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Long-term Overall and Disease-specific Mortality Associated with Benign Gynecologic Surgery Performed at Different Ages

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Abstract

Objective—As bilateral salpingo-oophorectomy is frequently performed with hysterectomy for nonmalignant conditions, defining health outcomes associated with benign bilateral salpingo-oophorectomy performed at different ages is critical.

Methods—We assessed mortality risk associated with benign total abdominal hysterectomy or bilateral salpingo-oophorectomy among 52,846 Breast Cancer Detection and Demonstration Project Follow-up Study participants. Surgery and risk factor data were ascertained via baseline interview (1979-1986) and three questionnaires (1987-1998). During follow-up through December 2005 (mean=22.1 years), 13,734 deaths were identified. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for overall and disease-specific mortality following total abdominal hysterectomy or bilateral salpingo-oophorectomy performed by ages 35, 40, 45, 50, or 55 years compared to not having surgery using landmark analyses and multivariable Cox regression.

Results—Undergoing bilateral salpingo-oophorectomy by age 35 was associated with increased mortality risk (HR_{35 years}=1.20, 95% CI: 1.08, 1.34), which decreased with age (HR_{40 years}=1.12, 95% CI: 1.04, 1.21; HR_{45 years}=1.10, 95% CI: 1.03, 1.17). Total abdominal hysterectomy alone performed by age 40 was associated with increased mortality risk to a lesser extent (HR_{40 years}=1.08, 95% CI: 1.01, 1.15). Analyses based on matched propensity scores related to having gynecological surgery yielded similar results. Elevated mortality risks were largely attributable to non-cancer causes.

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Conflicts of Interest: None.

Conclusions—Benign gynecologic surgeries among young women are associated with increased mortality risk, which attenuates with age.

Keywords

Bilateral oophorectomy; cohort studies; hysterectomy; mortality

Introduction

Defining the health outcomes associated with bilateral salpingo-oophorectomy (BSO) is important. BSO lowers breast and ovarian/fallopian tube cancer risk,¹ but may increase chronic disease risk.²⁻⁵ Results of prior studies assessing associations of BSO and mortality are inconsistent.⁵⁻⁹ Of approximately 600,000 hysterectomy procedures performed annually in the United States, half include incidental BSO;¹⁰ thus, any adverse effects of BSO affect public health.

Parker et al. reported that oophorectomy and hysterectomy were associated with a 13% increase in mortality, primarily from coronary heart disease and lung cancer, when compared with hysterectomy alone,⁵ supporting conclusions of a simulated analysis.⁶ Another analysis found that “prophylactic” oophorectomy was unrelated to mortality overall, but was related to increased mortality if performed before age 45 years.⁷ Similarly, another study linked oophorectomy to increased mortality, primarily due to cardiovascular disease, among obese women who underwent surgery before age 40 and did not use menopausal hormone therapy (HT).⁸ Finally, one investigation found that BSO was unrelated to mortality.⁹ Thus, data suggest that incidental BSO may be associated with increased mortality, but clarification of risks, particularly in relation to age at surgery are needed.

Defining whether BSO is related to increased mortality and identifying factors that modify this risk would inform discussions related to considering oophorectomy as an incidental procedure concurrent with hysterectomy as well as elective cancer-risk reducing surgery. To assess mortality risks associated with benign hysterectomy and BSO, we analyzed data from the Breast Cancer Demonstration Detection Project (BCDDP) follow-up study, which included an initial assessment of 61,431 women in 1979-1986 and follow-up for outcomes through 2005. Our analysis included a landmark analysis specifically designed to assess risks associated with BSO by predetermined ages, and an analysis in which women who underwent BSO were compared to women with a similar propensity to undergo this surgery, but did not (matched propensity scores). The large size and lengthy follow-up in the BCDDP cohort offers an important opportunity to assess long-term disease-specific mortality risks, which could reflect loss of ovarian function.

Methods

Study population

Briefly, BCDDP was a breast cancer screening program co-sponsored by the American Cancer Society and the National Cancer Institute that enrolled over 280,000 women at 29

U.S. centers between 1973 and 1980.¹¹ In 1979, 64,182 participants meeting the following criteria were enrolled in the BCDDP follow-up study: 1) breast cancer diagnosed during the screening program (n=4,275); 2) benign breast surgery (n=25,114); 3) recommended for follow-up but not biopsied (n=9,628) and 4) a subset of women who during screening had neither breast surgery performed nor recommended (n=25,165). The National Cancer Institute Institutional Review Board approved the study; all participants provided informed consent.

During BCDDP Follow-up Study Phase 1 (baseline: 1979-1986), 61,431 women (96%) completed a baseline telephone interview and up to six (usually four) annual telephone interviews. In Phases 2 (1987-1989), 3 (1993-1995) and 4 (1995-1998) participants completed self-administered, mailed questionnaires. When possible, living non-respondents were interviewed by telephone.

