). However, more than for any other cancer, the magnitude of the summary risk ratio and statistical significance was considerably greater when the meta-analysis was restricted to studies with low / moderate risk of bias. This suggests that compared to the other cancers explored, biases may more strongly be masking a true association between endometriosis and cutaneous melanoma and 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 69% of the 42 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 these 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 require this temporality, the use of a prospective cohort design is recommended, allowing for time-varying covariate analysis with a 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 one 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 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 subphenotypic 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) (Correia et al. in press HR 2020 if ePub in time) or be along the causal pathway between endometriosis and cancer (mediation) (Farland et al. in press HR 2020 if ePub in time).

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 relative risk would be skewed to an inverse association if the population over-selected for cervical cancers, but skewed to a direct 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 toward populations within Europe or of European descent, and thus if risk heterogeneity by race/ethnicity or region exist, 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 rASRM stage (Becker *et al.*, 2014) and its absence from ICD coding (Whitaker *et al.*, 2019). Recording (Becker *et al.*, 2014; Vitonis *et al.*, 2014) and using such data is 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) (Zondervan *et al.*, 2018). 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.

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. attempted to explore cancer risk (endometrial cancer) by endometriosis macro-phenotype (Kok *et al.*, 2015). 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 provides 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 toward 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) is 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

938 endometriosis case ascertainment nor did they consider the potential influence of diagnostic
939 biases.
940
941 Known shared risk factors between endometriosis and cancer include demographics,
942 anthropometry, menstrual cycle characteristics, lifestyle, and environmental toxins, which
943 may confer classic confounding of the quantified association between the conditions if not
944 accounted for in study design or statistical analyses. Too few studies adjusted for any
945 potential confounders beyond age, let alone comparable confounding adjustment among the
946 studies, to compare meta-analytic results stratified by the confounders considered in the
947 study-specific multivariable analyses. However, when we restricted the analysis to those
948 studies with low or moderate risk of bias, which were required by the ROBINS-I tool to
949 consider potential confounders, the magnitude of associations was often strengthened,
950 suggesting an overall negative confounding effect of such factors.
951
952 As noted above, the inverse association between endometriosis and cervical cancer may be
953 unique in this footprint as it could be modified by selection bias toward a population with
954 high access to care (women who were successfully diagnosed with endometriosis also have
955 access to routine screening) or be mediated by the detrimental impact of endometriosis-
956 specific symptoms on sexual health that may unintentionally lower risk of HPV infection
957 (Johnson *et al.*, 2019).
958
959 It may be that independent of overlapping risk factors and their resulting neoplastic pathways,
960 endometriosis has a causal effect on malignancy. Quantifying mediation between
961 endometriosis and cancer risk would lend insight into the pathways to which these
962 associations are attributable. Mediators – factors occurring after endometriosis but before the

963 cancer that are along the potential causal pathways (Farland et al. in press HR 2020 if ePub in
964 time), may include infertility, depression, anxiety, chronic stress, or endometriosis symptom-
965 related lifestyle adaptations such as decreased physical activity (Sotelo *et al.*, 2014; Brinton,
966 2017; Tanbo and Fedorcsak, 2017; Shafrir *et al.*, 2018; Brasil *et al.*, 2019; McTiernan *et al.*,
967 2019) – all of which are more common in women with endometriosis compared to women
968 without and are also cancer risk factors.
969
970 Similarly, mediators may include treatment for endometriosis or endometriosis-associated
971 symptoms (analgesics, oral contraceptives, progestins, GnRH agonists, lesion
972 excision/ablation, hysterectomy, bilateral salpingo-oophorectomy) that have been associated
973 with risk of specific cancer types (Luo *et al.*, 2016; Iversen *et al.*, 2017; Barnard *et al.*, 2018;
974 Vercellini *et al.*, 2018). NSAID use is a potential mediator given that women with
975 endometriosis more frequently use NSAIDs on a long-term basis compared to women without
976 endometriosis, and NSAID use at high doses for durations over 10 years has been associated
977 with ovarian cancer risk (Trabert *et al.*, 2019). These data may simply suggest that high dose
978 long duration NSAID use is actually proxy for endometriosis, and thus formal mediation
979 analyses would be beneficial. An example of the potential for quantifying mediation is the
980 determination that while women with endometriosis are more likely to undergo
981 hysterectomy/oophorectomy compared to premenopausal women without endometriosis,
982 these surgeries have also been associated with a higher risk of coronary heart disease (Howard
983 *et al.*, 2005). Thus, a mediation analysis within the Nurses' Health Study II, quantified that
984 while endometriosis was associated with a 1.62-fold higher risk of coronary heart disease,
985 42% of this association was mediated by (attributed to) hysterectomy/oophorectomy (Mu *et*
986 *al.*, 2016).
987

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 endometriosis patients 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 relative risk 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 0.5% difference from women without endometriosis and still very low (Kvaskoff *et al.*, 2017). Updating this absolute estimate with quantified risk estimate from the present meta-analysis (SRR=1.93), this absolute risk increased to 2.5%, which is 1.2% greater 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.

Further, 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 NCI stated lifetime absolute risk of 1.3% translates (SRR=1.39) to 1.8% for women with endometriosis.

Therefore, while a statistically significant relative risk 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 to 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). So 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 bilateral salpingo-oophorectomy (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 (hyperlipidemia, 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 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 for women with of ovarian cancer, potentially obscuring its rarity, wome 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.

Further, 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 endometriosis patients given their lifetime absolute risk in exactly this range. We also cannot ignore this updated evidence that there is 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 give 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 relative risk 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 tumor. 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, while associations with other cancer types remain too sparsely documented. The association with endometrial cancer was null with evidence of diagnostic bias. 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 endometriosis patients: 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 macro-phenotype. 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.

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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;Available from: www.cancer.org/healthy/find-cancer-early/cancer-screening-guidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer.html.

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. *New England Journal of Medicine* 2017;**376**:1835–1848.

Atsma F, Bartelink M-LEL, Grobbee DE, Schouw YT van der. 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, WERF EPHect Working Group. World Endometriosis Research Foundation

1186 Endometriosis Phenome and Biobanking Harmonisation Project: I. Surgical phenotype
1187 data collection in endometriosis research. *Fertil Steril* 2014;**102**:1213–1222.
1188 Begg CB, Mazumdar M. Operating Characteristics of a Rank Correlation Test for Publication
1189 Bias. *Biometrics* 1994;**50**:1088–1101.
1190 Berek JS, Chalas E, Edelson M, Moore DH, Burke WM, Cliby WA, Berchuck A, Society of
1191 Gynecologic Oncologists Clinical Practice Committee. Prophylactic and risk-reducing
1192 bilateral salpingo-oophorectomy: recommendations based on risk of ovarian cancer.
1193 *Obstet Gynecol* 2010;**116**:733–743.
1194 Bertelsen L, Mellemkjaer L, Frederiksen K, Kjaer SK, Brinton LA, Sakoda LC, Van IV,
1195 Olsen JH. Risk for breast cancer among women with endometriosis. *Int J Cancer*
1196 2007;**120**:1372–1375.
1197 Bodmer M, Becker C, Meier C, Jick SS, Meier CR. Use of metformin and the risk of ovarian
1198 cancer: A case–control analysis. *Gynecologic Oncology* 2011;**123**:200–204.
1199 Borgfeldt C, Andolf E. Cancer risk after hospital discharge diagnosis of benign ovarian cysts
1200 and endometriosis. *Acta Obstetricia et Gynecologica Scandinavica* 2004;**83**:395–400.
1201 Braganza MZ, González AB de, Schonfeld SJ, Wentzensen N, Brenner AV, Kitahara CM.
1202 Benign Breast and Gynecologic Conditions, Reproductive and Hormonal Factors, and
1203 Risk of Thyroid Cancer. *Cancer Prev Res* 2014;**7**:418–425.
1204 Brasil DL, Montagna E, Trevisan CM, La Rosa VL, Laganà AS, Barbosa CP, Bianco B, Zaia
1205 V. Psychological stress levels in women with endometriosis: systematic review and
1206 meta-analysis of observational studies. *Minerva Med* 2019;
1207 Brinton L, Westhoff C, Scoccia B, Lamb E, Althuis M, Mabie J, Moghissi K. Causes of
1208 Infertility as Predictors of Subsequent Cancer Risk. *Epidemiology* 2005a;**16**:500–507.
1209 Brinton LA. Fertility Status and Cancer. *Semin Reprod Med* 2017;**35**:291–297.

1210 Brinton LA, Gridley G, Persson I, Baron J, Bergqvist A. Cancer risk after a hospital discharge
1211 diagnosis of endometriosis. *American Journal of Obstetrics and Gynecology*
1212 1997;**176**:572–579.
1213 Brinton LA, Lamb EJ, Moghissi KS, Scoccia B, Althuis MD, Mabie JE, Westhoff CL.
1214 Ovarian cancer risk associated with varying causes of infertility. *Fertility and Sterility*
1215 2004;**82**:405–414.
1216 Brinton LA, Sakoda LC, Sherman ME, Frederiksen K, Kjaer SK, Graubard BI, Olsen JH,
1217 Mellemkjaer L. Relationship of Benign Gynecologic Diseases to Subsequent Risk of
1218 Ovarian and Uterine Tumors. *Cancer Epidemiol Biomarkers Prev* 2005b;**14**:2929–
1219 2935.
1220 Brinton LA, Scoccia B, Moghissi KS, Westhoff CL, Niwa S, Ruggieri D, Trabert B, Lamb
1221 EJ. Long-term Relationship of Ovulation-Stimulating Drugs to Breast Cancer Risk.
1222 *Cancer Epidemiol Biomarkers Prev* 2014;**23**:584–593.
1223 Buis CCM, Leeuwen FE van, Mooij TM, Burger CW. Increased risk for ovarian cancer and
1224 borderline ovarian tumours in subfertile women with endometriosis. *Hum Reprod*
1225 2013;**28**:3358–3369.
1226 Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, Reding DJ, Greenlee RT,
1227 Yokochi LA, Kessel B, *et al.* Effect of screening on ovarian cancer mortality: the
1228 Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized
1229 Controlled Trial. *JAMA* 2011;**305**:2295–2303.
1230 Chang W-H, Wang K-C, Lee W-L, Huang N, Chou Y-J, Feng R-C, Yen M-S, Huang B-S,
1231 Guo C-Y, Wang P-H. Endometriosis and the subsequent risk of epithelial ovarian
1232 cancer. *Taiwanese Journal of Obstetrics and Gynecology* 2014;**53**:530–535.

1233 Chen X, Guo T, Li B. Influence of prophylactic oophorectomy on mood and sexual function
1234 in women of menopausal transition or postmenopausal period. *Arch Gynecol Obstet*
1235 2013;**288**:1101–1106.
1236 Chuang S-C, Wu G-J, Lu Y-S, Lin C-H, Hsiung CA. Associations between Medical
1237 Conditions and Breast Cancer Risk in Asians: A Nationwide Population-Based Study
1238 in Taiwan. *PLoS One* [Internet] 2015;**10**:.
1239 Coburn SB, Bray F, Sherman ME, Trabert B. International patterns and trends in ovarian
1240 cancer incidence, overall and by histologic subtype. *Int J Cancer* 2017;**140**:2451–
1241 2460.
1242 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–188.
1243 Dunselman G a. J, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B,
1244 Heikinheimo O, Horne AW, Kiesel L, Nap A, *et al.* ESHRE guideline: management of
1245 women with endometriosis. *Hum Reprod* 2014;**29**:400–412.
1246 Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple,
1247 graphical test. *BMJ* 1997;**315**:629–634.
1248 Farland L, Tamimi R, Eliassen A, Spiegelman D, Hankinson S, Chen W, Missmer S.
1249 Laparoscopically Confirmed Endometriosis and Breast Cancer in the Nurses' Health
1250 Study II. *Obstetrics & Gynecology* 2016a;**128**:1025–1031.
1251 Farland LV, Correia KF, Wise LA, Williams PL, Ginsburg ES, Missmer SA. P-values and
1252 reproductive health: what can clinical researchers learn from the American Statistical
1253 Association? *Hum Reprod* 2016b;**31**:2406–2410.
1254 Farland LV, Lorrain S, Missmer SA, Dartois L, Cervenka I, Savoye I, Mesrine S, Boutron-
1255 Ruault M-C, Kvaskoff M. Endometriosis and the risk of skin cancer: a prospective
1256 cohort study. *Cancer causes & control : CCC* 2017;**28**:1011.

1257 Fortuny J, Sima C, Bayuga S, Wilcox H, Pulick K, Faulkner S, Zauber AG, Olson SH. Risk
1258 of endometrial cancer in relation to medical conditions and medication use. *Cancer*
1259 *epidemiology, biomarkers & prevention : a publication of the American Association*
1260 *for Cancer Research, cosponsored by the American Society of Preventive Oncology*
1261 2009;**18**:1448.
1262 Gandini S, Lazzeroni M, Peccatori FA, Bendinelli B, Saieva C, Palli D, Masala G, Caini S.
1263 The risk of extra-ovarian malignancies among women with endometriosis: A
1264 systematic literature review and meta-analysis. *Critical Reviews in*
1265 *Oncology/Hematology* 2019;**134**:72–81.
1266 Ghiasi M, Kulkarni MT, Missmer SA. Is Endometriosis More Common and More Severe
1267 Than It Was 30 Years Ago? *J Minim Invasive Gynecol* 2020;**27**:452–461.
1268 Glynn RJ, Colditz GA, Tamimi RM, Chen WY, Hankinson SE, Willett WW, Rosner B.
1269 Comparison of Questionnaire-Based Breast Cancer Prediction Models in the Nurses'
1270 Health Study. *Cancer Epidemiol Biomarkers Prev* 2019;**28**:1187–1194.
1271 Greenland S, Senn SJ, Rothman KJ, Carlin JB, Poole C, Goodman SN, Altman DG.
1272 Statistical tests, P values, confidence intervals, and power: a guide to
1273 misinterpretations. *Eur J Epidemiol* 2016;**31**:337–350.
1274 Guenego A, Mesrine S, Dartois L, Leenhardt L, Clavel-Chapelon F, Kvaskoff M, Boutron-
1275 Ruault M-C, Bonnet F. Relation between hysterectomy, oophorectomy and the risk of
1276 incident differentiated thyroid cancer: The E3N cohort. 2018;Available from:
1277 https://hal-univ-rennes1.archives-ouvertes.fr/hal-01952338.
1278 Hamling J, Lee P, Weitkunat R, Ambühl M. Facilitating meta-analyses by deriving relative
1279 effect and precision estimates for alternative comparisons from a set of estimates
1280 presented by exposure level or disease category. *Stat Med* 2008;**27**:954–970.

