Long-term outcomes of hysterectomy with bilateral salpingo-oophorectomy: a systematic review and meta-analysis

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OBJECTIVE: This study aimed to provide an up-to-date systematic review of "the long-term outcomes of bilateral salpingo-oophorectomy at the time of hysterectomy" and perform a meta-analysis for the reported associations.

DATA SOURCES: Our study updated a previous systematic review by searching the literature using PubMed, Web of Science, and Embase for publications between January 2015 and August 2022.

STUDY ELIGIBILITY CRITERIA: Our study included studies of women who had a hysterectomy with bilateral salpingo-oophorectomy vs women who had a hysterectomy with ovarian conservation or no surgery.

METHODS: The quality of the evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluations. Adjusted hazard ratios were extracted and combined to obtain fixed effect estimates.

RESULTS: Compared with hysterectomy or no surgery, hysterectomy with bilateral salpingo-oophorectomy in young women was associated with decreased risk of breast cancer (hazard ratio, 0.78; 95% confidence interval, 0.73—0.84) but with an increased risk of colorectal cancer (hazard ratio, 1.27; 95% confidence interval, 1.10—1.47). In addition, it was associated with an increased risk of total cardiovascular diseases, coronary heart disease, and stroke with hazard ratios of 1.18 (95% confidence interval, 1.11—1.25), 1.17 (95% confidence interval, 1.10—1.25), and 1.20 (95% confidence interval, 1.10—1.31), respectively. Compared with no surgery, hysterectomy with bilateral salpingo-oophorectomy before the age of 50 years was associated with an increased risk of hyperlipidemia (hazard ratio, 1.44; 95% confidence interval, 1.25—1.65), diabetes mellitus (hazard ratio, 1.16; 95% confidence interval, 1.09—1.24), hypertension (hazard ratio, 1.13; 95% confidence interval, 1.06—1.20), dementia (hazard ratio, 1.70; 95% confidence interval, 1.07—2.69), and depression (hazard ratio, 1.39; 95% confidence interval, 1.22—1.60). The evidence on the association with all-cause mortality in young women showed substantial heterogeneity between the studies (I^2=85%; P<.01).

CONCLUSION: Hysterectomy with bilateral salpingo-oophorectomy was associated with multiple long-term outcomes. The benefits of the addition of bilateral salpingo-oophorectomy to hysterectomy should be balanced against the risks.

Key words: all-cause mortality, anxiety, bilateral salpingo-oophorectomy, cancer, cardiovascular diseases, dementia, depression, diabetes mellitus, hyperlipidemia, hypertension, hysterectomy, parkinsonism

Introduction

Hysterectomy is one of the most commonly performed gynecologic procedures with more than 600,000 women undergoing hysterectomy each year[1] in the United States. In the United Kingdom between 2004 and 2014, more than 100,000 premenopausal women had a hysterectomy for benign indications, and 32% of those women had a concomitant bilateral salpingo-oophorectomy (BSO).[2] Hysterectomy is indicated for various benign conditions, such as fibroids, adenomyosis, and endometriosis. Many women who have hysterectomy also have BSO, for no immediate clinical indication but to prevent ovarian cancer. The removal of the ovaries leads to the sudden cessation of estrogen release and the immediate start of menopause, whereas hysterectomy

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This study was registered in the International Prospective Register of Systematic Reviews on August 25, 2022 (registration number: CRD42022349899).

All data were taken directly from the published articles.

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AJOG at a Glance

Why was this study conducted?

This study aimed to provide an up-to-date systematic review of the long-term outcomes of hysterectomy with bilateral salpingo-oophorectomy (BSO).

Key findings

Hysterectomy with BSO was associated with decreased risk of ovarian cancer and breast cancer but an increased risk of colorectal cancer, thyroid cancer, renal cancer, cardiovascular diseases (CVDs) and CVD risk factors.

What does this add to what is known?

Our findings show that hysterectomy with BSO at any age reduces the risk of ovarian cancer and that hysterectomy with BSO at a young age is associated with a reduced risk of breast cancer. Nevertheless, this risk reduction should be balanced against the possible increase in the risk of CVD, colorectal cancer, and all-cause mortality in young women. Furthermore, more evidences on the efficacy of hormone replacement therapy in mitigating the adverse effects of the premature cessation of estrogen are needed.

alone is associated with premature ovarian failure.[3,4] Despite the reduction in the incidence of ovarian cancer and ovarian cancer–related mortality,[5,6] women who undergo oophorectomy, especially before menopause, are at risk of unfavorable health outcomes. Most of these surgeries are performed in women at a general population-level risk of ovarian cancer. Therefore, the reduction in ovarian cancer risk should be balanced against other long-term outcomes. Evans et al[7] conducted a systematic review of the health sequelae of BSO at the time of hysterectomy in January 2015, but the authors did not perform a meta-analysis for the associations with the long-term outcomes.

Objectives

This study aimed to update the systematic review conducted by Evans et al[7] and, when possible, conduct a meta-analysis of the reported associations.

Methods

Institutional review board approval was not needed before conducting this systematic review.

