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Breast Cancer Risk After Hysterectomy: A Health Insurance Database-Based Analysis

Yeonjin Shin [1], **Gyuho Nahm** [1], **Jiwon Seo** [1], **Jin Li Lee** [2], **Gwan Hee Han** [3], **Sang-Hee Yoon** [3], **Ji Hyun Noh** [3], **Myounghwan Kim** [3], **Jin-Sung Yuk** [3]

[1]Independent Researcher, Seoul, Korea
[2]Applewoman Clinic, Seoul, Korea
[3]Department of Obstetrics and Gynecology, Sanggye Paik Hospital, School of Medicine, Inje University, Seoul, Korea

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Correspondence to
Jin-Sung Yuk
Department of Obstetrics and Gynecology, Sanggye Paik Hospital, School of Medicine, Inje University, 1342 Dongil-ro, Nowon-gu, Seoul 01757, Korea.
Email: dryjs01@gmail.comS5600@paik.ac.kr

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ORCID iDs
Yeonjin Shin
https://orcid.org/0009-0006-7901-2419
Gyuho Nahm
https://orcid.org/0009-0002-9705-1287
Jiwon Seo
https://orcid.org/0009-0002-9847-6068
Jin Li Lee
https://orcid.org/0009-0006-6218-7175
Gwan Hee Han
https://orcid.org/0000-0001-5263-4855
Sang-Hee Yoon
https://orcid.org/0000-0002-5723-5105
Ji Hyun Noh
https://orcid.org/0009-0002-3713-7986
Myounghwan Kim
https://orcid.org/0000-0002-8914-4267
Jin-Sung Yuk
https://orcid.org/0000-0002-5478-634X

ABSTRACT

Purpose: Despite numerous previous studies, the relationship between hysterectomies and breast cancer risk remains unclear. This study aimed to assess whether hysterectomies are significantly associated with a reduced risk of breast cancer in Korean women using data from the National Health Insurance Service database of South Korea.
Methods: We conducted a retrospective cohort study of South Korean women aged 40–59 years who underwent hysterectomies for benign reasons or underwent a health check-up between 2003 and 2011. To minimize confounding factors, a 1:1 propensity score matching (PSM) was used to balance the groups based on key covariates. The participants were followed up until December 31, 2020. Stratified Cox proportional hazards regression analysis was performed to assess the association between hysterectomies and breast cancer risk.
Results: After 1:1 PSM, 13,148 women were assigned to the hysterectomy or non-hysterectomy groups. Breast cancer occurred in 242 (1.8%) and 233 (1.8%) women in the non-hysterectomy and hysterectomy groups, respectively ($p = 0.711$). After adjusting for confounders, hysterectomy with or without adnexal surgery was not significantly associated with breast cancer risk (hazard ratio [HR], 0.937; 95% confidence interval [CI], 0.775–1.132 for hysterectomy with/without adnexal surgery; HR, 0.957; 95% CI, 0.779–1.176 for hysterectomy without adnexal surgery; and HR, 0.833; 95% CI, 0.513–1.353 for hysterectomy with adnexal surgery). No significant association was found when analyzing surgical methods or age at natural menopause.
Conclusion: Our study found no association between hysterectomies and breast cancer risk, which is consistent with previous studies that reported a null association.

Keywords: Breast Neoplasms; Hormones; Hysterectomy; Risk

INTRODUCTION

Breast cancer has the highest worldwide oncological incidence and mortality rate among women [1]. Many risk factors are associated with exposure to endogenous and exogenous sex hormones [2]. Breast cancer is also more likely to occur when an individual's breast tissue is positive for estrogen receptors [3]. Breast cancer is closely associated with both endogenous and exogenous sex hormones [4,5].

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Conflict of Interest
The authors declare that they have no competing interests.

Data Availability
Per the National Health Insurance Service's (NHIS) privacy policy, raw data cannot be provided.

Author Contributions
Conceptualization: Kim M, Yuk JS; Formal analysis: Yuk JS; Investigation: Shin Y, Nahm G, Yuk JS; Methodology: Yuk JS; Supervision: Kim M, Yuk JS; Writing - original draft: Shin Y, Yuk JS; Writing - review & editing: Shin Y, Nahm G, Seo J, Lee JL, Han GH, Yoon SH, Noh JH, Yuk JS.

Hysterectomy involves the surgical removal of the uterus. It is the most commonly performed major gynecological surgery [6]. According to Organisation for Economic Co-operation and Development data, the number of hysterectomies performed in 2021 was 28,176 in Australia (217.8 per 10,000 women), 40,278 in the United Kingdom (118.2 per 10,000 women), and 41,237 in South Korea (159.5 per 10,000 women) [7]. In the United States, approximately 600,000 hysterectomies are performed annually [8]. Most hysterectomies are performed for benign conditions such as uterine fibroids and dysfunctional uterine bleeding [6].

Some studies have shown that patients who undergo hysterectomies with ovarian preservation experience earlier menopause than those who do not [9,10]. During a hysterectomy, the ovarian branch of the uterine artery may be ligated, leading to reduced blood flow to the ovaries, which could impair hormone production [11]. However, other studies have concluded that there is no evidence of ovarian damage after hysterectomies due to increased ovarian blood flow, as suggested by the increased ovarian volume and reduced ovarian pulsatility index [12]. This is a controversial topic; however, if there is a possibility of impaired ovarian function after hysterectomies, hysterectomies may also reduce the risk of breast cancer, given the link between breast cancer and endogenous and exogenous sex hormones [13].

