Hysterectomy and Risk of Breast, Colorectal, Thyroid, and Kidney Cancer – an Australian Data Linkage Study

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ABSTRACT

Background: This study aimed to investigate the associations between hysterectomy for benign indications and risk of breast, colorectal, kidney, and thyroid cancer, and to explore whether these associations are modified by removal of ovaries at the time of surgery or by age at surgery.

Methods: We conducted a retrospective cohort study of the female population of Western Australia ($n = 839,332$) linking data from electoral, hospital, births, deaths, and cancer records. We used Cox regression to estimate HRs and 95% confidence intervals (CI) for the associations between hysterectomy and diagnosis of breast, colorectal, kidney, and thyroid cancers.

Results: Compared with no surgery, hysterectomy without oophorectomy (hysterectomy) and hysterectomy with bilateral salpingo-oophorectomy (hysterectomy-BSO) were associated with higher risk of kidney cancer (HR, 1.32; 95% CI, 1.11–1.56 and HR, 1.29; 95% CI, 0.96–1.73, respectively). Hysterectomy, but not hysterectomy-BSO, was related to higher risk of thyroid cancer (HR, 1.38; 95% CI, 1.19–1.60). In contrast, hysterectomy (HR, 0.94; 95% CI, 0.90–0.98) and hysterectomy-BSO (HR, 0.92; 95% CI, 0.85–1.00) were associated with lower risk of breast cancer. We found no association between hysterectomy status and colorectal cancer.

Conclusions: The associations between hysterectomy and cancer varied by cancer type with increased risks for thyroid and kidney cancer, decreased risk for breast cancer, and no association for colorectal cancer.

Impact: As breast, colorectal, and gynecologic cancers comprise a sizeable proportion of all cancers in women, our results suggest that hysterectomy is unlikely to increase overall cancer risk; however, further research to understand the higher risk of thyroid and kidney cancer is warranted.

Introduction

A hysterectomy is the surgical removal of a woman's uterus and it is one of the most common gynecologic procedures performed worldwide (1). Australia has high rates of hysterectomy, behind only the United States and Canada (2). An estimated 27% of women aged over 45 years in Australia have had a hysterectomy (3). Approximately 30% of these women have also had both ovaries removed (bilateral salpingo-oophorectomy; ref. 4).

Most hysterectomies are performed to treat symptomatic benign gynecologic conditions (e.g., uterine fibroids, endometriosis, and dysfunctional uterine bleeding). Hysterectomy for these benign indications prevents uterine cancer, and hysterectomy with bilateral salpingo-oophorectomy (hysterectomy-BSO) substantially reduces the risk of ovarian cancer (5). Our previous research has shown that, among women with endometriosis and/or fibroids, hysterectomy without oophorectomy was also associated with a decreased risk of ovarian cancer (6). While the associations between these gynecologic surgeries and endometrial and ovarian cancer may principally relate to the physical removal of the organs, both hysterectomy and oophorectomy also have the potential to cause considerable changes in hormone levels (7, 8), which may affect the risk of other hormone-related cancers.

The associations between hysterectomy and other hormone-related cancers are less clear. Most (9–11), but not all (12), population-based studies have found a lower risk of breast cancer in women who had a hysterectomy-BSO compared with those with no surgery, with stronger associations seen in women who had surgery when they were premenopausal (9). In contrast, most studies have found no association between hysterectomy without oophorectomy and risk of breast cancer (10, 12, 13); however, one study found a lower risk in women who had a hysterectomy alone before the age of 45 years (11). While the development of colorectal cancer appears to be influenced by sex hormones (14), associations with hysterectomy (with or without bilateral salpingo-oophorectomy) have been inconsistent, with studies finding either lower (15) or higher (16) risks as well as no association (10–12).

A meta-analysis of six prospective studies reported a higher risk of kidney cancer associated with hysterectomy irrespective of surgery age or oophorectomy (17). Similarly, a number of studies have suggested that hysterectomy, irrespective of oophorectomy status, is associated with a 40%–70% increased risk of thyroid cancer (18–20).

Overall, there has been limited longitudinal research on hysterectomy and cancer outcomes and further investigation is warranted. In addition, most studies have relied on self-report of hysterectomy and oophorectomy (10, 11, 13, 20–28), which may have contributed to the degree of uncertainty in their results.

The aim of this study was to investigate the associations between hysterectomy for benign indications and risk of breast, colorectal, kidney, and thyroid cancer, using linked administrative data; and to explore whether these associations were modified by removal of ovaries at the time of surgery or by age at surgery.

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Materials and Methods

Study population

We conducted a population-based retrospective cohort study using linked administrative data for women from Western Australia (WA). WA is Australia's fourth most populous state (11% of the total Australian population, ∼1.3 million women).

The study included all adult women (18 years and over) who were on the WA Electoral Roll in 1988 (when electronic records began) or who were added to the Roll up until 31 December 2014. It is a legislative requirement that all Australian citizens over the age of 18 years register and maintain an up-to-date residential address on the Electoral Roll. The cohort was linked with the WA Hospital Morbidity Data Collection (HMDC; 1970–2014), the WA Cancer Registry (1982–2015), the Midwives Notification System (MNS; 1980–2013), and WA Births (1950–1979) and Deaths (1988–2015) Registrations. The data were linked using probabilistic linkage by the WA Data Linkage Branch and deidentified before being provided to the research team. The study received approval from the QIMR Berghofer and WA Health Human Research Ethics Committees.