Search strategy

We searched the literature using PubMed, Web of Science, and Embase for relevant publications using the search terms described in Appendix S1. The search was limited to studies published in English between January 2015 and August 2022. Retrieved studies were saved into an Endnote Library for deduplication using the method outlined by Bramer et al.[8]

Eligibility criteria

We included observational studies comparing the incidence of long-term outcomes between women who had a hysterectomy with BSO and women who had either hysterectomy with ovarian conservation or no surgery. Long-term outcomes of interest were mortality, cancer, neuropsychiatric outcomes, bone health, cardiovascular diseases (CVDs), and CVD risk factors. We excluded studies on hysterectomy with BSO undertaken for cancer treatment or for gender affirmation surgery, studies focusing on women at high risk of ovarian cancer, studies with <3 years of follow-up, and studies on short-term outcomes, such as sexual satisfaction, pelvic pain, and reoperation outcomes.

Study selection

Titles and abstracts were screened in Abstrackr[9], a free online tool for abstracts screening, by I.A. and H.H. Any conflicts were resolved by Y.W. We assessed the studies from the literature search and the Evans et al's[7] systematic review for inclusion in this review.

Data extraction

Data were extracted from the included studies into a formatted Excel spreadsheet as described in Appendix S2. When the analysis was stratified by the indication for surgery, we chose the estimates reported for benign indications. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for reporting systematic reviews.[10]

Assessment of Grading of Recommendations Assessment, Development, and Evaluations

The Grading of Recommendations, Assessment, Development, and Evaluations[11–16] (GRADE) was used to assess the quality of the evidence. The GRADE ratings were made for each outcome separately. Evidence was rated as very low, low, moderate, or high and could be downgraded because of the risk of bias, imprecision, indirectness, or inconsistency. More details on the GRADE assessment are included in Appendix S3, Table S1.

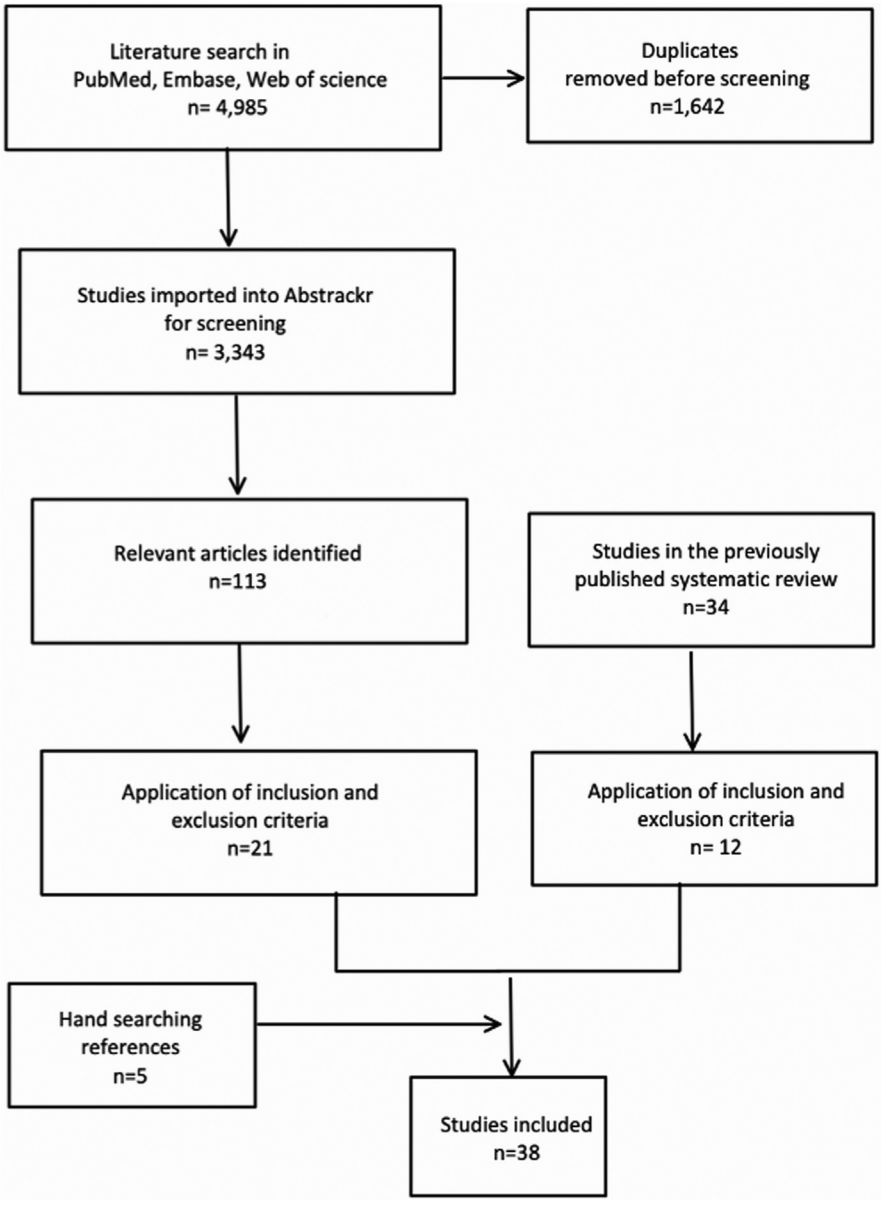
Data synthesis

Most of the studies included in the systematic review (34 of 38) reported hazard ratios (HRs) for the associations. Of note, 1 study reported an odds ratio, 1 study reported a mean difference, and 2 studies reported standardized incidence ratios. Reported adjusted HRs were combined to obtain fixed effect estimates using the standard inverse-variance weighted meta-analysis[17] technique. The meta-analyses were performed using the overall and age-specific estimates reported by the studies. We attempted to perform the meta-analysis for the associations between the outcomes and hysterectomy with BSO performed before or after the age of 50 years. The age strata included in the <50 years analyses were "<50" years when available; if not, we used "<45," "<48," "<43," "35–45," and "<40" years. For some of the outcomes, all the included studies reported <45-year estimates; for these outcomes, we reported that any association is for women who had a

hysterectomy with BSO before the age of 45 years. The age strata included in the >50 years analyses were ">50" years when available; if not, we used ">55," ">48" "50–59," or "55–65" years. The age at surgery strata of "<35" or ">65" years were not included for being restricted to extremes of age. In addition, the age stratum of "45–55" years was not included as it overlaps with ages in the 2 prespecified analysis groups. The exact age cutoff points used by each study are shown in all meta-analysis plots (Appendix S4, Figures 1-16).