Exposure assessment

Each phase collected data about gynecologic surgeries, including total abdominal hysterectomy (TAH, or simple hysterectomy), unilateral salpingo-oophorectomy (USO), bilateral-salpingo oophorectomy (BSO), and surgery dates. To assess outcomes following benign gynecologic surgeries, we defined women who underwent gynecologic surgeries prior to or within 12 months of ovarian cancer diagnosis or death (n=265, including 162 deaths) or endometrial cancer diagnosis or death (n=511, including 150 deaths) as not having had benign gynecologic surgery.

BCDDP screening phase interviews collected demographic data, including race/ethnicity and education level. Measured height and weight recorded at the last screening visit were used to calculate body mass index (BMI, kg/m²). Each phase included questions about use and duration of HT; Phase 1 did not distinguish between estrogen-only and estrogen-progestin therapy as the former was the primary formulation in use at that time. Other risk factors ascertained included reproductive history (Phase 1), alcohol use and smoking status (Phase 2, with smoking status updated in Phase 3), diagnoses of cardiovascular disease, diabetes, stroke, or osteoporosis (Phases 2-4), and family histories of breast cancer (baseline with updates in Phases 1-4) and ovarian cancer (Phase 4).

Ascertainment of cancer diagnoses and vital status

Incident cancers were identified through self-report, linkage to 19 state cancer registries, and the National Death Index. Self-reported cancers were verified through medical record review with standardized data abstraction. Vital status was ascertained by regular searches of the National Death Index through December 31, 2005. The primary cause of death was coded as listed on the death certificate using the International Classification of Diseases (ICD-9 and ICD-10). Women who were not identified as deceased in the National Death Index were presumed to be alive.

Analytic population

Of 61,431 women who completed the Phase 1 interview, we excluded women for the following: unknown menopausal status (n=50); never having menstruated (n=10); unknown

date of gynecologic surgery (n=1,570) or death (n=18); recorded death date earlier than that of baseline interview (n=6); and diagnosis of cancer prior to follow-up (n=6,931). The present analysis included 52,846 women, with follow-up questionnaire data at Phase 2 for 44,622 (84.4%), Phase 3 for 39,007 (73.8%), and Phase 4 for 37,171 (70.3%).

Statistical analysis

The exposure of interest in this analysis was benign gynecological surgery; therefore, women who underwent gynecological cancer surgery were considered unexposed. We categorized benign gynecological surgery as: none (i.e., intact uterus with retention of at least one ovary); TAH (with or without USO); and BSO (with or without TAH).

We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) associated with benign gynecologic surgery for all-cause and cause-specific mortality, using age as the time scale. Study entry began at the baseline interview and person-years accrued until death or December 31, 2005. Exit age was censored at 90 years (n=3,368 women) to ensure proportionality of the hazards. In all-cause mortality analyses, endometrial and ovarian cancer deaths were combined with deaths among women who did not undergo surgery because neither group had the exposure of interest (i.e., benign gynecological surgery). We evaluated cause-specific mortality for diseases that resulted in over 100 deaths. Examination of hazard plots and tests for interaction between gynecologic surgery status and the natural log of age were consistent with proportional hazards.

We examined the relation between benign gynecologic surgery status and mortality using two approaches: 1) a time-dependent exposure, in which women whose surgery status changed during follow-up contributed person-time to multiple exposure categories; and 2) landmark analyses,¹² which assessed mortality risk based on whether surgery was performed at or before pre-specified landmark ages. We highlight the latter as more clinically relevant. Specifically, fixed landmark ages (35, 40, 45, 50, or 55 years) were selected to conduct survival analysis of women with and without benign gynecological surgery by that age. Women who died prior to the landmark age were excluded, and women who underwent benign surgery after that age were considered unexposed. Thus, we compared the risk of death among women who had benign gynecologic surgery by specific landmark ages to those who did not.

We adjusted for the following potential confounders in our final multivariable models: BMI (<25, 25-<30, 30+ kg/m², unknown), alcohol use (never, ever, unknown), smoking (never, ever, unknown), HT use (never used, estrogen therapy <10 years, estrogen therapy use 10+ years, used other/unknown hormone formulations), and birth cohort (1891-<1911, 1911-<1931, 1931+). Smoking status and HT were treated as time-dependent exposures, allowing women to contribute person-time to multiple categories. Further adjustment for race/ethnicity, education, income, marital status, history of cardiovascular disease, diabetes, stroke, osteoporosis, age at menarche, parity, oral contraceptive use and duration, and family history of breast or ovarian cancers had minimal effects on risk estimates; we therefore do not show these results.

To reduce the possibility of bias due to differences in covariate distributions between women who underwent benign gynecologic surgery and those who did not, we matched women in these groups using propensity scores,¹³ defined as the conditional probability of undergoing TAH or BSO, given all covariates listed above. We computed deciles of the propensity score and created two matched datasets, one for TAH and another for BSO, selecting one woman who did not undergo surgery from each decile of the propensity score for every woman who underwent benign gynecologic surgery who fell into the same propensity score decile, and we repeated the landmark analyses.

In landmark sensitivity analyses, we censored exit age at 70 years to ensure that observed associations were not being driven by unique characteristics of long-term survivors. To explore whether the cumulative risk estimates observed at older landmark ages were driven by benign gynecologic surgeries conducted earlier in life, we also analyzed benign gynecologic surgery status as a time-dependent exposure in five-year age intervals in standard Cox models.