We excluded women with inconsistent data, for example, implausible birthdates, male-specific procedure codes, hysterectomy prior to birth records ($n = 1{,}597$), and women with missing data on socioeconomic disadvantage or remoteness category ($n = 9{,}267$, ∼1%). To minimize the inclusion of women who had hysterectomies, oophorectomies, or cancer diagnoses prior to hospital data being available (1970), we excluded women born before 1930 (aged >40 years in 1970; $n = 118{,}156$; **Fig. 1**). In a sensitivity analysis, we additionally excluded women who entered the study after 1988 and were 25 years or older at electoral enrollment, as they may have had a hysterectomy outside WA ($n = 297{,}993$).

Cancer ascertainment

We considered risk of four types of incident invasive cancer separately in our analyses—breast cancer [International Classification of Diseases (ICD) 10 code C50], colorectal cancer (C18-C20), thyroid cancer (C73), and kidney cancer (C64). Associations between hysterectomy and ovarian cancer have been reported separately (6). Cancer diagnoses up to 30 June 2015 were identified via the WA Cancer Registry.

Hysterectomy/oophorectomy status

Our exposure of interest was hysterectomy with or without salpingo-oophorectomy (bilateral or unilateral) for a benign indication and was included as a time-varying variable. The HMDC includes all WA private and public hospital admissions, including same-day procedures. Procedures and diagnoses for each separation were coded according to the ICD code version in use at the time of admission. Details of the procedure codes used to identify hysterectomy and salpingo-oophorectomy (unilateral and bilateral) are included in Supplementary Table S1. If the oophorectomy procedure code did not specify the number of ovaries removed, we assumed a bilateral salpingo-oophorectomy had been performed as this was the most common oophorectomy procedure. In a sensitivity analysis, we created an additional oophorectomy category (unknown oophorectomy). Women with an exact date match for hysterectomy and unilateral salpingo-oophorectomy or bilateral salpingo-oophorectomy procedures were categorized as "hysterectomy and unilateral salpingo-oophorectomy" (hysterectomy-USO) or "hysterectomy and bilateral salpingo-oophorectomy" (hysterectomy-BSO), respectively. Women who had a hysterectomy and oophorectomy on different dates were categorized as "hysterectomy with separate oophorectomy" (from the date when the second surgery occurred); we do not report results for these women as they were not our exposure of interest ($n = 16{,}754$).

Age at surgery was categorized into four groups approximating reproductive life stages (no surgery; <45 years, premenopausal; 45–54 years, perimenopausal; 55+ years, postmenopausal) and stratified by hysterectomy/oophorectomy status.

Covariates

For privacy reasons, year of birth from the WA Electoral Roll records was provided in 5-year bands (birth cohorts), so we used the midpoint of the band to estimate approximate age at study entry.

Information on parity was obtained from the WA Births Register and the MNS. Similar to other analyses using these linked datasets, we dichotomized our time-varying parity variable into women who gave birth to none, one or two children, and women who gave birth to three or more children (29).

Postcode at study entry was obtained from the WA Electoral Roll and used to assign remoteness of residence using the Accessibility and Remoteness Index of Australia (ARIA; ref. 30; major cities, inner regional, outer regional, remote, and very remote) and area-based quintiles of socioeconomic disadvantage using the Index of Relative Socioeconomic Disadvantage (IRSD; ref. 31).

We created dichotomous variables (yes/no) for ever being diagnosed with endometriosis, uterine fibroids, or genital prolapse (the three most common indications for hysterectomy) using ICD diagnosis codes (both principal and other diagnoses; Supplementary Table S1).

Statistical analysis

We used Cox regression models, with time-varying covariates (32), to investigate the associations between hysterectomies for benign indications (categorized by type of oophorectomy procedure) and diagnosis of breast, colorectal, kidney, and thyroid cancers. Age was used as the underlying time scale. A woman's estimated age at her first electoral record was her age at study entry, and age at study exit was her age at the earliest of: the cancer diagnosis of interest, death, hysterectomy/oophorectomy for a malignant condition, emigration out of WA, or end of observation (June 30, 2015). Women who had a hysterectomy in the 12 months prior to their diagnosis of the cancer of interest were treated as unexposed, as their surgery was unlikely to have played a causal role in the development of the cancer.

In our base model (Model 1 – age adjusted), we adjusted for age at entry and stratified by birth cohort. We then assessed the effect of adding parity, remoteness of residence, and IRSD quintile to Model 1 (Model 2 – minimally adjusted). Finally, we added the endometriosis, uterine fibroids, and genital prolapse variables to the model (Model 3 – fully adjusted).

The data analysis for this article was performed using SAS software, version 9.4 of the SAS system for Windows Copyright 2002–2012 by SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names or registered trademarks or trademarks of SAS Institute Inc.

Data availability

The datasets generated and/or analyzed during this study are not publicly available because of the terms of the ethics approval granted by the Western Australian Department of Health Human Research Ethics Committee (WADOH HREC) and data disclosure policies of the Data Providers. The datasets may be available from the corresponding author upon request and subject to approval from the WADOH HREC and relevant custodians.

