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Endometriosis and menopausal hormone therapy impact the hysterectomy-ovarian cancer association

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HIGHLIGHTS

- Examining the hysterectomy-ovarian cancer association requires consideration of hormone therapy (HT) use and endometriosis.
- After considering HT use, hysterectomy was not associated with ovarian cancer risk among women without endometriosis.
- Among women with endometriosis, hysterectomy was inversely associated with ovarian cancer risk after considering HT use.

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ABSTRACT

Objective. To evaluate the association between hysterectomy and ovarian cancer, and to understand how hormone therapy (HT) use and endometriosis affect this association.

Methods. We conducted a pooled analysis of self-reported data from 11 case-control studies in the Ovarian Cancer Association Consortium (OCAC). Women with ($n = 5350$) and without ovarian cancer ($n = 7544$) who never used HT or exclusively used either estrogen-only therapy (ET) or estrogen+progestin therapy (EPT) were included. Risk of invasive epithelial ovarian cancer adjusted for duration of ET and EPT use and stratified on history of endometriosis was determined using odds ratios (ORs) with 95% confidence intervals (CIs).

Results. Overall and among women without endometriosis, there was a positive association between ovarian cancer risk and hysterectomy (OR = 1.19, 95% CI 1.09–1.31 and OR = 1.20, 95% CI 1.09–1.32, respectively), but no association upon adjusting for duration of ET and EPT use (OR = 1.04, 95% CI 0.94–1.16 and OR = 1.06, 95% CI 0.95–1.18, respectively). Among women with a history of endometriosis, there was a slight inverse association between hysterectomy and ovarian cancer risk (OR = 0.93, 95% CI 0.69–1.26), but this association became stronger and statistically significant after adjusting for duration of ET and EPT use (OR = 0.69, 95% CI 0.48–0.99).

Conclusions. The hysterectomy-ovarian cancer association is complex and cannot be understood without considering duration of ET and EPT use and history of endometriosis. Failure to take these exposures into account in prior studies casts doubt on their conclusions. Overall, hysterectomy is not risk-reducing for ovarian cancer, however the inverse association among women with endometriosis warrants further investigation.

1. Introduction

The literature on the association between hysterectomy and risk of invasive epithelial ovarian cancer (ovarian cancer) is equivocal. While earlier studies observed an inverse association between hysterectomy and ovarian cancer [1–6], most recent studies have not seen this protective association [7–13], with some reporting a possible increased risk [11,12,14]. This apparent discrepancy between earlier and more recent studies was observed in a systematic review and meta-analysis by Jordan and colleagues, and they hypothesized that this may be due to temporal changes in menopausal hormone therapy (HT) use [15].

HT is more commonly used among women who had a hysterectomy with ovarian preservation than in women who did not have a hysterectomy and experienced natural menopause [16,17]. Also, the standard of care for women who have had a hysterectomy is to use estrogen-only therapy (ET) rather than estrogen+progestin therapy (EPT) because there is no need to protect the uterus from 'unopposed' estrogen. ET use is associated with increased risk of ovarian cancer in a duration-dependent manner [18]. Thus, duration of ET use has the potential to be a mediator of the hysterectomy-ovarian cancer relationship and under some circumstances could also act as a confounder depending on the temporal sequence between hysterectomy and ET use. Accounting for duration of ET use allows us to better understand the direct relationship between hysterectomy and ovarian cancer risk. The association between EPT use and ovarian cancer risk is less clear; taking duration of EPT use into account in assessing the hysterectomy-ovarian cancer association may also be important.

A recent longitudinal record-linkage study by Dixon-Suen et al. found hysterectomy to be associated with a substantially decreased risk of ovarian cancer among women with a history of endometriosis whereas no association was observed among women who had not had endometriosis [10]. These findings were also observed in a pooled analysis of four case-control studies by Modugno et al [13] However, neither study [10,13] considered the hysterectomy-ovarian cancer association in the context of duration and type of HT use.

Hysterectomy is one of the most common gynecologic surgical procedures worldwide [19]. As such, a more complete understanding of its association with ovarian cancer risk, particularly with respect to the impact of duration of ET and EPT use and endometriosis, is needed. In the analysis presented here, we pooled primary data from 11 epidemiologic studies participating in the Ovarian Cancer Association Consortium (OCAC) to examine the association between hysterectomy and ovarian cancer risk while taking into consideration the duration of ET and EPT use as well as history of endometriosis.

2. Materials and methods

All studies included in this analysis obtained institutional ethics committee approval. All participants provided written informed consent.