We used a likelihood ratio test, comparing models with and without interaction terms, to separately examine effect modification by HT and BMI. Probability values of <0.05 were considered statistically significant. All tests of significance were two-tailed. Analyses were performed using SAS software (SAS Institute Inc., Cary, NC).

Results

Distribution of participant characteristics by benign gynecologic surgery status

Women were predominantly non-Hispanic white (86.4%), with a mean (SD) age at baseline of 55.3 (8.7) years. At the end of follow-up, 11,247 (21%) women reported having TAH (with or without a USO), and 12,652 (24%) women reported having BSO (with or without a TAH) (Table 1). Among women categorized as having undergone benign TAH, 3,248 (29%) also reported having a USO. Among women reporting having BSO, the vast majority (98%) also reported having TAH.

Compared with women who did not undergo benign gynecologic surgery, women who underwent BSO were more likely to have birth dates between 1911-1930, higher BMIs, histories of chronic disease, used HT, and family histories of ovarian cancer. Women who underwent TAH or BSO were less likely than women who did not undergo benign gynecologic surgery to have ever smoked or consumed alcohol and to have post-high school education. Gynecologic surgery status did not vary substantially by other factors. Mortality risk increased with increasing BMI; increased risks were also observed for smokers and those who reported having a history of cardiovascular disease, diabetes or stroke (Table 2). Mortality risk was inversely associated with education, alcohol use, increasing parity and HT duration.

Relationships between gynecologic surgery and all-cause mortality

Over an average of 22 years of follow-up, 52,846 women contributed 1,167,514 person-years. Of 13,734 deaths, 4,326 (31%) were cancer-related, 9,014 (66%) non-cancer deaths, and 394 (3%) of unknown causes. Among all women, TAH and BSO were not associated

with all-cause mortality (HR=1.01, 95% CI: 0.96, 1.05, and HR=0.99, 95% CI: 0.95, 1.04, respectively) in time-dependent analyses (see Table, Supplemental Digital Content 1, which shows the relation between time-dependent gynecologic surgery status and all-cause mortality). However, risk estimates varied according to age at surgery. Results from landmark analyses (Figure 1) demonstrated that women who underwent BSO by age 35 years had an increased risk of death from any cause (HR_{35 years}=1.20, 95% CI: 1.08, 1.34), which progressively decreased if surgery was performed by later ages, until age 50 years, after which risk was not increased. TAH alone by ages 35 or 40 years was associated with increased all-cause mortality (HR_{35 years}=1.10, 95% CI: 1.00, 1.20; HR_{40 years}=1.08, 95% CI: 1.01, 1.15), but statistically significant associations were not observed by later landmark ages. Landmark analyses based on matched propensity scores related to having benign gynecological surgery were consistent with results for the entire cohort (see Table, Supplemental Digital Content 2, which describes results from landmark analyses with propensity score matching). Numbers were too sparse to separately examine risk associations for women who underwent TAH with USO (categorized in our benign TAH group) or for women who underwent BSO without TAH (categorized in our benign BSO group). Results from landmark analyses excluding these subgroups were also consistent with results for the entire cohort, though findings for risk associations with TAH were somewhat attenuated (data not shown).

Sensitivity analyses in which follow-up was censored at age 70 years indicated stronger shorter-term risk estimates related to gynecologic surgery as compared with those observed in the main analysis for which follow-up was censored at age 90 years (see Table, Supplemental Digital Content 3, which shows results from sensitivity analyses with follow-up censored at age 70 years). Time-dependent analyses stratified by age at surgery implicated BSO prior to age 35 years as the main cause of excess mortality (see Table, Supplemental Digital Content 1).

Relationships between benign gynecologic surgery and disease-specific mortality

Findings for common cancer and non-cancer causes of death with potential hormonal etiology are shown in Table 3 and Table 4 (findings for less common causes of death may be found in Table, Supplemental Digital Content 4). BSO was associated with a reduction in risk of cancer-related death if performed by age 50 (HR_{50 years}=0.89, 95% CI: 0.81, 0.98) or by age 55 years (HR_{55 years}=0.88, 95% CI: 0.80, 0.97) (Table 3). BSO was associated with increased risk of death from colorectal and pancreatic cancers; however, findings were only statistically significant at selected ages at surgery, based on limited data. Brain cancer deaths were increased among women who underwent BSO by age 55 years (HR_{55 years}=1.67, 95% CI: 1.05, 2.67), based on 32 fatal cases (see Table, Supplemental Digital Content 4). TAH by any of the landmark ages was not associated with cancer mortality.

BSO was related to increased risk of non-cancer deaths, with the strongest associations among women undergoing surgery by age 35 years (HR_{35 years}=1.25, 95% CI: 1.10, 1.42) (Table 4). The associations were progressively attenuated at older ages, though risk remained increased up to age 55 years (HR_{55 years}=1.08, 95% CI: 1.01, 1.14). BSO at all landmark ages was associated with a statistically significant increased risk of death from

coronary heart disease (CHD). Increased risk of death from diabetes was observed for BSO at all landmark ages, but was statistically significant only for women who underwent BSO by ages 40 and 45 years ($HR_{40\text{ years}}=1.60$, 95% CI: 1.02, 2.52; $HR_{45\text{ years}}=1.45$, 95% CI: 1.00, 2.10). TAH at all landmark ages was associated with increased CHD mortality, but risk estimates showed attenuation with increasing age and were lower than those observed for BSO.

