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Article

The association between hysterectomy and ovarian cancer risk: A population-based record-linkage study

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List of abbreviations

ARIA   Accessibility and Remoteness Index of Australia

CI   confidence interval

HMDC   Hospital Morbidity Data Collection

HR   hazard ratio

ICD   International Classification of Diseases

MHT   menopausal hormone therapy

MNS   Midwives Notifications System

SEIFA   Socio-Economic Indexes for Areas

WA   Western Australia

WADLS   Western Australian Data Linkage System

Abstract

Background: Recent studies have called into question the long-held belief that hysterectomy without oophorectomy protects against ovarian cancer. This population-based longitudinal record-linkage study aimed to explore this relationship, overall and by age at hysterectomy, time period, surgery type, and indication for hysterectomy.

Methods: We followed the female adult Western Australian population (837,942 women) across a 27-year period using linked electoral, hospital, births, deaths, and cancer records. Surgery dates were determined from hospital records, and ovarian cancer diagnoses (n=1,640) were ascertained from cancer registry records. We used Cox regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between hysterectomy and ovarian cancer incidence.

Results: Hysterectomy without oophorectomy (n=78,594) was not associated with risk of invasive ovarian cancer overall (HR = 0.98, 95% CI = 0.85-1.11), or with the most common serous subtype (HR = 1.05, 95% CI = 0.89-1.23). Estimates did not vary statistically significantly by age at procedure, time period or surgical approach. However, among women with endometriosis (5.8%) or with fibroids (5.7%), hysterectomy was associated with substantially decreased ovarian cancer risk, overall (HR = 0.17, 95% CI = 0.12-0.24 and HR = 0.27, 95% CI = 0.20-0.36, respectively) and across all subtypes.

Conclusions: Our results suggest that for most women, having a hysterectomy with ovarian conservation is not likely to substantially alter their risk of developing ovarian cancer. However, our results, if confirmed, suggest that ovarian cancer risk reduction could be considered as a possible benefit of hysterectomy when making decisions about surgical management of endometriosis or fibroids.

Keywords: ovarian cancer, hysterectomy, record-linkage, endometriosis, fibroids

Introduction

Hysterectomy without oophorectomy has been traditionally considered protective against ovarian cancer, supported by a considerable body of older research (summarized in (1-3)). However, many studies including women diagnosed more recently have not seen a protective association; indeed, some reported modest increases in risk, as seen in a recent meta-analysis (4) and subsequent studies (5, 6). This apparent shift could arise from changing surgical practices or patient characteristics, changes in menopausal hormone therapy (MHT) use, or perhaps improved reporting of oophorectomy status.

Hysterectomy is one of the most common major surgeries among women globally (7, 8); understanding the true relationship between hysterectomy alone and ovarian cancer risk is important to inform the current debate over the relative advantages of prophylactically removing ovaries at hysterectomy. Our aim was to explore the association between hysterectomy for benign indications and ovarian cancer risk, overall and by time period, age at surgery, hysterectomy type, and indication for hysterectomy. We examined this question using 45 years of administrative data from the Western Australian Data Linkage System (WADLS) (9).

Methods

Study population and linkage

We conducted a retrospective cohort study including all women on the Western Australian (WA) Electoral Roll (enrollment to vote is compulsory) when electronic records began in 1988, or who registered subsequently. We restricted the cohort to women aged ≤45 years in 1975, when hysterectomy began to be reliably recorded, to minimize inclusion of

women who had hysterectomies, oophorectomies, or cancer diagnoses before observation. Women born from 1930 to 1998 (the last birth-year for which women would reach electoral enrollment age within our observation period) were therefore eligible for the analysis. This cohort was linked with the WA Hospital Morbidity Data Collection (HMDC; 1970-2014), WA Cancer Registry (1982-2015), Midwives Notifications System (MNS; 1980-2013), and WA Births (1950-1979) and Deaths (1988-2015) Registers, allowing follow-up from 1988 until mid-2015. The Western Australian Data Linkage Branch linked the datasets using probabilistic linkage matching on identifying and demographic fields and provided de-identified data to the researchers. We excluded women with: recorded ovarian cancer, oophorectomy, or hysterectomy for malignancy before their first electoral record (n=9805); or data inconsistencies (implausible birthdates, births after hysterectomy, first electoral record after death, or male-specific codes: n=1313).