2.1. Study population

Primary data from 11 population-based case-control studies in the OCAC (http://ocac.ccge.medschl.cam.ac.uk/) were included in this pooled analysis. One study was from Australia, two were from Europe, and eight were from the United States [20]. Their main characteristics are presented in Table 1; details regarding each study have been published previously [21–31]. There is overlap in participants included in the Modugno et al. paper [13] and the current analysis: the HAW [26] study participants from 1993 to 1999 (~60% of HAW cases), the USC [30] study participants from 1994 to 1999 (~40% of USC cases), and the NCO [31] study participants from 1999 to 2001 (~25% of NCO cases). Women who were aged 50 years or older and were reported by each study as post-menopausal at their reference date (date of diagnosis for cases, date of interview for controls) were included. Whether the woman was pre-menopausal or post-menopausal at date of hysterectomy was not available. Requiring women to be 50 years or older at diagnosis will have excluded those who only reported being post-menopausal because of their hysterectomy and did not know when their menses would have ceased naturally.

Table 1
Description of the 11 OCAC studies included in the analysis.

OCAC study abbreviation	Study location	Recruitment period	Data collection method	Cases				Controls			
				N	% with hysterectomy	% with endometriosis	% with ET or EPT use	N	% with hysterectomy	% with endometriosis	% with ET or EPT use
AUS	Australia	2002–2005	Self-completed questionnaire	512	17.0	6.6	HT data n/a	454	21.8	4.2	HT data n/a
GER	Baden-Württemberg and Rhineland-Palatinate, Germany	1993–1998	Self-completed questionnaire	147	29.3	1.4	21.8	323	35.0	1.6	28.5
MAL	Denmark	1994–1999	In-person or phone interview	311	14.2	1	40.8	814	10.4	0.7	38
CON	Connecticut, USA	1999–2003	In-person interview	240	25.0	7.5	40	270	18.5	8.5	45.9
DOV	Washington, USA	2002–2009	In-person interview	669	27.1	10.5	59.5	1058	21.6	6.6	63.3
HAW	Hawai'i, USA	1993–2008	In-person interview	433	18.5	9	45.7	582	15.6	6.2	53.1
HOP	Western Pennsylvania, Northeast Ohio, Western New York, USA	2003–2009	In-person interview	456	27.0	6.6	41.9	1021	21.3	6.6	45.6
NCO	North Carolina, USA	1999–2008	In-person interview	286	21.0	8.7	HT data n/a	311	17.4	3.2	HT data n/a
NEC	New Hampshire and Eastern Massachussets, USA	1992–2008	In-person interview	847	13.2	9.2	29.4	1048	14.6	8.3	33.6
UCI	Orange County and San Diego County, California, USA	1996–2005	Self-completed questionnaire	211	37.0	13.7	70.6	296	40.5	14.2	73.3
USC	Los Angeles, California, USA	1994–2010	In-person interview	1238	23.3	8.3	45.5	1367	18.3	6.4	49.3
All Studies				5350	21.6	8.1	44.0	7544	19.4	6.0	47.4

Cases were women diagnosed with primary invasive epithelial ovarian, fallopian tube, or primary peritoneal tumors, hereafter referred to as ovarian cancer. The analyses included women with high-grade serous, low-grade serous, endometrioid, clear cell, and mucinous epithelial tumors, as well as other invasive epithelial ovarian cancers that were not classified as one of these five histotypes in the original pathology reports. Controls were women who reported having at least one intact ovary and had not been diagnosed with ovarian cancer on or before their reference date. Women who had never used ET or EPT were included as were women who exclusively used either ET or EPT. Women who used both ET and EPT and those for whom the type of HT used was unknown were excluded from the analysis.

2.2. Data analysis

All information used in these analyses was self-reported via in-person interviews or self-administered questionnaires (Table 1). The primary data were pooled across the 11 OCAC studies and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the association between hysterectomy and risk of ovarian cancer; hysterectomies that occurred more than one year prior to a woman's reference date were counted as such whereas women who had a hysterectomy within one year of diagnosis/interview date were coded as not having had the procedure ($n = 40$). These analyses were conducted among all women combined and then further stratified by endometriosis history.

Prior to pooling, we evaluated heterogeneity in the association between hysterectomy and ovarian cancer risk by OCAC study site for all women and for those without endometriosis using a standard meta-analytic approach. We observed only moderate evidence of heterogeneity across OCAC study sites in both instances (I^2: 51% for all women, I^2: 52% for women without endometriosis) and the fixed and random effects results were not materially different (Supplementary Figs. 1A and 1B). In addition, heterogeneity in the hysterectomy-ovarian cancer association by OCAC study site could not be adequately evaluated for women with endometriosis due to small sample sizes, thus we present the results using a pooled approach.