Risk associations by menopausal hormone therapy use and body mass index

Ever use of HT did not statistically significantly modify the relation between gynecologic surgery and all-cause mortality (see Table, Supplemental Digital Content 5, which shows survival model results for the association between benign gynecologic surgery status and all-cause mortality for never vs. ever users of menopausal HT). However, among never users of HT, increased mortality associated with BSO persisted at older ages, whereas risks among ever users dissipated after age 50 years. All-cause mortality was particularly elevated among lean women ($BMI < 25\text{ kg/m}^2$) who underwent BSO by age 50 years (P for interaction = 0.003), whereas risks associated with TAH were strongest for overweight and obese women ($BMI \geq 25\text{ kg/m}^2$) (see Table, Supplemental Digital Content 6, which shows survival model results for the relation between benign gynecologic surgery status and all-cause mortality for women with $BMI < 25\text{ kg/m}^2$ vs. $BMI \geq 25\text{ kg/m}^2$). For CHD mortality, we observed similar patterns of increased risk associated with BSO among never users of HT and lean women (data not shown).

Discussion

This analysis within a large prospective cohort with lengthy follow-up shows that BSO performed at young ages is associated with an increased risk of death, which declines progressively with aging, and disappears by age 50 years. In addition, TAH alone performed by age 40 years was associated with a smaller increase in mortality risk. For both procedures, excess risk is attributable largely to non-cancer causes, especially CHD. Our results in combination with the literature support caution in recommending BSO for younger women who are not at high-risk of breast and ovarian cancers.

Prior analyses have linked BSO performed by the fifth decade to increased mortality among all women⁵ or among subsets of women who are obese⁸ or never users of exogenous hormones.^{5, 7-8} Our results extend these findings to younger women, demonstrating a 20% increased risk of death among women undergoing BSO by age 35 years. The California Teachers Study reported that BSO was unrelated to mortality,⁹ but this result was based on only 11 average years of follow-up (vs. 22 years in our study), and 97% of women who underwent BSO and 66% with intact ovaries reported taking HT. In our data and others,^{5, 7-8} use of HT attenuates mortality risk related to BSO; thus, patterns of exogenous hormone use may have contributed to the divergent null finding.

Prior studies have linked BSO to increased CHD mortality,⁴⁻⁵ with some showing a greater prevalence of CHD risk factors³ or higher CHD risk² associated with BSO at age 50 years or younger. Surgical menopause is associated with an abrupt decrease in circulating endogenous estrogens, increases in lipids¹⁴ and subclinical atherosclerosis.¹⁵⁻¹⁶

Alternatively, the relationship between BSO and CHD mortality may not be causal because common risk factors may predispose to both gynecological surgery and CHD mortality. Although we adjusted for multiple factors, we cannot exclude residual confounding in our analyses of BSO and CHD mortality, and BMI was only available at baseline.

We also observed weaker CHD mortality risks associated with TAH alone, which could reflect acceleration of ovarian failure, as previously postulated,¹⁷ or misclassification of women who underwent BSO. In the Women's Health Initiative, TAH alone was not independently related to risk of CHD.¹⁸

Similar to findings from three^{5, 7-8} of four^{5, 7-9} prior cohorts, we observed higher mortality risks among women who underwent BSO and were non-users of menopausal HT. This finding has important public health implications, given the decline in HT use.¹⁹ Consistent with the mitigation of mortality risk associated with HT, we found that BSO was riskier for lean women, possibly reflecting protection associated with greater estrogen synthesis in adipose tissues²⁰ among heavier women. However, in the National Health and Nutrition Examination Survey, a population with higher average BMI than BCDDP, excess mortality following BSO was concentrated among young obese women.⁸

Our data suggest that BSO by age 50 or 55 years may reduce cancer mortality, although associations were not identified for the most common tumor types. For unclear reasons, mortality risks were elevated for colorectal, pancreatic and brain cancers at selected ages.

Although use of self-reported surgical history is a potential limitation of our analysis, prior studies have reported excellent reliability and validity for these data.²¹⁻²³ While we were unable to account for possible effects of surgical indications, our analysis of women matched on propensity scores related to the probability of undergoing benign gynecologic surgery yielded results similar to those for the entire cohort. In addition, we think that it is unlikely that risk information related to surgical indication that was not captured by our questionnaire data would be influencing the risk of death decades later and producing the observed monotonic relationship between age at BSO and mortality risk. Furthermore, our results are generally compatible with the literature, while extending prior findings.

We present results from a landmark analysis and a Cox model, in which benign gynecologic surgery was treated as a time-dependent exposure. Both analytic approaches avoid biases involved in comparing time-to-event data for different exposure groups when exposure group membership for an individual arbitrarily varies during the time under study. Results that used surgery as a time-dependent variable were consistent with findings from the landmark analysis showing that benign gynecologic surgeries among young women are associated with increased mortality risk. We focused on results from the landmark analysis as it is simple in its execution and its interpretation and provides the clinically relevant quantities. While the results of the landmark analysis depend on the somewhat arbitrary choice of the particular landmark time, we lessened the impact of this selection by choosing several landmark ages.