As hysterectomy alone is associated with premature ovarian failure[3,4] and the anticipated outcomes are possibly linked to the cessation of estrogen release, it is possible that the associations would be weaker when hysterectomy with BSO was compared with hysterectomy alone than compared with no surgery. In contrast, when hysterectomy with BSO is compared with no surgery, there is a possibility that any associations are confounded by the indication for hysterectomy. Therefore, we performed subgroup analyses and divided the studies based on the reference category used for comparison (hysterectomy or no surgery). We assessed between study heterogeneity in effect estimates using the I^2 statistic and chi-square test.[12] When evidence of substantial heterogeneity (I^2 of >50%)[17] was found, we repeated the meta-analysis after the exclusion of the outlier studies. This was applied to the age-stratified meta-analyses and the unstratified meta-analyses (in the absence of age-stratified meta-analysis for the same outcome). All the analyses were performed using R (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria).[18]

FIGURE
Search process



A diagram showing the summary of the search review process.

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Results

Study selection

The search strategy identified 4985 references. After removing 1642 duplicates, we identified 113 potentially relevant studies. Among these studies, 21 met the eligibility criteria.

Evans et al's[7] systematic review included 34 studies, of which 12 met the eligibility criteria for our review and an additional 5 articles were identified from hand searching the references (Figure). Overall, 38 studies were included that consisted of 12 prospective cohort studies, 24 retrospective cohort studies, 1 case-control study, and 1 case-cohort study.

Study characteristics

The sample sizes ranged from 2900 to more than 5 million. Most studies presented analyses stratified by the age at surgery and the use of hormone replacement therapy (HRT). Outcomes studied were CVDs, hypertension, diabetes mellitus, hyperlipidemia, cancer, dementia, depression, parkinsonism, carpal tunnel syndrome, restless leg syndrome, changes in fat and lean body mass, bone fracture, all-cause mortality, and cause-specific mortalities (description of the included studies is shown in Table 1). The methods of selection of the study

TABLE 1
Description of the included studies

Study	Year	Outcome	Population	Size[a]	Design	Follow-up (y)		
						Measure	Exposed[b]	Unexposed[c]
Huo et al[25]	2022	Cancer	American	3172	Retrospective cohort	Median (IQR)	18 (13.6–22.5)	17.8 (13.5–22.6)
Starlinger et al[41]	2022	Carpal tunnel syndrome	American	2479	Retrospective cohort	Median (IQR)[d]	7.1 (3.8–13.9)	7.0 (3.0–12.4)
Poorthuis et al[31]	2022	Stroke and heart disease	Chinese	272,884	Prospective cohort	Mean	9.8	
Cusimano et al[21]	2022	Ovarian cancer	Canadian	195,282	Retrospective cohort	Median (IQR)	17 (13–21)	16 (12–20)
Cusimano et al[55]	2021	All-cause mortality, cause-specific mortality	Canadian	200,549	Retrospective cohort	Median (IQR)	12 (7–17)	
Huo et al[42]	2021	Restless legs syndrome	American	3306	Retrospective cohort	Median (IQR)	14.5 (10.3–19.1)	14.4 (10.4–19.3)
Wilson et al[26]	2021	Breast, colorectal, thyroid and kidney cancer	Australian	745,713	Retrospective cohort	Max	27	
Karia et al[56]	2021	Fat and lean body mass	American	4209	Retrospective cohort	Median (IQR)	6 (2–10)[e] 16 (7–23)[f]	
Madika et al[37]	2021	Hypertension	French	44,189	Prospective cohort	Median	16.4	
Luo et al[57]	2021	Renal cell carcinoma	American	144,599	Prospective cohort	Mean	15.9	
Tuesley et al[58]	2020	All-cause mortality, cause-specific mortality	Australian	666,588	Retrospective cohort	Median	24.2	
Chow et al[24]	2020	Breast cancer	American	49,215	Retrospective cohort	Median (IQR)	1.80 (1.10–3.40)	1.80 (0.87–3.10)
Gottschau et al[22]	2020	Breast cancer	Danish	119,340	Retrospective cohort	Median (range)	13.3 (>0.0–39.0)	15.2 (>0.0–39.0)
Chiang et al[34]	2020	Diabetes mellitus	Taiwanese	26,281	Retrospective cohort	Median	7.1	
Ding et al[36]	2018	Hypertension	Taiwanese	26,338	Retrospective cohort	Median	6.7	
Guenego et al[28]	2018	Thyroid cancer	French	81,717	Prospective cohort	Median	Cases: 9.9 Noncases: 21.4	
Li et al[32]	2018	Hyperlipidemia	Taiwanese	28,587	Retrospective cohort	Mean (SD)	7.06 (4.05)	5.96 (2.84)
Luo et al[33]	2017	Diabetes mellitus	American	56,296	Prospective cohort	Mean	13.4	
Mytton et al[2]	2017	All-cause mortality, IHD-mortality,IHD, cancer, suicide	English	113,679	Retrospective cohort	Mean (SD)	6.20 (2.84)	
Rocca et al[29]	2016	Multimorbidity	American	3306	Retrospective cohort	Median (IQR)	14.5 (10.3–19.1)	
Altman et al[27]	2016	Cancer	Swedish	5,401,203	Retrospective cohort	Mean (SD)	9.61 (7.20)	22.50 (12.30)