All models were adjusted for reference age (five-year age categories from 50 to 74, 75+ years), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian, other), education level (less than high school, high school graduate, some college, college graduate), and OCAC study. The impact of duration of ET use (continuous) and duration of EPT use (continuous) was examined. ET duration had a material impact on all models and was therefore included as an adjustment factor. Duration of EPT use was also included in all models although it only affected the association among women with endometriosis. Results with and without adjustment for duration of ET and duration of EPT use are presented. We also evaluated whether HT use modified the association between hysterectomy and ovarian cancer by fitting a model with an interaction term between hysterectomy and ET duration and hysterectomy and EPT duration.

In addition, the potential confounding effects of the following exposures were evaluated: duration of combined oral contraceptive (COC) use (never and < 1, 1 to <5, 5 to <10, 10+ years), parity (0, 1, 2, 3, 4 + births), tubal ligation (yes/no), body mass index (<18.5, 18.5 to <25, 25 to <30, 30+ kg/m^2), age at menarche (continuous), first-degree family history of ovarian cancer (yes/no), and history of endometriosis (yes/no; in the unstratified analysis). Only parity confounded the hysterectomy-ovarian cancer association based on a 10% or greater change in the hysterectomy beta coefficient; this exposure was, therefore, also included in all models.

Education level was missing for 3.7% of women. When models with and without education level were evaluated (both restricted to those with no missing data), there was no difference in the hysterectomy-ovarian cancer effect estimate. Therefore, a missing category for education was created so that no women were excluded from the analysis based on this variable. Overall, 180 women were excluded due to missing data for any of the other variables included in the analysis.

Histotype-specific analyses were carried out among women without endometriosis; sample sizes were too small to evaluate histotype-

specific associations among women with endometriosis. In addition, there was a suggestion in the literature that the effect of hysterectomy in the pre-menopausal period may differ from the effect of hysterectomy in the post-menopausal period [32]. Age at menopause was not available in the OCAC, but we were able to restrict our analysis to hysterectomies that occurred before the age of 50 as a proxy for pre-menopausal hysterectomies. 85.6% of hysterectomies occurred under the age of 50 in our data.

All tests of statistical significance were two-sided. All analyses were performed using SAS software, release 9.4 (SAS Institute, Inc., Cary, North Carolina) with the exception of the OCAC study site heterogeneity evaluation meta-analyses which were done with R version 4.0.2 meta and tidyverse packages.

3. Results

The analyses presented here included 5350 women with ovarian cancer and 7544 control women. The prevalence of hysterectomy among women with ovarian cancer was 22% compared to 19% among control women (Table 1). The overall prevalence of endometriosis was 8% and 6% among women with ovarian cancer and control women, respectively. In the nine studies with HT data available, among women with ovarian cancer, 44% had ever used HT, compared to 47% of control women.

In the analysis of all women (regardless of history of endometriosis) unadjusted for duration of ET or EPT use or history of endometriosis, there was increased risk of ovarian cancer associated with having had a hysterectomy (OR = 1.19, 95% CI 1.09–1.31; Table 2). However, duration of ET use had a strong effect on this estimate. After considering duration of ET and EPT use, there was no association between hysterectomy and ovarian cancer risk (OR = 1.04, 95% CI 0.94–1.16; Table 2). Among women without endometriosis, there was also no association between ovarian cancer and hysterectomy (OR = 1.06, 95% CI 0.95–1.18) after taking duration of ET and EPT use into account. There was, however, an inverse association among women with endometriosis after duration of ET and EPT use was considered (OR without adjustment = 0.93, 95% CI 0.69–1.26; OR with adjustment = 0.69, 95% CI 0.48–0.99; adjusted model endometriosis-hysterectomy p-interaction = 0.047; Table 2).

When examining the hysterectomy-ovarian cancer association by histotype among women without a history of endometriosis, there were no significant associations (Supplementary Table 1). There was also no association between hysterectomy and ovarian cancer risk when restricting to hysterectomies that occurred before age 50 (OR = 1.03, 95% CI 0.91–1.16).