Strengths of our study include repeated risk factor and gynecological surgery data collection, the large size of the cohort, and lengthy follow-up. Sensitivity analyses demonstrated that

results were not driven by deaths among the very old, where biases could come into play. We attempted to account for changes in surgical practices and treatment for chronic diseases by adjusting for birth cohort. We also observed that the prevalence of gynecologic surgeries was stable within different birth cohorts, lending relevance of our findings to current clinical practice.

Conclusions

In summary, we demonstrate that BSO among younger women is associated with a substantial increase in mortality risk, primarily due to CHD, which declines with aging and disappears by age 50 years. TAH alone at younger ages demonstrated a weaker increase in mortality, which requires confirmation given the complexities of this analysis. Although women at extremely high genetic risk for breast and ovarian cancer clearly benefit from risk-reducing BSO,¹ other women must weigh the risks of developing gynecological cancer against those of CHD mortality. Further research on effects of BSO may enable women to make improved choices based on their individual risks of gynecologic cancer and CHD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

BSO	bilateral salpingo-oophorectomy
BMI	body mass index
BCDDP	Breast Cancer Demonstration Detection Project
CI	confidence interval
CHD	coronary heart disease
HR	hazard ratio
HT	hormone therapy

TAH total abdominal hysterectomy
USO unilateral salpingo-oophorectomy

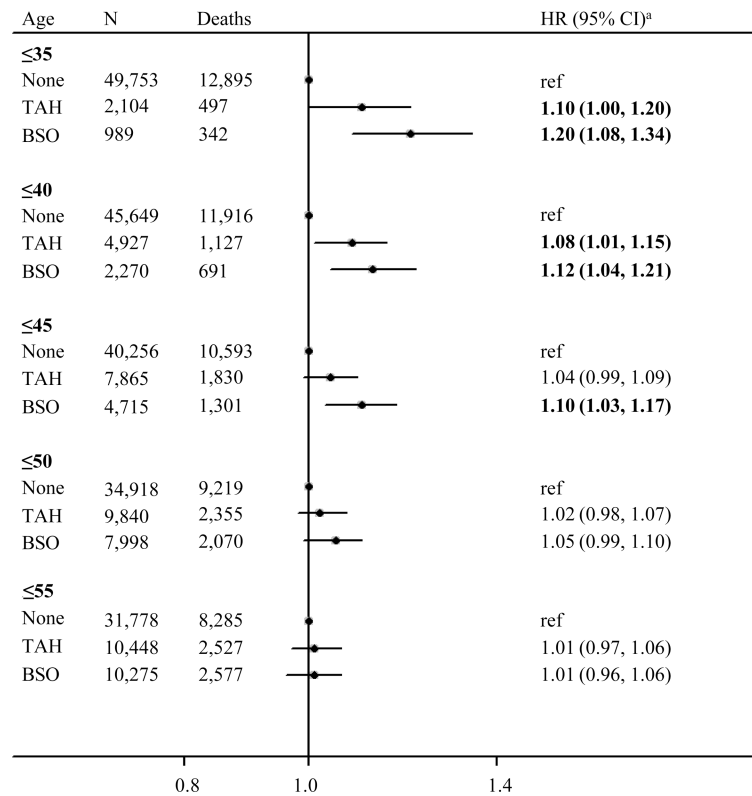


Figure 1. Survival Model Results for Landmark Analyses Relating Between Benign Gynecologic Surgery Status to All-cause Mortality, According to the Age by Which Surgeries Were Performed, BCDDP Follow-up Study, Follow-up From 1979-1986 to 2005 (n=52,846)
^a Landmark analyses, using Cox proportional hazards models, adjusted for body mass index, alcohol use, smoking, menopausal hormone therapy use, and birth cohort.
 BCDDP, Breast Cancer Detection and Demonstration Project; BSO, bilateral salpingo-oophorectomy; CI, confidence interval; TAH, transabdominal hysterectomy; HR, hazard ratio.

Table 1
Distribution of Select Participant Characteristics by Benign Gynecologic Surgery Status Among 52,846 Women in the US BCDDP Follow-up Study With Follow-up From 1979-1986 to 2005