Despite ongoing studies by many researchers, no consistent conclusions have been drawn about the link between hysterectomies and breast cancer [10,14-18]. Moreover, current studies have several limitations, including a lack of correction for hormone-related factors, such as menopausal hormone therapy (MHT), obesity, the indications for the surgery, and previous gynecological conditions [19-21]. Additionally, some studies were based on self-reports rather than hospital records; therefore, the accuracy of the data could not be guaranteed [10,14,17]. A self-reported history of a hysterectomy showed high accuracy, whereas a self-reported history of an oophorectomy demonstrated lower accuracy, requiring caution in interpretation [22,23]. Therefore, a new study is needed to address the limitations of existing research.

We hypothesized that hysterectomies are significantly associated with a reduced risk of breast cancer. The primary objective of this study was to determine the risk of breast cancer in Korean women who underwent hysterectomies for benign conditions.

METHODS

Database

This study used data extracted from the National Health Insurance Service (NHIS) database of South Korea. This extensive database offers a rich repository of health insurance information encompassing variables such as age, medical insurance type, surgical procedure codes, gender, diagnostic codes, hospitalization and outpatient visit records, and prescription details [24]. The NHIS conducts routine medical examinations every two years for people over the age of 40 years, collecting valuable anthropometric and health history data [24]. Data for this population-based retrospective cohort study were obtained from the NHIS Health Examination and Health Insurance Database, covering the period from January 1, 2002, to December 31, 2020.

Selection of participants

This retrospective cohort study investigated the long-term health outcomes of hysterectomies for benign diseases in women aged 40–59 years between January 1, 2002, and December 1, 2011. Participants who underwent surgery between January 1, 2002, and December 1, 2011, formed the "hysterectomy group." To ensure generalizability, a group of women in the same age range who underwent a medical examination during the same period at the NHIS was established (the "non-hysterectomy group"). Stringent inclusion criteria were employed based on validated data sources, including Korea Health Insurance Medical Care Expenses (2016, 2020 versions) and the International Classification of Diseases, 10th revision (ICD-10) codes. To manage the NHIS server capacity, a random sample of 25% eligible women within each group was selected.

The exclusion criteria were implemented to minimize confounding factors. These included women who had undergone hysterectomies or a national health examination in 2002 (to calculate the washout and Charlson Comorbidity Index [CCI]), individuals who had undergone a hysterectomy after the initial medical examination in the non-hysterectomy group, and participants with cancer or benign breast diagnoses within the first year of study registration. The observation period for all the participants was extended to December 31, 2020.

A thorough dataset of variables was carefully extracted and equitably matched through 1:1 propensity score matching (PSM) using a logistic regression model with stepwise selection to balance the hysterectomy and non-hysterectomy groups based on propensity scores derived from key covariates. These variables included demographics (age, socioeconomic status [SES], residential area), medical history (diabetes mellitus, hypertension, CCI, reproductive factors [age at menarche and menopause, parity]), lifestyle habits (physical exercise, smoking, alcohol consumption), and specific gynecological conditions (uterine fibroids, endometriosis, previous adnexal surgery, and menopausal hormone therapy history). We applied 1:1 nearest-neighbor matching without replacement using a greedy matching algorithm. This rigorous matching aimed to control for potential confounders and enhance the comparability of the two groups.

Outcome

Breast cancer was identified based on the presence of three or more relevant ICD-10 diagnostic codes within the category C50 (C50, C50.0, and C50.9).

Investigated factors

This study investigated a range of factors that could potentially influence the participants' health, including demographics, reproductive history, lifestyle habits, and comorbidity burden. SES was categorized as low for women eligible for medical and health insurance benefits, and age was grouped into 5-year increments. The CCI, calculated using diagnosis codes from health insurance data collected one year before study enrollment, served as a measurement of the comorbidity burden [25]. Furthermore, we also considered self-reported habits such as smoking, alcohol consumption, and physical activity, and categorized them based on the questionnaire responses.

Hysterectomies and adnexal surgeries were identified through procedure codes. The procedure codes for the different types of hysterectomies are listed in **Supplementary Table 1**. Information on comorbidities, including dyslipidemia, diabetes mellitus, hypertension, uterine fibroids, and endometriosis, was obtained based on ≥ two diagnosis codes before

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baseline presentation. In the assessment of reproductive history, menarche age was classified as occurring either before or after 13 years, while parity was classified as 0 or unspecified and 1, 2, or 3 or more births. Menopausal status and menarcheal age were determined using a questionnaire, and menopausal hormone therapy was defined as any usage extending beyond six months before the initiation of the study. The study considered both residency type (urban or non-urban) and body mass index (BMI), calculated using the Asia-Pacific perspective criteria [26]. Adnexal surgical procedures included unilateral or bilateral excision of benign adnexal tumors, cystectomies, oophorectomies, and salpingectomies. Additionally, these procedures included the incision and drainage of ovarian cysts, as well as ovarian wedge resections.

Statistical analyses

Statistical significance was set at a two-tailed *p*-value of less than 0.050. Missing values in the Cox regression analysis were handled using list-wise deletion. All analyses were performed using the R software version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria). Following PSM, categorical variables were analyzed using the Cochran-Mantel-Haenszel test, whereas continuous variables were compared using the paired *t*-test or Wilcoxon signed-rank test, depending on normality assessments using the Anderson-Darling test. Standardized mean differences were used to evaluate the balance of matched individual covariates.

Stratified Cox proportional hazards regression analysis was performed to assess the association between hysterectomies and breast cancer risk. The study participation date was defined as the date of hysterectomy in the hysterectomy group and the date of initial health checkup in the non-hysterectomy group. Censoring occurred at the earliest confirmed breast cancer diagnosis in the health insurance data, date of death, or last day of healthcare utilization (e.g., visit or prescription), reflecting death, emigration, or coverage loss. To ensure the validity of the Cox proportional-hazards model, we assessed the proportional-hazards assumption using the Schoenfeld residual test. To verify the robustness of our results, we performed an additional stratified Cox regression analysis explicitly comparing women who underwent laparoscopic hysterectomies with those who did not.