1281 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*
1282 2002;**21**:1539–1558.
1283 Holly EA, Cress RD, Ahn DK. Cutaneous Melanoma in Women III. Reproductive Factors
1284 and Oral Contraceptive Use. *Am J Epidemiol* 1995;**141**:943–950.
1285 Howard BV, Kuller L, Langer R, Manson JE, Allen C, Assaf A, Cochrane BB, Larson JC,
1286 Lasser N, Rainford M, *et al.* Risk of cardiovascular disease by hysterectomy status,
1287 with and without oophorectomy: the Women's Health Initiative Observational Study.
1288 *Circulation* 2005;**111**:1462–1470.
1289 Hsu H-C, Tseng K-Y, Wang H-C, Sung F-C, Ma W-F. Risk of Endometriosis and Subsequent
1290 Ovary and Breast Cancers in Nurses: A Population-Based Cohort Study in Taiwan.
1291 *International Journal of Environmental Research and Public Health* 2019;**16**:3469.
1292 Iversen L, Sivasubramaniam S, Lee AJ, Fielding S, Hannaford PC. Lifetime cancer risk and
1293 combined oral contraceptives: the Royal College of General Practitioners' Oral
1294 Contraception Study. *Am J Obstet Gynecol* 2017;**216**:580.e1-580.e9.
1295 Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, Amso NN,
1296 Apostolidou S, Benjamin E, Cruickshank D, *et al.* Ovarian cancer screening and
1297 mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a
1298 randomised controlled trial. *Lancet* 2016;**387**:945–956.
1299 Jegerlehner S, Bulliard J-L, Aujesky D, Rodondi N, Germann S, Konzelmann I, Chiolero A,
1300 NICER Working Group. Overdiagnosis and overtreatment of thyroid cancer: A
1301 population-based temporal trend study. *PLoS ONE* 2017;**12**:e0179387.
1302 Johnson CA, James D, Marzan A, Armaos M. Cervical Cancer: An Overview of
1303 Pathophysiology and Management. *Semin Oncol Nurs* 2019;**35**:166–174.

1304 Johnson NP, Hummelshoj L, Adamson GD, Keckstein J, Taylor HS, Abrao MS, Bush D,
1305 Kiesel L, Tamimi R, Sharpe-Timms KL, *et al.* World Endometriosis Society
1306 consensus on the classification of endometriosis. *Hum Reprod* 2017;**32**:315–324.
1307 Kim HS, Kim TH, Chung HH, Song YS. Risk and prognosis of ovarian cancer in women with
1308 endometriosis: a meta-analysis. *British Journal of Cancer* 2014;**110**:1878.
1309 Kobayashi H, Sumimoto K, Moniwa N, Imai M, Takakura K, Kuromaki T, Morioka E,
1310 Arisawa K, Terao T. Risk of developing ovarian cancer among women with ovarian
1311 endometrioma: a cohort study in Shizuoka, Japan. *International Journal of*
1312 *Gynecologic Cancer* 2007;**17**:37–43.
1313 Kok VC, Tsai H-J, Su C-F, Lee C-K. The Risks for Ovarian, Endometrial, Breast, Colorectal,
1314 and Other Cancers in Women With Newly Diagnosed Endometriosis or Adenomyosis:
1315 A Population-Based Study. *International Journal of Gynecologic Cancer*
1316 2015;**25**:968–976.
1317 Koushik A, Grundy A, Abrahamowicz M, Arseneau J, Gilbert L, Gotlieb WH, Lacaille J,
1318 Mes-Masson A-M, Parent M-É, Provencher DM, *et al.* Hormonal and reproductive
1319 factors and the risk of ovarian cancer. 2017;Available from: https://hal-riip.archives-
1320 ouvertes.fr/pasteur-01534637.
1321 Kvaskoff M, Horne AW, Missmer SA. Informing women with endometriosis about ovarian
1322 cancer risk. *The Lancet* 2017;**390**:2433–2434.
1323 Kvaskoff M, Mu F, Terry KL, Harris HR, Poole EM, Farland L, Missmer SA. Endometriosis:
1324 a high-risk population for major chronic diseases? *Hum Reprod Update* 2015;**21**:500–
1325 516.
1326 Lac V, Nazeran TM, Tessier-Cloutier B, Aguirre-Hernandez R, Albert A, Lum A, Khattra J,
1327 Praetorius T, Mason M, Chiu D, *et al.* Oncogenic mutations in histologically normal
1328 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. Evidence of a genetic link between endometriosis and ovarian cancer. *Fertility and sterility* 2016;**105**:35.

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* [Internet] 2015;**94**:.

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 (Phila)* 2018;**11**:735–778.

Lu Y, Cuellar-Partida G, Painter JN, Nyholt DR, Study AOC, Consortium (IEC) TIE, Morris AP, Fasching PA, Hein A, Burghaus S, *et al.* Shared genetics underlying epidemiological association between endometriosis and ovarian cancer. *Human Molecular Genetics* 2015;**24**:5955.

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 Obstetricia et Gynecologica Scandinavica* 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. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *International Journal of 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. *Human Reproduction (Oxford, England)* 2013;**28**:1406.

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. *Journal of Epidemiology and Global 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.

1401 Mu F, Rich-Edwards J, Rimm EB, Spiegelman D, Missmer SA. Endometriosis and Risk of
1402 Coronary Heart Disease. *Circ Cardiovasc Qual Outcomes* 2016;**9**:257–264.
1403 Nagle CM, Olsen CM, Webb PM, Jordan SJ, Whiteman DC, Green AC. Endometrioid and
1404 clear cell ovarian cancers – A comparative analysis of risk factors. *European Journal*
1405 *of Cancer* 2008;**44**:2477–2484.
1406 National Cancer Institute. SEER cancer statistics review (CSR) 1975–2014. Available
1407 https://seer.cancer.gov/csr/1975_2014 (accessed June 26, 2017).
1408 (accessed.https://seer.cancer.gov/csr/1975_2014. 2017;
1409 Ness RB, Cramer DW, Goodman MT, Kjaer SK, Mallin K, Mosgaard BJ, Purdie DM, Risch
1410 HA, Vergona R, Wu AH. Infertility, Fertility Drugs, and Ovarian Cancer: A Pooled
1411 Analysis of Case-Control Studies. *Am J Epidemiol* 2002;**155**:217–224.
1412 Nichols HB, Visvanathan K, Newcomb PA, Hampton JM, Egan KM, Titus-Ernstoff L,
1413 Trentham-Dietz A. Bilateral Oophorectomy in Relation to Risk of Postmenopausal
1414 Breast Cancer: Confounding by Nonmalignant Indications for Surgery? *American*
1415 *Journal of Epidemiology* 2011;**173**:1111.
1416 Nnoaham KE, Hummelshoj L, Webster P, Hooghe T d', Nardone F de C, Nardone C de C,
1417 Jenkinson C, Kennedy SH, Zondervan KT. Impact of endometriosis on quality of life
1418 and work productivity: a multicenter study across ten countries. *Fertility and sterility*
1419 2011;**96**:366.
1420 Olson JE, Cerhan JR, M.s CAJ, Anderson KE, Vachon CM, Sellers TA. Postmenopausal
1421 cancer risk after self-reported endometriosis diagnosis in the Iowa Women's Health
1422 Study. *Cancer* 2002;**94**:1612–1618.
1423 Painter JN, O'Mara TA, Morris AP, Cheng THT, Gorman M, Martin L, Hodson S, Jones A,
1424 Martin NG, Gordon S, *et al.* Genetic overlap between endometriosis and endometrial

cancer: evidence from cross-disease genetic correlation and GWAS meta-analyses. *Cancer medicine* 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, *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. *The Lancet Oncology* 2012;**13**:385.

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.

1449 Prescott J, Farland LV, Tobias DK, Gaskins AJ, Spiegelman D, Chavarro JE, Rich-Edwards
1450 JW, Barbieri RL, Missmer SA. A prospective cohort study of endometriosis and
1451 subsequent risk of infertility. *Hum Reprod* 2016;**31**:1475–1482.
1452 Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of
1453 cancer: a systematic review and meta-analysis of prospective observational studies.
1454 *Lancet* 2008;**371**:569–578.
1455 Rocca WA, Gazzuola-Rocca L, Smith CY, Grossardt BR, Faubion SS, Shuster LT, Kirkland
1456 JL, Stewart EA, Miller VM. Accelerated Accumulation of Multimorbidity After
1457 Bilateral Oophorectomy: A Population-Based Cohort Study. *Mayo Clin Proc*
1458 2016;**91**:1577–1589.
1459 Rosner B, Glynn RJ, Tamimi RM, Chen WY, Colditz GA, Willett WC, Hankinson SE. Breast
1460 cancer risk prediction with heterogeneous risk profiles according to breast cancer
1461 tumor markers. *Am J Epidemiol* 2013;**178**:296–308.
1462 Rossing MA, Cushing-Haugen KL, Wicklund KG, Doherty JA, Weiss NS. Risk of Epithelial
1463 Ovarian Cancer in Relation to Benign Ovarian Conditions and Ovarian Surgery.
1464 *Cancer causes & control : CCC* 2008;**19**:1357.
1465 Rothman KJ. Disengaging from statistical significance. *Eur J Epidemiol* 2016;**31**:443–444.
1466 Rowlands IJ, Nagle CM, Spurdle AB, Webb PM. Gynecological conditions and the risk of
1467 endometrial cancer. *Gynecologic Oncology* 2011;**123**:537–541.
1468 Ruderman R, Pavone ME. Ovarian cancer in endometriosis: an update on the clinical and
1469 molecular aspects. *Minerva Ginecol* 2017;**69**:286–294.
1470 Ruiz MP, Morales-Ramirez PB, Dziadek OL, Algren SD. Epithelial ovarian cancer and type
1471 of peritoneal insult: a case-control study. *European journal of obstetrics, gynecology,*
1472 *and reproductive biology* 2016;**205**:170–173.

1473 Saavalainen L, Lassus H, But A, Tiitinen A, Härkki P, Gissler M, Heikinheimo O, Pukkala E.
1474 A Nationwide Cohort Study on the risk of non-gynecological cancers in women with
1475 surgically verified endometriosis. *International Journal of Cancer* 2018a;**143**:2725–
1476 2731.
1477 Saavalainen L, Lassus H, But A, Tiitinen A, Härkki P, Gissler M, Pukkala E, Heikinheimo O.
1478 Risk of Gynecologic Cancer According to the Type of Endometriosis. *Obstetrics &*
1479 *Gynecology* 2018b;**131**:1095–1102.
1480 Saraswat L, Ayansina D, Cooper KG, Bhattacharya S, Horne AW, Bhattacharya S. Impact of
1481 endometriosis on risk of further gynaecological surgery and cancer: a national cohort
1482 study. *BJOG: An International Journal of Obstetrics & Gynaecology* 2018;**125**:64–72.
1483 Shafrir AL, Farland LV, Shah DK, Harris HR, Kvaskoff M, Zondervan K, Missmer SA. Risk
1484 for and consequences of endometriosis: A critical epidemiologic review. *Best Pract*
1485 *Res Clin Obstet Gynaecol* 2018;**51**:1–15.
1486 Simoens S, Hummelshoj L, Dunselman G, Brandes I, Dirksen C, D'Hooghe T, Consortium E.
1487 Endometriosis Cost Assessment (the EndoCost Study): A Cost-of-Illness Study
1488 Protocol. *GOI* 2011a;**71**:170–176.
1489 Simoens S, Meuleman C, D'Hooghe T. Non-health-care costs associated with endometriosis.
1490 *Hum Reprod* 2011b;**26**:2363–2367.
1491 Sotelo JL, Musselman D, Nemeroff C. The biology of depression in cancer and the
1492 relationship between depression and cancer progression. *Int Rev Psychiatry*
1493 2014;**26**:16–30.
1494 Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D,
1495 Altman DG, Ansari MT, Boutron I, *et al.* ROBINS-I: a tool for assessing risk of bias
1496 in non-randomised studies of interventions. *BMJ* [Internet] 2016;**355**:.

Stewart LM, Holman CDJ, Aboagye-Sarfo P, Finn JC, Preen DB, Hart R. In vitro fertilization, endometriosis, nulliparity and ovarian cancer risk. *Gynecol Oncol* 2013;**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 Epidemiology* 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. *Journal of Women's 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, *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* [Internet] 2019;Available from:

https://academic.oup.com/humrep/advance-article/doi/10.1093/humrep/dez165/5584449.

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. *Nature Reviews Cancer* 2011;**11**:719–725. Nature Publishing Group.

Venn A, Watson L, Bruinsma F, Giles G, Healy D. Risk of cancer after use of fertility drugs with in-vitro fertilisation. *The 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**:.

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* [Internet] 2014;**14**:.

Wasserstein RL, Lazar NA. The ASA Statement on p-Values: Context, Process, and Purpose. *The American Statistician* 2016;**70**:129–133. Taylor & Francis.

1547 Weiss HA, Brinton LA, Potischman NA, Brogan D, Coates RJ, Gammon MD, Malone KE,
1548 Schoenberg JB. Breast cancer risk in young women and history of selected medical
1549 conditions. *Int J Epidemiol* 1999;**28**:816–823.
1550 Wentzensen N, Poole EM, Trabert B, White E, Arslan AA, Patel AV, Setiawan VW,
1551 Visvanathan K, Weiderpass E, Adami H-O, *et al.* Ovarian Cancer Risk Factors by
1552 Histologic Subtype: An Analysis From the Ovarian Cancer Cohort Consortium.
1553 *Journal of Clinical Oncology* 2016;**34**:2888.
1554 Whitaker LHR, Byrne D, Hummelshoj L, Missmer SA, Saraswat L, Saridogan E, Tomassetti
1555 C, Horne AW. Proposal for a new ICD-11 coding classification system for
1556 endometriosis. *Eur J Obstet Gynecol Reprod Biol* 2019;**241**:134–135.
1557 Williams CL, Jones ME, Swerdlow AJ, Botting BJ, Davies MC, Jacobs I, Bunch KJ, Murphy
1558 MFG, Sutcliffe AG. Risks of ovarian, breast, and corpus uteri cancer in women treated
1559 with assisted reproductive technology in Great Britain, 1991-2010: data linkage study
1560 including 2.2 million person years of observation. *BMJ* [Internet] 2018;**362**:.
1561 Yeh C-C, Su F-H, Tzeng C-R, Muo C-H, Wang W-C. Women with adenomyosis are at higher
1562 risks of endometrial and thyroid cancers: A population-based historical cohort study.
1563 *PLOS ONE* 2018;**13**:e0194011.
1564 Yland J, Carvalho LFP, Beste M, Bailey A, Thomas C, Abrão MS, Racowsky C, Griffith L,
1565 Missmer SA. Endometrioma, the follicular fluid inflammatory network and its
1566 association with oocyte and embryo characteristics. *Reprod Biomed Online* 2019;
1567 Young P, Purdie D, Jackman L, Molloy D, Green A. A study of infertility treatment and
1568 melanoma. *Melanoma Res* 2001;**11**:535–541.
1569 Zondervan K, Becker C, Missmer SA. Endometriosis. *NEJM, in press* 2020;
1570 Zondervan KT, Becker CM, Koga K, Missmer SA, Taylor RN, Viganò P. Endometriosis. *Nat*
1571 *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. *European Journal of Cancer Prevention* 2009;**18**:316–321.