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TABLE 1
Description of the included studies *(continued)*

Study	Year	Outcome	Population	Size[a]	Design	Follow-up (y)		
						Measure	Exposed[b]	Unexposed[c]
Harrington et al[59]	2016	DVT	American	1979	Case-control		NA	NA
Falconer et al[6]	2015	Ovarian cancer	Swedish	5,486,467	Retrospective cohort	Mean (SD)	8.00 (6.60)	23.10 (12.40)
Chan et al[5]	2014	Ovarian or peritoneal cancer	American	52,716	Prospective cohort	Median (range)	5.90 (0.25–19.00)	4.50 (0.25–19.00)
Gaudet et al[19]	2014	Cancer	American	51,052	Prospective cohort	Median (range)	13.9 (0.01–16.72)	
Appiah et al[35]	2014	Diabetes mellitus	American	2046	Prospective cohort	Mean (SD)	8.70 (1.90)	
Parker et al[52]	2013	Cause specific, all-cause mortality	American	30,117	Prospective cohort	Max	28	
Jacoby et al[23]	2011	Cancer, hip fracture, cardiovascular	American	25,448	Prospective cohort	Mean (SD)	7.60 (1.60)	
Ingelsson et al[60]	2010	Cardiovascular diseases	Swedish	367,710	Retrospective cohort	Median (IQR)	10.4 (5.0–17.1)	
Parker et al[20]	2009	Cancer, hip fracture, cardiovascular	American	29,380	Prospective cohort	Max	24	
Rivera et al[61]	2009	Cardiovascular mortality	American	3474	Retrospective cohort	Median (range)	25.00 (0.01–53.80)	26.40 (0.18–55.10)
Rocca et al[40]	2008	Parkinsonism	American	2912	Retrospective cohort	Median (range)	28.70 (0.15–55.70)	
Rocca et al[38]	2008	Depression, anxiety	American	2194	Retrospective cohort	Median (range)	23.70 (0.48–53.30)	
Rocca et al[39]	2007	Cognitive impairment or dementia	American	3487	Retrospective cohort	Median (range)	25.1 (0.01-53.8)	26.5 (0.45-53.6)
Rocca et al[62]	2006	All-cause mortality	American	2937	Retrospective cohort	Median (range)	25.00 (0.01–53.80)	26.40 (0.20–55.10)
Howard et al[30]	2005	Cardiovascular	American	70,660	Prospective cohort	Mean	5.1	
Falkeborn et al[63]	2000	Myocardial infarction	Swedish	17,126 [g]	Case-cohort	Mean	8.9	
Melton et al[43]	1996	Fracture	American	436	Retrospective cohort	Median	15.1	

BSO, bilateral salpingo-oophorectomy; *DVT*, deep vein thrombosis; *DXA*, dual-energy x-ray absorptiometry; *IHD*, ischaemic heart disease; *IQR*, interquartile range; *NA*, not available; *SD*, standard deviation.

[a] Number of women who had a hysterectomy and BSO and referent cohort in cohort studies and number of cases and controls in case-control and cross-sectional studies; [b] Exposed refers to women who had a hysterectomy with BSO; [c] Unexposed refers to the reference group that is either hysterectomy alone or no surgery; [d] Time from study entry to the development of outcome; [e] Median time since surgery in women who had their outcome assessment (DXA scan) below the age of 45 years; [f] Median time since surgery in women who had their outcome assessment (DXA scan) above the age of 45 years; [g] Number of people who had a hysterectomy or oophorectomy. Comparisons are made to the general population.

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participants and ascertainment of the surgeries and outcomes in each study are summarized in Table S2.

The results of the reported associations for each study are shown in Table S3. The results of the meta-analyses examining associations between hysterectomy with BSO and the long-term outcomes are shown in Table 2.

TABLE 2
Meta-analysis results for the associations between hysterectomy and bilateral salpingo-oophorectomy and the long-term outcomes