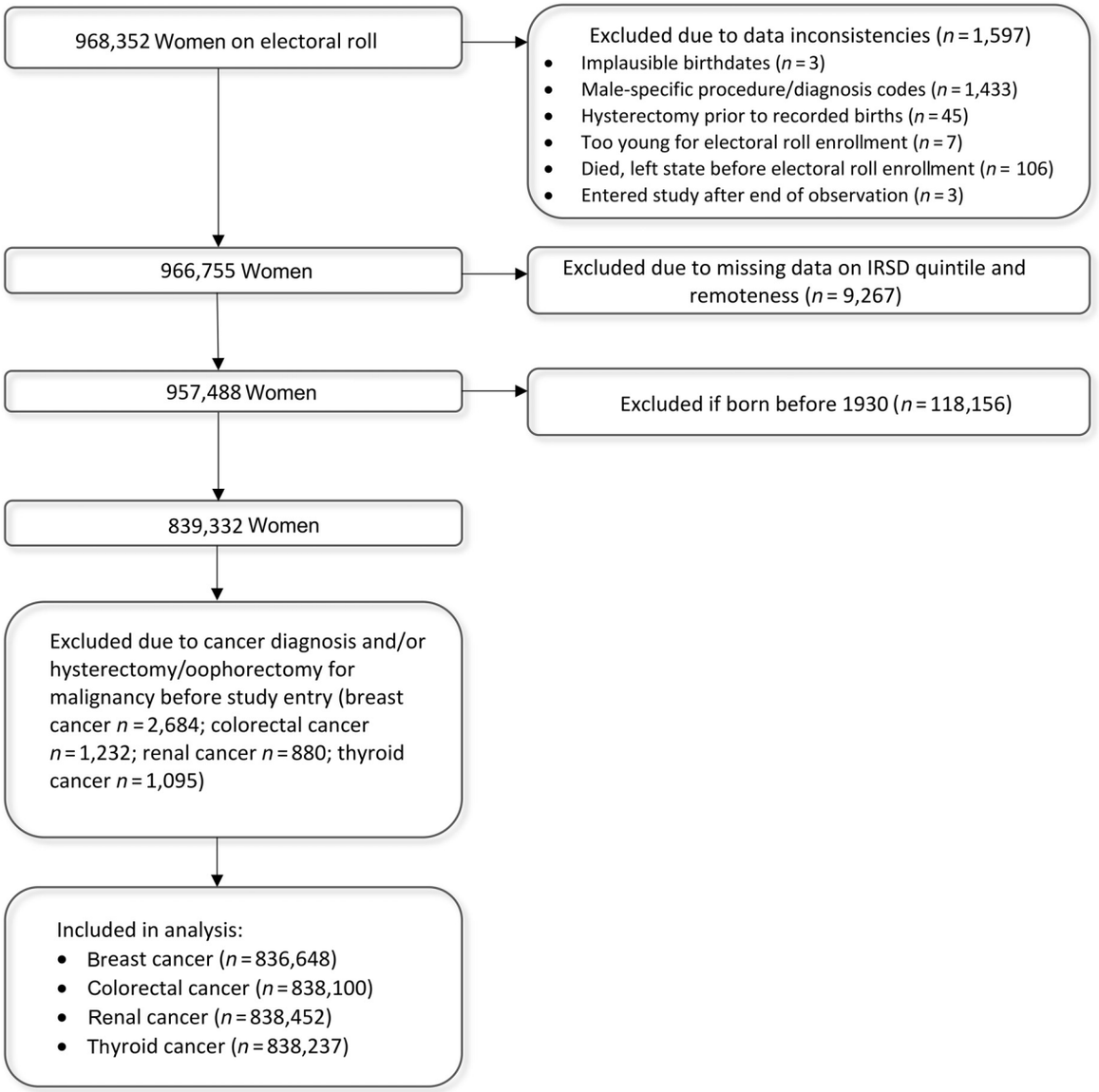

Figure 1.
Flowchart of participants included in each cancer analysis.

Results

The final study population included 839,332 women in one or more of our analyses; the women excluded because of a cancer diagnosis and/or hysterectomy/oophorectomy for malignancy before study entry were specific to each individual cancer analysis (**Fig. 1**). Characteristics of the study population by hysterectomy status at study exit are summarized in **Table 1**. Women who had a hysterectomy during follow-up were older at study entry than women who did not. They were also more likely to have given birth to three or more children and have lived in more disadvantaged areas. On average women who had a hysterectomy-BSO were older at the time of surgery than women who had a hysterectomy only or a hysterectomy-USO.

Breast cancer

In the fully adjusted model (with adjustment for hospital-diagnosed fibroids, endometriosis, and prolapse, Model 3), compared with no hysterectomy, hysterectomy and hysterectomy-BSO were associated with a lower risk of breast cancer [HR, 0.94; 95% confidence interval (CI), 0.90–0.98 and HR, 0.92; 95% CI, 0.85–1.00, respectively; **Table 2**]. In this model, hospital-diagnosed fibroids and endometriosis were associated with a higher risk of breast cancer (HR, 1.24; 95% CI, 1.18–1.30 and HR, 1.08; 95% CI, 1.03–1.15, respectively), while prolapse was associated with a reduced risk of breast cancer (HR, 0.96; 95% CI, 0.92–1.00). The associations did not vary appreciably by age at surgery (**Table 2**).

Table 1. Descriptive characteristics by hysterectomy status[a,b].