Table 1. Risk of bias for the 49 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 et al., 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., 2005, Denmark	Low	Low	Low	Low	Low	Low	Low	Low
Brinton et al., 2005, 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
Pearce et al., 2012 Multiple locations	Moderate	Moderate	Serious	Moderate	Low	Moderate	Low	Serious
Stewart et al., 2012, Australia	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Buis et al., 2013, The Netherlands	Low	Moderate	Low	Low	Moderate	Low	Low	Moderate
Morales et al., 2013, Puerto Rico	Low	Moderate	Serious	Moderate	Moderate	Low	Moderate	Serious
Stewart et al., 2013, Australia	Low	Moderate	Low	Low	No information	Low	Low	Moderate
Braganza et al., 2014, USA	Low	Low	Serious	Low	Low	Low	Low	Serious
Brinton et al., 2014, USA	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
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., 2016, USA	Low	Low	Low	Low	No information	Low	Low	Low
Mogensen et al., 2016, Denmark	Low	Low	Low	Low	No information	Low	Low	Low
Ruiz et al., 2016, USA	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., 2018, Finland	Critical	Low	Low	Low	No information	Low	Low	Critical
Saavalainen et al., 2018, Finland	Critical	Low	Low	Low	No information	Low	Low	Critical
Saraswat et al., 2018, Scotland	Moderate	Low	Low	Low	Low	Low	Low	Moderate
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

Table 2. Summary relative risks (SRR) and 95% confidence intervals (CI) for the associations between endometriosis and cancer risk, overall and by cancer type for those cancer types with at least 4 studies published through 2019

	Number of studies	SRR (95% CI)	I^2 (%)	P^a_{within}	$P^b_{between}$
Overall cancer					
All Studies	5	1.07 (0.98-1.16)	87.9	<0.0001	
By Study Design					
Case-Control	0	--	--	--	
Cohort	5	1.07 (0.98-1.16)	87.9	<0.0001	
Retrospective cohort	4	1.10 (1.00-1.21)	90.4	<0.0001	0.33
Prospective cohort	1	0.90 (0.77-1.05)	--	--	
By Geographical Location					
North America	1	0.90 (0.77-1.05)	--	--	0.20
Europe	3	1.03 (0.97-1.11)	84.8	0.001	
Asia	1	1.80 (1.37-2.36)	--	--	
Australia	0	--	--	--	
Multiple Locations	0	--	--	--	
By Assessment of Endometriosis					
Self-reported	1	0.90 (0.77-1.05)	--	--	0.33
Medical Records / Registry	4	1.10 (1.00-1.21)	90.4	<0.0001	
Required Temporality[c]					
No	0	--	--	--	
Yes	5	1.07 (0.98-1.16)	87.9	<0.0001	
ROBINS-I Risk of Bias					
Low/moderate	2	1.45 (0.98-2.13)	86.0	0.008	0.08
Serious/critical	3	0.99 (0.96-1.02)	36.6	0.21	
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 Geographical 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	

Table 2. Summary relative risks (SRR) and 95% confidence intervals (CI) for the associations between endometriosis and cancer risk, overall and by cancer type for those cancer types with at least 4 studies published through 2019

	Number of studies	SRR (95% CI)	I^2 (%)	P^a_{within}	$P^b_{between}$
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 Geographical 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	--	--	--	
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	

Table 2. Summary relative risks (SRR) and 95% confidence intervals (CI) for the associations between endometriosis and cancer risk, overall and by cancer type for those cancer types with at least 4 studies published through 2019

	Number of studies	SRR (95% CI)	I^2 (%)	P^a_{within}	$P^b_{between}$
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 Geographical 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	
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 Geographical 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	

Table 2. Summary relative risks (SRR) and 95% confidence intervals (CI) for the associations between endometriosis and cancer risk, overall and by cancer type for those cancer types with at least 4 studies published through 2019

	Number of studies	SRR (95% CI)	I^2 (%)	P^a_{within}	$P^b_{between}$
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 Geographical 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					
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 Geographical 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	

Table 2. Summary relative risks (SRR) and 95% confidence intervals (CI) for the associations between endometriosis and cancer risk, overall and by cancer type for those cancer types with at least 4 studies published through 2019

	Number of studies	SRR (95% CI)	I^2 (%)	P^a_{within}	$P^b_{between}$
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 Geographical 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	

Footnote: SRR summary relative risk; CI confidence interval

I^2 (%) is a measure of the proportion of the heterogeneity attributed to between study variation rather than due to chance. I^2-valuesof 25%, 50% and 75% indicates 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

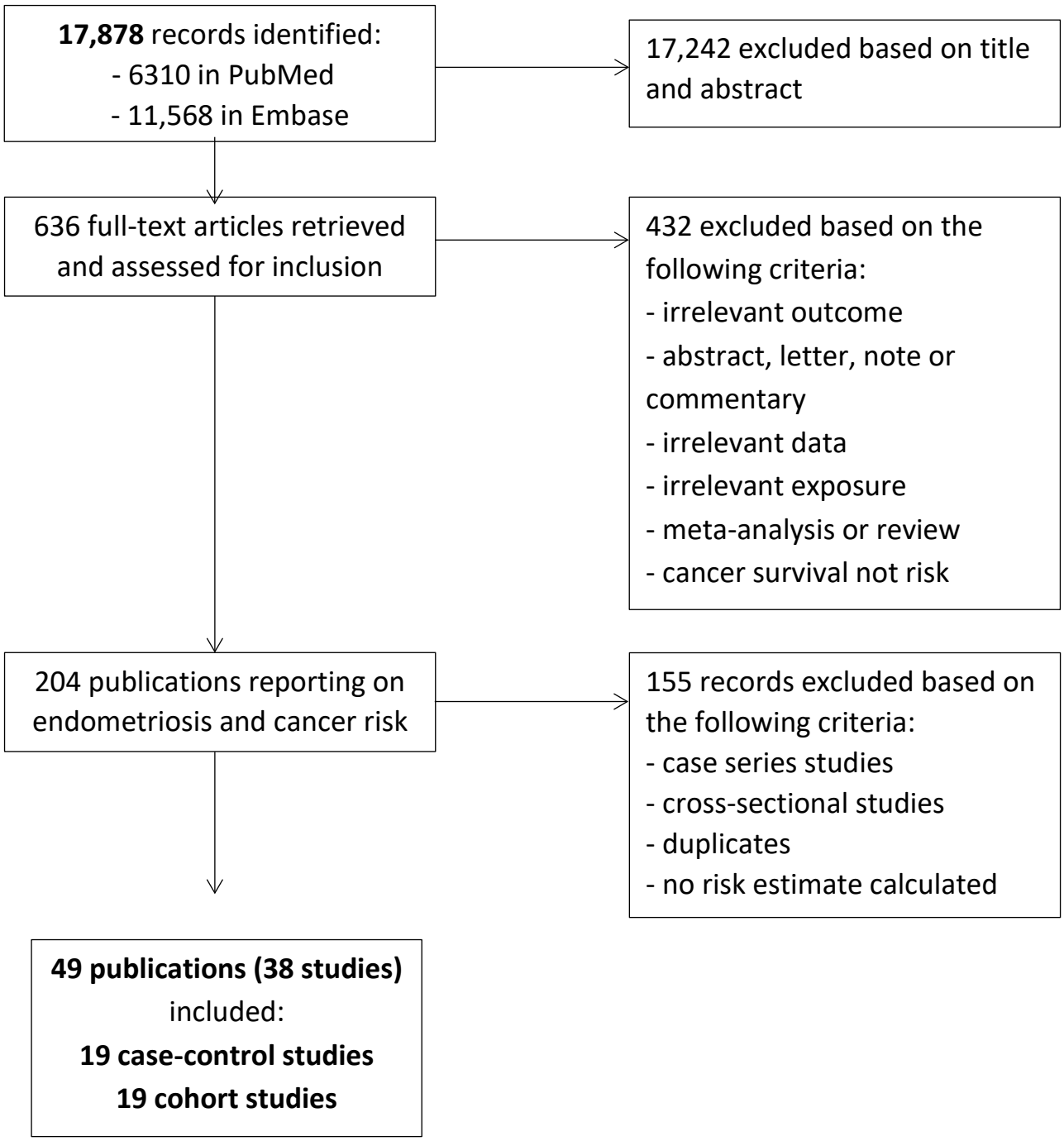


Figure 1. Flow-chart of study selection

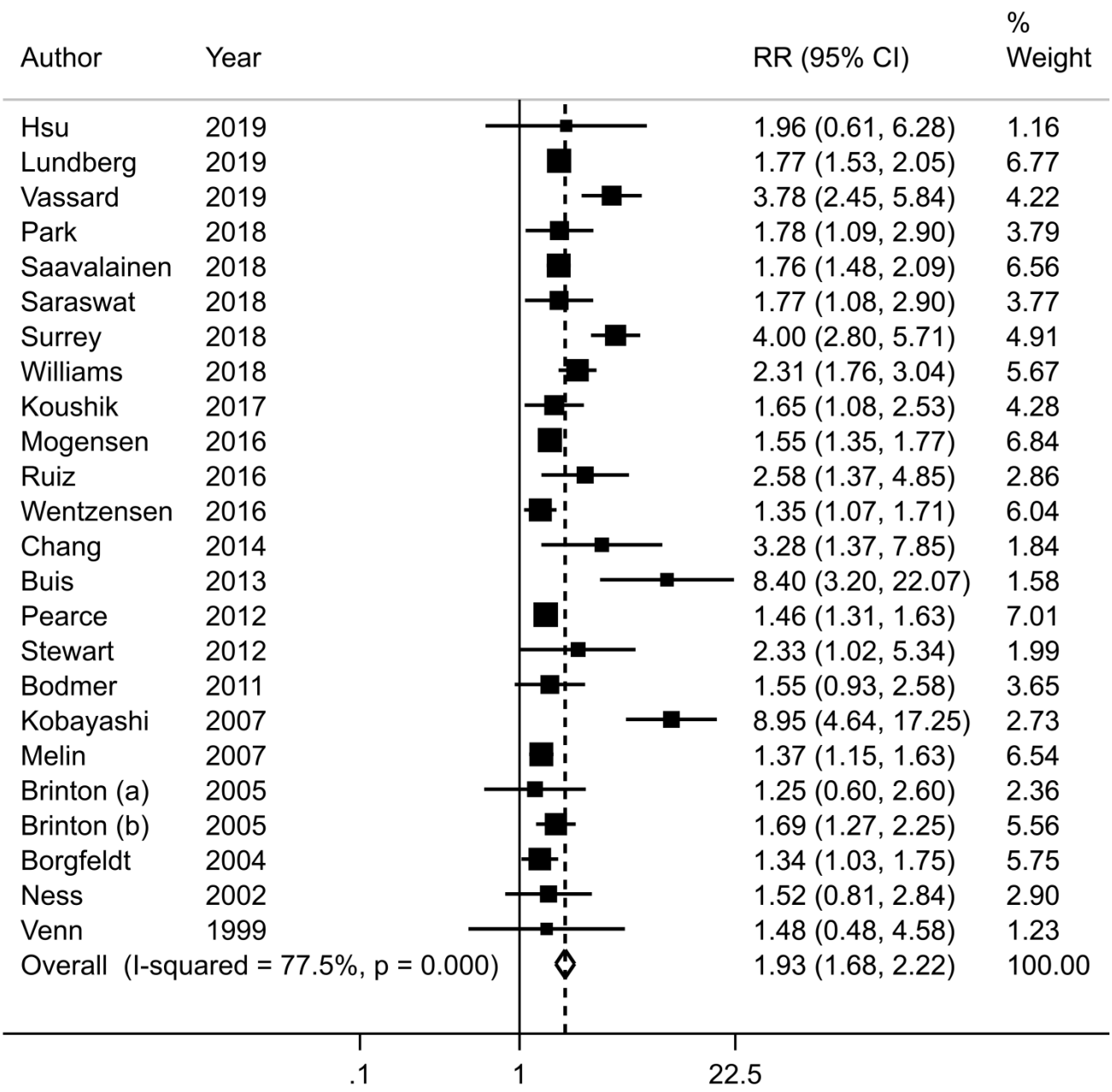


Figure 2. Association between endometriosis and ovarian cancer risk among 24 studies published through 2019.

* Note: Brinton (a) conducted in the US 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, CI=confidence interval, p=p-value, test for between study heterogeneity

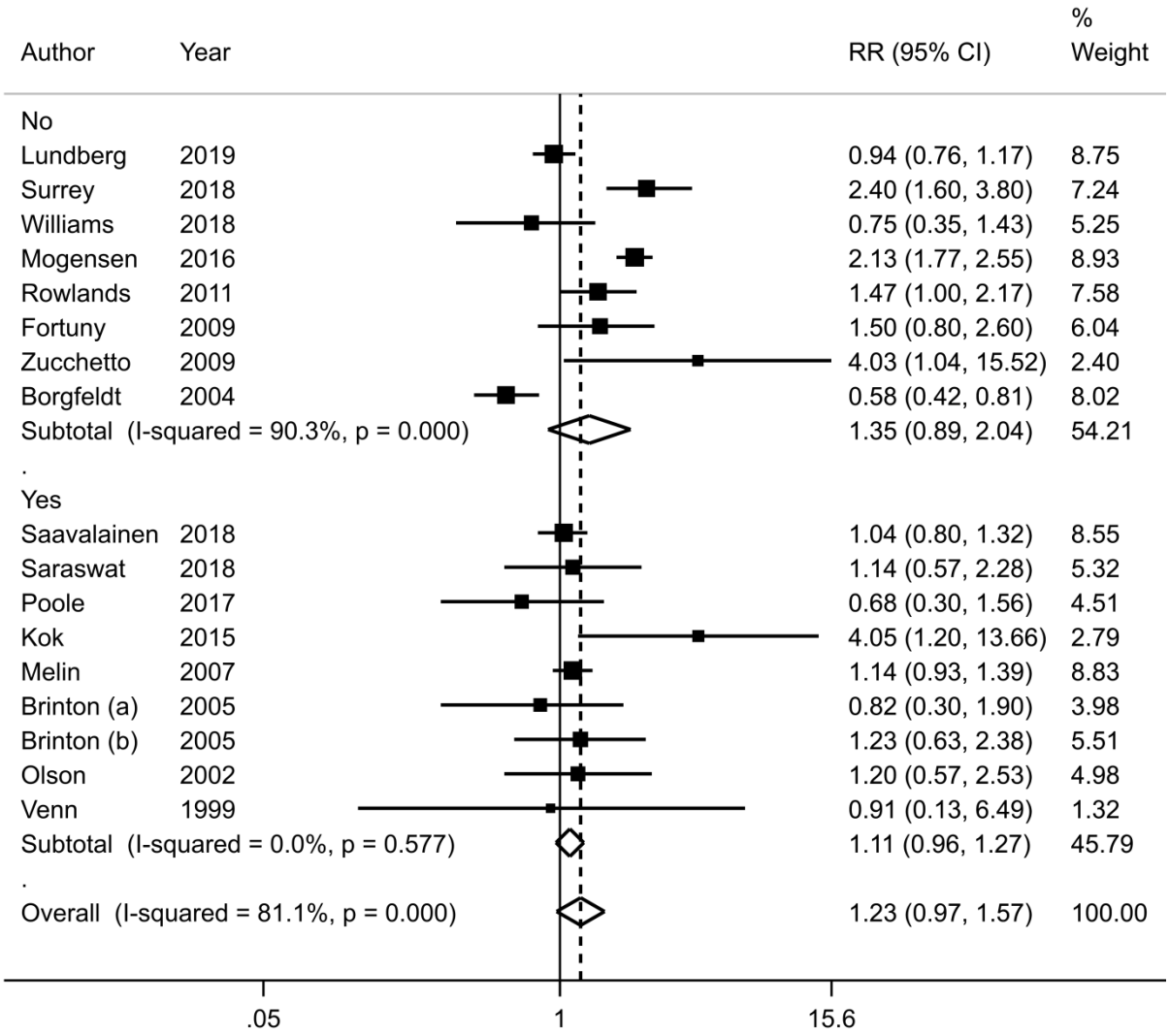


Figure 3. Evaluation of the association between endometriosis and endometrial cancer risk among 17 studies published through 2019; 8 that did not require temporality in the analyses, and 9 that did (i.e. endometriosis diagnosis had to precede the endometrial cancer diagnosis, not diagnosed concurrently)