Outcome	Reference	Age[a]	n[b]	HR	95% CI	I^2[c]; *P* value[d]
Breast cancer	Hysterectomy or no surgery	Unstratified	8	0.90	0.87–0.94	74%; <.01
		<45	7	0.78	0.73–0.84	49%;.07
		>50	5	1.05	0.96–1.15	0%;.99
	Hysterectomy	Unstratified	6	0.90	0.86–0.94	81%; <.01
		<45	5	0.75	0.69–0.82	56%;.06
		>50	4	1.05	0.94–1.17	0%;.95
	No surgery	Unstratified	2	0.92	0.85–0.99	0%;.76
		<45	2	0.86	0.75–0.98	0%; 1.00
		>50	1	1.04	0.88–1.23	NA
Colorectal cancer	Hysterectomy or no surgery	Unstratified	6	1.09	1.00–1.18	78%; <.01
		<45	5	1.27	1.10–1.47	72%; <.01
		>50	4	1.25	1.04–1.51	0%;.98
	Hysterectomy	Unstratified	4	1.30	1.14–1.48	70%;.02
		<45	4	1.52	1.26–1.83	46%;.14
		>50	3	1.27	0.92–1.76	0%;.92
	No surgery	Unstratified	2	0.97	0.87–1.07	0%;.92
		<45	1	0.97	0.77–1.22	NA
		>55	1	1.24	0.99–1.56	NA
Thyroid cancer	No surgery	Unstratified	3	1.56	1.30–1.87	86%; <.01
Kidney cancer	Hysterectomy or no surgery	Unstratified	3	1.23	1.01–1.48	35%;.21
	Hysterectomy		1	0.75	0.42–1.34	NA
	No surgery		2	1.30	1.06–1.59	0%;.94
Ovarian cancer	Hysterectomy or no surgery	Unstratified	5	0.11	0.09–0.15	77%; <.01
	Hysterectomy		3	0.14	0.09–0.20	85%; <.01
	No surgery		2	0.09	0.06–0.14	57%;.13
All cancer risk	Hysterectomy or no surgery	Unstratified	5	0.94	0.90–0.98	47%;.11
		<50	6	0.88	0.83–0.94	49%;.08
		>50	4	0.93	0.90–0.97	0%;.39
	Hysterectomy	Unstratified	3	0.93	0.89–0.97	6%;.35
		<50	3	0.86	0.80–0.93	0%;.53
		>50	3	1.02	0.91–1.14	0%;.89
	No surgery	Unstratified	2	1.00	0.86–1.15	79%;.03
		<50	3	0.95	0.83–1.08	72%;.03
		>50	1	0.92	0.88–0.96	NA
CVD	Hysterectomy or no surgery	Unstratified	3	1.13	1.08–1.18	81%; <.01
		<50	3	1.18	1.11–1.25	67%;.05
		>50	3	1.04	0.96–1.12	45%;.16

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TABLE 2
Meta-analysis results for the associations between hysterectomy and bilateral salpingo-oophorectomy and the long-term outcomes *(continued)*

Outcome	Reference	Age[a]	n[b]	HR	95% CI	I^2[c]; *P* value[d]
	Hysterectomy	Unstratified	1	0.99	0.90–1.09	NA
		<50	1	0.98	0.84–1.15	NA
		>50	1	1.03	0.86–1.23	NA
	No surgery	Unstratified	2	1.17	1.11–1.23	17%;.27
		<50	2	1.22	1.14–1.30	0.0%;.73
		>50	2	1.04	0.95–1.14	72%;.06
CVD mortality	Hysterectomy or no surgery	Unstratified	3	1.12	1.01–1.24	17%;.30
		<50	3	1.24	1.08–1.43	0.0%;.95
		>50	3	0.85	0.71–1.03	0.0%;.91
	Hysterectomy	Unstratified	1	1.19	1.02–1.39	NA
		<50	1	1.24	1.03–1.50	NA
		>50	1	0.82	0.54–1.24	NA
	No surgery	Unstratified	2	1.08	0.94–1.23	32%;.23
		<50	2	1.25	1.01–1.54	0.0%;.75
		>50	2	0.86	0.70–1.06	0.0%;.71
CHD	Hysterectomy or no surgery	Unstratified	5	1.16	1.10–1.23	0.0%;.40
		<50	5	1.17	1.10–1.25	0.0%;.67
		>50	3	1.21	1.05–1.39	0.0%;.67
	Hysterectomy	Unstratified	3	1.14	1.07–1.23	35%;.21
		<50	3	1.18	1.09–1.28	0.0%;.43
		>50	2	1.08	0.81–1.44	0.0%;.47
	No surgery	Unstratified	2	1.19	1.00–1.30	0.0%;.52
		<50	2	1.17	1.06–1.29	0.0%;.42
		>50	1	1.25	1.07–1.46	NA
Stroke	Hysterectomy or no surgery	Unstratified	4	1.15	1.08–1.24	5.0%;.37
		<50	4	1.20	1.10–1.31	0.0%;.61
		>50	3	1.08	0.93–1.25	0.0%;.43
	Hysterectomy	Unstratified	2	1.10	0.98–1.23	0.0%;.44
		<50	2	1.17	0.97–1.41	0.0%;.80
		>50	2	1.11	0.82–1.51	38%;.20
	No surgery	Unstratified	2	1.19	1.09–1.29	27%;.24
		<50	2	1.21	1.10–1.33	39%;.20
		>50	1	1.07	0.91–1.26	NA
Hypertension	No surgery	Unstratified	3	1.13	1.06–1.20	6.0%;.35
Hyperlipidemia	No surgery	Unstratified	2	1.40	1.29–1.53	32%;.23
		<45	2	1.44	1.25–1.65	0.0%;.34
		>45	2	1.29	1.14–1.45	0.0%;.52
Diabetes mellitus	No surgery	Unstratified	4	1.16	1.09–1.24	0.0%;.46

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TABLE 2
Meta-analysis results for the associations between hysterectomy and bilateral salpingo-oophorectomy and the long-term outcomes *(continued)*