Ethics

To protect participants' confidentiality, a rigorous de-identification process removed all personally identifiable information from the NHIS data. The subsequent analysis was restricted to secure NHIS servers that adhered to strict data governance policies. While the analysis was confined to the NHIS secure server, the anonymized study findings, including figures, tables, and numerical data, were allowed to be exported, thus ensuring participant confidentiality. Informed consent was waived for this study in accordance with the Bioethics and Safety Act of South Korea. Ethical approval was granted by the Institutional Review Board of the Sanggye Paik Hospital (approval number: SGPAIK 2021-12-005).

RESULTS

This study reviewed a sample population of 4,580,240 women aged 40–59 years who underwent hysterectomies or health check-ups between 2003 and 2011 (**Figure 1**). A final sample of 26,296 participants (13,148 in each group) was included in the study (**Figure 1**).

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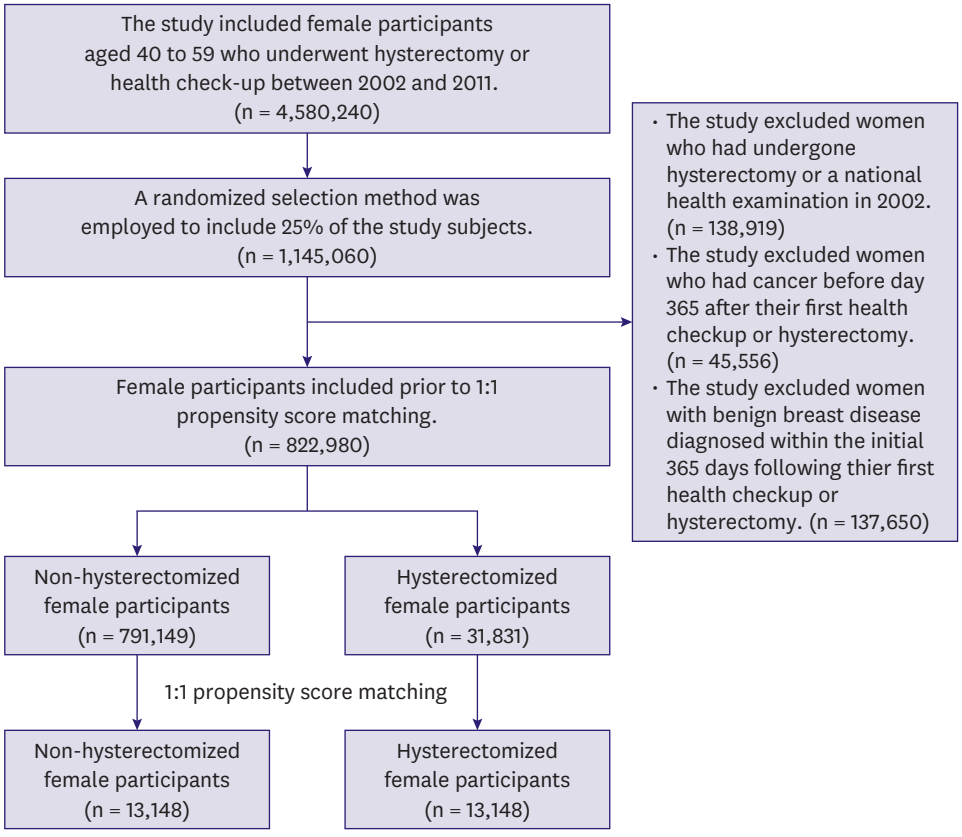


Figure 1. Patient selection flowchart for the hysterectomy and non-hysterectomy groups.

The detailed baseline characteristics of the patients after 1:1 PSM are shown in **Table 1**. The median duration of follow-up for the non-hysterectomy and hysterectomy groups was 11.4 years (interquartile range [IQR]: 10.1–13.4) and 11.4 years (IQR: 10.0–13.3), respectively. After matching, most covariates were well balanced (standardized mean difference [SMD] < 0.1), although a notable imbalance remained in age at inclusion (SMD = 0.134) and adnexal surgery (SMD = 0.200). The characteristics of the hysterectomy and non-hysterectomy groups before 1:1 PSM are shown in **Supplementary Table 2**.

There were 242 (1.8%) patients with breast cancer in the non-hysterectomy group and 233 (1.8%) patients in the hysterectomy group ($p = 0.711$). The breast cancer rates per 100,000 person-years were 157 in the non-hysterectomy group and 151 in the hysterectomy group. Detailed breast cancer incidence rates for each variable are presented in **Supplementary Table 3**.

Cox proportional hazards analysis was performed on a subgroup of hysterectomy participants classified according to adnexal surgery. The analysis revealed that hysterectomy with or without adnexal surgery (hazard ratio [HR], 0.937; 95% confidence interval [CI], 0.775–1.132), hysterectomy without adnexal surgery (HR, 0.957; 95% CI, 0.779–1.176) and hysterectomy with adnexal surgery (HR, 0.833; 95% CI, 0.513–1.353) did not show a significant difference in breast cancer risk, as outlined in **Table 2**. To address potential residual confounding due to the previously noted imbalance in adnexal surgery, we added the adjusted HRs from the multinomial Cox model after PSM (**Table 2**). However, these adjustments did not significantly

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Table 1. Characteristics of the hysterectomy and non-hysterectomy groups among subjects after propensity score matching