	No hysterectomy–no oophorectomy *N* = 719,793 N (%)	Hysterectomy–no oophorectomy *N* = 74,056 N (%)	Hysterectomy-USO *N* = 2,809 N (%)	Hysterectomy-BSO *N* = 25,920 N (%)
Mean age (years) at entry (SD)	29.9 (12.3)	39.2 (10.2)	39.6 (7.3)	39.4 (11.2)
Mean age (years) at hysterectomy (SD)	–	43.5 (9.1)	42.9 (6.9)	49.2 (10.1)
Birth cohort				
1930–1939	51,021 (7.1)	12,183 (16.5)	191 (6.8)	4,861 (18.8)
1940–1949	73,134 (10.2)	21,830 (29.5)	1,118 (39.8)	7,318 (28.2)
1950–1959	116,563 (16.2)	22,915 (30.9)	1,224 (43.6)	6,640 (25.6)
1960–1969	151,459 (21.0)	13,694 (18.5)	269 (9.6)	5,195 (20.0)
1970+	327,616 (45.5)	3,434 (4.6)	7 (0.3)	1,907 (7.4)
Hospital-diagnosed endometriosis				
No	700,301 (97.3)	56,771 (76.7)	1,646 (58.6)	17,655 (68.1)
Yes	19,492 (2.7)	17,285 (23.3)	1,163 (41.4)	8,265 (31.9)
Hospital-diagnosed fibroids				
No	707,695 (98.3)	51,720 (69.8)	1,639 (58.4)	15,643 (60.4)
Yes	12,098 (1.7)	22,336 (30.2)	1,170 (41.7)	10,277 (39.7)
Hospital-diagnosed prolapse				
No	702,468 (97.6)	44,101 (59.6)	2,077 (73.9)	20,685 (79.8)
Yes	17,325 (2.4)	29,955 (40.5)	732 (26.1)	5,235 (20.2)
Parity (at study exit)				
0–2 births	537,872 (74.7)	44,144 (59.6)	1,906 (67.9)	17,622 (68.0)
3+ births	181,921 (25.3)	29,912 (40.4)	903 (32.2)	8,298 (32.0)
Remoteness of residence				
Major cities	542,473 (75.4)	52,621 (71.1)	2,138 (76.1)	20,030 (77.3)
Inner regional	62,699 (8.7)	7,546 (10.2)	244 (8.7)	2,168 (8.4)
Outer regional	62,689 (8.7)	8,447 (11.4)	211 (7.5)	2,085 (8.0)
Remote	35,313 (4.9)	4,071 (5.5)	179 (6.4)	1,140 (4.4)
Very remote	16,619 (2.3)	1,371 (1.9)	37 (1.3)	497 (1.9)
IRSD quintile				
1 (most disadvantaged)	121,086 (16.8)	13,569 (18.3)	517 (18.4)	4,736 (18.3)
2	158,232 (22.0)	20,558 (27.8)	765 (27.2)	6,594 (25.4)
3	97,417 (13.5)	9,406 (12.7)	362 (12.9)	3,270 (12.6)
4	116,207 (16.1)	10,308 (13.9)	337 (12.0)	3,628 (14.0)
5 (least disadvantaged)	226,851 (31.5)	20,215 (27.3)	828 (29.5)	7,692 (29.7)

Abbreviation: N, number.

[a]Hysterectomy status at study exit.

[b]Results for women who had hysterectomy and separate oophorectomy (n = 7,457) or oophorectomy only (9, 297) are not reported because they were not the exposure of interest.

Colorectal cancer

We found no statistically significant associations between hysterectomy status and colorectal cancer overall (fully adjusted, Model 3 HR, 0.98; 95% CI, 0.91–1.06 for hysterectomy and 0.97; 95% CI, 0.85–1.11 for hysterectomy-BSO; **Table 2**). However, there was a suggestion that hysterectomy-BSO undertaken in women aged 55+ years was associated with a higher risk of colorectal cancer (fully adjusted, Model 3 HR, 1.24; 95% CI, 0.99–1.56) compared with women without a hysterectomy/oophorectomy.

Kidney cancer

In our minimally adjusted model (Model 2), hysterectomy, hysterectomy-USO, and hysterectomy-BSO were associated with a higher risk of kidney cancer, although the event numbers for hysterectomy-USO were small and the CIs were wide and included one (**Table 2**). The addition of hospital-diagnosed endometriosis, fibroids, and prolapse to the model made little difference (fully adjusted, Model 3 hysterectomy HR, 1.32; 95% CI, 1.11–1.56; and hysterectomy-BSO HR, 1.29; 95% CI, 0.96–1.73; **Table 2**). For age at surgery, the point estimates were highest in women who had their surgery before age 45 (fully adjusted, Model 3 HR, 1.47; 95% CI, 1.21–1.78 for hysterectomy; HR, 1.49; 95% CI, 0.94–2.37 for hysterectomy-BSO, **Table 2**); however, the CIs across the age at surgery categories overlapped.

Thyroid cancer

In our minimally adjusted model (Model 2), hysterectomy and hysterectomy-BSO were associated with a higher risk of thyroid cancer (HR, 1.64; 95% CI, 1.44–1.87 and HR, 1.54; 95% CI, 1.20–1.99, respectively). In the fully adjusted model (Model 3), the associations were attenuated (HR, 1.38; 95% CI, 1.19–1.60 for hysterectomy and HR, 1.18; 95% CI, 0.90–1.54 for hysterectomy-BSO); this was because of the addition of hospital-diagnosed fibroids, which was associated with a higher risk of thyroid cancer (HR, 1.99; 95% CI, 1.76–2.25). For age at surgery, a statistically significant higher risk of thyroid cancer was seen in women who had a hysterectomy without oophorectomy before age 55 years (**Table 2**). The number of cases for hysterectomy after age 55 years and hysterectomy-BSO in all age groups was small and results were not statistically significant in the fully adjusted model.

Table 2. HRs and 95% CIs for the associations between hysterectomy status and breast, colorectal, kidney, and thyroid cancer.