Outcome	Reference	Age[a]	n[b]	HR	95% CI	I^2[c]; *P* value[d]
Dementia	No surgery	Unstratified	2	1.36	0.99−1.85	0.0%;.39
		<45	2	1.70	1.07−2.69	0.0%;.89
Depression	No surgery	Unstratified	2	1.39	1.22−1.60	0.0%;.40
		<45	2	1.39	1.17−1.64	8.0%;.30
Anxiety	No surgery	Unstratified	2	1.31	1.13−1.52	77%;.04
		<45	2	1.14	0.94−1.38	62%;.10
Hip fracture	Hysterectomy	Unstratified	2	0.87	0.72−1.03	0.0%;.71
		<45	2	0.79	0.58−1.08	0.0%;.80
		>50	2	0.76	0.49−1.18	0.0%;.69
All-cause mortality	Hysterectomy or no surgery	Unstratified	5	1.10	1.06−1.15	89%; <.01
		<50	6	1.22	1.16−1.28	85%; <.01
		>50	5	0.98	0.91−1.05	4.0%;.39
	Hysterectomy	Unstratified	4	1.11	1.06−1.15	92%; <.01
		<50	4	1.22	1.16−1.29	90%; <.01
		>50	3	1.02	0.93−1.11	0.0%;.45
	No surgery	Unstratified	1	1.07	0.90−1.27	NA
		<50	2	1.19	1.07−1.33	68%;.08
		>50	2	0.92	0.82−1.03	0.0%;.40

CHD, coronary heart disease; *CI*, confidence interval; *CVD*, cardiovascular disease; *HR*, hazard ratio; *NA*, not applicable.

[a] Age at surgery; [b] Number of studies included in the meta-analysis; [c] The I^2 statistic is the proportion of total statistical heterogeneity caused by true variation between studies rather than chance; [d] The *P* value for the chi-square test to evaluate the null hypothesis that all studies are homogenous.

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Grading of Recommendations Assessment, Development, and Evaluations assessment

The GRADE assessments for the evidence of association with each outcome are shown in Table 3. Evidence for the association between hysterectomy with BSO and breast cancer (before or after the age of 50 years) had a high GRADE rating. The evidence for the association with all-cause mortality (<50 and >50 years), coronary heart disease (CHD; <50 years), and all-cancers risk (<50 years) was of moderate GRADE rating. The evidence for the rest of the outcomes was of low and very low GRADE.

Synthesis of results

Cancer outcomes

Hysterectomy with BSO was associated with a substantial reduction in ovarian cancer risk and ovarian cancer−related mortality[5,6,19−21] (HR, 0.11; 95% confidence interval [CI], 0.09−0.15; I^2=77%). This analysis excluded the study conducted by Mytton et al,[2] which reported a more than 4-fold increase in the hazard of ovarian cancer in women who had a hysterectomy with BSO. However, the authors included ovarian cancer cases occurring within the first year after the surgery, and the excess cancer cases were diagnosed within a few weeks after the removal of the ovaries. We conducted a second meta-analysis after excluding 2 outlier studies, which reduced the heterogeneity between the studies (I^2=42%; *P*=.18) and maintained the strong protective association (HR, 0.16; 95% CI, 0.12−0.23).

The association between hysterectomy with BSO and breast cancer was reported in 8 studies.[2,19,20,22−26] Compared with hysterectomy or no surgery, hysterectomy with BSO before the age of 45 years was associated with a reduction in breast cancer risk (fixed effect HR, 0.78; 95% CI, 0.73−0.84), with moderate heterogeneity between the studies (I^2=49%; *P*=.07). There was no association for women who had the procedure after the age of 50 years (HR, 1.05; 95% CI, 0.96−1.15; I^2=0%). Of note, 3 studies stratified the analysis by the use of HRT in different age groups[22,23,25] but yielded conflicting results (Table S2). None of the studies examined the association with estrogen receptor subtypes of breast cancer.

Of note, 6 studies[2,19,20,23,26,27] examined the association with colorectal cancer. Compared with hysterectomy or no surgery, hysterectomy with BSO was associated with an increased risk of colorectal cancer in women who had the surgery before the age of 45 years and after the age of 50 years, with HRs of 1.27 (95% CI, 1.10−1.47) and 1.25 (95% CI, 1.04−1.51), respectively. There was

TABLE 3
Assessment of GRADE

Outcome	Age (y)[a]	GRADE
Breast cancer	<45	High
	>50	High
Thyroid cancer	Unstratified	Very low
Kidney cancer	Unstratified	Low
Colon cancer	<45	Very low
	>50	Low
All cancer	<50	Moderate
	>50	Low
Cardiovascular diseases	<50	Very low
	>50	Very low
Coronary heart disease	<50	Moderate
	>50	Low
Stroke	<50	Low
	>50	Low
Diabetes mellitus	Unstratified	Low
Hypertension	Unstratified	Low
Hyperlipemia	<50	Low
	>50	Low
Dementia	Unstratified	Very low
Depression	Unstratified	Very low
Anxiety	Unstratified	Very low
Hip fracture	<50	Low
	>50	Low
All-cause mortality	<50	Moderate
	>50	Moderate

Very low: the true effect is probably markedly different from the estimated effect.

Low: the true effect might be markedly different from the estimated effect.

Moderate: the authors believe that the true effect is probably close to the estimated effect.

High: the authors have a lot of confidence that the true effect is like the estimated effect.

GRADE, Grading of Recommendations, Assessment, Development, and Evaluations.

[a] Age at surgery.

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evidence of substantial heterogeneity in the analysis of younger women (I^2=72%; P<.01), and the association was mainly driven by Mytton et al.[2] A second meta-analysis was conducted after excluding Mytton et al,[2] which yielded a weaker association with an HR of 1.11 (95% CI, 0.94−1.31) and showed no evidence of heterogeneity. In addition, hysterectomy with BSO before the age of 50 years was associated with an increased risk of colorectal cancer mortality (HR, 1.78; 95% CI, 1.24−2.55; I^2=0%).