4. Conclusions

Our findings demonstrate that the association between hysterectomy and risk of ovarian cancer cannot be understood without considering duration of ET and EPT use and history of endometriosis. Failing to take duration of ET and EPT use into account can lead to positive bias of the hysterectomy-ovarian cancer relationship as we observed in our analysis. Overall, after adjusting for duration of ET and EPT use, there was no association between hysterectomy and ovarian cancer among women without endometriosis and an inverse association among women with a history of endometriosis (Fig. 1).

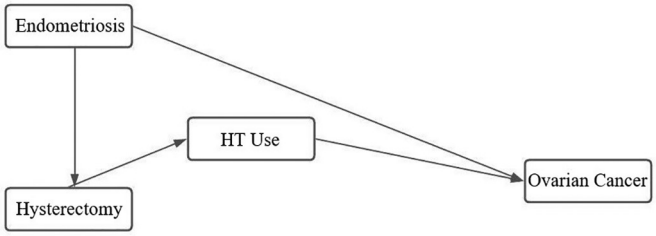

Fig. 1. The relationships among hysterectomy, endometriosis, menopausal hormone therapy (HT) use, and risk of ovarian cancer.

Our overall result is in line with that of the Ovarian Cancer Cohort Consortium (OC3) [7]; their analysis adjusted for duration of HT (all types) use and found a null association between hysterectomy and ovarian cancer risk among all women (HR = 0.95, 95% CI 0.89–1.03). Furthermore, in the Nurse's Health Study [9], the relative risk for hysterectomy and ovarian cancer was 1.11 before adjusting for duration of ET use and 0.84 after adjustment. Peres and colleagues also noted a difference in the hysterectomy-ovarian cancer relationship based on ET use [32]. In addition, our results by history of endometriosis are consistent with the findings from a country-wide administrative data analysis in Australia that also found an inverse association between hysterectomy and ovarian cancer among women with endometriosis [10]. This protective association was also noted by Modugno and colleagues [13] although there is some overlap in the studies included in their analysis and the studies in the present results (see Methods for details).

Several recent studies have found that hysterectomy was associated with a modestly increased risk of ovarian cancer [11,12,14], however none of these studies adjusted for duration of ET or EPT use in their analysis. Failing to adjust for duration of ET or EPT use likely accounts for this observation. In our unadjusted analysis we observed a positive association consistent with the contemporary literature, illustrating the importance of adjusting for duration of ET use as a potential confounder or mediator to see the direct effect of hysterectomy on ovarian cancer risk. Although we do not have data on the temporal sequence of HT use and hysterectomy, it is likely that most HT use came after the hysterectomy given that 86% of hysterectomies occurred under the age of 50 such that HT use would be a mediator of the hysterectomy-ovarian cancer relationship. Adjusting for duration of ET and EPT use allows us to evaluate the direct effect of hysterectomy on ovarian cancer which was our goal with this analysis. This allows us to better understand disease etiology and evaluate the potential for hysterectomy to be a primary prevention strategy. Most older studies found hysterectomy to be associated with decreased risk of ovarian cancer [1–6]. A possible explanation for the protective association in older studies may be that more women who had their ovaries removed were incorrectly included in the control group than in contemporary studies. It is not uncommon for women to be less aware of the number of ovaries they have following gynecologic procedures [33].

The underlying explanation for the inverse association between hysterectomy and ovarian cancer risk among women with endometriosis may be multifaceted. The association may be due to the hysterectomy procedure being accompanied with more extensive surgery that removes the endometriotic lesions [34], a hypothesized cell of origin for endometrioid, clear cell, and low-grade serous ovarian cancer histotypes [35]. Removal of endometriosis is associated with reduced ovarian cancer risk [36], and our histotype-specific analyses among

Table 2
The association between hysterectomy and invasive ovarian cancers in post-menopausal women overall and stratified by endometriosis history.

	Cases	Controls	OR[a]	95% CI			OR[b]	95% CI		
All Women										
No Hysterectomy	4193	6084	1.0				1.0			
Hysterectomy	1157	1460	1.19	1.09	–	1.31	1.04	0.94	–	1.16
Women without endometriosis										
No Hysterectomy	3924	5818	1.0				1.0			
Hysterectomy	995	1274	1.20	1.09	–	1.32	1.06	0.95	–	1.18
Women with endometriosis										
No Hysterectomy	269	266	1.0				1.0			
Hysterectomy	162	186	0.93	0.69	–	1.26	0.69	0.48	–	0.99

[a] Adjusted for age, race, education, OCAC site, and parity.
[b] Adjusted for age, race, education, OCAC site, parity, ET duration, and EPT duration; endometriosis-hysterectomy p-interaction = 0.047.

women without endometriosis did show hysterectomy being inversely associated with clear cell ovarian cancer and perhaps endometrioid although the results were neither statistically significant nor different across histotypes. The OC3 study found an inverse association between hysterectomy and clear cell and endometrioid cancers as well [15]. It is also possible that one or both ovaries and/or the fallopian tubes were removed during the hysterectomy procedure for some control women with endometriosis, and they were unaware of this. However, Dixon-Suen et al.'s study did have oophorectomy information from hospital records and the inverse association they observed between hysterectomy and ovarian cancer among women with endometriosis was for women who still had their ovaries [10].