Characteristics	Non-hysterectomy	Hysterectomy	Total	*p*-value	SMD	Missing (%)
No. of women	13,148	13,148	26,296			
Follow-up period (yr)	11.4 [10.1–13.4]	11.4 [10.0–13.3]	11.4 [10.1–13.4]	0.960	0.002	0
Median age (yr)	48 [44–50]	47 [45–50]	47 [45–50]	0.125	0.055	0
Age at inclusion (yr)				< 0.001	0.134	0
40–44	3,347 (25.5)	3,160 (24.0)	6,507 (24.7)			
45–49	5,434 (41.3)	6,232 (47.4)	11,666 (44.4)			
50–55	3,483 (26.5)	3,106 (23.6)	6,589 (25.1)			
55–60	884 (6.7)	650 (4.9)	1,534 (5.8)			
Year at inclusion				< 0.001	0.042	0
2003–2005	1,357 (10.3)	1,512 (11.5)	2,869 (10.9)			
2006–2008	4,572 (34.8)	4,400 (33.5)	8,972 (34.1)			
2009–2011	7,219 (54.9)	7,236 (55.0)	14,455 (55.0)			
Median BMI (kg/m^2)	23.6 [21.8–25.8]	23.7 [21.8–25.8]	23.6 [21.8–25.8]	0.396	0.008	0
BMI (kg/m^2)				0.012	0.030	0
< 18.5	221 (1.7)	196 (1.5)	417 (1.6)			
18.5–22.9	5,057 (38.5)	5,106 (38.8)	10,163 (38.6)			
23–24.9	3,397 (25.8)	3,406 (25.9)	6,803 (25.9)			
25–29.9	3,844 (29.2)	3,879 (29.5)	7,723 (29.4)			
≥ 30	629 (4.8)	561 (4.3)	1,190 (4.5)			
SES	46 (0.3)	64 (0.5)	110 (0.4)	0.073	0.021	0
Region	9,490 (72.2)	9,512 (72.3)	19,002 (72.3)	0.772	0.004	0
CCI				< 0.001	0.038	0
0	10,541 (80.2)	10,734 (81.6)	21,275 (80.9)			
1	2,093 (15.9)	1,955 (14.9)	4,048 (15.4)			
≥ 2	514 (3.9)	459 (3.5)	973 (3.7)			
Parity				< 0.001	0.042	0
0 or not respond	1,888 (14.4)	1,999 (15.2)	3,887 (14.8)			
1	1,767 (13.4)	1,633 (12.4)	3,400 (12.9)			
2	8,707 (66.2)	8,792 (66.9)	17,499 (66.5)			
≥ 3	786 (6.0)	724 (5.5)	1,510 (5.7)			
Age at menarche (≥ 13 yr)	10,359 (78.8)	10,314 (78.4)	20,673 (78.6)	0.234	0.008	0
Menopause before inclusion	2,055 (15.6)	1,952 (14.8)	4,007 (15.2)	< 0.001	0.022	0
Smoking				0.007	0.029	0
Never	12,454 (94.7)	12,384 (94.2)	24,838 (94.5)			
Past	210 (1.6)	206 (1.6)	416 (1.6)			
Current	484 (3.7)	558 (4.2)	1,042 (4.0)			
Alcohol (per week)				< 0.001	0.053	0
None	9,325 (70.9)	9,270 (70.5)	18,595 (70.7)			
Up to 2/week	3,608 (27.4)	3,596 (27.4)	7,204 (27.4)			
3–6/week	135 (1.0)	213 (1.6)	348 (1.3)			
Daily	80 (0.6)	69 (0.5)	149 (0.6)			
Physical exercise (per week)				0.088	0.035	0
None	8,701 (66.2)	8,521 (64.8)	17,222 (65.5)			
1–2	2,411 (18.3)	2,513 (19.1)	4,924 (18.7)			
3–4	1,229 (9.3)	1,296 (9.9)	2,525 (9.6)			
5–6	395 (3.0)	371 (2.8)	766 (2.9)			
Daily	412 (3.1)	447 (3.4)	859 (3.3)			
DM before inclusion	1,284 (9.8)	1,275 (9.7)	2,559 (9.7)	0.866	0.002	0
Hypertension before inclusion	2,523 (19.2)	2,557 (19.4)	5,080 (19.3)	0.594	0.007	0
Dyslipidemia before inclusion	2,082 (15.8)	1,944 (14.8)	4,026 (15.3)	0.017	0.029	0
MHT before inclusion	260 (2.0)	159 (1.2)	419 (1.6)	< 0.001	0.061	0
Adnexal surgery before inclusion	531 (4.0)	123 (0.9)	654 (2.5)	< 0.001	0.200	0
Uterine fibroids before inclusion	9,630 (73.2)	9,583 (72.9)	19,213 (73.1)	< 0.001	0.008	0
Endometriosis before inclusion	2,251 (17.1)	2,310 (17.6)	4,561 (17.3)	0.001	0.012	0

Descriptive statistics are presented as both frequencies and percentages for categorical variables, and medians with interquartile ranges for continuous variables.
SMD = standardized mean difference; BMI = body mass index; SES = socioeconomic status; CCI = Charlson Comorbidity Index; DM = diabetes mellitus; MHT = menopausal hormone therapy.

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Table 2. Comparison of breast cancer risk in women with and without hysterectomy

Variables	Breast cancer incidence/ 100,000 person-years	Crude HR (95% CI)	*p*-value	Adjusted HR (95% CI)*	*p*-value (adjusted)
Non-hysterectomy	242/154,230 (157)	1		1	
Hysterectomy					
Hysterectomy (with/without adnexal surgery)	233/154,306 (151)	0.937 (0.775–1.132)	0.499	0.975 (0.790–1.205)	0.817
Hysterectomy without adnexal surgery	199/128,372 (155)	0.957 (0.779–1.176)	0.674	1.040 (0.825–1.314)	0.737
Hysterectomy with adnexal surgery	34/25,933 (131)	0.833 (0.513–1.353)	0.461	0.709 (0.825–1.314)	0.202

HR = hazard ratio; CI = confidence interval.
*Adjusted using multinomial Cox model after propensity score matching, including adnexal surgery as a covariate.