The study received approval from QIMR Berghofer and WA Health Human Research Ethics Committees.

Variable measurement

Our main outcome was diagnosis of primary invasive epithelial cancer in the ovary (International Classification of Diseases [ICD]-10 code C56), fallopian tube (C57.0) or peritoneum (C48), recorded in the WA Cancer Registry, hereafter referred to collectively as 'ovarian cancer'. Available data included date/basis of diagnosis, and tumor site, behavior, grade, and morphology. Using morphology ICDO-3 codes we classified cancers as serous, mucinous, endometrioid, clear cell, or other.

The HMDC contains information on all public and private WA hospital separations, including admission/discharge month and year, diagnosis codes (principal, 21 additional), and surgical procedure codes (principal, 10 additional) (see **Supplementary Tables 1 and 2**

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for codes). We used procedure codes to ascertain hysterectomies, oophorectomies, and tubal ligations, and diagnosis codes to identify hysterectomy indications and ovarian cancer diagnoses before cancer registry records began.

Birth-year (from electoral records) was provided in 5-year bands to protect anonymity; we derived age by assigning birthdate as the lowermost end. Electoral records include postcode, from which we derived remoteness of residence (major cities/inner regional/outer regional/remote/very remote) using the Accessibility and Remoteness Index of Australia (ARIA+) (10, 11), and socio-economic disadvantage quintiles using the Socio-Economic Indexes for Areas (SEIFA) (12), at study entry. We determined parity using the Births Register and MNS, assuming nulliparity at 1950 for women (n=68,218) who reached reproductive age before records began.

Statistical analysis

We calculated person-time for each woman as the interval between study entry (her first appearance in the available electoral records) and exit, determined as the earliest of: ovarian cancer diagnosis; hysterectomy or unilateral/bilateral oophorectomy if followed within 6 months by ovarian cancer diagnosis (surgery date was then assigned as diagnosis date, as we considered these surgeries were likely related to their cancer); or a censoring condition, at which follow-up ceased. Censoring conditions were: all other unilateral/bilateral oophorectomies (including at hysterectomy); hysterectomy for other malignancies (predominantly endometrial); diagnosis of non-epithelial ovarian cancer; death; emigration; or end of observation (30/06/2015). We calculated exposed and unexposed person-time considering hysterectomy, parity, and tubal ligation as time-varying using the counting process method (13). Thus person-time from entry until hysterectomy (or until exit, for

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unexposed women) was considered unexposed; any observed time after hysterectomy (from study entry, for women with prior hysterectomies) was considered exposed.

We performed Cox proportional-hazards regression, estimating hazard ratios (HRs) and 95% confidence intervals (CI) for the association between hysterectomy and ovarian cancer incidence, overall and for different histologic subtypes, using age as the underlying time scale (14). We stratified models by birth decade, and adjusted for age at entry, parity (≥3 vs 0-2 births), and tubal ligation (yes/no). We omitted SEIFA and ARIA from final models because they did not change HRs for the main association. The proportional hazards assumption was confirmed graphically by plotting Schoenfeld residuals against time.

We conducted additional analyses comparing risk associated with hysterectomy performed in three eras (<1990, 1990-2002, >2002). Time periods were chosen based on trends in MHT use, which may influence the association (15). MHT use decreased in the 1970s then increased again (1980s), became widespread during the 1990s, then declined sharply from 2002 (16), when Women's Health Initiative investigators reported that combined MHT use was associated with adverse health outcomes (17). We examined whether the association varied by age (as a proxy for menopausal status) at hysterectomy, considering <45 (mostly premenopausal women), 45-54 (peri-menopausal women), and ≥55 years (mostly post-menopausal women). We compared risk associated with abdominal or vaginal hysterectomy (numbers were insufficient to examine solely laparoscopic hysterectomy). Lastly, we performed analyses considering hysterectomy indication, focusing on three common indications (endometriosis, uterine leiomyoma [fibroids], and genital prolapse).