The lack of an association between hysterectomy and ovarian cancer, particularly the lack of association for hysterectomies performed in the pre-menopausal period, is interesting. Tubal ligation is protective against ovarian cancer with one presumed mechanism being blocking retrograde menstruation [37]. If this is the case, having a hysterectomy in the pre-menopausal period should be protective through a similar mechanism at least for endometrioid, clear cell, and low-grade serous cancers which are thought to arise from endometriosis [35]. Although we do observe a non-significant inverse association for clear cell and endometrioid cancers, there was a non-significant positive association with low-grade serous cancers (Supplementary Table 1). Investigation into the mechanism(s) behind the protective effect of tubal ligations is needed to better understand why hysterectomy is not inversely associated with ovarian cancer risk with the exception of women with endometriosis. Interestingly, the study by Peres and colleagues did observe an inverse association between hysterectomies done in the pre-menopausal period and ovarian cancer [42]. It is possible that our failure to observe this association is due to chance.

A strength of our analysis was our large sample size, which included 5350 women with ovarian cancer and 7544 control women. In addition, we had comprehensive data available in the OCAC, which allowed us to examine the hysterectomy-ovarian cancer association within strata of endometriosis history while adjusting for duration of ET and EPT use.

The use of self-report data is a limitation, particularly since the studies we have included in our analysis are case-control studies, making recall bias a concern. However, there is little reason to believe that women with ovarian cancer versus women without would differentially misreport their hysterectomy status, duration of ET and EPT use, or endometriosis history, as these are not exposures likely to be subject to recall bias. Non-differential misclassification could explain a null finding, but it is unlikely to result in the inverse association we observed among women with endometriosis. We also considered the potential for selection bias given that hysterectomy is less common among more educated women [38,39] and some case-control studies have observed higher education and socioeconomic levels to be inversely associated with ovarian cancer risk [40,41]. However, in our analyses, the prevalence of cases and controls who have less than a high school education (19% versus 20%, respectively) and at least a high school education (25% versus 27%, respectively) were similar. Controls were slightly more likely to have a college degree compared to cases (30% versus 26%), but this is a minor difference that is unlikely to introduce selection bias. In addition, the percent of control women with a history of endometriosis in our analysis was 6%, which is in line with the 5–10% endometriosis prevalence that others have reported [42,43].

It is possible, as mentioned above, that the inverse association with hysterectomy observed among women with endometriosis is because some control women also had their ovaries and/or their fallopian tubes removed during their hysterectomy and this removal was unbeknownst to them [33]. Unfortunately, we did not have data on women's oophorectomy and/or salpingectomy status nor their indications for having a hysterectomy. However, our findings are in line with Dixon-Suen et al.'s study [10] who in their analysis of claims data, which would have accurately captured this information for women, observed an inverse association between hysterectomy and ovarian cancer risk among those with endometriosis. Further, our results are consistent with those of the OC3 analysis [7]. Also, while we were able to assess histotype-specific associations among all women and women without endometriosis, we were unable to do this for women with endometriosis due to small numbers.

Overall, there was no association between hysterectomy and ovarian cancer risk among women without endometriosis whereas among women with endometriosis, there was an inverse association when duration of ET use and duration of EPT use were taken into account. From a clinical standpoint, our results indicate that hysterectomy should not be considered a primary prevention strategy for ovarian cancer for most women. Although we do observe hysterectomy to be associated with decreased risk of ovarian cancer among women with endometriosis further research into the mechanisms underlying this apparent protective association is needed.

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Author contributions

The Australian Ovarian Cancer Study Group made substantial contributions in the acquisition of data for the work.

Hoda Anton-Culver made substantial contributions in the acquisition of data for the work, in interpreting the data for the work, and in revising the work critically for important intellectual content.

Andrew Berchuck made substantial contributions in the interpretation of data for the work, and revised the work critically for important intellectual content.