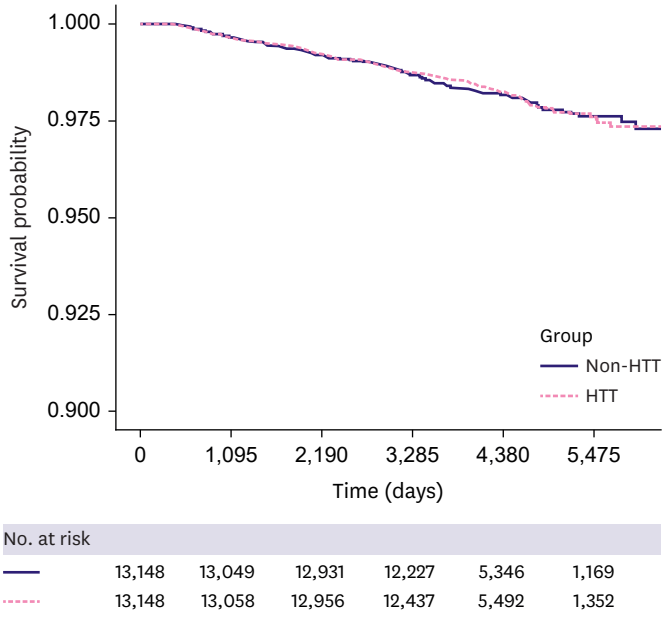


Figure 2. Kaplan-Meier curves (stratified log-rank test $p = 0.500$).
HTT = hysterectomy.

affect the results. The Kaplan–Meier plots for the non-hysterectomy and hysterectomy groups are presented in **Figure 2** (stratified log-rank test: $p = 0.500$).

The HRs for breast cancer were analyzed in subgroups based on age (**Table 3**). In the 40–49 year age group, there was no significant association with an increased risk of breast cancer after hysterectomies with or without adnexal surgery (HR, 1.022; 95% CI, 0.807–1.293), hysterectomy without adnexal surgery (HR, 1.061; 95% CI, 0.822–1.371), and hysterectomy with adnexal surgery (HR, 0.826; 95% CI, 0.450–1.517). The analysis also indicated that none of the hysterectomy groups—hysterectomy with or without adnexal surgery (HR, 0.800; 95%

Table 3. Comparison of breast cancer risk in women with and without hysterectomy according to age

Breast cancer risk	40–49 yr			50–59 yr		
	Breast cancer incidence/100,000 person-years	Crude HR (95% CI)	*p*-value	Breast cancer incidence/100,000 person-years	Crude HR (95% CI)	*p*-value
Non-hysterectomy	163/103,112 (158)	1		79/51,118 (155)	1	
Hysterectomy						
Hysterectomy (with/without adnexal surgery)	177/111,059 (159)	1.022 (0.807–1.293)*	0.857	56/43,247 (129)	0.800 (0.538–1.189)*	0.270
Hysterectomy without adnexal surgery		1.061 (0.822–1.371)†	0.648		0.841 (0.543–1.302)†	0.437
Hysterectomy with adnexal surgery		0.826 (0.450–1.517)‡	0.538		0.636 (0.247–1.642)‡	0.350

HR = hazard ratio; CI = confidence interval.
*Breast cancer with hysterectomy (with/without adnexal surgery); †Breast cancer with hysterectomy without adnexal surgery; ‡Breast cancer with hysterectomy with adnexal surgery.

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CI, 0.538–1.189), hysterectomy without adnexal surgery (HR, 0.841; 95% CI, 0.543–1.302), and hysterectomy with adnexal surgery (HR, 0.636; 95% CI, 0.247–1.642)— were significantly associated with an increased risk of breast cancer compared with the non-hysterectomy group in the 50–59 years age group.

In a sensitivity analysis specifically focusing on laparoscopic hysterectomies, we found that none of the laparoscopic hysterectomy with or without adnexal surgery (HR, 0.879; 95% CI, 0.709–1.095), hysterectomy without adnexal surgery (HR, 0.897; 95% CI, 0.707–1.139), and hysterectomy with adnexal surgery (HR, 0.786; 95% CI, 0.450–1.373) procedures were associated with an increased risk of breast cancer. These findings are consistent with our key results. In addition, multiple Cox analysis was performed on all variables included in **Table 1**, including adnexal surgery before inclusion, and there was no difference in breast cancer risk between the two groups (HR, 0.975; 95% CI, 0.790–1.210).

DISCUSSION

This study found no association between hysterectomies and breast cancer risk, regardless of whether adnexal surgery was performed. Given that the average age of natural menopause in Korean women is 49.3 years, no association between hysterectomies and breast cancer risk was found, even when stratifying the age at which hysterectomies were performed at 50 years [27].

Our findings align with previous studies, including that by Altman et al. [18], a population-based cohort study of Swedish women, which showed that hysterectomies with or without bilateral salpingo-oophorectomies (BSOs) were not associated with breast cancer risk. Similarly, a multi-ethnic cohort study in Hawaii and Los Angeles found no significant association between hysterectomies and breast cancer [10].

Several studies, including the findings of Lovett et al. [14] from the Sister Study, a prospective cohort of women with a sister diagnosed with breast cancer, have found a significant association between hysterectomies alone and an increased risk of breast cancer (HR, 1.12; 95% CI, 1.02–1.23).