We conducted sensitivity analyses, including: varying elements of the methods (using years as the time-scale); varying the population (to women <45 years when hospital [1970] or

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cancer registry [1982] records began, vs. applying no age restriction; excluding women entering after 1988 after usual enrollment age [>25 years; therefore women migrating into WA]; examining associations by birth cohort); selecting different comparison groups (estimating associations for later vs. earlier hysterectomies in age/period analyses); and restricting the outcome to cancer of the ovary (censoring at fallopian tube/peritoneal cancer diagnosis).

Analyses were performed in SAS 9.4 (SAS Institute Inc., N.C.). Tests of statistical significance were two-sided and we used an alpha level of 5% to determine statistical significance; to determine the statistical significance of the hazard ratios in our analysis, we assessed whether the 95% CI crossed 1.00.

Results

We included 837,942 women (aged 17-82 [median 30] years at entry, 17-87 [median 50] at exit) contributing 15,738,607 person-years of follow-up. The cohort included 223,049 women (26.6%) who entered in 1988 (median age at entry/exit 38/65) and 614,893 women (73.4%) who entered later (median age at entry/exit 26/45). Overall 78,594 women had a recorded hysterectomy for a benign indication before study exit (28,091 occurred before entry) and contributed 1,335,989 exposed person-years. There were 81,927 tubal ligations before exit. At their study entry, 715,329 (85.4%) of women had 0-2 children and 122,613 (14.6%) had 3 or more; by study exit, 610,857 (72.9%) had 0-2 children, and 227,085 (27.1%) had 3 or more. At entry, 622,446 (74.3%) lived in major cities, 147,874 (17.6%) in inner/outer regional and 60,228 (7.2%) in remote/very remote areas; 31.3% were in the least and 16.9% in the most disadvantaged SEIFA quintile. There were 48,870 (5.8%) women with a diagnosis of endometriosis (most at hysterectomy), 47,407 (5.7%) with fibroids (15,037 had

both conditions), and 55,752 (6.7%) with prolapse. During the study window 1,640 women were diagnosed with invasive epithelial ovarian cancer (including 1020 serous, 125 mucinous, 146 endometrioid, and 90 clear cell cancers). **Table 1** presents population characteristics by hysterectomy/exposure status.

Hysterectomy was not associated with decreased risk of invasive epithelial ovarian cancer overall (HR 0.98, 95%CI 0.85-1.11), or for the most common serous subtype (HR 1.05, 95%CI 0.89-1.23), after adjusting for age, tubal ligation, and parity. Effect estimates were in the protective direction for mucinous (HR 0.55, 95%CI 0.28-1.06), endometrioid (HR 0.69, 95%CI 0.41-1.18) and clear cell (HR 0.56, 95%CI 0.27-1.16) tumors, but were not statistically significant (**Table 2**).

Analyses by time period (**Figure 1A**) showed no association with ovarian cancer overall for hysterectomies performed <1990 (HR 0.93, 95%CI 0.79-1.10), and a slightly positive but statistically nonsignificant association for hysterectomies performed 1990-2002 (HR 1.14, 95%CI 0.93-1.40). The association for hysterectomies performed >2002 was inverse (HR 0.60, 95%CI 0.34-1.06), although not statistically significant. The association did not vary substantively by age at hysterectomy: <45 years, HR 0.94 (95%CI 0.77-1.15); 45-55 years, HR 1.01 (95%CI 0.84-1.21); >55 years, HR 0.96 (95%CI 0.68-1.34) (**Figure 1B**). Results by type of hysterectomy are presented in **Supplementary Table 3**. There were too few cancers to conduct period, age, or surgical type analyses by histologic subtype.