Jenny Chang-Claude made substantial contributions in the acquisition of data for the work, in interpreting the data for the work, and in revising the work critically for important intellectual content.

Kathleen Cho made substantial contributions in the interpretation of data for the work, and revised the work critically for important intellectual content.

Daniel Cramer made substantial contributions in the acquisition of data for the work, in interpreting the data for the work, and in revising the work critically for important intellectual content.

Jennifer Anne Doherty made substantial contributions in the acquisition of data for the work, in interpreting the data for the work, and in revising the work critically for important intellectual content.

Renée Fortner made substantial contributions to conception or design of the work, aided in the interpretation of data for the work, and revised the work critically for important intellectual content.

Marc Goodman made substantial contributions in the acquisition of data for the work and in revising the work critically for important intellectual data.

Gillian E Hanley made substantial contributions in the interpretation of data for the work, and revised the work critically for important intellectual content.

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References

[1] A.S. Whittemore, R. Harris, J. Itnyre, Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative ovarian cancer group, Am. J. Epidemiol. 136 (10) (1992) 1184–1203, https://doi.org/10.1093/oxfordjournals.aje.a116427.

[2] R. Luoto, A. Auvinen, E. Pukkala, M. Hakama, Hysterectomy and subsequent risk of cancer, Int. J. Epidemiol. 26 (3) (1997) 476–483, https://doi.org/10.1093/ije/26.3.476.

[3] H.A. Risch, L.D. Marrett, G.R. Howe, Parity, contraception, infertility, and the risk of epithelial ovarian cancer, Am. J. Epidemiol. 140 (7) (1994) 585–597, https://doi.org/10.1093/oxfordjournals.aje.a117296.

[4] D.W. Cramer, H. Xu, Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer, Ann. Epidemiol. 5 (4) (1995) 310–314, https://doi.org/10.1016/1047-2797(94)00098-E.

[5] A. Loft, O. Lidegaard, A. Tabor, Incidence of ovarian cancer after hysterectomy: a nationwide controlled follow up, Br. J. Obstet. Gynaecol. 104 (11) (1997) 1296–1301, https://doi.org/10.1111/j.1471-0528.1997.tb10978.x.

[6] N. Kreiger, M. Sloan, M. Cotterchio, P. Parsons, Surgical procedures associated with risk of ovarian cancer, Int. J. Epidemiol. 26 (4) (1997) 710–715, https://doi.org/10.1093/ije/26.4.710.

[7] N. Wentzensen, E.M. Poole, B. Trabert, et al., Ovarian cancer risk factors by histologic subtype: an analysis from the ovarian cancer cohort consortium, J. Clin. Oncol. 34 (24) (2016) 2888–2898, https://doi.org/10.1200/JCO.2016.66.8178.