In contrast, some studies have found a link between hysterectomies and a reduced risk of breast cancer. A multicenter case-control study by Press et al. [17] in the United States showed that both hysterectomies with ovarian conservation (odds ratio [OR], 0.83; 95% CI, 0.72–0.96) and partial ovary removal (OR, 0.73; 95% CI, 0.59–0.91) were associated with a reduced risk of breast cancer. A retrospective cohort study of Western Australian women by Wilson et al. [15] also found that both the hysterectomy group (HR, 0.94; 95% CI, 0.90–0.98) and the hysterectomy with BSO group (HR, 0.92; 95% CI, 0.85–1.00) showed a reduction in breast cancer rates. The Carolina Breast Cancer Study, a population-based case-control study of black and white premenopausal women in the U.S., found that both hysterectomy with bilateral oophorectomy (OR, 0.60; 95% CI, 0.47–0.77) and hysterectomy with bilateral ovarian preservation (OR, 0.68; 95% CI, 0.55–0.84) were associated with a reduced risk of breast cancer [16].

However, many previous studies relied on self-reporting and did not account for factors such as hormone replacement therapy, obesity, alcohol use, surgery indications, age at menarche, and previous gynecologic diseases, which are closely linked to endogenous and exogenous

sex hormones [10,15-18]. Additionally, the focus of the Carolina Breast Cancer Study on women with a close family history of breast cancer limits the applicability of these findings to the general population [14].

The role of the ovaries in breast cancer development has been suspected for approximately 130 years [28]. The hypothesis is that estrogen and its metabolites cause alkylation of cellular molecules, generating active radicals that can damage deoxyribonucleic acid, leading to the development of breast cancer [5]. Additionally, a model suggested that accumulated estrogen promotes the progression of breast tissue from normal growth to hyperplasia and neoplasia [5].

Based on the association between hysterectomies and decreased ovarian function, we expected a reduced risk of breast cancer after a hysterectomy. However, no significant association was observed. The reasons for this null association are unclear; however, a combination of factors may have contributed to this discrepancy.

First, there may be an effect of hormonal treatment, including possible contraceptive use, administered before the hysterectomy for the treatment of the surgical indication. For abnormal uterine bleeding (AUB), a common indication for hysterectomy, the American College of Obstetricians and Gynecologists [29] recommends that hormone-related medications be tried first before surgical treatment. In fact, 62.3% of women who had a hysterectomy for benign conditions considered at least one alternative treatment before surgery, with more than half of them considering hormonal therapy and the levonorgestrel-releasing intrauterine system [30]. Several studies have linked hormone treatments to an increased risk of breast cancer [31]. Other drugs used to treat AUB include gonadotropin-releasing hormone (GnRH) agonists. GnRH agonists inhibit the secretion of endogenous sex hormones, thereby reducing the size of uterine fibroids and relieving dysmenorrhea and bleeding symptoms [32,33]. GnRH agonists are also used in the adjuvant treatment of breast cancer because of their effectiveness in suppressing estrogen secretion [34]. Therefore, the hormone treatment history of the participants in this study may have had different significant effects on breast cancer development depending on the type of hormone treatment.

Second, MHT administered after hysterectomies may affect breast cancer risk. Several studies have shown that patients who underwent hysterectomies experienced earlier menopause than those who did not [6,9]. If a hysterectomy is accompanied by a BSO, surgical menopause occurs, which can cause more rapid and severe menopausal symptoms than natural menopause [35,36]. MHT is recommended for these patients [36,37]. Since MHT is associated with an increased risk of breast cancer, it is possible that MHT administered after hysterectomies may have influenced breast cancer rates [38,39]. However, after hysterectomies, estrogen monotherapy (ET) is used, except in special cases, as women are free from the risk of endometrial cancer after hysterectomies [40,41]. ET has a limited effect on breast cancer risk or is associated with a reduced risk of breast cancer [38,39,42]. However, if there is a history of endometriosis or a subtotal hysterectomy that left part of the cervix in situ was performed, combined estrogen-progestogen therapy or tibolone is indicated [43].

Third, hysterectomy may not affect ovarian function, as some studies have shown [44,45]. However, no definitive conclusions have been reached regarding the association between hysterectomies and decreased ovarian function. Lee et al. [45] evaluated ovarian function by measuring ovarian arterial blood flow indices and serum anti-Müllerian hormone in patients who underwent ovarian-sparing hysterectomies. There was no decrease in ovarian function

over a three-month period. Studies that have explored the link between changes in ovarian function and early menopause have hypothesized that, after a hysterectomy, the ramus of the uterine artery that supplies blood to the ovaries becomes disconnected, reducing blood flow to the ovaries and leading to decreased ovarian function [6,9]. However, according to Lee et al. [45], the decrease in blood flow to the ovaries after hysterectomies is sufficiently compensated for by the ovarian artery; as a result, a hysterectomy does not cause changes in ovarian function.

The link between hysterectomies and breast cancer has been the subject of ongoing research with conflicting conclusions until recently [14-17]. This study supports previous studies that found no association between hysterectomies and breast cancer [10,18]. Several studies have identified an association between hysterectomies and a reduced risk of breast cancer, leading some to attribute the increased incidence of breast cancer in African Americans to a decrease in hysterectomy practices [15-17]. However, future studies are needed to re-examine the significance of the association between hysterectomies and breast cancer.

Given the strong association between breast cancer and endogenous and exogenous sex hormones, this study adjusted for factors that may affect these hormones [4,5]. Participants were examined for an MHT use history, obesity, menarche, and parity. To correct for certain gynecological conditions caused by excessive endogenous sex hormones, prior life experiences with adnexal surgery, endometriosis, and fibroids were examined, and a 1:1 PSM was performed. We also performed 1:1 PSM to determine the indication for the hysterectomy. Hysterectomies are most often performed for benign conditions in which endogenous sex hormones play a pathogenic role, such as uterine fibroids, adenomyosis, and endometriosis [4,20,21].

In addition, this study was conducted using data from the NHIS, a large and reliable data source. To our knowledge, this is the first study to examine the association between hysterectomies and breast cancer in Korean women, and compared to other studies on similar topics, it is one of the largest studies of a single ethnic group.