Our two *a priori* approaches to assess whether the association varied by indication were: first, to adjust the main models for the indication(s) for hysterectomy; and second, to examine in a separate model the association between hysterectomy for each indication coded at surgery (a single multi-level variable) and risk, compared to no hysterectomy. Implementing the first approach, we observed that after adjusting models for ever-diagnosis of

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endometriosis or fibroids, estimates of the association decreased for ovarian cancer overall (HR 0.65, 95%CI 0.56-0.75), and for each subtype (serous HR 0.76 [95%CI 0.63-0.91], mucinous HR 0.38, 95%CI 0.19-0.75; endometrioid HR 0.30, 95%CI 0.17-0.52; clear cell HR 0.19, 95%CI 0.09-0.41) (**Table 2**). Further adjustment for prolapse did not substantially alter effect estimates.

Implementing our second approach, we constructed a model estimating risk associated with hysterectomy performed for each indication. We observed that, compared to women without hysterectomy (which includes women with/without diagnosis of each indication), estimates were in the direction of slightly increased ovarian cancer risk for hysterectomy for endometriosis (without fibroids/prolapse) (HR 1.18, 95%CI 0.71-1.96), or fibroids (without endometriosis/prolapse) (HR 1.10, 95%CI 0.79-1.55), and apparent slight decreased ovarian cancer risk for hysterectomy for prolapse (without endometriosis/fibroids) (HR 0.89, 95%CI 0.67-1.18), although none were statistically significant (**Table 3**). However, these conditions were associated with ovarian cancer risk irrespective of hysterectomy. Ever-diagnosis of endometriosis was associated with increased ovarian cancer risk (HR 2.74, 95%CI 2.32-3.22), with particularly strong associations for endometrioid (HR 7.42, 95%CI 4.80-11.48) and clear cell (HR 12.24, 95%CI 7.23-20.73) cancers (**Supplementary Table 4**). Ever-diagnosis of fibroids was associated with increased risk overall (HR 1.97, 95%CI 1.69-2.30), with little variation by subtype (**Supplementary Table 4**). Ever-diagnosis of prolapse was associated with decreased risk overall (HR 0.68, 95%CI 0.57-0.80), with little variation by subtype except a stronger inverse association for clear cell cancers (HR 0.38, 95%CI 0.16-0.89) (**Supplementary Table 4**).

To distinguish the effect of hysterectomy for a particular indication from the effect of the condition itself, we implemented a third approach, stratifying by each condition and repeating our analysis within those strata. We observed that among women ever diagnosed with

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endometriosis, hysterectomy was associated with substantially decreased ovarian cancer risk (HR 0.17, 95%CI 0.12-0.24, overall) (**Table 4**), with fairly consistent HRs across subtypes (**Supplementary Table 5**). Similarly, hysterectomy was associated with decreased risk among women with fibroids (HR 0.27, 95%CI 0.20-0.36 overall) (**Table 4**), which again was similar across subtypes (**Supplementary Table 5**). The strong inverse relationship among women with endometriosis or fibroids remained, although was slightly attenuated, after excluding women with the other condition (data not shown). Among women without endometriosis, without fibroids, and with neither condition, there was no protective effect of hysterectomy (for example, HR 1.15, 95%CI 0.98-1.35, overall, among women with neither condition) (**Table 4**). In women with prolapse, the effect estimate was slightly elevated but not statistically significant (HR 1.24, 95%CI 0.91-1.69) (**Table 4**).

Our results were robust to the method used to estimate person-years. Including older women (relaxing/removing the age restriction) yielded similar estimates although some became slightly inverse (**Supplementary Table 6**), consistent with the hypothesis that including older women increases misclassification of women with prior oophorectomy. Restricting analyses to younger women (<45 in 1982), or excluding women migrating into WA, made little difference to estimates (**Supplementary Table 6**). There were no obvious patterns by birth cohort, although numbers were generally too low to draw clear conclusions. Estimates were similar when we repeated analyses defining outcome strictly as cancer of the ovary (ICD code C56), except for a stronger inverse association for mucinous cancers (data not shown).