Characteristic	Benign gynecologic surgery status, N (%) ^a		
	None N=28,947	Simple hysterectomy N=11,247	Bilateral salpingo-oophorectomy N=12,652
Age, y			
<50	9,103 31.4%	3,647 32.4%	3,663 29.0%
50-54	6,455 22.3%	2,499 22.2%	2,875 22.7%
55-59	5,463 18.9%	2,173 19.3%	2,533 20.0%
60-64	3,512 12.1%	1,355 12.0%	1,673 13.2%
65-69	2,179 7.5%	854 7.6%	1,052 8.3%
70-74	1,496 5.2%	501 4.5%	605 4.8%
75-79	634 2.2%	194 1.7%	212 1.7%
80+	105 0.4%	24 0.2%	39 0.3%
Birth cohort			
1891-<1911	2,108 7.3%	673 6.0%	808 6.4%
1911-<1931	17,353 59.9%	6,805 60.5%	8,056 63.7%
1931+	9,486 32.8%	3,769 33.5%	3,788 29.9%
Race/ethnicity			
Non-Hispanic white	24,974 86.3%	9,689 86.1%	10,992 86.9%
Other/unknown	3,973 13.7%	1,558 13.9%	1,660 13.1%
Education			
<High school or high school graduate	3,639 12.7%	1,665 15.0%	1,963 15.6%
Post-high school	25,071 87.3%	9,468 85.0%	10,591 84.4%
BMI, kg/m ²			
<25	18,827 66.8%	6,968 63.1%	7,876 63.8%
25-<30	6,780 24.0%	2,933 26.6%	3,121 25.3%
30+	2,596 9.2%	1,139 10.3%	1,343 10.9%
Smoking			
Never	13,909 56.4%	5,823 59.6%	6,670 59.8%

Characteristic	Benign gynecologic surgery status, N (%) ^a		
	None N=28,947	Simple hysterectomy N=11,247	Bilateral salpingo-oophorectomy N=12,652
Ever	10,772 43.6%	3,951 40.4%	4,491 40.2%
Alcohol			
Never	10,406 44.0%	4,490 47.7%	5,213 48.5%
Ever	13,254 56.0%	4,922 52.3%	5,528 51.5%
Cardiovascular disease			
No	18,283 83.6%	6,739 78.7%	7,768 78.9%
Yes	3,579 16.4%	1,821 21.3%	2,082 21.1%
Diabetes			
No	19,909 91.0%	7,537 88.5%	8,669 88.5%
Yes	1,963 9.0%	982 11.5%	1,125 11.5%
Stroke			
No	22,303 96.5%	8,630 94.7%	9,853 95.0%
Yes	820 3.5%	481 5.3%	522 5.0%
Osteoporosis			
No	16,914 78.9%	6,475 76.9%	7,433 77.4%
Yes	4,532 21.1%	1,947 23.1%	2,174 22.6%
Parity			
Nulliparous/missing	4,524 15.6%	1,110 9.9%	1,888 14.9%
One	3,528 12.2%	1,212 10.8%	1,670 13.2%
Two	8,454 29.2%	3,223 28.7%	3,710 29.3%
Three or more	12,441 43.0%	5,702 50.7%	5,384 42.6%
Menopausal hormone therapy			
Never used	13,631 47.1%	2,679 23.8%	1,904 15.0%
ET <10 years	3,497 12.1%	3,798 33.8%	3,536 27.9%
ET 10+years	584 2.0%	2,771 24.6%	4,501 35.6%
Used hormones, type other/unknown	11,235 38.8%	1,999 17.8%	2,711 21.4%
Family history of ovarian			
No	17,881 94.7%	7,179 94.5%	8,012 92.8%
Yes	1,009 5.3%	419 5.5%	623 7.2%

BCDDP, Breast Cancer Detection and Demonstration Project; BMI, body mass index; ET, estrogen therapy

^aBenign gynecologic surgery status at end of follow-up. Missing values were excluded from column percentage calculations.

Table 2
Survival Model Results for the Relation Between Select Participant Characteristics and All-cause Mortality Among 52,846 Women in the US BCDDP Follow-up Study With Follow-up From 1979-1986 to 2005

Characteristic	No. of deaths	HR	95% CI
Birth cohort			
1891-<1911	1,960	1.00	referent
1911-<1931	10,042	0.93	0.88 , 0.98
1931+	1,732	0.92	0.85 , 1.00
Race/ethnicity			
Non-hispanic white	11,961	1.00	referent
Other/unknown	1,773	1.03	0.98 , 1.08
Education			
<High school or high school	2,696	1.00	referent
Post-high school	10,917	0.84	0.80 , 0.87
BMI, kg/m ²			
<25	7,742	1.00	referent
25-<30	3,791	1.17	1.12 , 1.21
30+	1,885	1.71	1.62 , 1.79
Smoking ^{df}			
Never	5,191	1.00	referent
Ever	4,413	1.49	1.43 , 1.55
Alcohol			
Never	4,790	1.00	referent
Ever	4,574	0.95	0.91 , 0.99
Cardiovascular disease			
No	6,212	1.00	referent
Yes	2,473	1.30	1.24 , 1.36
Diabetes			
No	7,138	1.00	referent
Yes	1,502	1.82	1.72 , 1.93
Stroke			
No	8,518	1.00	referent
Yes	657	1.21	1.12 , 1.31
Osteoporosis			
No	6,517	1.00	referent
Yes	1,973	0.81	0.77 , 0.85
Parity			
Nulliparous/missing	2,508	1.00	referent
One	2,012	0.94	0.89 , 1.00
Two	3,883	0.84	0.80 , 0.89
Three or more	5,331	0.84	0.80 , 0.88

Characteristic	No. of deaths	HR	95% CI
Menopausal hormone therapy ^a			
Never used	5,712	1.00	referent
ET <10 years	2,919	0.85	0.81 , 0.89
ET 10+years	2,021	0.83	0.79 , 0.87
Used hormones, type other/unknown	3,082	0.80	0.77 , 0.84
Family history of ovarian cancer			
No	4,050	1.00	referent
Yes	259	1.00	0.88 , 1.13

BCDDP, Breast Cancer Detection and Demonstration Project; BMI, body mass index; CI, confidence interval; ET, estrogen therapy; HR, hazard ratio

^aSmoking status and menopausal hormone therapy were treated as time-dependent exposures.