However, this study had several limitations. First, we did not identify the major risk factors for breast cancer. Information on family history, genetic variants in BReast CAncer gene (BRCA) 1 and BRCA2, and specific types of previous benign breast disease were unavailable in the study data [46]. Second, we corrected for MHT administered before the study start date, but not for MHT administered after the study start date. MHT, which can be administered before or after surgery, is associated with breast cancer development [31]. This omission may limit the interpretation of the results. Third, we lacked detailed information on adnexal surgeries, which included patients with both ovaries removed, one ovary preserved, or only the fallopian tubes removed; further research is needed to categorize this more accurately. Fourth, this study was conducted only with Korean women, limiting its generalizability to other ethnic groups. However, studies examining the association between hysterectomies and breast cancer risk across different ethnic groups have reported no significant differences [10,16]. Fifth, stepwise selection was used to build the propensity score model, which may have led to the exclusion of relevant confounders and slight imbalances in certain covariates. Although we performed additional analyses adjusting for these imbalanced variables and observed consistent results, the potential for residual confounding factors cannot be fully excluded. Sixth, death was treated as a censored event, which may not fully account for competing risks. This limitation should be addressed in future studies by using appropriate competing risk models.

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Despite these limitations, our study adjusted for variables influencing the association between endogenous and exogenous female hormones and breast cancer more thoroughly than previous studies did. Consequently, we did not find an association between breast cancer and hysterectomies, suggesting that the existing hypothesis regarding this relationship needs to be revisited.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Procedure codes for the different types of hysterectomies

Supplementary Table 2

The characteristics of the hysterectomy and non-hysterectomy groups before propensity score matching

Supplementary Table 3

Comparison of breast cancer cases per 100,000 person-years for women with and without hysterectomies using various variables

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49. PUBMED | CROSSREF
2. Atashgaran V, Wrin J, Barry SC, Dasari P, Ingman WV. Dissecting the biology of menstrual cycle-associated breast cancer risk. Front Oncol 2016;6:267. PUBMED | CROSSREF
3. Khan SA, Rogers MAM, Obando JA, Tamsen A. Estrogen receptor expression of benign breast epithelium and its association with breast cancer. Cancer Res 1994;54:993-7. PUBMED
4. Nounu A, Kar SP, Relton CL, Richmond RC. Sex steroid hormones and risk of breast cancer: a two-sample Mendelian randomization study. Breast Cancer Res 2022;24:66. PUBMED | CROSSREF
5. Clemons M, Goss P. Estrogen and the risk of breast cancer. N Engl J Med 2001;344:276-85. PUBMED | CROSSREF
6. 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. PUBMED | CROSSREF
7. OECD Data Explorer. Surgical Procedures. https://data-explorer.oecd.org/vis?fs[0]=Topic%2C1%7CHealth%23HEA%23%7CHealthcare%20use%23HEA_PRC%23&pg=0&fc=Topic&bp=true&snb=10&vw=tb&df[ds]=dsDisseminateFinalDMZ&df[id]=DSD_HEALTH_PROC%40DF_SURG_PROC&df[ag]=OECD.ELS.HD&df[vs]=1.1&dq=...CM683_687_689.....&pd=2010%2C&to[TIME_PERIOD]=false. Accessed March 22th, 2025.
8. Wu JM, Wechter ME, Geller EJ, Nguyen TV, Visco AG. Hysterectomy rates in the United States, 2003. Obstet Gynecol 2007;110:1091-5. PUBMED | CROSSREF
9. Farquhar CM, Sadler L, Harvey SA, Stewart AW. The association of hysterectomy and menopause: a prospective cohort study. BJOG 2005;112:956-62. PUBMED | CROSSREF
10. 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. PUBMED | CROSSREF
11. Xiangying H, Lili H, Yifu S. The effect of hysterectomy on ovarian blood supply and endocrine function. Climacteric 2006;9:283-9. PUBMED | CROSSREF
12. Abdelazim IA, Abdelrazak KM, Elbiaa AAM, Farghali MM, Essam A, Zhurabekova G. Ovarian function and ovarian blood supply following premenopausal abdominal hysterectomy. Przegl Menopauz 2015;14:238-42. PUBMED | CROSSREF