* Note: Brinton (a) conducted in the US and Brinton (b) conducted in Denmark. RR=relative risk, CI=confidence interval, p=p-value, test for between study heterogeneity

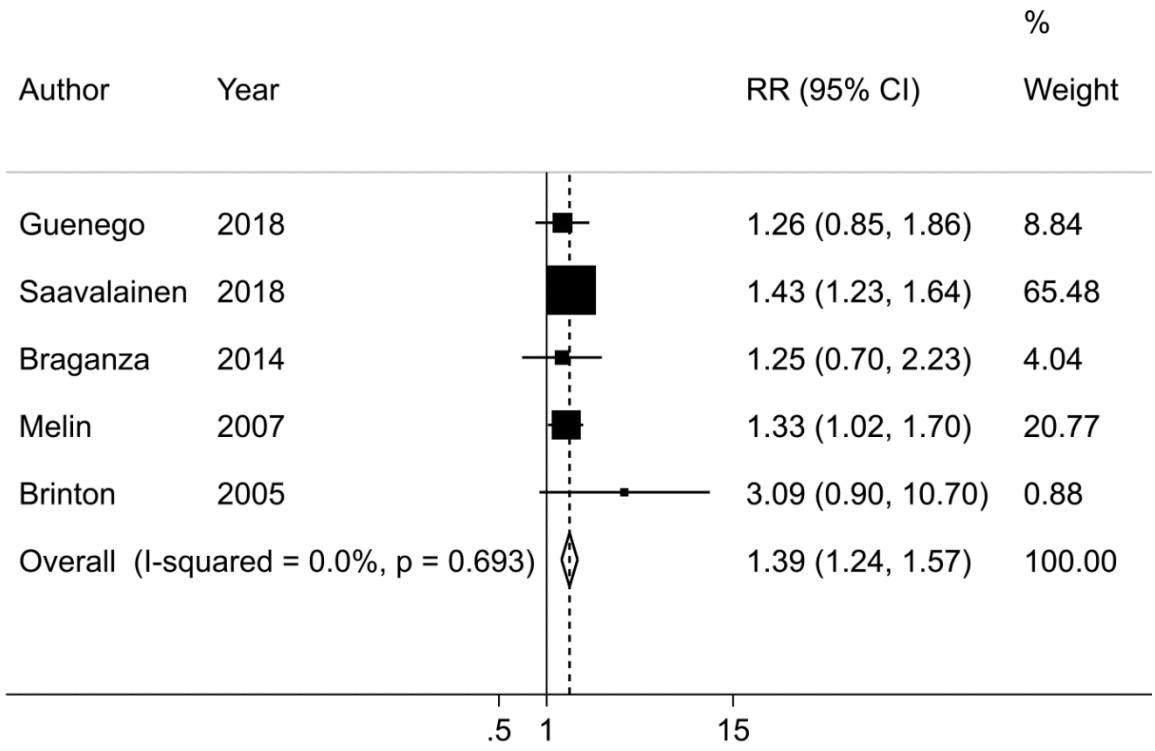


Figure 4. Evaluation of the association between endometriosis and thyroid cancer risk among 5 studies published through 2019.

*RR=relative risk, CI=confidence interval, p=p-value, test for between study heterogeneity

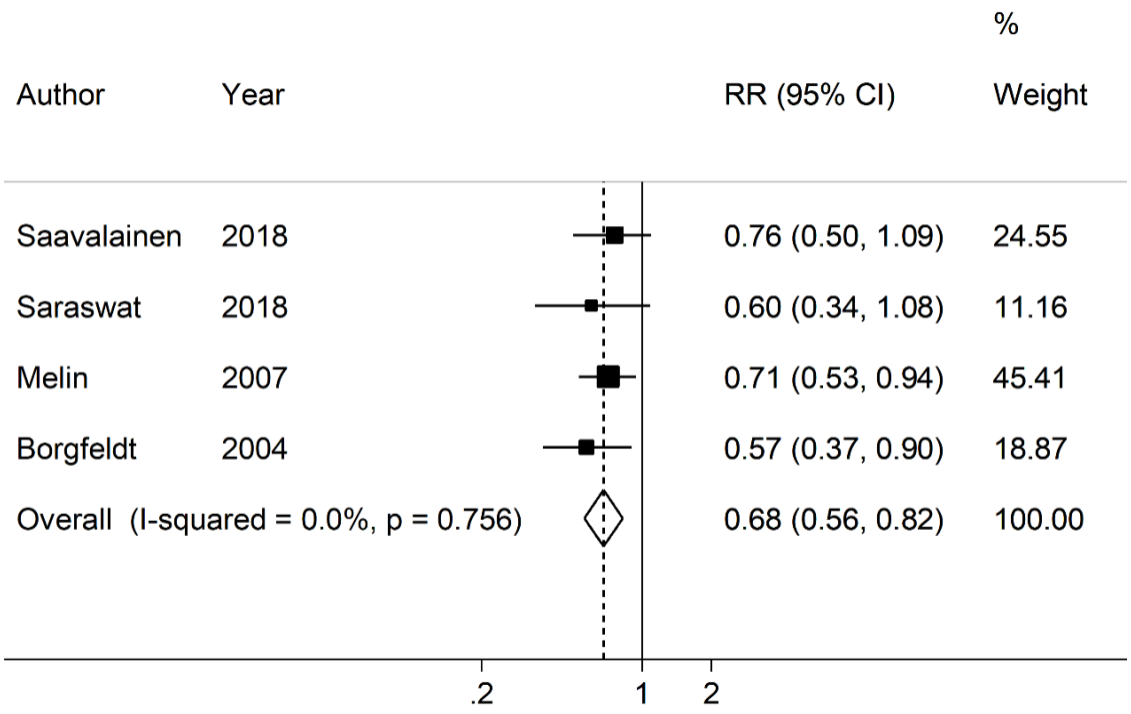


Figure 5. Evaluation of the association between endometriosis and cervical cancer risk among 4 studies published through 2019.

*RR=relative risk, CI=confidence interval, p=p-value, test for between study-heterogeneity

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
Moseson et al., 1993 USA	Case-control, population-based	1977–1981	20	Self-reported	354 BC	Medical records, histologically-confirmed	747; random sample of women screened at the same institute who were not diagnosed with BC by the end of 1981	**Cross-sectional:** Comparison of endometriosis in BC cases and controls; no information on years of dx	BC: OR=1.7 (0.6-5.1) Risk estimates by menopausal status	Age, family history of breast cancer, age at first full-term birth, nulliparity, height, menopausal status, screening variables, Jewish religion, and Latin American birthplace
Holly et al., 1995 USA	Case-control, population-based	1981-1986	–	Self-reported	452 MM	Medical records, histologically-confirmed	930; identified through random-digit dialing, matched on age and county of residence	**Cross-sectional:** Comparison of endometriosis in MM cases and controls; no information on years of dx	MM: 0.86 (0.53-1.4)	Age
Venn et al., 1999 Australia	Retrospective cohort of women with infertility	1981–1996	4809	Medical records (10 Australian IVF clinics)	143 BC 13 OvCa 12 EndCa	Medical records (population-based cancer registries and National Death Index)	Comparison to population rates	**Endometriosis dx preceded cancer dx:** Retrospective evaluation of cancer and endometriosis dx; information on years of dx	BC: SIR=1.04 (0.71–1.54) OvCa: SIR=1.48 (0.48–4.59) EndCa: SIR=0.91 (0.13–6.49)	Age, calendar time
Weiss et al., 1999 USA	Case-control, population-based	1990–1992	96	Self-reported	2173 BC	Medical records (cancer registries (Altanta, Seattle/Puget and 5 counties in central New jersey))	1990 controls; selected through random-digit dialing	**Cross-sectional**: Comparison of endometriosis in BC cases and controls; no information on years of dx	BC: OR=1.14 (0.7-1.8) Risk estimates by years since surgery and menopausal status	Age at diagnosis, race, site, menopausal status, age at first birth, number of births, family history, previous breast biopsy, alcohol consumption, BMI, and number of mammograms within the 5-year period prior to one year before diagnosis

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
Baron et al., 2001 USA	Case-control, population-based	1990–1994	11,366	Self-reported	5659 BC	Medical records (cancer registries (Wisconsin, Massachusetts, and New Hampshire))	5928; randomly selected from license drivers and Medicare lists, matched on age	**Cross-sectional:** Comparison of endometriosis in BC cases and controls; no information on years of dx	BC: OR=0.8 (0.7–1.0)	Age, state, age at first birth, BMI, family history of breast cancer, HRT use, menopausal status, age at menopause, OC use, parity, and alcohol use
Young et al., 2001 Australia	Case-control study of women with infertility, hospital-based	1980–1990	32	Medical records (large fertility clinic in Queensland)	14 MM	Medical records (QLD, NSW, and VIC Cancer registries)	93; randomly selected from the total cohort (women attending a large fertility clinic in Queesland), based on age strata	**Cross-sectional:** Retrospective evaluation of endometriosis and MM dx; no information on years of dx	MM: OR=0.62 (0.16-2.41)	Cohort entry year and entry age
Ness et al., 2002 Multiple locations (USA, Denmark, Canada, and Australia)	Pooled analysis of 8 population-based case-control studies	1989–1999	90	Self-reported	5207 OvCa	Medical records (treatment centers; national and cancer registries; hospitals)	7705; Random digit dialing, town lists, population registers	**Cross-sectional**: Retrospective evaluation of cancer and endometriosis dx; no information on years of dx	OvCa: OR=1.52 (0.81-2.83)	Age, gravidity, race, education, family history of ovarian cancer, tubal ligation, duration of oral contraceptive use, and research site plus other infertility types
Olson et al., 2002 USA	Prospective cohort of post-menopausal women	1986–1998	1392	Self-reported	1795 BC 188 OvCa 243 NHL	Medical records (State Health Registry of Iowa)	36,042; women from the cohort without cancer	**Endometriosis dx preceded cancer dx**: Prospective evaluation of cancer and endometriosis dx; exclusion of women with a prevalent cancer at baseline or bilateral oophorectomy/hysterectomy/mastectomy/chemotherapy (for OvCa/EndCa/BC/NHL)	TotCa: RR=0.90 (0.77–1.05) BC: RR=0.96 (0.75–1.23) CRC: RR=0.73 (0.48–1.10) EndCa: RR=1.20 (0.57–2.53) Lung cancer: RR=1.11 (0.74–1.66) MM: RR=0.67 (0.25–1.80)	Any cancer: smoking, pack-years, age at first live birth/parity, alcohol intake, hormone replacement, body mass index. Breast cancer: age at first live birth/parity, education, alcohol intake, hormone

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
									NHL: RR=1.67 (0.97–2.87) OvCa: RR=0.78 (0.25–2.44) Urinary tract cancer: RR=0.81 (0.38–1.73)	replacement, body mass index. Lung cancer: smoking history, pack-years, body mass index. NHL: transfusion history, marital status, and alcohol intake. CRC, EndCa, melanoma, OvCa, urinary tract cancer: age
Borgfeldt et al., 2004 Sweden	Case-control, hospital-based	1969–1997	28,163	Medical records (Swedish Hospital Discharge Registry)	81 OvCa 427 BC 39 EndCa 22 CervCa	Medical records (Swedish Hospital Discharge Register)	81,073; Swedish Population Register, 3 controls per case matched on date of birth	**Cross-sectional**: Retrospective evaluation of cancer and endometriosis; cancer dx was considered starting from 1 year after hospital discharge for endometriosis; information on years of dx but no time-varying analysis	OvCa: OR=1.34 (1.03–1.75) BC: OR=1.10 (0.98–1.23) EndCa: OR=0.58 (0.42–0.81) CervCa: OR=0.57 (0.37–0.90)	None
Brinton et al., 2004 USA	Retrospective cohort of women with infertility	1965–1999	1919	Medical records (large reproductive endocrinology and infertility practices in 5 areas in the US)	45 OvCa	Self-reported (n=13), medical records/cancer registries (n=21), or National Death Index (n=10)	Comparison to population rates (SEER data)	**Endometriosis dx preceded cancer dx:** Retrospective evaluation of cancer and endometriosis at 5 large practices; information on years of dx; exclusion of women with bilateral oophorectomy or OvCa within 1 year of inclusion	OvCa: SIR=2.48 (1.3–4.2)	None

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
Brinton et al., 2005 Denmark	Retrospective cohort	1978-1998	71 occurring prior to cancer	Medical records (Hospital Discharge Register)	2491 OvCa (860 BOT, 932 serous, 344 mucinous, 300 endometrioid, 123 clear-cell) 1389 EndCa (1178 CIT, 137 sarcomas)	Medical records (Danish Cancer Register)	99,421 / 99,172; Central Population Register	**Endometriosis dx preceded cancer dx:** Retrospective evaluation of cancer and endometriosis dx; information on years of dx; exclusion of prevalent hysterectomy, bilateral oophorectomy, and OvCa or EndCa	OvCa: RR=1.69 (1.27-2.25) BOT: RR=1.22 (0.69-2.17) Serous: RR=1.20 (0.70-2.04) Mucinous: RR=1.01 (0.38-2.71) Endometrioid: RR=3.37 (1.92-5.91) Clear-cell: RR=3.03 (1.23-7.44) EndCa: RR=1.23 (0.63-2.38) CIT: RR=1.14 (0.54-2.42) Sarcomas: RR=2.72 (0.66-11.12) - Risk estimates by years since endometriosis dx	Calendar time, parity, number of births, and age at first birth as time-dependent variables
Brinton et al., 2005 USA	Retrospective cohort of women with infertility	1965–1999	-	Medical records (large reproductive endocrinology and infertility practices in 5 areas in the US)	45 OvCa 39 EndCa 292 BC 28 Colon 42 MM 18 ThyrCa	Self-reported, medical records, and cancer registries	women from the cohort who did not develop any cancer	**Endometriosis dx preceded cancer dx:** Retrospective evaluation of cancer and endometriosis at 5 large practices; information on years of dx; exclusion of the 1st year of follow-up	OvCa: RR=1.25 (0.6–2.6) EndCa: RR=0.82 (0.3–1.9) BC: RR=0.78 (0.6-1.1) Colon: RR=2.00 (0.7-5.4) MM: RR=2.06 (1.0–4.4) ThyrCa: RR=3.09 (0.9-10.7)	Age at follow-up, calendar time, study sites, gravidity at entry, and all causes of infertility

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
Melin et al., 2006 Sweden	Retrospective cohort	1969–2000	64,492	Medical records (Swedish Hospital Discharge Register)	3,349 TotCa 51 Buccal/pharynx 54 Gastric 81 Pancreatic 181 Lung 64 Bladder 75 NMSC 214 Haematopoetic 113 NHL 23 Liver 188 Large intestine 118 Rectal	Medical records (National Swedish Cancer Register)	Comparison to population rates	**Endometriosis dx preceded cancer dx:** Retrospective evaluation of cancer and endometriosis in a national patient register; information on years of dx; exclusion of the 1st year of follow-up	TotCa: SIR=1.04 (1.00–1.07) Buccal: SIR=1.13 (0.84–1.49) Gastric: SIR=0.91 (0.68–1.19) Pancreatic: SIR=1.20 (0.95–1.49) Lung: SIR=0.94 (0.81-1.09) Bladder: SIR=0.95 (0.74–1.22) NMSC: SIR=1.05 (0.82–1.31) Haematopoetic: SIR=1.12 (0.98–1.28) NHL: SIR=1.24 (1.02–1.49) Liver: SIR=1.21 (0.77–1.82) Large intestine: SIR=0.95 (0.82–1.10) Rectal: SIR=1.05 (0.87–1.25)	None