Discussion

In this large retrospective study using linked administrative data we found that hysterectomy was not associated with decreased ovarian cancer risk either overall or for the most common and aggressive form (serous cancer), and that reductions in risk were not observed in earlier time periods. There was a suggestion of decreased risk of non-serous ovarian cancers which was not statistically significant. The association varied minimally by age at surgery or type of hysterectomy. Among women with endometriosis or fibroids, two common indications for this procedure, hysterectomy was associated with substantially decreased ovarian cancer risk.

While older studies had suggested a protective effect of hysterectomy on ovarian cancer (18, 19), almost all recent studies have not shown this (20, 21). Our results are consistent with recent findings; we did not see inverse associations even for hysterectomies performed in the 1970s/1980s. The discrepancy between older and newer studies may arise from better self-reporting of oophorectomy. Many women with documented bilateral oophorectomy report that their ovaries have not been removed (22). It may be that women in older studies, with hysterectomies undertaken further back in time, were less likely to be aware that oophorectomy had been simultaneously performed. Our study avoids this bias by ascertaining oophorectomy using hospital records.

Fluctuations in MHT use may have also influenced associations over time. MHT is prescribed more frequently to women with hysterectomy than those without, and is associated with modestly increased ovarian cancer risk (23). Two large studies have reported that hysterectomy is associated with slightly increased ovarian cancer risk among ever-users of MHT, but decreased risk among never-users (24, 25). Without data on MHT use we could not

directly explore its influence, but the slight increased risk associated with hysterectomies in the 1990s, when MHT was common, and reduced risk thereafter, when MHT use fell, is consistent with this pattern. However, we had short follow-up and few hysterectomies and cancer diagnoses after 2002.

Some previous studies have suggested that hysterectomy at younger ages particularly (<45 or <50) may be associated with reduced ovarian cancer risk (4). However, we found little variation in the association by surgery age.

We found some evidence that the association varies by histologic subtype, with no association seen for serous cancers but a suggestion of inverse relationships with non-serous tumors, particularly mucinous and clear cell. These results closely match subtype-specific estimates from a recent pooled analysis of 21 cohorts (6). Some (5, 26-28), but not all (29, 30), large case-control studies have also reported risk reductions for non-serous tumors.

A novel finding of our study was that hysterectomy appeared to substantially reduce risk among women with endometriosis or fibroids (both of which were associated with considerably increased ovarian cancer risk in our population). Few studies have considered indication for hysterectomy. One case-control study reported that adjustment for endometriosis, fibroids, and ovarian cysts decreased the odds ratio for the hysterectomy/ovarian cancer association (24), as we found. An analysis pooling four case-control studies (2098 cases) compared women with/without endometriosis and, consistent with our results, reported that hysterectomy was associated with possible decreased ovarian cancer risk among women with endometriosis (OR 0.69, 95%CI 0.38-1.24) but not without (OR 1.02, 95%CI 0.86-1.23) (31). Use of self-reported endometriosis, consequently including a broader disease spectrum with more misclassification, may explain their weaker association, as self-reported endometriosis is associated with lower ovarian cancer risk than

surgically confirmed endometriosis (32). Another study of women with endometriosis found that removal of endometriotic lesions substantially reduced ovarian cancer risk, while hysterectomy did not (33). It is possible that the protective effect we observed is primarily due to simultaneous removal of lesions. Fibroids have rarely been assessed in relation to ovarian cancer. One Danish record-linkage study reported that women with fibroids are at increased risk of ovarian cancer (RR 1.36, 95%CI 1.16-1.60), particularly endometrioid tumors (RR 1.57, 95%CI 1.05-2.34) (34), a similar although slightly weaker association than we observed. We know of no studies examining the hysterectomy/ovarian cancer relationship by the presence/absence of fibroids. Our findings among women with these conditions, while intriguing and plausible, were obtained from post-hoc subgroup analyses and require replication.