	Person-years	Cases	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)	Model 3[c] HR (95% CI)
Breast cancer					
No hysterectomy–no oophorectomy	14,578,354	16,500	Ref.	Ref.	Ref.
Hysterectomy–no oophorectomy	1,284,582	2,977	1.00 (0.97–1.04)	0.99 (0.95–1.03)	0.94 (0.90–0.98)
Hysterectomy-USO	59,912	154	1.20 (1.02–1.40)	1.16 (0.99–1.36)	1.04 (0.88–1.22)
Hysterectomy-BSO	274,626	730	1.04 (0.97–1.04)	1.02 (0.95–1.10)	0.92 (0.85–1.00)
Hysterectomy–no oophorectomy (vs. no surgery)					
<45 years	870,701	1,779	1.00 (0.96–1.05)	0.98 (0.93–1.03)	0.95 (0.91–1.00)
45–54 years	349,162	989	1.02 (0.96–1.09)	1.01 (0.94–1.07)	0.92 (0.86–0.99)
55+ years	64,720	209	0.94 (0.82–1.08)	0.93 (0.81–1.07)	0.87 (0.75–1.00)
Hysterectomy-BSO (vs. no surgery)					
<45 years	118,975	230	0.93 (0.82–1.06)	0.91 (0.80–1.04)	0.86 (0.76–0.99)
45–54 years	118,078	345	1.06 (0.95–1.18)	1.04 (0.93–1.15)	0.91 (0.81–1.01)
55+ years	37,572	155	1.21 (1.04–1.42)	1.20 (1.02–1.40)	1.04 (0.89–1.23)
Colorectal cancer					
No hysterectomy–no oophorectomy	14,692,737	4,900	Ref.	Ref.	
Hysterectomy–no oophorectomy	1,307,740	948	0.99 (0.92–1.06)	0.95 (0.88–1.02)	0.98 (0.91–1.06)
Hysterectomy-USO	61,159	34	0.93 (0.67–1.31)	0.93 (0.66–1.30)	0.88 (0.63–1.24)
Hysterectomy-BSO	283,552	258	1.04 (0.92–1.18)	1.01 (0.89–1.15)	0.97 (0.85–1.11)
Hysterectomy–no oophorectomy (vs. no surgery)					
<45 years	883,678	518	1.03 (0.94–1.13)	0.99 (0.91–1.09)	1.02 (0.93–1.12)
45–54 years	356,870	333	0.95 (0.85–1.06)	0.91 (0.81–1.02)	0.92 (0.82–1.04)
55+ years	67,192	97	0.90 (0.73–1.10)	0.87 (0.71–1.06)	0.98 (0.79–1.21)
Hysterectomy-BSO (vs. no surgery)					
<45 years	121,223	75	1.02 (0.81–1.28)	0.99 (0.86–1.24)	0.97 (0.77–1.22)
45–54 years	122,338	102	0.90 (0.74–1.09)	0.88 (0.72–1.07)	0.82 (0.67–1.01)
55+ years	39,991	81	1.34 (1.07–1.67)	1.31 (1.05–1.63)	1.24 (0.99–1.56)
Kidney cancer					
No hysterectomy–no oophorectomy	14,719,496	814	Ref.	Ref.	
Hysterectomy–no oophorectomy	1,313,180	218	1.41 (1.21–1.64)	1.37 (1.17–1.59)	1.32 (1.11–1.56)
Hysterectomy-USO	61,347	9	1.45 (0.75–2.79)	1.46 (0.75–2.81)	1.38 (0.71–2.70)
Hysterectomy-BSO	285,381	53	1.35 (1.02–1.79)	1.35 (1.02–1.79)	1.29 (0.96–1.73)
Hysterectomy–no oophorectomy (vs. no surgery)					
<45 years	886,563	133	1.55 (1.29–1.87)	1.52 (1.26–1.83)	1.47 (1.21–1.78)
45–54 years	358,877	65	1.21 (0.94–1.57)	1.17 (0.91–1.52)	1.08 (0.82–1.42)
55+ years	67,741	20	1.25 (0.80–1.96)	1.21 (0.77–1.89)	1.07 (0.67–1.63)
Hysterectomy-BSO (vs. no surgery)					
<45 years	121,619	19	1.55 (0.98–2.44)	1.55 (0.98–2.44)	1.49 (0.94–2.37)
45–54 years	123,107	26	1.46 (0.99–2.16)	1.46 (0.99–2.17)	1.34 (0.89–2.01)
55+ years	40,655	8	0.87 (0.43–1.76)	0.87 (0.44–1.76)	0.79 (0.39–1.60)
Thyroid cancer					
No hysterectomy–no oophorectomy	14,707,135	1,630	Ref.	Ref.	
Hysterectomy–no oophorectomy	1,310,973	300	1.59 (1.39–1.80)	1.64 (1.44–1.87)	1.38 (1.19–1.60)
Hysterectomy-USO	61,291	9	1.03 (0.53–1.98)	1.08 (0.56–2.09)	0.84 (0.44–1.64)
Hysterectomy-BSO	284,825	64	1.50 (1.16–1.93)	1.54 (1.20–1.99)	1.18 (0.90–1.54)
Hysterectomy–no oophorectomy (vs. no surgery)					
<45 years	885,212	187	1.50 (1.29–2.73)	1.56 (1.33–1.82)	1.38 (1.18–2.53)
45–54 years	358,067	101	1.90 (1.55–2.35)	1.97 (1.60–2.42)	1.46 (1.16–1.83)
55+ years	67,695	12	1.13 (0.63–2.00)	1.15 (0.64–2.04)	0.87 (0.48–1.56)
Hysterectomy-BSO (vs. no surgery)					
<45 years	121,530	23	1.32 (0.87–2.00)	1.37 (0.91–2.07)	1.19 (0.78–1.80)
45–54 years	122,782	29	1.55 (1.07–2.25)	1.59 (1.10–2.30)	1.11 (0.76–1.63)
55+ years	40,513	12	1.88 (1.06–1.33)	1.91 (1.07–3.39)	1.31 (0.73–2.35)

Abbreviations: Ref., reference category; vs., versus.

[a]Adjusted for age at entry.

[b]Adjusted for age at entry, parity, remoteness category, and SEIFA quintile, and stratified by birth cohort.

[c]Adjusted for age at entry, parity, remoteness category, SEIFA quintile, hospital-diagnosed fibroids, hospital-diagnosed endometriosis, and hospital-diagnosed prolapse, and stratified by birth cohort.

Sensitivity analyses

When we further restricted our cohort (additionally excluding women who entered the study after 1988 and were aged over 25 years), the effect estimates were in the same direction and of a similar magnitude (Supplementary Table S2). We were unable to consider hysterectomy status by age at surgery in this sensitivity analysis because the small number of cases in some categories.