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
Bertelsen et al., 2007 Denmark	Case–cohort study	1978–1998	1978	Medical records (Danish Hospital Discharge Register)	16,983 BC	Medical records (Danish Cancer Registry)	97,344 women in the remaining sub-cohort	**Endometriosis dx preceded cancer dx:** Retrospective evaluation of endometriosis and BC; information on years of dx; exclusion of BC cases occurring prior to baseline; time-varying analysis (women with endometriosis occurring after BC were considered unexposed); latency of 1 year between endometriosis and BC dx	BC: RR=0.97 (0.85-1.11) - OMA: RR=0.92 (0.73-1.14) Uterus: RR=1.04 (0.83-1.30) Pelvis: RR=0.89 (0.62-1.17) - **Follow-up >=1 year afer endo dx** BC: RR=0.91 (0.79–1.06) - OMA: RR=0.84 (0.67-1.07) Uterus: RR=0.96 (0.76-1.22) Pelvis: RR=0.87 (0.63-1.20) - Risk estimates by year of and age at endometriosis dx	Parity, parental status, age at birth of first child, benign breast disease, bilateral oophorectomy, and calendar year
Kobayashi et al., 2007 Japan	Prospective cohort	1985–2002	6398 OMA	Medical records of a positive ultrasound (registration at the local hospitals)	46 OvCa	Medical records (Shizuoka Cancer Registry)	Comparison of OvCa rates in the endometriosis cohort and the cancer registry	**Endometriosis dx preceded cancer dx:** Retrospective evaluation of OvCa and OMA in a cancer registry; information on years of dx	OvCa: SIR=8.95 (4.12–15.3) Risk estimates by years of follow-up and age at OMA dx	Age and calendar year

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
Melin et al., 2007 Sweden	Retrospective cohort	1958-2002	63,630	Medical records (Swedish Hospital Discharge Register)	3822 TotCa 134 OvCa 1465 BC 64 ThyrCa 186 BrainCa 217 MM 104 KidneyCa 97 EndCa 49 CervCa	Medical records (National Swedish Cancer Register)	Comparison to population rates	**Endometriosis dx preceded cancer dx:** Retrospective evaluation of endometriosis and cancer dx in a national patient register; information on years of dx; follow-up for cancer started 1 year after endometriosis dx to exclude prevalent cancers	TotCa: SIR=1.01 (0.98-1.05) OvCa: SIR=1.37 (1.14–1.62) BC: SIR=1.08 (1.02–1.13) ThyrCa: SIR=1.33 (1.02–1.70) BrainCa: SIR=1.27 (1.09–1.46) MM: SIR=1.23 (1.07–1.40) KidneyCa: SIR=1.36 (1.11–1.64) EndCa: SIR=1.14 (0.93–1.39) CervCa: SIR=0.71 (0.53–0.94)	None
Fortuny et al., 2009 USA	Case-control, population-based	2001-2005	59	Self-reported	469 EndCa	Medical records (histologically-confirmed)	467; selected through random-digit dialing (n=175), Centers for Medicare and Medicaid lists (n=68), and area sampling (n=224)	**Cross-sectional:** Comparison of endometriosis in EndCa cases and controls; no information on years of dx	EndCa: OR=1.5 (0.8-2.6)	Age and BMI
Zucchetto et al., 2009 Italy	Case-control, hospital-based	1992–2006	11	Self-reported	454 EndCa	Medical records (histologically-confirmed)	908; women admitted to the same hospital with non-neoplastic conditions; 2 controls per case matched on study center and age	**Cross-sectional:** Comparison of endometriosis in EndCa cases and controls; no information on years of dx	EndCa: OR=4.03 (1.04-15.52)	Stratified on center and age, and adjusted for period of interview, BMI, age at menarche, age at menopause, parity, and OC use

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
Bodmer et al., 2011 United Kingdom	Case-control, hospital-based	1995–2009	88	Medical records (UK-based General Practice Research Database)	1611 OvCa	Medical records (UK-based General Practice Research Database)	9170; up to 6 controls per case, women without any evidence for OvCa matched on calendar time, age, sex, general practice, and number of years of active history in the GPRD prior to the index date	**Cross-sectional:** Comparison of endometriosis in OvCa cases and controls, with no information on years of dx; exclusion of women with a history of ovarian disease prior to the index date	OvCa: OR=1.55 (0.93–2.57)	None
Nichols et al., 2011 USA	Case-control study of postmenopausal women, population-based	1992–1995	426	Self-reported	4935 BC	Medical records (cancer registries (Wisconsin, Massachusetts, and New Hampshire))	5111; randomly selected from license drivers and Medicare lists, matched on age	**Cross-sectional:** Comparison of endometriosis in BC cases and controls; no information on years of dx; exclusion of exposures occurring prior to the reference date	BC: OR=0.99 (0.80-1.21)	Age, US state, age at menarche, duration of oral contraceptive use, parity, age at first birth, age at menopause, postmenopausal hormone use, BMI, mammography screening, and family history of breast cancer
Rowlands et al., 2011 Australia	Case-control, population-based	2003-2007	119	Self-reported	1399 EndCa (1077 type I 322 type II)	Medical records (cancer registries)	1539; selected from the national electoral roll, matched on state of residence and age	**Endometriosis dx preceded cancer dx:** Comparison of endometriosis in EndCa cases and controls; information on age at endometriosis dx; exclusion of women diagnosed in the 12 months prior to cancer dx (cases) or first approach (controls)	EndCa: OR=1.41 (1.00-2.17) Type I: OR=1.48 (0.98-2.23) Type II: OR=1.44 (0.80-2.59) - **Excluding last 12 months** EndCa: OR=1.04 (0.69-1.56) Type I: OR=1.10	Age, age at menarche, parity, duration of OC use, HRT use, smoking, and BMI

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
									(0.71-1.70) Type II: OR=0.82 (0.41-1.66)	
Pearce et al., 2012 Multiple locations (USA, Europe, and Australia)	Pooled analysis of case-control studies	1993–2010	–	Self-reported	7911 OvCa	–	13,226; multiple sources: population, hospital, clinic	**Cross-sectional**: Comparison of endometriosis in OvCa cases and controls, with no information on years of dx	OvCa: OR=1.46 (1.31–1.63) Serous: OR=1.20 (0.95-1.52) Mucinous: OR=1.02 (0.69-1.50) Endometrioid: OR=2.04 (1.67-2.48) Clear-cell: OR=3.05 (2.43-3.84)	Conditioned on age and race/ethnicity
Stewart et al., 2012 Australia	Retrospective cohort of women with infertility	1982–2002	2978 in women with IVF treatment	Medical records (Western Australia Data Linkage System)	38 OvCa	Medical records (cancer registry)	21,646 women in the total cohort; women seeking hospital care for infertility at all hospitals in Western Australia	**Endometriosis dx preceded cancer dx:** Retrospective evaluation of cancer and endometriosis dx; information on years of diagnosis; time-varying analysis	OvCa: HR=2.33 (1.02-5.53)	IVF, socio-economic status, age, and calendar year at the first infertility admission
Buis et al., 2013 The Netherlands	Retrospective cohort of women with subfertility problems	1989–2007	3657	Histo/cytopathology records (968); medical records (1883); self-report (806)	31 OvCa (19 invasive, 15 BOT)	Medical records (Dutch Pathology Database and Netherlands Cancer Registry)	5247; women with subfertility problems without endometriosis	**Endometriosis dx preceded cancer dx**: Retrospective evaluation of endometriosis and cancer dx; information on years of dx; inclusion of events in women diagnosed with OvCa after the date of 1st dx of endometriosis only	OvCa: HR=8.4 (3.2–22.1) Invasive OvCa: HR=12.7 (2.9-55.5) Borderline: HR=5.5 (1.5-20.4) OMA: OvCa: HR=11.3 (4.0-31.8) Non-OMA: OvCa: HR=7.7 (2.1-28.7)	Age, oral contraceptive use, parity

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
Morales et al., 2013 Puerto Rico	Case-control, hospital-based	2006–2012	94	Self-reported	465 BC	Medical records (histologically-confirmed)	661; women recruited in collaborating private clinical practices with a negative mammogram in previous 6 months, who had undergone a clinical breast examination, and who had not received blood transfusion within previous 5 years	**Cross-sectional:** Comparison of endometriosis in BC cases and controls, with no information on years of dx	BC: OR=0.61 (0.3-1.0)	Age, BMI, family history of breast cancer, menopause, number of children, alcohol use, smoking, and vitamin use
Stewart et al., 2013 Australia	Retrospective cohort of women with infertility	1982–2002	2978 in women with IVF treatment	Medical records (Western Australia Data Linkage System)	31 BOT	Medical records (cancer registry)	21,639 women in the total cohort; women seeking hospital care for infertility at all hospitals in Western Australia	**Endometriosis dx preceded cancer dx:** Retrospective evaluation of cancer and endometriosis dx; information on years of diagnosis; time-varying analysis	BOT: HR=0.31 (0.04-2.29)	IVF, socio-economic status, age, and calendar year at the first infertility admission
Braganza et al., 2014 USA	Prospective cohort	1993–2009	5549	Self-reported	127 ThyrCa (99 papillary 20 follicular)	Medical records (histologically-confirmed)	women from the cohort who did not report any cancer	**Endometriosis dx preceded cancer dx:** Prospective evaluation of endometriosis and ThyrCa dx; time-varying analysis	ThyrCa: HR=1.25 (0.70–2.23) Papillary: HR=1.52 (0.83-2.79)	Age, education, race, marital status, family history of thyroid cancer, baseline BMI status, and smoking status
Brinton et al., 2014 USA	Retrospective cohort of women with infertility	1965–2010	189 endometriosis among BC cases	Medical records (large reproductive endocrinology and infertility practices in 5 areas in the US)	749 BC	Medical records (cancer registries (n=607), medical records (n=61), death certificates (n=28)) or self-rported (n=53)	9143 women who sought infertility advice at 5 reproductive endocrinology practices	**Endometriosis dx preceded cancer dx**: Retrospective evaluation of cancer and endometriosis dx; information on years of dx and time-varying analysis	BC: HR: 1.12 (0.93–1.35)	Study site and calendar year of first infertility evaluation

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
Chang et al. 2014, Taiwan	Retrospective cohort	2000-2010	5468	Medical records (Taiwan National Health Insurance Research Database)	22 OvCa	Medical records (Taiwan National Health Insurance Research Database; at least 3 medical records)	15,074; comparison cohort: 2 non-endometriosis controls from the same database and matched by age, index year, obstetric history, socioeconomic status, work, urbanization	**Endometriosis dx preceded cancer dx**: Retrospective evaluation of endometriosis and cancer dx in a national health insurance database; exclusion of women with OvCa, endometriosis, or total hysterectomy before endometriosis dx; exclusion of women with synchronous endometriosis and OvCa and of those with OvCa dx within 1 year after endometriosis dx in a sensitivity analysis	OvCa: HR=3.28 (1.37-7.85) **Follow-up>=1 yr after 1st endo dx** OvCa: HR=3.87 (1.58-9.47)	Age, socioeconomic status, work, urbanization, pelvic inflammatory disease, infertility status, cardiovascular disease, diabetes mellitus, chronic liver disease, rheumatic disease, and Charlson Comorbidity Index
Chuang et al., 2015 Taiwan	Nested case-control	2002-2010	507	Medical records (Taiwan National Health Insurance Research Database)	4884 BC	Medical records (Taiwan National Health Insurance Research Database)	19,536; 4 controls per case selected from the health insurance database; matched to cases on year and month of birth, and year of Longitudinal Health Insurance Database	**Cross-sectional**: Retrospective evaluation of endometriosis and cancer dx in a national health insurance database; information on years of dx but no time-varying analysis	BC: OR=1.44 (1.15-1.80)	Occupation, number of screening tests before index date, and average outpatient visits 6 months before index date

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
Kok et al., 2015 Taiwan	Retrospective cohort	2003-2008	2266 (768 adenomyosis, 165 OMA, 1333 other/mixed)	Medical records (Taiwan National Health Insurance Research Database)	248 TotCa 22 OvCa 17 EndCa 69 BC 10 CRC	Medical records (Taiwan National Health Insurance Research Database)	9064; comparison cohort: 4 non-endometriosis controls sampled from the same database and matched on age and index date	**Endometriosis dx preceded cancer dx**: Retrospective evaluation of endometriosis and cancer dx in a national health insurance database; exclusion of women with prevalent cancer, hysterectomy or oophorectomy	TotCa: HR=1.8 (1.4-2.4) OvCa: HR=4.56 (1.72-12.11) EndCa: HR=4.05 (1.20-13.66) BC: HR=1.15 (0.61-2.15) CRC: HR=2.99 (0.72-12.51) OMA: OvCa: HR=4.37 (1.07-17.83) EndCa: HR=3.23 (0.54-19.27) BC: HR=0.54 (0.12-2.40) Adenomyosis: OvCa: HR=5.50 (1.95-15.50) EndCa: HR=4.38 (1.22-15.72) BC: HR=1.24 (0.62-2.48) CRC: HR=3.51 (0.75-16.47)	Age group, diabetes mellitus, chronic kidney disease, liver cirrhosis, rheumatoid arthritis, and (for specific cancer types) use of medroxyprogesterone acetate, norethindrone acetate, danazol, and GnRH agonist
Farland et al., 2016 USA	Prospective cohort	1989-2013	5389	Medical records (reported as laparoscopically-confirmed, validation study confirmation rate=97.4%)	4979 BC	Medical records (histologically-confirmed)	Women from the cohort who did not report any cancer	**Endometriosis dx preceded cancer dx**: Prospective evaluation of endometriosis and cancer dx; time-varying analysis; exclusion of prevalent BC and endometriosis	BC: HR=0.96 (0.88–1.06) Premenopausal: HR=1.05 (0.89-1.23) Postmenopausal: HR=0.93 (0.80-1.07) ER+/PR+: HR=1.00 (0.87-1.14) ER+/PR-: HR=1.90	Age, calendar time, family history of breast cancer in a mother or sister, age at menarche, body mass index, body mass index at age 18 years, smoking history,

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
									(1.44-2.50) ER-/PR-: HR=0.90 (0.67-1.21)	biopsy-confirmed benign breast disease, alcohol intake, recent health-seeking behavior, height, oral contraceptive use history, parity/age at first birth, total breastfeeding, and birth weight
Mogensen et al., 2016 Denmark	Retrospective cohort	1977–2012	45,790	Medical records (Danish National Patient Register)	221 OvCa (70 serous, 10 mucinous, 28 endometrioid, 25 clear-cell) 118 EndCa (67 type I, 4 type II) 1452 BC (1034 ductal, 176 lobular)	Medical records (Danish Cancer Register)	45,356/43,784/45,790; women from the general population	**Endometriosis dx preceded cancer dx**: Retrospective evaluation of endometriosis and cancer dx; information on years of dx; exclusion of cancer cases diagnosed during the 1st year after endometriosis dx to ensure temporality; for OvCa and EndCa, exclusion of women with a history of bilateral oophorectomy/hysterectomy before (or on the same date as) endometriosis dx	OvCa: SIR=1.55 (1.35–1.77) EndCa: SIR=2.13 (1.77–2.55) BC: SIR=1.05 (1.00–1.11) **Follow-up>=1 yr after 1st endo dx** OvCa: SIR=1.34 (1.16–1.55) EndCa: SIR=1.43 (1.13–1.79) BC: SIR=1.05 (0.99–1.10) OvCa: Serous: SIR=1.05 (0.82-1.32) Mucinous: SIR=0.75 (0.36-1.37) Endometrioid: SIR=1.64 (1.09-2.37) Clear-cell: SIR=3.64 (2.36-5.38)	Age, calendar year, and parity