Notable strengths of our study include its large size, population-based design, long-term follow-up, and measurement of exposure and outcome using medical records. Compulsory electoral enrollment allowed us to include virtually all female WA residents. Ascertaining hysterectomy/oophorectomy status using hospital data eliminates recall error, a concern in many previous studies. Misclassification of hysterectomy status is likely to be minimal, since: the HMDC records all surgeries in WA; residents infrequently receive care elsewhere due to geographic isolation (35); we restricted the analysis to younger women at the start of hospital records; and excluding women migrating into WA during observation did not change our findings. Precise information on surgery date allowed accurate classification of exposed time. Reporting diagnoses of malignant solid tumors to the cancer registry is mandatory, so most ovarian cancers after 1982 should be captured.

Our study is not without limitations. We may not have captured exposures or outcomes occurring prior to available hospital records. We mitigated this by restricting to women aged ≤45 years in 1975 (the start of reliable hysterectomy data). Residual misclassification

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resulting from unrecorded early hysterectomies (perhaps chiefly among 6.7% of women without recorded hysterectomy, who entered in 1988 and were aged 30-45 in 1975) would have reduced the difference between exposed and unexposed groups, attenuating any association. However, restricting our analysis to younger women resulted in similar estimates, suggesting that misclassification was minimal. Our study design limited access to information on some possible confounding factors, which are not usually recorded in administrative data sources. However, the confounders we were able to include had negligible influence on our effect estimates, and confounders which were unrecorded would be expected to have modest effects (for instance, oral-contraceptive use is not strongly related to hysterectomy [for example, (36)]). For the same reason we could not directly assess the effect of any changes in MHT use over time. We compared the association between time-periods chosen to reflect different levels of MHT use, and observed suggestive differences. MHT use is only moderately associated with ovarian cancer risk (23) but could account for a portion of the difference. Future studies examining this association should incorporate MHT use if possible.

In summary, we conducted a large, population-based record-linkage study using up to 45 years of data for women in Western Australia. Our results for women with endometriosis and fibroids require replication, but suggest that hysterectomy may reduce ovarian cancer risk among these women. However, women without these conditions should not be advised that hysterectomy alone will reduce their ovarian cancer risk.

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Notes

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Table 1: Demographic and reproductive characteristics of included women, by final hysterectomy status recorded 1970-2015

Characteristic	No hysterectomy (N=733,832) No. (%)	Hysterectomy contributing exposed time* (N=78,594) No. (%)	Hysterectomy contributing no exposed time † (N=25,516) No. (%)
Age at study entry, y			
<30	385,380 (52.5)	12,054 (15.3)	5,428 (21.3)
30-<40	159,300 (21.7)	23,759 (30.2)	7,840 (30.7)
40-<50	107,808 (14.7)	26,584 (33.8)	8,159 (32.0)
50-<60	66,378 (9.0)	14,794 (18.8)	3,690 (14.5)
60-<70	12,870 (1.8)	1,331 (1.7)	373 (1.5)
≥70	2,096 (0.3)	72 (0.1)	26 (0.1)
Tubal ligation at end of observation			
No	672,377 (91.6)	62,509 (79.5)	20,677 (81.0)
Yes	61,455 (8.4)	16,085 (20.5)	4,839 (19.0)
Parity at end of observation			
0	342,192 (46.6)	21,170 (26.9)	8,481 (33.2)
1	62,582 (8.5)	6,272 (8.0)	2,176 (8.5)
2	142,476 (19.4)	19,240 (24.5)	6,268 (24.6)
≥3	186,582 (25.4)	31,912 (40.6)	8,591 (33.7)
Endometriosis ‡			
No	713,013 (97.2)	59,725 (76.0)	16,334 (64.0)
Yes	20,819 (2.8)	18,869 (24.0)	9,182 (36.0)
Fibroids ‡			
No	721,137 (98.3)	54,977 (70.0)	14,421 (56.5)
Yes	12,695 (1.7)	23,617 (30.0)	11,095 (43.5)
Prolapse ‡			
No	715,643 (97.5)	46,408 (59.0)	20,139 (78.9)
Yes	18,189 (2.5)	32,186 (41.0)	5,377 (21.1)
Socio-economic disadvantage score (SEIFA§) quintile at study entry ‖			
1 (most disadvantaged)	122,758 (16.7)	14,213 (18.1)	4,590 (18.0)
2	160,028 (21.8)	21,514 (27.4)	6,364 (24.9)
3	98,783 (13.5)	9,912 (12.6)	3,202 (12.5)
4	118,065 (16.1)	10,863 (13.8)	3,577 (14.0)
5 (least disadvantaged)	232,575 (31.7)	21,847 (27.8)	7,722 (30.3)