Of note, 3 studies examined the association between hysterectomy with BSO vs no surgery and thyroid cancer.[26−28] The fixed effect HR was 1.56 (95% CI, 1.30−1.87), but there was substantial heterogeneity among the studies (I^2=86%; P<.01). The meta-analysis was repeated after excluding the outlier study,[28] and the association was attenuated (HR, 1.17; 95% CI, 0.92−1.48) with no evidence of heterogeneity.

Moreover, 3 of the studies examined the association between kidney cancer and hysterectomy or no surgery. Hysterectomy with BSO was associated with an increased risk of kidney cancer (HR, 1.23; 95% CI, 1.01−1.48), with moderate heterogeneity between the studies (I^2=35%; P=.21).

In addition, 6 studies[2,19,20,23,26,29] reported the association with the risk of any cancer. The meta-analysis for the association was conducted after excluding the study conducted by Mytton et al.[2] The fixed effect HR for hysterectomy with BSO vs hysterectomy or no surgery before the age of 50 years was 0.88 (95% CI, 0.83−0.94; I^2=49%; P=.08). Moreover, there was a small reduction in the risk of any cancer in women who had the surgery after the age of 50 years (HR, 0.93; 95% CI, 0.90−0.97), with no evidence of heterogeneity.

Cardiovascular diseases

In addition, 6 studies examined the association of hysterectomy with BSO with different CVDs.[2,19,22,28−30] Based on the meta-analysis of 3 studies,[23,30,31] compared with hysterectomy or no surgery, hysterectomy with BSO was associated with the risk of total CVD in women who had the surgery before the age of 50 years (HR, 1.18; 95% CI, 1.11−1.25). We observed a substantial heterogeneity between the studies (I^2=67%; P=.05). The outlier was the only study that used hysterectomy as the reference category. Excluding this study yielded a somewhat stronger association (HR, 1.22; 95% CI, 1.14−1.30), with no evidence of heterogeneity. There was no association between hysterectomy with BSO and CVD in women who had the surgery after the age of 50 (HR, 1.04; 95% CI, 0.96−1.12). Furthermore, hysterectomy with BSO was associated with an increased risk of CVD mortality in women who underwent the surgery before the age of 50 years (fixed-effect HR, 1.24; 95% CI, 1.08−1.43), but not in older women.

Compared with hysterectomy or no surgery, hysterectomy with BSO was associated with an increased risk of CHD

in women who had the surgery before and after the age of 50 years with HRs of 1.21 (95% CI, 1.05−1.39; I^2=0%) and 1.17 (95% CI, 1.10−1.25; I^2=0%), respectively. In addition, hysterectomy with BSO was associated with an increased risk of stroke in women who had the surgery before the age of 50 years (HR, 1.20; 95% CI, 1.10−1.31; I^2=0%), but not in women who had the surgery after the age of 50 years.

Cardiovascular risk factors

Compared with no surgery, hysterectomy with BSO was associated with hyperlipidemia in women who had the surgery before and after the age of 45 years[29,32] with fixed effect HRs of 1.29 (95% CI, 1.14−1.45) and 1.44 (95% CI, 1.25−1.65), respectively, and no evidence of heterogeneity. However, one of the studies[27] showed that compared with no surgery, hysterectomy alone was associated with increased risk of hyperlipidemia in both older and younger women.

Compared with no surgery, hysterectomy with BSO was associated with increased risk of diabetes mellitus in 4 studies[29,33−35] (HR, 1.16; 95% CI, 1.09−1.24; I^2=0%), unstratified by age at surgery. Of note, 1 study[33] repeated the analysis but compared with hysterectomy alone stratified by the age at surgery and the use of HRT. There was no association in women younger or older than the age of 45 years, and the use of HRT did not change the association. In addition, in the analysis by Appiah et al,[35] the comparison between unadjusted survival curves for the development of diabetes mellitus for women with hysterectomy alone and women with hysterectomy with BSO was not statistically significant (*P*=.73).

Finally, the meta-analysis of 3 studies[29,36,37] with unstratified estimates showed that compared with no surgery, hysterectomy with BSO was associated with increased risk of hypertension (HR, 1.13; 95% CI, 1.06−1.20; I^2=6%).

Neuropsychiatric outcomes

The meta-analysis of 2 cohorts from the Mayo Clinic showed increased risk of depression[29,38] and dementia[29,39] in women who had the surgery before the age of 45 years with HRs of 1.70 (95% CI, 1.07−2.69) and 1.39 (95% CI, 1.22−1.60), respectively. In addition, these studies reported increased risk of anxiety,[29,38] with substantial heterogeneity (I^2=77%; *P*=.04). Of note, 1 study showed that compared with no surgery, hysterectomy with BSO in premenopausal women was associated with increased risk of parkinsonism (HR, 2.29; 95% CI, 1.33−3.95).[40] In addition, compared with no surgery, hysterectomy with BSO before the age of 50 years was associated with an increased risk of carpal tunnel syndrome[41] (HR, 1.65; 95%CI, 1.20−2.25) and restless leg syndrome[42] (HR, 1.44; 95% CI, 1.08−1.92).