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
									EndCa: Type I: SIR=1.54 (1.20-1.96) Type II: SIR=1.06 (0.28-2.71) BC: Ductal: SIR=1.04 (0.97-1.10) Lobular: SIR=1.14 (0.98-1.33) - Risk estimates by time since endo dx, calendar period of endo dx, and age at dx of endo	
Ruiz et al., 2016 USA	Case control, hospital-based	2003-2008	21	Self-reported	208 OvCa cases 53 type I 155 type II	Medical records (hospital dx)	224; wowen matched to case by age and selected from the same institution over the same time period	**Cross-sectional**: Comparison of endometriosis in OvCa cases and controls, with no information on years of dx	Type I OvCa: OR=5.07 (2.06–12.46) Type II OvCa: OR=1.34 (0.55–3.23)	None
Wentzensen et al., 2016 Multiple locations (North America, Asia, and Europe)	Prospective cohort	1980-2014	1503 exposed OvCa cases	Self-reported	5584 OvCa (3378 serous, 606 endometrioid, 331 mucinous, 269 clear-cell)	Medical records (cancer registries or medical record review)	1,279,002; women from the cohort who did not report any cancer	**Endometriosis dx preceded cancer dx**: Prospective evaluation of endometriosis and OvCa in 21 prospective studies; exclusion of women with a hx of cancer or bilateral oophorectomy before study entry	OvCa: RR=1.35 (1.07-1.71) Serous: RR=1.03 (0.74-1.46) Endometrioid: RR=2.32 (1.36-3.95) Mucinous: RR=1.62 (0.58-4.51) Clear-cell: RR=2.87 (1.53-5.39) Phomog=0.01 - Risk estimates by grade of	Stratified by birth year and cohort; adjusted for age at study entry, parity, and duration of oral contraceptive use by using pooled analyses of all (21) cohorts combined

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
									differentiation Association stronger in well-differentiated tumors (but NS heterog)	
Farland et al., 2017 France	Prospective cohort	1990-2011	2967	Medical records (reported as surgically-confirmed, validation study confirmation rate=81.5%)	535 MM 247 SCC 1712 BCC	Medical records (histologically-confirmed)	84,754; women from the cohort who did not report any cancer	**Endometriosis dx preceded cancer dx**: Prospective evaluation of endometriosis and MM; exclusion of women with a hx of cancer at inclusion; time-varying analysis	MM: HR=1.64 (1.15-2.35) NMSCs: HR=1.17 (0.93-1.46) SCC: HR=1.21 (0.62-2.36) BCC: HR=1.16 (0.91-1.48)	Stratified on birth cohort and adjusted for age, education, hair color, skin complexion, number of nævi, freckling, skin sensitivity to sun exposure, family history of skin cancer, and quartiles of residential sun exposure in county of birth and at baseline
Koushik et al., 2017 Canada	Case-control, population-based	2011-2016	84	Self-reported	496 OvCa (103 type I, 261 type II, 132 borderline)	Medical records (histologically-confirmed)	908; women from the electoral list throughout the case recruitment period and matched to cases on age in 5-year groups and electoral district	**Cross-sectional:** Comparison of endometriosis in OvCa cases and controls, with no information on years of dx	OvCa: OR=1.65 (1.08–2.54) Invasive: OR=1.70 (1.07-2.71) Borderline: OR=1.55 (0.77-3.13) Phomog=0.81 Type I: OR=2.96 (1.54-5.67) Type II: OR=1.33 (0.76-2.32) P homog: 0.04	Age, duration of oral contraceptive use, parity, and education

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
Poole et al., 2017 USA	Prospective cohort	1989-2011	5910	Medical records (reported as laparoscopically-confirmed, validation study confirmation rate=97.4%)	228 OvCa (107 serous, 62 endometrioid or clear-cell, 22 mucinous) 166 EndCa	Medical records (histologically-confirmed)	101,797 / 96,943; women from the cohort who did not report any cancer	**Endometriosis dx preceded cancer dx**: Prospective evaluation of endometriosis and cancer dx; exclusion of prevalent endometriosis or cancer cases; sensitivity analyses moving dx date backwards to account for dx delays	OvCa: HR=2.28 (1.54-3.38) EndCa: HR=0.68 (0.30-1.56) Serous OvCa: HR=1.69 (0.92-3.11) Non-serous OvCa: HR=2.44 (1.48-4.01) Phomog: 0.36 Serous OvCa: HR=1.70 (0.93-3.12) Endometrioid/clear-cell OvCa: HR=1.78 (0.84-3.78) Mucinous OvCa: HR=2.90 (0.97-8.68) Phomog: 0.72	OvCa: Stratified by age and time period; adjusted for parity, duration of oral contraceptive use, menopausal status, tubal ligation, family history of ovarian cancer + additionally (except for analyses by tumor type) post-menopausal hormone use, infertility history, IUD use, hysterectomy, and menstrual cycle irregularity EnCa: Stratified by age and time period; adjusted for BMI, parity, duration of post-menopausal hormones (by type), age at menopause, age at menarche, menstrual irregularity, infertility history, and duration of oral contraceptive use

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
Saavalainen et al., 2018 Finland	Retrospective cohort	1987-2014	49,933 (23,210 OMA 20,187 SPE 2372 DE)	Medical records (Finnish Hospital Discharge Register)	129 OvCa 46 BOT 55 EndCa 28 CervCa	Medical records (Finnish Cancer Registry)	Comparison to population rates	**Endometriosis dx preceded cancer dx**: Retrospective evaluation of cancer and endometriosis in a national patient register; information on years of dx; time-varying analysis from endometriosis diagnosis	OvCa: SIR=1.76 (1.47–2.08) EndCa: SIR=1.04 (0.80–1.32) CervCa: SIR=0.76 (0.50–1.09) **OvCa** Serous: SIR=1.37 (1.02-1.80) Mucinous: SIR=0.88 (0.42-1.62) Endometrioid: SIR=3.12 (2.15-4.38) Clear-cell: SIR=5.17 (3.20-7.89) BOT: SIR=1.29 (0.95-1.72) **Endo x OvCa** OMA: SIR=2.56 (1.98-3.27) SPE: SIR=1.32 (0.99-1.72) DE: SIR=1.41 (0.29-4.10) **EndCa** Endometrioid: SIR=1.06 (0.80-1.38) **Endo x EndCa** OMA: SIR=1.12 (0.77-1.57) SPE: SIR=1.04 (0.70-1.49) DE: SIR=0.74 (0.02-4.12) **CervCa** Adenocarcinoma:	None

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
									SIR=1.06 (0.53-1.88) SCC: SIR=0.46 (0.20-0.91) **Endo x CervCa** OMA: SIR=0.96 (0.54-1.58) SPE: SIR=0.53 (0.24-1.00) DE: SIR=1.80 (0.37-5.25)	
Saavalainen et al., 2018 Finland	Retrospective cohort	1987-2014	49,933 (23,210 OMA 20,187 SPE 2372 DE)	Medical records (Finnish Hospital Discharge Register)	3619 TotCa 1555 BC 31 Buccal 62 Gastric 267 CRC 16 Small intestine 20 Liver 62 Pancreas 145 Lung 156 MM 62 NMSC 904 BCC 80 Kidney 36 Urinary 207 Brain 179 ThyrCa 135 NHL 269 Lymphoid and hematopoietic	Medical records (Finnish Cancer Registry)	–	**Endometriosis dx preceded cancer dx**: Retrospective evaluation of cancer and endometriosis in a national patient register; information on years of dx; time-varying analysis from endometriosis diagnosis	TotCa: SIR=0.98 (0.95-1.01) BC: SIR=0.99 (0.94-1.03) Buccal: SIR=0.60 (0.41-0.85) Gastric: SIR=1.03 (0.79-1.32) Colon: SIR=0.95 (0.80-1.10) Rectal: SIR=1.14 (0.93-1.37) Small Intestine: SIR=1.32 (0.76-2.14) Liver: SIR=0.89 (0.54-1.37) Pancreas: SIR=0.76 (0.58-0.96) Lung: SIR=0.91 (0.77-1.06) MM: SIR=1.03 (0.87-1.19) BCC: SIR=1.18 (1.10-1.25) NMSC: SIR=1.08	None

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
									(0.83-1.38) Kidney: SIR=1.05 (0.83-1.30) Urinary: SIR=0.91 (0.63-1.25) Brain: SIR=1.10 (0.95-1.25) ThyrCa: SIR=1.43 (1.23-1.64) NHL : SIR=1.06 (0.89-1.25) Lymphoid and hematopoietic: SIR=1.07 (0.95-1.20) Risk estimates by tumor type and type of endometriosis	
Saraswat et al., 2018 Scotland	Retrospective cohort	1981-2010	17,834	Medical records (laparoscopically-confirmed)	1224 TotCa 69 OvCa 32 EndCa 48 CervC 448 BC	Medical records (cancer registry)	17,384; age-matched women from the general population	**Endometriosis dx preceded cancer dx**: Retrospective evaluation of endometriosis and cancer dx; information on years of dx; exclusion of women with cancer at the time of endometriosis surgery	TotCa: HR=1.21 (1.08-1.35) OvCa: HR=1.77 (1.08-2.89) EndCa: HR=1.14 (0.57-2.28) CervCa: HR=0.60 (0.34-1.08) BC: HR=1.28 (1.06-1.54)	Matched by year of birth and time of entry in the study (univariate analyses only)
Stewart et al., 2018 Australia	Retrospective cohort	1970-2014	34,552	Medical records (Western Australia Data Linkage System)	454 cases of high-grade serous OvCa	Medical records (cancer registry)	406,830; women with no cancer record	**Endometriosis dx preceded cancer dx**: Retrospective evaluation of endometriosis and cancer dx; information on years of dx; time-varying analysis of the association between endometriosis and HGSOC	OvCa: HR=0.82 (0.55-1.22)	Age, infertiliy, pelvic inflammatory disease, hysterectomy, salpingectomy, oophorectomy, tubal ligation, plural delivery, high parity, breast

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
										cancer, parity
Surrey et al., 2018 USA	Retrospective cohort	2006-2015	26,961	Medical records (commercial insurance claims)	_	Medical records (commercial insurance claims)	107,844; comparison cohort: 4 controls per case matched on state of residence, insurance plan type, and age	**Endometriosis dx preceded cancer dx:** Retrospective evaluation of cancer and endometriosis; information on years of dx; exclusion of patients in whom the comorbidity under study occurred before the index date; time-varying analysis from the index date to time to the first comorbidity claim	OvCa: HR=4.0 (2.8-5.7) EndCa: HR=2.4 (1.6-3.8) BC: HR=1.4 (1.1-1.7)	15 Charlson-Deyo comorbidities measured during the year preceding the index date: rheumatologic disease, diabetes, diabetes with chronic complications, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, peptic ulcer disease, mild liver disease, hemiplegia, paraplegia, renal disease, moderate or severe liver disease, AIDS

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
Williams et al., 2018 United Kingdom	Prospective cohort of women who had assisted reproduction	1991-2011	18,630	Medical records (Human Fertilisation and Embryology Authority database)	2578 BC 164 EndCa 405 OvCa	Medical records (National Health Service Central Registers of England, Wales, and Scotland)	252,631 women with no cancer dx in the cohort; Human Fertilisation and Embryology Authority (HFEA)	**Endometriosis dx preceded cancer dx:** Prospective evaluation of cancer and endometriosis dx; information on years of dx; exclusion of cancer dx recorded in the 1st year of follow-up in a sensitivity analysis	BC: SIR=0.98 (0.86-1.12) EndCa: SIR=0.75 (0.35-1.43) OvCa: SIR=2.31 (1.74-3.01) Invasive BC: SIR=0.96 (0.92-1.00) In situ BC: SIR=1.14 (1.01-1.28) Invasive OvCa: SIR=1.31 (1.14-1.49) BOT: SIR=1.30 (1.08-1.55) - **Follow-up>=1 yr after 1st endo dx** BC: SIR=0.98 (0.85-1.12) EndCa: SIR=0.78 (0.35-1.47) OvCa: SIR=2.19 (1.62-2.89) Invasive BC: SIR=0.94 (0.81-1.09) In situ BC: SIR=1.28 (0.84-1.88) Invasive OvCa: SIR=2.51 (1.77-3.47) BOT: SIR=1.57 (0.81-2.73)	None

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
Guenego et al., 2018 France	Prospective cohort	1990-2012	6606	Medical records (reported as surgically-confirmed, validation study confirmation rate=81.5%)	412 ThyrCa	Medical records (histologically-confirmed)	80,197; women from the cohort who did not report any cancer	**Endometriosis dx preceded cancer dx**: Prospective evaluation of endometriosis and Thyroids cancer; exclusion of women with a hx of cancer at inclusion; time-varying analysis	ThyrCa Self-reported endometriosis: HR=1.27 (0.90-1.79) Medically confirmed: HR= 1.26 (0.85-1.86) Surgically confirmed: HR= 1.19 (0.76; 1.88)	Age, and stratified by 5-year category birth cohort, smoking status, history of dysthyroidism, history of other benign thyroid disease and BMI, age at menarche, infertility treatment, parity and age at first full-term pregnancy, age at menopause and use of MHT
Park et al., 2018 USA	Case-control, population-based (African-American women)	2010-2015	82	Self-reported	600 OvCa	Medical records (histologically-confirmed)	908; identified through random digit dialing	**Cross-sectional:** Comparison of endometriosis in OvCa cases and controls, with no information on years of dx	OvCa: HR=1.78 (1.09-2.90) OvCa serous: HR=1.29 (0.71-2.35)	age at diagnosis, study site, marital status, education, BMI, parity, tubal ligation, duration of oral contraceptive use, family history of breast or ovarian cancer, talc use, endometriosis, fibroid, PID, ovarian cyst
Vassard et al., 2019 Denmark	Retrospective cohort of women who had assisted reproduction treatment	1994-2016	1734	Medical records (Danish IVF Register)	393 OvCa	Medical records (cancer registry)	566,858 untreated women with no cancer dx in the cohort; in the Danish National ART-couple II	**Endometriosis dx preceded cancer dx:** Prospective evaluation of cancer and endometriosis dx; with no information on years of dx	OvCa: HR= 3.78 (2.45-5.84)	Educational level, parity, partnership status, treatment year and age

Supplementary Table S1. Characteristics of the included 49 publications (1993-2019) from 38 studies of associations between endometriosis and cancer