13. Collaborative Group on Hormonal Factors in Breast Cancer. Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. Lancet Oncol 2012;13:1141-51. PUBMED | CROSSREF
14. Lovett SM, Sandler DP, O'Brien KM. Hysterectomy, bilateral oophorectomy, and breast cancer risk in a racially diverse prospective cohort study. J Natl Cancer Inst 2023;115:662-70. PUBMED | CROSSREF
15. Wilson LF, Tuesley KM, Webb PM, Dixon-Suen SC, Stewart LM, Jordan SJ. Hysterectomy and risk of breast, colorectal, thyroid, and kidney cancer - an Australian data linkage study. Cancer Epidemiol Biomarkers Prev 2021;30:904-11. PUBMED | CROSSREF
16. Robinson WR, Nichols HB, Tse CK, Olshan AF, Troester MA. Associations of premenopausal hysterectomy and oophorectomy with breast cancer among black and white women: the Carolina Breast Cancer Study, 1993-2001. Am J Epidemiol 2016;184:388-99. PUBMED | CROSSREF
17. Press DJ, Sullivan-Halley J, Ursin G, Deapen D, McDonald JA, Strom BL, et al. Breast cancer risk and ovariectomy, hysterectomy, and tubal sterilization in the women's contraceptive and reproductive experiences study. Am J Epidemiol 2011;173:38-47. PUBMED | CROSSREF
18. 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. PUBMED | CROSSREF
19. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet 2019;394:1159-68. PUBMED | CROSSREF
20. Zhai J, Vannuccini S, Petraglia F, Giudice LC. Adenomyosis: mechanisms and pathogenesis. Semin Reprod Med 2020;38:129-43. PUBMED | CROSSREF
21. Zondervan KT, Becker CM, Missmer SA. Endometriosis. N Engl J Med 2020;382:1244-56. PUBMED | CROSSREF
22. Phipps AI, Buist DSM. Validation of self-reported history of hysterectomy and oophorectomy among women in an integrated group practice setting. Menopause 2009;16:576-81. PUBMED | CROSSREF
23. Rosland TE, Johansen N, Åsvold BO, Pripp AH, Liavaag AH, Michelsen TM. Validity of self-reported hysterectomy and oophorectomy in a population-based cohort: the HUNT study. BJOG 2024;131:1555-62. PUBMED | CROSSREF
24. National Health Insurance Service. Health Security System. http://www.nhis.or.kr/english/wbheaa02300m01.do. Accessed October 24th, 2021.
25. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson Comorbidity Index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 2011;173:676-82. PUBMED | CROSSREF
26. World Health Organization, Regional Office for the Western Pacific. The Asia-Pacific Perspective: Redefining Obesity and Its Treatment. Sydney: Health Communications Australia; 2000.
27. Park CY, Lim JY, Park HY. Age at natural menopause in Koreans: secular trends and influences thereon. Menopause 2018;25:423-9. PUBMED | CROSSREF
28. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. Trans Med Chir Soc Edinb 1896;15:153-79. PUBMED
29. Practice Bulletin No. 136: Management of abnormal uterine bleeding associated with ovulatory dysfunction. Obstet Gynecol 2013;122:176-85. PUBMED | CROSSREF
30. Corona LE, Swenson CW, Sheetz KH, Shelby G, Berger MB, Pearlman MD, et al. Use of other treatments before hysterectomy for benign conditions in a statewide hospital collaborative. Am J Obstet Gynecol 2015;212:304.e1-7. PUBMED | CROSSREF
31. Barańska A, Błaszczuk A, Kanadys W, Malm M, Drop K, Polz-Dacewicz M. Oral contraceptive use and breast cancer risk assessment: a systematic review and meta-analysis of case-control studies, 2009-2020. Cancers (Basel) 2021;13:5654. PUBMED | CROSSREF
32. Management of symptomatic uterine leiomyomas: ACOG Practice Bulletin, Number 228. Obstet Gynecol 2021;137:e100-15. PUBMED | CROSSREF
33. Hartmann KE, Fonnesbeck C, Surawicz T, Krishnaswami S, Andrews JC, Wilson JE, et al. Management of Uterine Fibroids. Rockville: Agency for Healthcare Research and Quality; 2017.
34. Huerta-Reyes M, Maya-Núñez G, Pérez-Solis MA, López-Muñoz E, Guillén N, Olivo-Marin JC, et al. Treatment of breast cancer with gonadotropin-releasing hormone analogs. Front Oncol 2019;9:943. PUBMED | CROSSREF
35. C Pillay O, Manyonda I; C. Pillay O. The surgical menopause. Best Pract Res Clin Obstet Gynaecol 2022;81:111-8. PUBMED | CROSSREF

36. Rocca WA, Mielke MM, Gazzuola Rocca L, Stewart EA. Premature or early bilateral oophorectomy: a 2021 update. Climacteric 2021;24:466-73. PUBMED | CROSSREF

37. Piszczek C, Ma J, Gould CH, Tseng P. Cancer risk-reducing opportunities in gynecologic surgery. J Minim Invasive Gynecol 2018;25:1179-93. PUBMED | CROSSREF

38. Yuk JS, Kim T, Cho H, Gwak G. Breast cancer risk association with postmenopausal hormone therapy: Health Insurance Database in South Korea-based cohort study. Eur J Endocrinol 2024;190:1-11. PUBMED | CROSSREF

39. Abenhaim HA, Suissa S, Azoulay L, Spence AR, Czuzoj-Shulman N, Tulandi T. Menopausal hormone therapy formulation and breast cancer risk. Obstet Gynecol 2022;139:1103-10. PUBMED | CROSSREF

40. Stuenkel CA. Menopausal hormone therapy and the role of estrogen. Clin Obstet Gynecol 2021;64:757-71. PUBMED | CROSSREF

41. Garg N, Behbehani S, Kosiorek H, Wasson M. Hormone replacement therapy prescription after premature surgical menopause. J Minim Invasive Gynecol 2020;27:1618-23. PUBMED | CROSSREF

42. Chlebowski RT, Anderson GL, Aragaki AK, Manson JE, Stefanick ML, Pan K, et al. Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the women's health initiative randomized clinical trials. JAMA 2020;324:369-80. PUBMED | CROSSREF

43. Academic Committee of the Korean Society of Menopause, Lee SR, Cho MK, Cho YJ, Chun S, Hong SH, et al. The 2020 menopausal hormone therapy guidelines. J Menopausal Med 2020;26:69-98. PUBMED | CROSSREF

44. Atay V, Ceyhan T, Baser I, Gungor S, Goktolga U, Muhcu M. Hysterectomy with preservation of both ovaries does not result in premature ovarian failure. J Int Med Res 2007;35:416-21. PUBMED | CROSSREF

45. Lee DY, Park HJ, Kim BG, Bae DS, Yoon BK, Choi D. Change in the ovarian environment after hysterectomy as assessed by ovarian arterial blood flow indices and serum anti-Müllerian hormone levels. Eur J Obstet Gynecol Reprod Biol 2010;151:82-5. PUBMED | CROSSREF

46. Practice Bulletin No 182: Hereditary breast and ovarian cancer syndrome. Obstet Gynecol 2017;130:e110-26. PUBMED | CROSSREF