Table 3

Survival Model Results for the Relation Between Benign Gynecologic Surgery Status and Cancer Mortality, According to the Age by Which Surgeries Were Performed: US BCDDP Follow-up Study With Follow-up From 1979-1986 to 2005 (n=52,846)

Benign gynecological surgery status	All cancers (No. deaths=4,326)	Lung (No. deaths=914)	Breast (No. deaths=734)	CRC (No. deaths=384)	Pancreas (No. deaths=322)	NHL (No. deaths=236)
<u>Age at surgery</u>						
35 years						
None						
No. of deaths	4,076	859	697	362	299	222
HR ^a	ref	ref	ref	ref	ref	ref
TAH						
No. of deaths	153	33	25	7	9	10
HR ^a	1.00	1.00	0.93	0.51	0.76	1.20
95% CI	0.85, 1.18	0.70, 1.42	0.62, 1.38	0.24, 1.08	0.39, 1.49	0.63, 2.28
BSO						
No. of deaths	97	22	12	15	14	4
HR ^a	1.14	1.17	0.88	1.92	2.09	0.84
95% CI	0.93, 1.39	0.77, 1.80	0.49, 1.56	1.13, 3.23	1.21, 3.60	0.31, 2.28
40 years						
None						
No. of deaths	3,779	784	646	338	283	200
HR ^a	ref	ref	ref	ref	ref	ref
TAH						
No. of deaths	374	85	66	27	22	28
HR ^a	1.04	1.12	1.04	0.83	0.76	1.50
95% CI	0.94, 1.17	0.89, 1.41	0.80, 1.35	0.55, 1.23	0.49, 1.19	1.00, 2.25
BSO						
No. of deaths	173	45	22	19	17	8
HR ^a	0.92	1.14	0.73	1.09	1.09	0.79
95% CI	0.79, 1.08	0.84, 1.55	0.47, 1.12	0.68, 1.74	0.66, 1.80	0.39, 1.62
45 years						

Benign gynecological surgery status		All cancers (No. deaths=4,326)	Lung (No. deaths=734)	Breast (No. deaths=914)	CRC (No. deaths=384)	Pancreas (No. deaths=322)	NHL (No. deaths=236)
None							
No. of deaths	3,374	694	579	303	247	173	
HR ^a	ref	ref	ref	ref	ref	ref	
TAH							
# of deaths	595	130	103	49	39	37	
HR ^o	1.00	1.04	0.99	0.89	0.83	1.23	
95% CI	0.91, 1.09	0.85, 1.26	0.80, 1.23	0.65, 1.22	0.58, 1.18	0.85, 1.79	
BSO							
No. of deaths	355	90	52	32	36	26	
HR ^a	0.95	1.16	0.85	0.90	1.17	1.36	
95% CI	0.84, 1.06	0.92, 1.47	0.63, 1.14	0.61, 1.32	0.81, 1.70	0.88, 2.11	
<50 years							
None							
No. of deaths	2,957	612	500	268	199	150	
HR ^a	ref	ref	ref	ref	ref	ref	
TAH							
No. of deaths	742	149	123	62	57	46	
HR ^a	0.96	0.92	0.96	0.84	1.06	1.18	
95% CI	0.88, 1.04	0.76, 1.11	0.78, 1.19	0.62, 1.13	0.77, 1.45	0.83, 1.68	
BSO							
No. of deaths	575	144	98	51	64	38	
HR ^a	0.89	1.08	0.97	0.81	1.40	1.17	
95% CI	0.81, 0.98	0.88, 1.32	0.76, 1.22	0.58, 1.12	1.02, 1.93	0.79, 1.73	
55 years							
None							
No. of deaths	2,630	557	430	238	175	136	
HR ^a	ref	ref	ref	ref	ref	ref	
TAH							
No. of deaths	783	155	126	65	61	48	
HR ^a	0.96	0.88	1.01	0.81	1.08	1.13	

Benign gynecological surgery status	All cancers (No. deaths=4,326)	Lung (No. deaths=914)	Breast (No. deaths=734)	CRC (No. deaths=384)	Pancreas (No. deaths=322)	NHL (No. deaths=236)
95% CI	0.88, 1.04	0.73, 1.07	0.81, 1.25	0.60, 1.09	0.79, 1.49	0.79, 1.62
BSO						
No. of deaths	723	169	127	64	72	47
HR ^a	0.88	0.97	1.05	0.78	1.26	1.10
95% CI	0.80, 0.97	0.80, 1.18	0.84, 1.31	0.57, 1.06	0.92, 1.72	0.76, 1.60

BSO, bilateral salpingo-oophorectomy; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; NHL, non-Hodgkins lymphoma; TAH, total abdominal hysterectomy.