In the sensitivity analysis where we created an additional oophorectomy category (unknown number of ovaries removed), the results for hysterectomy-BSO and hysterectomy with unknown oophorectomy were generally similar (Supplementary Table S3).

Discussion

In this retrospective data-linkage study of over 800,000 women, hysterectomy (with and without bilateral salpingo-oophorectomy) was associated with a higher risk of kidney cancer (particularly in women who had surgery before age 45 years) and hysterectomy (without oophorectomy) was associated with a higher risk of thyroid cancer. In contrast, hysterectomy (with and without bilateral salpingo-oophorectomy) was associated with a lower risk of breast cancer. We found no association between hysterectomy and colorectal cancer.

Our results for kidney cancer are largely consistent with previous findings. A meta-analysis of seven cohort studies found a summary relative risk of 1.26 (95% CI, 1.11–1.42) for the association between hysterectomy and kidney cancer (17). Only one of the studies included in the meta-analysis (using data from the Hawaii-Los Angeles Multiethnic Cohort) had an effect estimate below 1 (27). The higher risk in the meta-analysis was observed irrespective of oophorectomy status, age at surgery, time since hysterectomy and adjustment for body mass index, hypertension, and smoking status (17). In our study, the point estimates were highest in women aged <45 years at surgery; however, the CIs across age groups overlapped and the number of cases in older age groups was small.

Similar to our study, prospective studies conducted in Sweden (12), France (21), Finland (33), and the United States (20) found a higher risk of thyroid cancer in women who had a hysterectomy without oophorectomy. Some prospective studies also found that hysterectomy-BSO (compared with no surgery) was associated with a higher risk of thyroid cancer (20, 21, 28). In contrast, a Swedish record linkage study reported a similar effect estimate for hysterectomy-BSO to our study (HR, 1.11; 95% CI, 0.66–1.88; ref. 12)

We found a lower risk of breast cancer in women who had a hysterectomy-BSO compared with those with no surgery and this is consistent with most prospective studies (9–11, 13). While we also found a lower risk of breast cancer in women with hysterectomy with both ovaries conserved, only one other prospective cohort study (using data from the Cancer Prevention Study-II Nutrition Cohort; ref. 11) found similar results. Three other studies reported no association (10, 12, 13); however, two of these reported point estimates below 1 (12, 13), and the other was in a population of black women who may have different characteristics to the population in our study, which was largely of European origin (10).

The existing evidence for the associations between hysterectomy (with and without bilateral salpingo-oophorectomy) and colorectal cancer is inconsistent, with studies reporting lower risk (15), higher risk (10, 16), and (like our study) no association (11, 34). These inconsistencies do not appear to be explained by self-report of surgery or adjustment for menopausal hormone therapy (MHT) use.

Strengths of our study include the large number of women in our sample (including almost the entire female population of WA), the length of follow-up (27 years), and the small amount of missing data (<1%). Hysterectomy and oophorectomy status were ascertained using hospital records, minimizing recall error that might be present in studies using self-report of surgery and age at surgery; this is particularly the case for oophorectomy status where self-report has been shown to be considerably less reliable than self-report of hysterectomy (35). We were also able to adjust for common indications for hysterectomy (endometriosis, uterine fibroids, and prolapse) using hospital diagnosis codes. In addition, reporting of cancer diagnosis to the Western Australia Cancer Registry is required by law, so our study should have included essentially all cancers occurring in the study population from 1982 onward.

Our study also has some limitations. Principal among these is that we did not have information on MHT use, which may mediate or modify associations between hysterectomy and cancer development. The majority of women with a hysterectomy who are MHT users, use estrogen-only MHT (20). The International Agency for Research on Cancer has concluded that recent use of exogenous estrogen reduces risk of colorectal cancer, but probably increases risk (after at least 5 years duration) of breast cancer (36). Most (22, 24, 27, 37), but not all studies (26, 38), have shown no association between MHT use and either kidney or thyroid cancer. If we had been able to consider MHT use in our models, we may have seen a statistically significant higher risk of colorectal cancer in women with a hysterectomy while the risk reductions in breast cancer for women with a hysterectomy may have been greater. The absence of information on MHT use may also explain why we did not see a substantial difference in our results between hysterectomy and hysterectomy-BSO and these two cancers as women with hysterectomy-BSO are more likely to take MHT than women with a hysterectomy alone (39). We could not adjust for obesity, which has been positively associated with both hysterectomy and the cancers of interest (40, 41); in particular, if we had been able to include this confounder in our analysis, the associations between hysterectomy and kidney and thyroid cancer may have been attenuated (although some studies (23, 28), but not others (27, 38), have seen a higher risk of these cancers with hysterectomy even after adjustment for body mass index).

There was also potential for misclassification of exposure if a woman had surgery before hospital records were available (1970) or in a different state prior to moving to WA. However, in our primary analysis, we excluded women who were aged 40 years or over in 1970 (as most hysterectomies are performed after this age), and the results of our sensitivity analysis (where we further excluded women who entered the study after 1988 and were 25 years or older at electoral enrollment) were in the same direction and of a similar magnitude to the primary analysis, suggesting that any misclassification would not be likely to change the interpretation of the results. Finally, despite the long follow-up period and size of the cohort, the number of women with hysterectomy-USO as well as the numbers of thyroid and kidney cancers were relatively small.