Author, year, location	Design	Study period	Endometriosis: #cases	Endometriosis: ascertainment	Cancer: #cases	Cancer: ascertainment	Controls: number, source population	Temporality	RR (95% CI)	Adjustment factors
Hsu et al., 2019 Taiwan	Retrospective cohort	2000-2011	5586	Medical records (Taiwan National Health Insurance Research Database)	10 OvCa 37 BC	Medical records (Taiwan National Health Insurance Research Database)	143,096; women without history of endometriosis or cancer from general female population frequency; matched to the rest of cohort by age	**Endometriosis dx preceded cancer dx:** Retrospective evaluation of endometriosis and cancer dx in a national health insurance database; with no information on years of dx	OvCa: HR= 1.28 (1.19-1.37) in nurse cohorts HR=1.64 (0.20-13.7) other hospital employees BC: HR= 0.62 (0.22-1.78) in nurse cohorts HR= 1.97 (0.75-5.13) other hospital employees	Age, and comorbidities
Lundberg et al., 2019 Sweden	Retrospective cohort of women with infertility	1942-1992	53,687	Medical records (Swedish Hospital Discharge Register)	6435 OvCa 6112 EndCa 53,687 BC	Medical records (National Swedish Cancer Register)	Comparison to population rates	**Endometriosis dx preceded cancer dx:** Retrospective evaluation of endometriosis and cancer dx in a national patient register with no information on years of dx	OvCa: HR= 1.77 (1.53-2.05) EndCa: HR=1.02 (0.96-1.07) BC: HR=0.94 (0.76-1.17)	Age, calendar time, education level, country of birth, parity and age at first birth, salpingectomy and bilatera oophorectomy

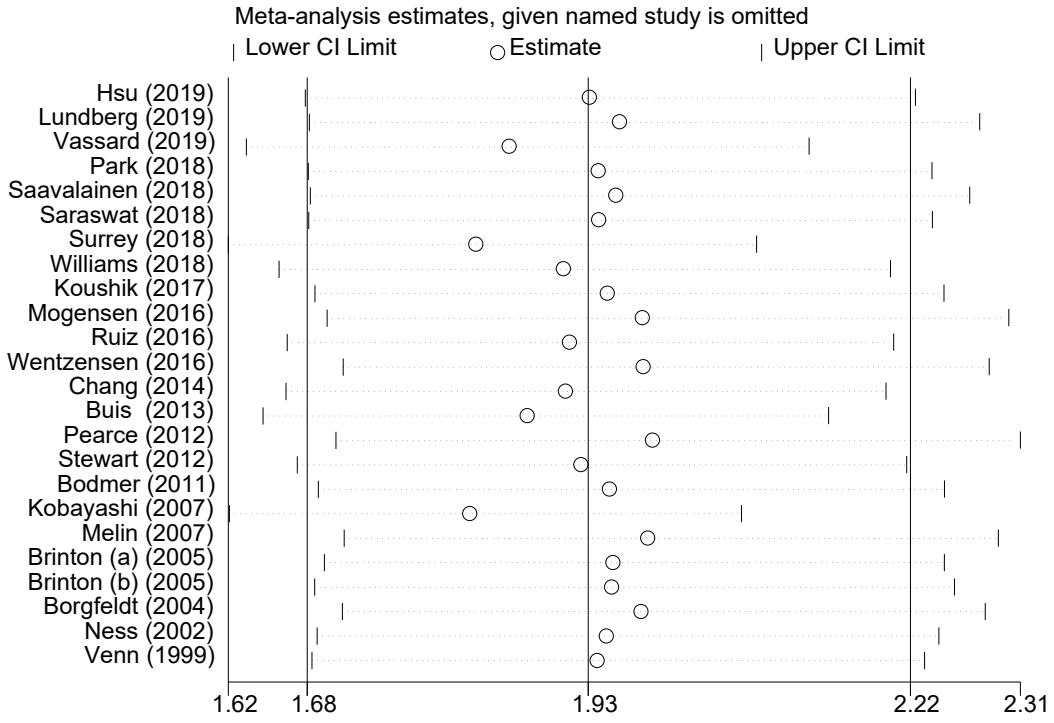
Footnote: RR relative risk; CI confidence interval; OR odds ratio; BC breast cancer; MM multiple myeloma; OvCA ovarian cancer; EndCA endometrial cancer MM melanoma malignant; ThyrCa tyroids cancer; TotCa total cancer; NMSC non melanoma skin cancer; NHL Non-Hodgkin lymphoma; BOT Borderline ovarian tumour; CervCa cervical cancer; BrainCa Brain cancer; KidneyCa Kidney cancer; SCC squamous cell carcinoma; BCC Basal cell carcinoma; BMI Body mass index, OC Oral contraceptive; IVF In vitro fertilisation, MHT menopausal hormone therapy; PID Pelvic inflammatory disease. AIDS acquired immunodeficiency syndrome; HRT hormone replacement therapy;

Supplementary Table S2. Summary relative risks (SRR) and 95% confidence intervals (CI) for the associations between endometriosis and cancer by cancer types with < 4 studies published as of 2019.				
	Number of studies	SRR (95% CI)	I^2 (%)	P^a_{within}
Keratinocyte cancers	3	1.10 (0.96-1.26)	0.0	0.79
Basal-cell carcinoma	2	1.18 (1.11-1.25)	0.0	0.89
Lymphatic/haematopoietic cancers	2	1.09 (1.00-1.19)	0.0	0.61
Non-Hodgkin lymphoma	3	1.18 (1.00-1.41)	40.6	0.18
Leukaemia	2	1.07 (0.88-1.31)	14.3	0.28
Brain cancer	2	1.18 (1.02-1.36)	49.3	0.16
Lung cancer	3	0.94 (0.84-1.04)	0.0	0.67
Gastric cancer	2	0.97 (0.81-1.18)	0.0	0.52
Liver cancer	2	1.05 (0.77-1.44)	0.0	0.34
Pancreatic cancer	2	0.96 (0.61-1.50)	85.8	0.008
Urinary cancer	2	0.99 (0.83-1.18)	0.0	0.60
Bladder cancer	2	0.94 (0.76-1.15)	0.0	0.84
Renal cancer	2	1.20 (0.93-1.55)	65.6	0.09
Buccal cancer	2	0.83 (0.45-1.55)	86.0	0.007

Footnote: SRR summary relative risk; CI confidence interval

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.

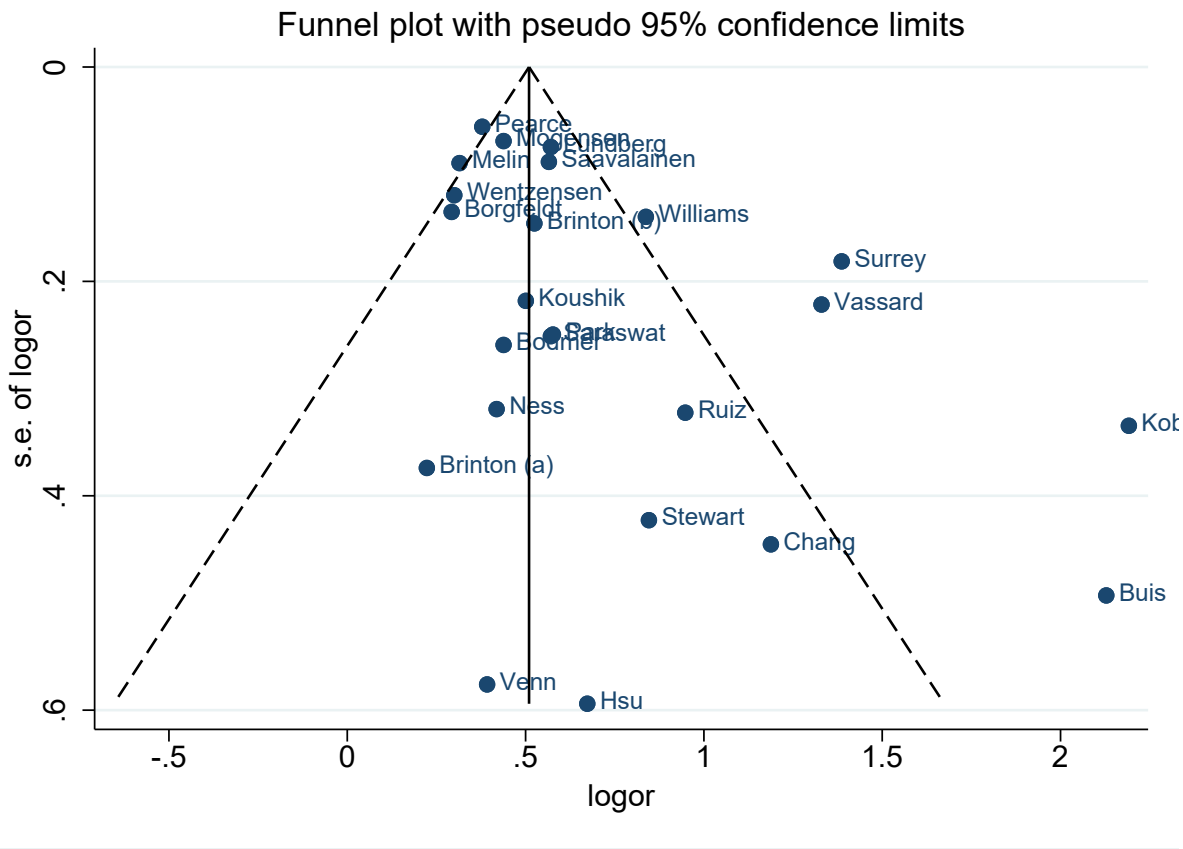
[a]P-value testing for heterogeneity among the studies within each cancer type



Study omitted	Estimate	[95% Conf.	Interval]
Hsu (2019)	1.9332196	1.6832901	2.2202578
Lundberg (2019)	1.9597607	1.6868342	2.2768459
Vassard (2019)	1.8626285	1.6313814	2.1266544
Park (2018)	1.9410294	1.6858954	2.2347739
Saavalainen (2018)	1.9564782	1.6877016	2.2680593
Saraswat (2018)	1.9414203	1.686263	2.2351868
Surrey (2018)	1.8332846	1.6154995	2.0804293
Williams (2018)	1.9103692	1.6601797	2.198262
Koushik (2017)	1.9490139	1.6917695	2.2453742
Mogensen (2016)	1.9798468	1.7024627	2.3024256
Ruiz (2016)	1.9157109	1.6673318	2.2010906
Wentzensen (2016)	1.9805933	1.7166094	2.2851734
Chang (2014)	1.9121628	1.6662681	2.1943448
Buis (2013)	1.8785173	1.6460669	2.1437933
Pearce (2012)	1.9887435	1.7102326	2.3126099
Stewart (2012)	1.9257933	1.6762004	2.2125516
Bodmer (2011)	1.9509244	1.6947575	2.2458117
Kobayashi (2007)	1.8279574	1.6164461	2.0671449
Melin (2007)	1.9845668	1.7174559	2.293221
Brinton (a) (2005)	1.9539349	1.7000763	2.2457004
Brinton (b) (2005)	1.9528441	1.6915002	2.2545669
Borgfeldt (2004)	1.978653	1.7158593	2.2816949
Ness (2002)	1.9481601	1.6936715	2.2408876
Venn (1999)	1.9400594	1.6891245	2.2282732
Combined	1.9322576	1.6849565	2.2158552

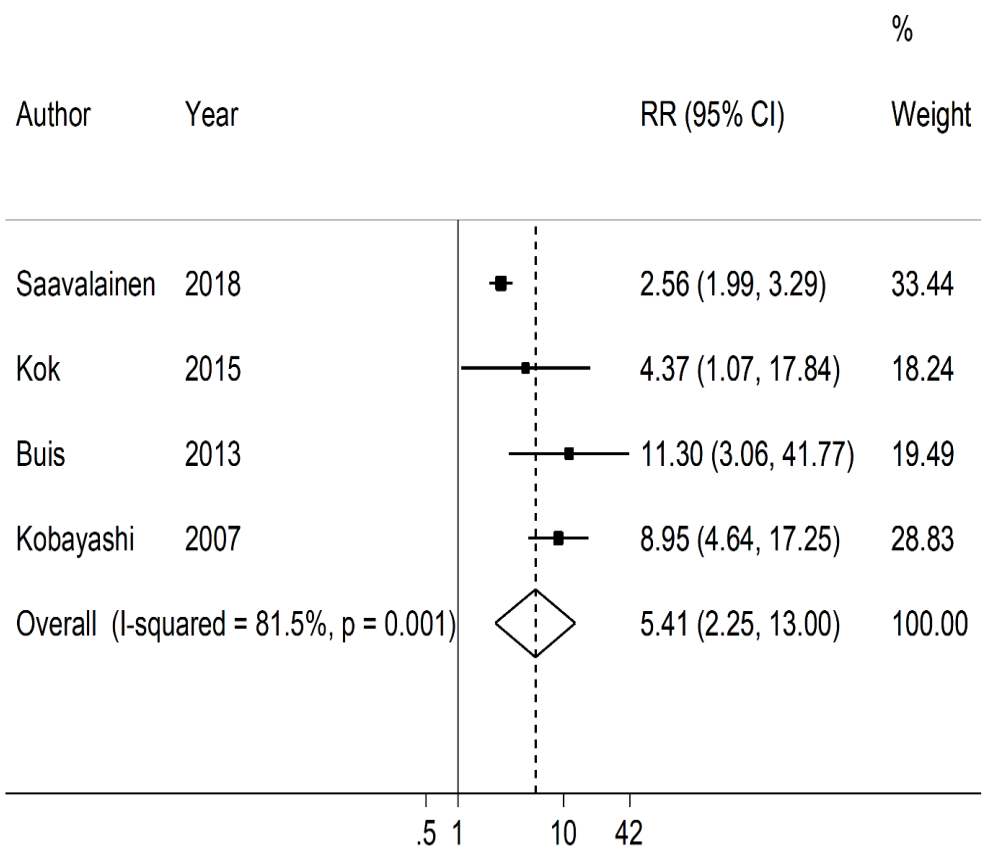
Supplementary Figure S1. Influence analysis for 24 studies evaluating the association between endometriosis and ovarian cancer risk published through 2019

*Note 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 this supplementary analysis for ovarian cancer.