^aLandmark analyses, using Cox proportional hazards models, adjusted for body mass index, smoking, menopausal hormone therapy use, and birth cohort.

Table 4
Survival Model Results for the Relation Between Benign Gynecologic Surgery Status and Noncancer Mortality, According to the Age by Which Surgeries Were Performed: US BCDDP Follow-up Study With Follow-up From 1979-1986 to 2005 (n=52,846)

Benign gynecological surgery status	All non-cancers (No. deaths=9,014)	CHD (No. deaths=3,453)	Stroke (No. deaths=1,177)	COPD (No. deaths=537)	Alzheimer's disease (No. deaths=349)	Diabetes (No. deaths=295)
<i>Age at surgery</i>						
35 years						
None						
No. of deaths	8,442	3,208	1,123	494	335	267
HR ^a	ref	ref	ref	ref	ref	ref
TAH						
No. of deaths	334	131	32	28	10	18
HR ^a	1.17	1.21	0.85	1.72	1.01	1.75
95% CI	1.04, 1.30	1.02, 1.44	0.59, 1.20	1.17, 2.53	0.54, 1.90	1.08, 2.83
BSO						
No. of deaths	238	114	22	15	4	10
HR ^a	1.25	1.56	0.84	1.35	0.59	1.50
95% CI	1.10, 1.42	1.29, 1.89	0.55, 1.29	0.81, 2.27	0.22, 1.57	0.79, 2.82
40 years						
None						
No. of deaths	7,788	2,963	1,020	459	312	238
HR ^a	ref	ref	ref	ref	ref	ref
TAH						
No. of deaths	727	276	93	48	25	36
HR ^a	1.11	1.13	1.09	1.25	1.07	1.67
95% CI	1.03, 1.20	0.99, 1.28	0.88, 1.36	0.92, 1.70	0.71, 1.62	1.16, 2.39
BSO						
No. of deaths	499	214	64	30	12	21
HR ^a	1.22	1.37	1.15	1.28	0.80	1.60
95% CI	1.11, 1.34	1.19, 1.58	0.89, 1.48	0.88, 1.86	0.45, 1.43	1.02, 2.52
45 years						

Benign gynecological surgery status	All non-cancers (No. deaths=9,014)	CHD (No. deaths=3,453)	Stroke (No. deaths=1,177)	COPD (No. deaths=537)	Alzheimer's disease (No. deaths=349)	Diabetes (No. deaths=295)
None						
HR ^a	6,912	2,626	901	429	282	212
HR [§]	ref	ref	ref	ref	ref	ref
TAH						
No. of deaths	1,182	455	148	64	47	47
HR ^a	1.06	1.10	1.01	0.89	1.13	1.33
95% CI	1.00, 1.13	0.99, 1.22	0.85, 1.21	0.68, 1.17	0.82, 1.55	0.96, 1.84
BSO						
No. of deaths	913	371	126	44	20	35
HR ^a	1.18	1.28	1.19	0.90	0.69	1.45
95% CI	1.10, 1.27	1.14, 1.43	0.98, 1.45	0.65, 1.24	0.43, 1.10	1.00, 2.10
<50 years						
None						
No. of deaths	5,992	2,280	781	369	248	184
HR ^a	ref	ref	ref	ref	ref	ref
TAH						
No. of deaths	1,546	600	193	90	53	57
HR ^a	1.06	1.11	0.99	0.96	0.92	1.26
95% CI	1.00, 1.13	1.01, 1.22	0.84, 1.17	0.75, 1.23	0.68, 1.26	0.92, 1.72
BSO						
No. of deaths	1,441	567	197	78	47	51
HR ^a	1.13	1.20	1.12	0.97	0.96	1.28
95% CI	1.06, 1.20	1.08, 1.32	0.95, 1.33	0.74, 1.27	0.69, 1.35	0.91, 1.78
<55 years						
None						
No. of deaths	5,410	2,086	687	336	213	170
HR ^a	ref	ref	ref	ref	ref	ref
TAH						
No. of deaths	1,677	642	214	98	67	56

Benign gynecological surgery status	All non-cancers (No. deaths=9,014)	CHD (No. deaths=3,453)	Stroke (No. deaths=1,177)	COPD (No. deaths=537)	Alzheimer's disease (No. deaths=349)	Diabetes (No. deaths=295)
HR ^a	1.04	1.07	1.02	0.94	1.12	1.09
95% CI	0.99, 1.11	0.97, 1.17	0.86, 1.20	0.74, 1.20	0.83, 1.50	0.79, 1.51
BSO						
No. of deaths	1,792	684	253	100	68	65
HR ^a	1.08	1.10	1.14	0.93	1.12	1.24
95% CI	1.01, 1.14	1.00, 1.21	0.97, 1.34	0.72, 1.19	0.83, 1.52	0.90, 1.70

BSO, bilateral salpingo-oophorectomy; CHD, coronary heart disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; TAH, total abdominal hysterectomy.

^aLandmark analyses, using Cox proportional hazards models, adjusted for body mass index, alcohol use, smoking, menopausal hormone therapy use, and birth cohort.