There may be a range of potential pathways and mechanisms underpinning our results, and these are likely to differ by cancer type. Exposure to circulating ovarian hormones affects the risk of breast cancer, and this is a likely explanation for the lower risk of breast cancer for women with a hysterectomy seen in our study (11). It has been suggested that the association between hysterectomy and kidney cancer may be the result of underlying conditions rather than the surgery itself (23). In our analysis, we adjusted for the most common indications for hysterectomy (fibroids, endometriosis, and prolapse)

and found the association between hysterectomy and kidney cancer remained (while the other conditions for hysterectomy were no longer statistically significant in the fully-adjusted model—results not shown) suggesting indication for surgery is a less likely explanation for our finding. Alternative explanations are increased ascertainment [as women who have had a hysterectomy have more frequent ongoing contact with medical practitioners in the years subsequent to surgery than women without a hysterectomy (42)], and/or accidental damage to the ureter as a result of the surgery, which may lead to renal damage (23).

We found that hysterectomy with ovarian conservation and uterine fibroids were risk factors for thyroid cancer, with fibroids attenuating the association between hysterectomy-BSO and thyroid cancer. Dysfunctional menstrual bleeding, a common symptom of fibroids, is often correlated with thyroid dysfunction (12), and uterine fibroids have been associated with thyroid nodules and hypothyroidism (which are in turn associated with thyroid cancer; ref. 21). The surgery itself may also have a direct effect on the thyroid gland through changes in reproductive hormones resulting from removal of the uterus (19). The association between hysterectomy and thyroid cancer may also be because of greater case ascertainment, as women with dysfunctional bleeding may be more likely to have thyroid function tests leading to ongoing monitoring and further investigative procedures (21). Notably, both kidney and thyroid cancers are considered to have high levels of overdiagnosis (an estimated 58% of kidney and 78% of thyroid cancers diagnosed in Australian women in 2012; ref. 43).

In conclusion, hysterectomy is used for the treatment of benign and malignant indications; it removes the risk of cervical and endometrial cancer and reduces the risk of ovarian cancer. In our study, we found hysterectomy was not associated with colorectal cancer but was associated with a reduced risk of breast cancer, and a slightly higher risk of thyroid and kidney cancer. As breast, colorectal, and gynecologic cancers combined comprise approximately 50% of all cancers diagnosed in Australian women, our results suggest that hysterectomy is unlikely to increase overall cancer risk. However, further research to understand the small positive associations with thyroid and kidney cancer, particularly with respect to the role that enhanced surveillance may play, is warranted.

Authors' Disclosures

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Authors' Contributions

L.F. Wilson: Conceptualization, data curation, formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **K.M. Tuesley:** Data curation, methodology, writing–review and editing. **P.M. Webb:** Conceptualization, methodology, writing–review and editing. **S.C. Dixon-Suen:** Conceptualization, data curation, methodology, writing–review and editing. **L.M. Stewart:** Writing–review and editing. **S.J. Jordan:** Conceptualization, supervision, methodology, writing–review and editing.

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References

1. Hammer A, Rositch AF, Kahlert J, Gravitt PE, Blaakaer J, Sogaard M. Global epidemiology of hysterectomy: possible impact on gynecological cancer rates. Am J Obstet Gynecol 2015;213:23–9.
2. McPherson K, Gon G, Scott M. International variations in a selected number of surgical procedures. Paris, France: OECD; 2013.
3. Australian Bureau of Statistics. National Health Survey: summary of results. 4364.0. 2004–05. Canberra, Australia: Australian Bureau of Statistics; 2006.
4. Wilson LF, Pandeya N, Mishra GD. Hysterectomy trends in Australia, 2000–2001 to 2013–2014: joinpoint regression analysis. Acta Obstet Gynecol Scand 2017;96:1170–9.
5. Chan JK, Urban R, Capra AM, Jacoby V, Osann K, Whittemore A, et al. Ovarian cancer rates after hysterectomy with and without salpingo-oophorectomy. Obstet Gynecol 2014;123:65–72.
6. Dixon-Suen SC, Webb PM, Wilson LF, Tuesley K, Stewart LM, Jordan SJ. The association between hysterectomy and ovarian cancer risk: a population-based record-linkage study. J Natl Cancer Inst 2019;111:1097–1103.
7. Moorman PG, Myers ER, Schildkraut JM, Iversen ES, Wang F, Warren N. Effect of hysterectomy with ovarian preservation on ovarian function. Obstet Gynecol 2011;118:1271–9.
8. Whiteman MK, Staropoli CA, Benedict JC, Borgeest C, Flaws JA. Risk factors for hot flashes in midlife women. J Womens Health 2003;12:459–72.
9. Schairer C, Persson I, Falkeborn M, Naessen T, Troisi R, Brinton LA. Breast cancer risk associated with gynecologic surgery and indications for such surgery. Int J Cancer 1997;70:150–4.
10. Boggs DA, Palmer JR, Rosenberg L. Bilateral oophorectomy and risk of cancer in African American women. Cancer Causes Control 2014;25:507–13.
11. Gaudet MM, Gapstur SM, Sun J, Teras LR, Campbell PT, Patel AV. Oophorectomy and hysterectomy and cancer incidence in the Cancer Prevention Study-II Nutrition Cohort. Obstet Gynecol 2014;123:1247–55.
12. Altman D, Yin L, Falconer H. Long-term cancer risk after hysterectomy on benign indications: population-based cohort study. Int J Cancer 2016;138:2631–8.
13. Woolcott CG, Maskarinec G, Pike MC, Henderson BE, Wilkens LR, Kolonel LN. Breast cancer risk and hysterectomy status: the Multiethnic Cohort Study. Cancer Causes Control 2009;20:539–47.
14. Haziman AA, Ravinderan S, Thangavelu T, Thomas W. A novel role for estrogen-induced signaling in the colorectal cancer gender bias. Ir J Med Sci 2019;188:389–95.
15. Cape DB, Kreiger N. Gynaecological surgical procedures and risk of colorectal cancer in women. Eur J Cancer Prev 1999;8:495–500.
16. Segelman J, Lindstrom L, Frisell J, Lu Y. Population-based analysis of colorectal cancer risk after oophorectomy. Br J Surg 2016;103:908–15.
17. Karami S, Daugherty SE, Purdue MP. Hysterectomy and kidney cancer risk: a meta-analysis. Int J Cancer 2014;134:405–10.
18. Caini S, Gibelli B, Palli D, Saieva C, Ruscica M, Gandini S. Menstrual and reproductive history and use of exogenous sex hormones and risk of thyroid cancer among women: a meta-analysis of prospective studies. Cancer Causes Control 2015;26:511–8.