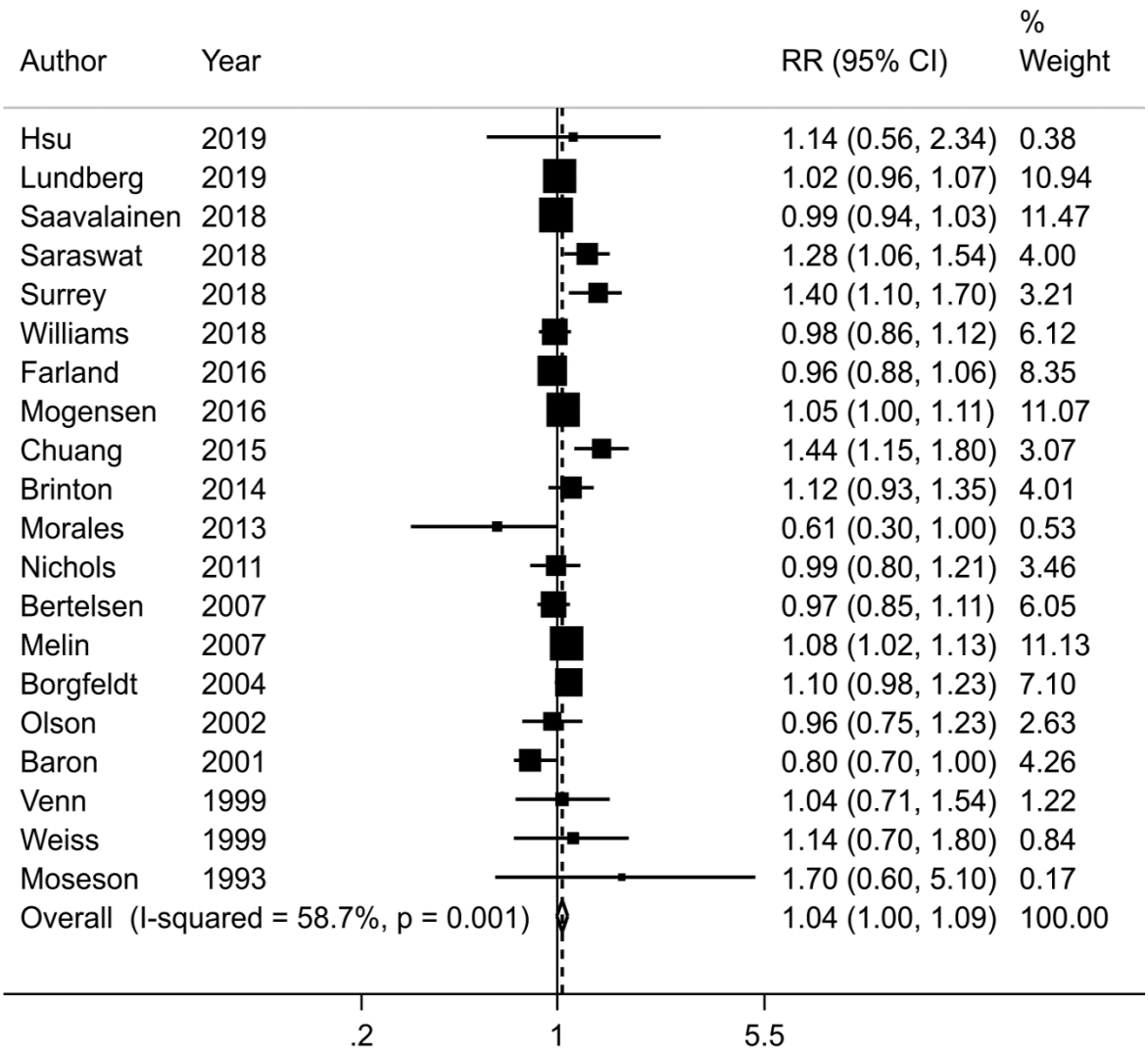
Supplementary Figure S2. Funnel plot for 24 studies evaluating the association between endometriosis and ovarian cancer risk published through 2019

*Note 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 this supplementary analysis for ovarian cancer.



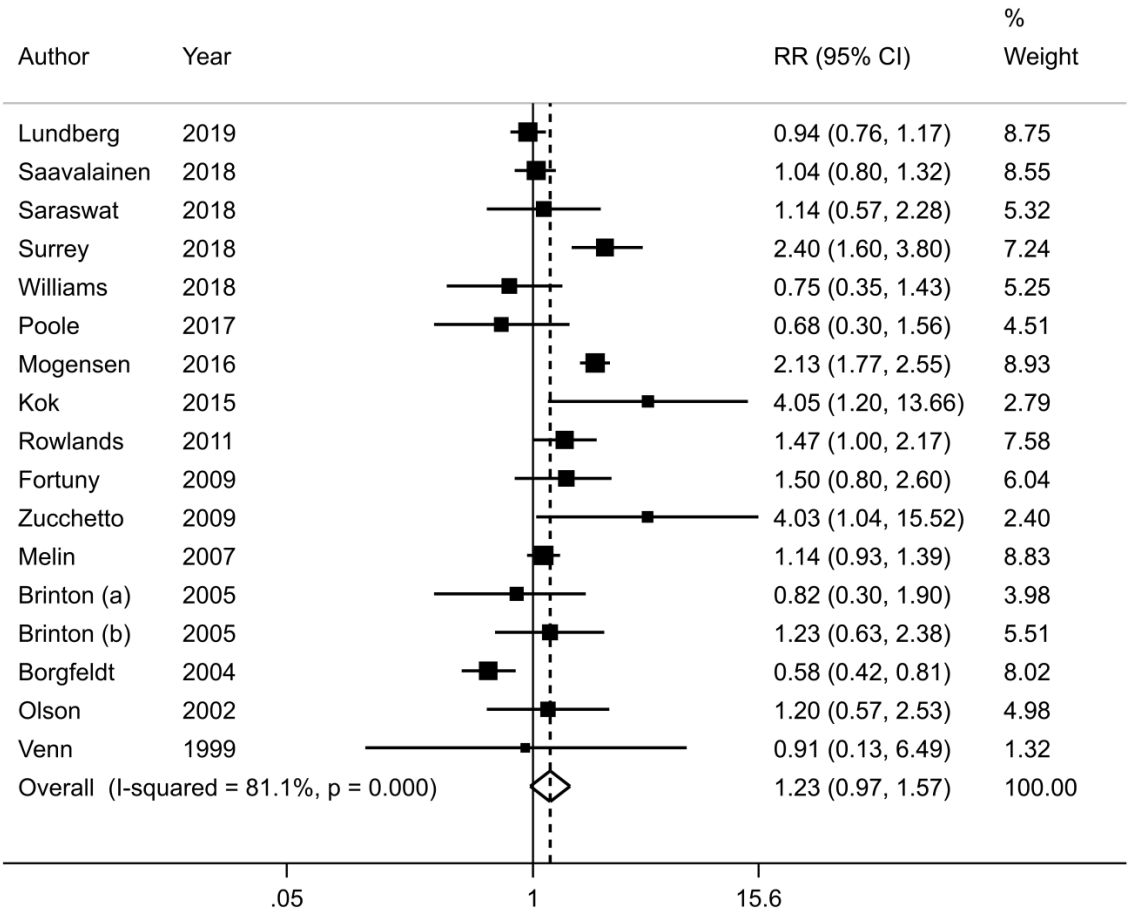
Supplementary Figure S3. Association between endometrioma (not exclusive, i.e. superficial peritoneal lesions or deep endometriosis could also have been present) and ovarian cancer risk

Footnote: RR relative risk, CI confidence interval, p=p-value, test for between study heterogeneity



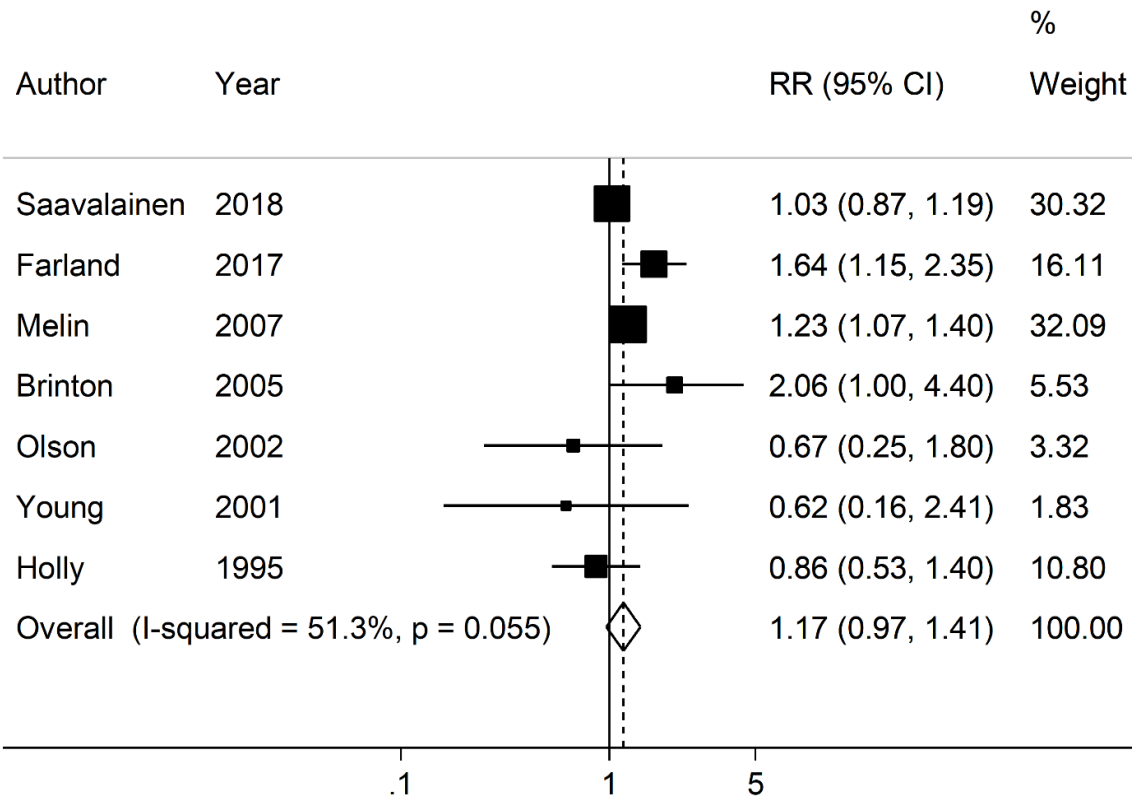
Supplementary Figure S4. Association between endometriosis and breast cancer risk among 20 studies published through 2019.

*RR=relative risk, CI=confidence interval, p=p-value, test for between study heterogeneity



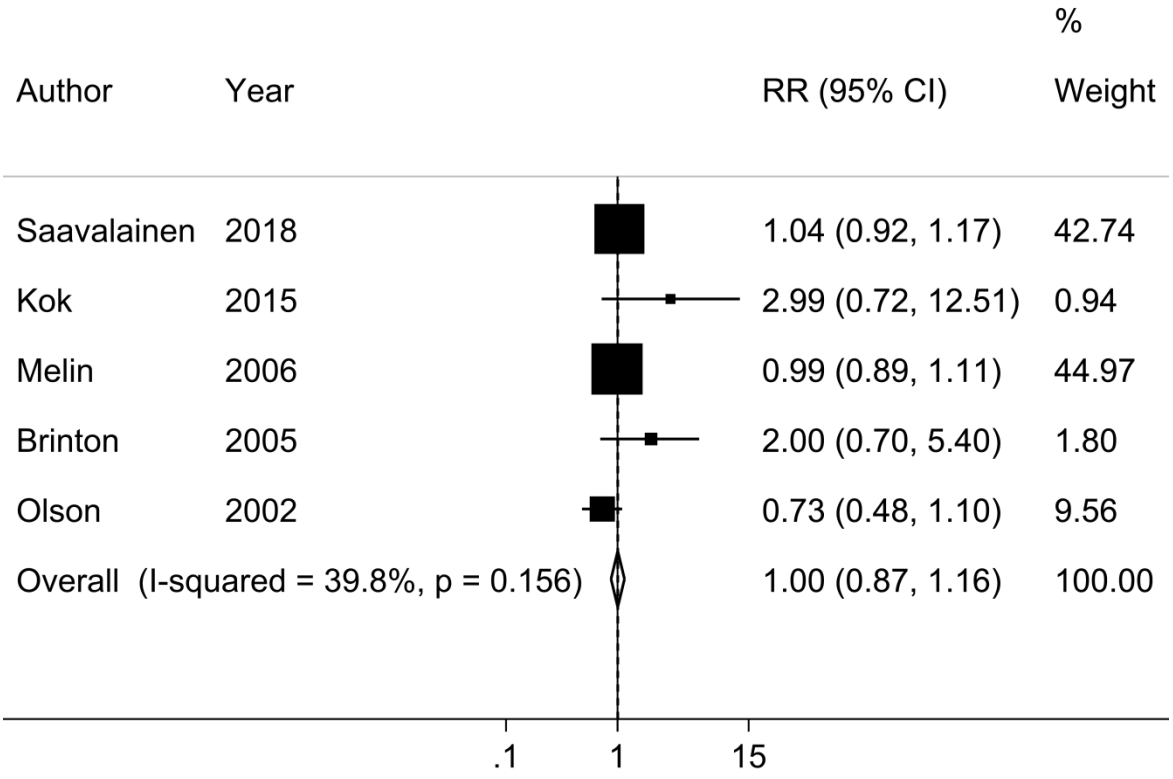
Supplementary Figure S5. Evaluation of the association between endometriosis and endometrial cancer risk among 17 studies published through 2019.

* Note: Brinton (a) conducted in the US and Brinton (b) conducted in Denmark. RR=relative risk, CI=confidence interval, p=p-value, test for between study heterogeneity



Supplementary Figure S6. Evaluation of the association between endometriosis and cutaneous melanoma risk among 7 studies published through 2019.

*RR=relative risk, CI=confidence interval, p=p-value, test for between study heterogeneity



Supplementary Figure S7. Evaluation of the association between endometriosis and colorectal cancer risk among 5 studies published through 2019.

*RR=relative risk, CI=confidence interval, p=p-value, test for between-study heterogeneity

A. Influence analysis for endometriosis and breast cancer risk

Study omitted	Estimate	[95% Conf.	Interval]
Hsu (2019)	1.0417918	.99550164	1.0902344
Lundberg (2019)	1.0461345	.99406683	1.1009294
Saavalainen (2018)	1.0495924	.99852318	1.1032735
Saraswat (2018)	1.0325894	.98834205	1.0788177
Surrey (2018)	1.03126	.98872292	1.0756272
Williams (2018)	1.0464802	.9983663	1.0969127
Farland (2016)	1.0498698	1.0015166	1.1005573
Mogensen (2016)	1.0426871	.99067062	1.0974348
Chuang (2015)	1.0307789	.98887807	1.074455
Brinton (2014)	1.0389574	.99203157	1.0881028
Morales (2013)	1.0444038	.99941623	1.0914166
Nichols (2011)	1.0441743	.9968968	1.0936939
Bertelsen (2007)	1.04706	.99907851	1.0973459
Melin (2007)	1.0383459	.98820931	1.0910263
Borgfeldt (2004)	1.0379018	.99008101	1.0880321
Olson (2002)	1.0445044	.99756569	1.0936517
Baron (2001)	1.0516464	1.0081979	1.0969671
Venn (1999)	1.0422194	.99563634	1.090982
Weiss (1999)	1.0413368	.99498391	1.0898491
Moseson (1993)	1.0411016	.99527645	1.0890367
Combined	1.0419527	.99621939	1.0897854

B. Influence analysis for endometriosis and endometrial cancer risk

Study omitted	Estimate	[95% Conf.	Interval]
Lundberg (2019)	1.2654675	.97343814	1.645105
Saavalainen (2018)	1.2536314	.96063733	1.6359885
Saraswat (2018)	1.2381101	.96200216	1.5934649
Surrey (2018)	1.1685135	.9138689	1.4941134
Williams (2018)	1.2665684	.98698252	1.6253537
Poole (2017)	1.2671235	.98895574	1.6235327
Mogensen (2016)	1.1495616	.93371409	1.4153069
Kok (2015)	1.1908191	.93384033	1.5185146
Rowlands (2011)	1.2157387	.9383328	1.5751561
Fortuny (2009)	1.217212	.94444954	1.5687499
Zucchetto (2009)	1.1968384	.93825042	1.5266949
Melin (2007)	1.2451015	.94457322	1.6412464
Brinton (a) (2005)	1.2534292	.97745055	1.6073291
Brinton (b) (2005)	1.2328626	.95741194	1.5875615
Borgfeldt (2004)	1.3148426	1.0467229	1.6516416
Olson (2002)	1.2343742	.9596985	1.5876647
Venn (1999)	1.2374282	.96813816	1.5816218
Combined	1.2321361	.96691225	1.5701108

Supplementary Figure S8. Influence analysis for studies evaluating the association between endometriosis and breast cancer risk (n=20 publications) (A) and between endometriosis and endometrial cancer risk (n=17 publications) (B)