Remoteness at study entry ‖			
Major cities	548,088 (74.7)	55,110 (70.1)	19,248 (75.4)
Inner regional	63,417 (8.6)	7,880 (10.0)	2,108 (8.3)
Outer regional	63,584 (8.7)	8,811 (11.2)	2,074 (8.1)
Remote	36,015 (4.9)	4,295 (5.5)	1,212 (4.7)
Very remote	16,772 (2.3)	1,423 (1.8)	511 (2.0)

* These women had a hysterectomy for benign indications before their study exit (their hysterectomies occurred either before their first electoral record, or during the study window) and therefore contribute exposed time to the analysis. Women whose hysterectomy was performed during the study window contribute both unexposed and exposed time.

† These women had a hysterectomy but contribute only unexposed time to the analysis as their hysterectomy occurred at, or after, their study exit (these women predominantly exited due to a bilateral/unilateral oophorectomy performed prior to, or at the time of, their hysterectomy), or was performed for a non-benign indication (n=4632; at which time follow-up was censored if the woman had not already exited the study).

‡ Condition included as a diagnosis during any hospitalisations 1970-2015.

§ Socio-Economic Indexes for Areas.

‖ Percentages do not add to 100% due to a small proportion of missing data.

Table 2: Association between hysterectomy for a benign indication and invasive epithelial ovarian cancer, by histologic subtype*

Adjustment models†	All invasive ovarian cancer HR (95% CI)	Serous HR (95% CI)	Mucinous HR (95% CI)	Endometrioid HR (95% CI)	Clear cell HR (95% CI)
Adjustment 1					
No hysterectomy	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Hysterectomy‡	0.98 (0.85 to 1.11)	1.05 (0.89 to 1.23)	0.55 (0.28 to 1.06)	0.69 (0.41 to 1.18)	0.56 (0.27 to 1.16)
Adjustment 2					
No hysterectomy	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Hysterectomy‡	0.65 (0.56 to 0.75)	0.76 (0.63 to 0.91)	0.38 (0.19 to 0.75)	0.30 (0.17 to 0.52)	0.19 (0.09 to 0.41)

*   Time was censored at hysterectomy for malignancy. Hysterectomy is time-varying. Ovarian cancer includes primary ovarian, fallopian tube, and peritoneal cancer. For each histologic subtype analysis, follow-up time is censored at diagnosis of other subtypes. HR = hazard ratio; CI = confidence interval.

†   Models were stratified by decade of birth and adjusted for age at study entry, tubal ligation (yes/no), and parity (3 or more vs 0-2 births) (Adjustment 1), and additionally endometriosis (yes/no) and fibroids (yes/no) (Adjustment 2). Adjusting for genital prolapse (a third common indication for hysterectomy) did not affect the association between hysterectomy and ovarian cancer, so this was not included in presented models.

‡   As hysterectomy is time-varying, the analysis compares exposed time ('hysterectomy', contributed by women after their hysterectomy) vs unexposed time ('no hysterectomy', contributed by women before their hysterectomy and by women who did not have a recorded hysterectomy). We assigned date of hysterectomy as date of hospital discharge. For the vast majority (99.9%) of the women in this analysis, admission and discharge dates for hospitalisation for hysterectomy were identical (78.9%) or only one month apart (21.0%), because recovery in hospital after hysterectomy is typically short and the provided HMDC data included admission/discharge month and year (not day).