19. Falconer H, Yin L, Bellocco R, Altman D. Thyroid cancer after hysterectomy on benign indications: findings from an observational cohort study in Sweden. Int J Cancer 2017;140:1796–801.
20. Luo J, Hendryx M, Manson JE, Liang X, Margolis KL. Hysterectomy, oophorectomy, and risk of thyroid cancer. J Clin Endocrinol Metab 2016;101:3812–9.
21. Guenego A, Mesrine S, Dartois L, Leenhardt L, Clavel-Chapelon F, Kvaskoff M, et al. Relation between hysterectomy, oophorectomy and the risk of incident differentiated thyroid cancer: the E3N cohort. Clin Endocrinol 2019;90:360–8.
22. Kabat GC, Silvera SA, Miller AB, Rohan TE. A cohort study of reproductive and hormonal factors and renal cell cancer risk in women. Br J Cancer 2007;96:845–9.
23. Karami S, Daugherty SE, Schonfeld SJ, Park Y, Hollenbeck AR, Grubb RL 3rd, et al. Reproductive factors and kidney cancer risk in 2 US cohort studies, 1993–2010. Am J Epidemiol 2013;177:1368–77.
24. Lee JE, Hankinson SE, Cho E. Reproductive factors and risk of renal cell cancer: the Nurses' Health Study. Am J Epidemiol 2009;169:1243–50.
25. Luoto R, Auvinen A, Pukkala E, Hakama M. Hysterectomy and subsequent risk of cancer. Int J Epidemiol 1997;26:476–83.
26. Molokwu JC, Prizment AE, Folsom AR. Reproductive characteristics and risk of kidney cancer: IOWA Women's Health Study. Maturitas 2007;58:156–63.
27. Setiawan VW, Kolonel LN, Henderson BE. Menstrual and reproductive factors and risk of renal cell cancer in the multiethnic cohort. Cancer Epidemiol Biomarkers Prev 2009;18:337–40.
28. Zamora-Ros R, Rinaldi S, Biessy C, Tjonneland A, Halkjaer J, Fournier A, et al. Reproductive and menstrual factors and risk of differentiated thyroid carcinoma: the EPIC study. Int J Cancer 2015;136:1218–27.
29. Stewart LM, Spilsbury K, Jordan S, Stewart C, Holman CDJ, Powell A, et al. Risk of high-grade serous ovarian cancer associated with pelvic inflammatory disease, parity and breast cancer. Cancer Epidemiol 2018;55:110–6.
30. Department of Health and Aged Care (GISCA). Measuring remoteness: accessibility/remoteness index of Australia (ARIA). Revised ed. Occasional paper new series no. 14. Phillip, Canberra: Department of Health and Aged Care; 2001.
31. Pink B. (Australian Statistician). Technical paper. Socio-Economic Indexes for Areas (SEIFA) 2011. ABS catalogue no. 2033.0.55.001 Canberra, Australia: Australian Bureau of Statistics; 2013.
32. Allison PD. Survival analysis using SAS: a practical guide. Carey, North Carolina: SAS Institute; 2010.
33. Luoto R, Grenman S, Salonen S, Pukkala E. Increased risk of thyroid cancer among women with hysterectomies. Am J Obstet Gynecol 2003;188:45–8.
34. Altman D, Falconer C, Cnattingius S, Granath F. Pelvic organ prolapse surgery following hysterectomy on benign indications. Am J Obstet Gynecol 2008;198:572 e1–6.
35. Phipps AI, Buist DS. Validation of self-reported history of hysterectomy and oophorectomy among women in an integrated group practice setting. Menopause 2009;16:576–81.
36. International Agency For Research On Cancer Working Group on the Evaluation of Carcinogenic Risks to Humans. Pharmaceuticals, Vol. 100 A. A review of human carcinogens. Lyon, France: IARC; 2012.
37. Moleti M, Sturniolo G, Di Mauro M, Russo M, Vermiglio F. Female reproductive factors and differentiated thyroid cancer. Front Endocrinol 2017;8:111.
38. Schonfeld SJ, Ron E, Kitahara CM, Brenner A, Park Y, Sigurdson AJ, et al. Hormonal and reproductive factors and risk of postmenopausal thyroid cancer in the NIH-AARP diet and health study. Cancer Epidemiol 2011;35:e85–90.
39. Million Women Study Collaborators. Patterns of use of hormone replacement therapy in one million women in Britain, 1996–2000. BJOG 2002;109:1319–30.
40. Cooper R, Hardy R, Kuh D. Is adiposity across life associated with subsequent hysterectomy risk? Findings from the 1946 British birth cohort study. BJOG 2008;115:184–92.
41. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, et al. Body fatness and cancer–viewpoint of the IARC working group. N Engl J Med 2016;375:794–8.
42. Byles J, Mishra G, Hockey R, Adane A, Chan H, Forder P, et al. Use, access to, and impact of medicare services for Australian women: findings from the Australian longitudinal study on women's health. Available from: https://alswh.org.au/wp-content/uploads/2020/02/2017_Major-Report_Summary.pdf.
43. Glasziou PP, Jones MA, Pathirana T, Barratt AL, Bell KJ. Estimating the magnitude of cancer overdiagnosis in Australia. Med J Aust 2020;212:163–8.