[8] M.S. Rice, M.A. Murphy, A.F. Vitonis, et al., Tubal ligation, hysterectomy and epithelial ovarian cancer in the New England case-control study, Int. J. Cancer 133 (10) (2013) 2415–2421, https://doi.org/10.1002/ijc.28249.
[9] M.S. Rice, S.E. Hankinson, S.S. Tworoger, Tubal ligation, hysterectomy, unilateral oophorectomy, and risk of ovarian cancer in the Nurses' Health Studies, Fertil. Steril. 102 (1) (2014) 192–198 , e3 https://doi.org/10.1016/j.fertnstert.2014.03.041.
[10] S.C. Dixon-Suen, P.M. Webb, L.F. Wilson, K. Tuesley, L.M. Stewart, S.J. Jordan, The association between hysterectomy and ovarian cancer risk: a population-based record-linkage study, J. Natl. Cancer Inst. 111 (10) (2019) 1097–1103, https://doi.org/10.1093/jnci/djz015.
[11] S.J. Jordan, A.C. Green, D.C. Whiteman, P.M. Webb, Australian ovarian cancer study group. Risk factors for benign, borderline and invasive mucinous ovarian tumors: epidemiological evidence of a neoplastic continuum? Gynecol. Oncol. 107 (2) (2007) 223–230, https://doi.org/10.1016/j.ygyno.2007.06.006.
[12] S.J. Jordan, A.C. Green, D.C. Whiteman, et al., Serous ovarian, fallopian tube and primary peritoneal cancers: a comparative epidemiological analysis, Int. J. Cancer 122 (7) (2008) 1598–1603, https://doi.org/10.1002/ijc.23287.
[13] F. Modugno, R.B. Ness, G.O. Allen, J.M. Schildkraut, F.G. Davis, M.T. Goodman, Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis, Am. J. Obstet. Gynecol. 191 (3) (2004) 733–740, https://doi.org/10.1016/j.ajog.2004.03.035.
[14] C.M. Nagle, C.M. Olsen, P.M. Webb, et al., Endometrioid and clear cell ovarian cancers: a comparative analysis of risk factors, Eur. J. Cancer 44 (16) (2008) 2477–2484, https://doi.org/10.1016/j.ejca.2008.07.009.
[15] S.J. Jordan, C.M. Nagle, M.D. Coory, et al., Has the association between hysterectomy and ovarian cancer changed over time? A systematic review and meta-analysis, Eur. J. Cancer 49 (17) (2013) 3638–3647, https://doi.org/10.1016/j.ejca.2013.07.005.
[16] C.B. Johannes, S.L. Crawford, J.G. Posner, S.M. McKinlay, Longitudinal patterns and correlates of hormone replacement therapy use in middle-aged women, Am. J. Epidemiol. 140 (5) (1994) 439–452, https://doi.org/10.1093/oxfordjournals.aje.a117266.
[17] Million Women Study Collaborators, Patterns of use of hormone replacement therapy in one million women in Britain, 1996-2000, BJOG. 109 (12) (2002) 1319–1330, https://doi.org/10.1016/s1470-0328(02)02914-2.
[18] A.W. Lee, R.B. Ness, L.D. Roman, et al., Association between menopausal estrogen-only therapy and ovarian carcinoma risk, Obstet. Gynecol. 127 (5) (2016) 828–836, https://doi.org/10.1097/AOG.0000000000001387.
[19] A. Hammer, A.F. Rositch, J. Kahlert, P.E. Gravitt, J. Blaakaer, M. Søgaard, Global epidemiology of hysterectomy: possible impact on gynecological cancer rates, Am. J. Obstet. Gynecol. 213 (1) (2015) 23–29, https://doi.org/10.1016/j.ajog.2015.02.019.
[20] R.A. Cannioto, B. Trabert, E.M. Poole, J.M. Schildkraut, Ovarian cancer epidemiology in the era of collaborative team science, Cancer Causes Control CCC. 28 (5) (2017) 487–495, https://doi.org/10.1007/s10552-017-0862-6.
[21] M.A. Merritt, A.C. Green, C.M. Nagle, P.M. Webb, Australian cancer study (ovarian Cancer), Australian ovarian Cancer study group. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer, Int. J. Cancer 122 (1) (2008) 170–176, https://doi.org/10.1002/ijc.23017.
[22] J. Royar, H. Becher, J. Chang-Claude, Low-dose oral contraceptives: protective effect on ovarian cancer risk, Int. J. Cancer 95 (6) (2001) 370–374, https://doi.org/10.1002/1097-0215(20011120)95:6<370::AID-IJC1065>3.0.CO;2-T.
[23] E. Glud, S.K. Kjaer, B.L. Thomsen, et al., Hormone therapy and the impact of estrogen intake on the risk of ovarian cancer, Arch. Intern. Med. 164 (20) (2004) 2253–2259, https://doi.org/10.1001/archinte.164.20.2253.
[24] H.A. Risch, A.E. Bale, P.A. Beck, W. Zheng, PGR +331 A/G and increased risk of epithelial ovarian cancer, Cancer Epidemiol. Biomark. Prev. 15 (9) (2006) 1738–1741, https://doi.org/10.1158/1055-9965.EPI-06-0272.
[25] M.A. Rossing, K.L. Cushing-Haugen, K.G. Wicklund, J.A. Doherty, N.S. Weiss, Risk of epithelial ovarian cancer in relation to benign ovarian conditions and ovarian surgery, Cancer Causes Control 19 (10) (2008) 1357–1364, https://doi.org/10.1007/s10552-008-9207-9.