Table 3: Association between hysterectomy for a benign indication and invasive epithelial ovarian cancer*, by indication

Recorded hysterectomy indication	HR (95% CI)†
No hysterectomy	1.00 (Reference)
Hysterectomy performed for: ‡	
Endometriosis (not fibroids or prolapse)	1.18 (0.71 to 1.96)
Fibroids (not endometriosis or prolapse)	1.10 (0.79 to 1.55)
Prolapse (not endometriosis or fibroids)	0.89 (0.67 to 1.18)
Fibroids and endometriosis (not prolapse)	0.80 (0.43 to 1.50)
Prolapse and endometriosis (not fibroids)	0.71 (0.32 to 1.58)
Prolapse and fibroids (not endometriosis)	1.16 (0.70 to 1.93)
Prolapse, fibroids and endometriosis	0.77 (0.32 to 1.85)
Other indications	0.98 (0.82 to 1.18)

*   Time was censored at hysterectomy for malignancy. Hysterectomy is time-varying. Ovarian cancer includes primary ovarian, fallopian tube, and peritoneal cancer.

†   Models were stratified by decade of birth and adjusted for age at study entry, tubal ligation (yes/no), and parity (3 or more vs 0-2 births). HR = hazard ratio; CI = confidence interval.

‡   We created a single time-varying variable for hysterectomy by indication. We defined indication using codes recorded in any of the diagnosis fields at the time of surgery, in order to capture the pathological context of the surgery as completely as possible. Women who had a hysterectomy before study exit contribute exposed time to one of the indication categories from their hysterectomy onwards. For each of the following categories, other conditions, such as those coded as uterine disorders or disorders of menstruation, may have been also noted in the hospital record.

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Table 4: Association between hysterectomy for a benign indication and invasive epithelial ovarian cancer*, by presence of endometriosis, fibroids, and prolapse†

Hysterectomy by presence of benign gynaecological conditions	HR (95% CI)‡
Women with endometriosis	
No hysterectomy	1.00 (Reference)
Hysterectomy	0.17 (0.12 to 0.24)
Women without endometriosis	
No hysterectomy	1.00 (Reference)
Hysterectomy	1.09 (0.95 to 1.26)
Women with fibroids	
No hysterectomy	1.00 (Reference)
Hysterectomy	0.27 (0.20 to 0.36)
Women without fibroids	
No hysterectomy	1.00 (Reference)
Hysterectomy	1.09 (0.94 to 1.27)
Women with endometriosis or fibroids	
No hysterectomy	1.00 (Reference)
Hysterectomy	0.26 (0.21 to 0.33)
Women without endometriosis or fibroids	
No hysterectomy	1.00 (Reference)
Hysterectomy	1.15 (0.98 to 1.35)
Women with prolapse	
No hysterectomy	1.00 (Reference)
Hysterectomy	1.24 (0.91 to 1.69)
Women without prolapse	
No hysterectomy	1.00 (Reference)
Hysterectomy	0.97 (0.83 to 1.15)

*   Time was censored at hysterectomy for malignancy. Hysterectomy is time-varying. Ovarian cancer includes primary ovarian, fallopian tube, and peritoneal cancer.

†   Strata (presence/absence of each condition) are defined by whether the condition was included as a diagnosis during any hospitalisations 1970-2015.

‡   Models were stratified by decade of birth and adjusted for age at study entry, tubal ligation (yes/no), and parity (3 or more vs 0-2 births). HR = hazard ratio; CI = confidence interval.

Figure legend

Figure 1: Association between hysterectomy for a benign indication and invasive epithelial ovarian cancer, by (A) period of hysterectomy and (B) age at hysterectomy, compared to no hysterectomy. Time was censored at hysterectomy for malignancy. Hysterectomy is time-varying. Ovarian cancer includes primary ovarian, fallopian tube, and peritoneal cancer. Models were stratified by decade of birth and adjusted for age at study entry, tubal ligation (yes/no), and parity (3 or more vs 0-2 births). In **B,** patterns were similar if we assigned birthdate at the electoral birth-year band midpoint.

Figure 1--FINAL