[26] G. Lurie, L.R. Wilkens, P.J. Thompson, et al., Combined oral contraceptive use and epithelial ovarian cancer risk: time-related effects, Epidemiology. 19 (2) (2008) 237–243, https://doi.org/10.1097/EDE.0b013e31816334c5.
[27] R.B. Ness, R.C. Dodge, R.P. Edwards, J.A. Baker, K.B. Moysich, Contraception methods, beyond oral contraceptives and tubal ligation, and risk of ovarian cancer, Ann. Epidemiol. 21 (3) (2011) 188–196, https://doi.org/10.1016/j.annepidem.2010.10.002.
[28] K.L. Terry, I. De Vivo, L. Titus-Ernstoff, M.-C. Shih, D.W. Cramer, Androgen receptor cytosine, adenine, guanine repeats, and haplotypes in relation to ovarian cancer risk, Cancer Res. 65 (13) (2005) 5974–5981, https://doi.org/10.1158/0008-5472.CAN-04-3885.
[29] A. Ziogas, M. Gildea, P. Cohen, et al., Cancer risk estimates for family members of a population-based family registry for breast and ovarian cancer, Cancer Epidemiol. Biomark. Prev. 9 (1) (2000) 103–111.
[30] A.H. Wu, C.L. Pearce, A.W. Lee, et al., Timing of births and oral contraceptive use influences ovarian cancer risk, Int. J. Cancer 141 (12) (2017) 2392–2399, https://doi.org/10.1002/ijc.30910.
[31] J.M. Schildkraut, P.G. Moorman, A.E. Bland, et al., Cyclin E overexpression in epithelial ovarian cancer characterizes an etiologic subgroup, Cancer Epidemiol. Biomark. Prev. 17 (3) (2008) 585, https://doi.org/10.1158/1055-9965.EPI-07-0596.
[32] L.C. Peres, A.J. Alberg, E.V. Bandera, et al., Premenopausal hysterectomy and risk of ovarian Cancer in African-American women, Am. J. Epidemiol. 186 (1) (2017) 46–53, https://doi.org/10.1093/aje/kwx055.
[33] A.I. Phipps, D.S.M. Buist, Validation of self-reported history of hysterectomy and oophorectomy among women in an integrated group practice setting, Menopause. 16 (3) (2009) 576–581, https://doi.org/10.1097/gme.0b013e31818ffe28.
[34] B. Rizk, A.S. Fischer, H.A. Lotfy, et al., Recurrence of endometriosis after hysterectomy, Facts Views Vis. ObGyn. 6 (4) (2014) 219–227.
[35] C.L. Pearce, C. Templeman, M.A. Rossing, et al., Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies, Lancet Oncol. 13 (4) (2012) 385–394, https://doi.org/10.1016/S1470-2045(11)70404-1.
[36] A.-S. Melin, C. Lundholm, N. Malki, M.-L. Swahn, P. Sparèn, A. Bergqvist, Hormonal and surgical treatments for endometriosis and risk of epithelial ovarian cancer, Acta Obstet. Gynecol. Scand. 92 (5) (2013) 546–554, https://doi.org/10.1111/aogs.12123.
[37] W. Sieh, S. Salvador, V. McGuire, et al., Tubal ligation and risk of ovarian cancer subtypes: a pooled analysis of case-control studies, Int. J. Epidemiol. 42 (2) (2013) 579–589, https://doi.org/10.1093/ije/dyt042.
[38] K.M. Brett, J.V. Marsh, J.H. Madans, Epidemiology of hysterectomy in the United States: demographic and reproductive factors in a nationally representative sample, J. Women's Health 6 (3) (1997) 309–316, https://doi.org/10.1089/jwh.1997.6.309.
[39] A. Stang, A. Kluttig, S. Moebus, et al., Educational level, prevalence of hysterectomy, and age at amenorrhoea: a cross-sectional analysis of 9536 women from six population-based cohort studies in Germany, BMC Womens Health 14 (2014) 10, https://doi.org/10.1186/1472-6874-14-10.
[40] K.-H. Tung, L.R. Wilkens, A.H. Wu, et al., Association of dietary vitamin a, carotenoids, and other antioxidants with the risk of ovarian cancer, Cancer Epidemiol. Biomark. Prev. 14 (3) (2005) 669–676, https://doi.org/10.1158/1055-9965.EPI-04-0550.
[41] A.J. Alberg, P.G. Moorman, S. Crankshaw, et al., Socioeconomic status in relation to the risk of ovarian cancer in African-American women: a population-based case-control study, Am. J. Epidemiol. 184 (4) (2016) 274–283, https://doi.org/10.1093/aje/kwv450.
[42] H.S. Taylor, A.M. Kotlyar, V.A. Flores, Endometriosis is a chronic systemic disease: clinical challenges and novel implications, Lancet. 397 (10276) (2021) 839–852, https://doi.org/10.1016/S0140-6736(21)00389-5.
[43] K.T. Zondervan, C.M. Becker, K. Koga, S.A. Missmer, R.N. Taylor, P. Vigano, Endometriosis, Nat. Rev. Dis. Primers. 19 (4) (2018) 9, https://doi.org/10.1038/s41572-018-0008-5.