Musculoskeletal outcomes

In 1 study, compared with no surgery, hysterectomy with BSO before the age of 45 years was associated with an increased risk of osteoporosis (HR, 1.51; 95% CI, 1.06−2.15).[29] In an analysis stratified by HRT use, the association was only significant in the non-HRT users (HR, 3.99; 95% CI, 1.29−12.34), *P*-value .02.[29]

The meta-analysis of 2 studies[20,23] that evaluated the association with hip fracture did not provide evidence of association for any of the age groups. Melton et al's[43] estimated standardized incidence ratios (SIR) for the association between hysterectomy with BSO and hip, forearm, and vertebral fractures. There was no increase in the risk of hip fractures or distal forearm fractures, but there was an increase in the risk of vertebral fractures (SIR, 1.90; 95% CI, 1.30−2.80).

All-cause mortality

Compared with hysterectomy or no surgery, hysterectomy with BSO was associated with an increased risk of all-cause mortality in women who had the surgery before the age of 50 years (HR, 1.22; 95% CI, 1.16−1.28), but there was substantial heterogeneity between the studies (I^2=85%; *P*<.01). Heterogeneity remained significant in subgroup analyses by reference category with I^2 estimates of 90% for the hysterectomy reference category and 68% for the no surgery reference category. We performed another meta-analysis after the exclusion of Mytton et al,[2] which reported the strongest positive association, and Jacoby et al,[23] which reported a protective association. This meta-analysis yielded an HR of 1.19 (95% CI, 1.12−1.25), with lower heterogeneity between the studies (I^2=59%; *P*=.06). In contrast, there was no association with all-cause mortality in women who had the surgery after the age of 50 years (HR, 0.98; 95% CI, 0.91−1.05; I^2=4%).

Comment

Principal findings

Compared with hysterectomy alone or no surgery, hysterectomy with BSO was associated with substantial reductions in ovarian cancer risk in all age groups and breast cancer risk in young women.[2,5,6,14−16] In contrast, hysterectomy with BSO was associated with increased risks of colorectal cancer, renal cancer, and potentially thyroid cancer. Overall, hysterectomy with BSO was associated with a reduction in the combined risk of all cancers in women below the age of 50 years and to a lesser extent in older women. Furthermore, hysterectomy with BSO was associated with an increased risk of total CVD, CHD, and stroke in women younger than 50 years. In addition, compared with no surgery, hysterectomy with BSO was associated with an increased risk of hyperlipidemia, diabetes mellitus, and hypertension, regardless of the age at surgery, and associated with dementia and depression in women younger than 45 years. There was an increase in the risk of all-cause mortality in young women, but there was substantial heterogeneity between the study estimates.

Age at surgery is an effect modifier for the associations between hysterectomy with BSO and the long-term outcomes, especially for the association with breast cancer and CVD.

Evidence was conflicting regarding the efficacy of HRT in modifying the reported associations. It is possibly caused by the reduced power of the studies after stratification by age at surgery and HRT as the studies that stratified by the "use of HRT" had smaller sample sizes.

The difference in HRT formulations, doses, and durations of use between included studies are also likely to limit power.

Strengths and limitations

This systematic review added 26 studies with more than 7 million women to the previously published one.[7] In addition, we performed meta-analyses for the associations with the long-term outcomes, which allowed us to observe more associations because of combining smaller studies. Unlike Evans et al's[7] systematic review, our analysis showed that hysterectomy with BSO in young women is associated with decreased risk of breast cancer and total cancer and an increased risk of colorectal cancer. Moreover, we noticed an increased risk of colorectal cancer in older women. In addition, we examined the association with other outcomes, including hyperlipidemia, diabetes mellitus, hypertension, thyroid cancer, and renal cancer.

We excluded studies, including women who had a hysterectomy with BSO, to treat cancer to minimize confounding by the indication for surgery. The meta-analyses were based on adjusted HRs, aimed at minimizing the effect of confounders. The meta-analyses were stratified by the age at surgery. Most of the age-stratified meta-analyses did not show evidence of significant heterogeneity between the studies.

One of the limitations is that there was a small number of studies for each outcome of interest and many meta-analyses were based only on 2 or 3 studies, which did not allow the assessment of the effect of publication bias.

Quality of the evidence, confounding, and bias

The high-quality evidence suggests a clear reduced risk of breast cancer for women who had the BSO before the age of 45 years and no association with breast cancer for women who had the BSO after the age of 50 years. Moderate quality evidence suggests a reduced risk of all cancers and an increased risk of CHD and all-cause mortality in women who had BSO before the age of 50 years. In addition, moderate GRADE evidence indicates no association with all-cause mortality in women who had BSO after the age of 50 years. For the other outcomes, the quality of evidence was low or very low.

Several factors could confound the reported associations. The most important factors are age, parity, and comorbidities. All studies were adjusted for age. The adjustment for parity would be more crucial when the comparison is against no surgery as hysterectomy most often takes place after family completion.[44] Not adjusting for parity could confound the associations with breast cancer, neuropsychiatric outcomes, and bone health. Of note, 5[19,20,22,23,26] of 8 studies on the association with breast cancer risk adjusted for parity. However, the included studies reported a similar association with breast cancer, regardless of adjusting for parity. For neuropsychiatric outcomes,[29,38–40] none of the studies adjusted for parity, and in all the studies, the comparison was against no surgery. The association between parity and brain function is controversial. Some studies reported that higher parity is associated with lower brain age,[45] improved memory, and protection against Alzheimer disease,[46,47] whereas others reported the opposite.[48,49] For bone health, it is thought that because of the changes in calcium metabolism during pregnancy parity would be associated with a reduction in bone mineral density. However, repeated evidence showed higher hip bone mineral density[50] and lower risk of hip fracture in parous women.[51] Thus, it is unlikely that the reported associations with osteoporosis[29] and vertebral fracture[43] are confounded by parity. Women who had a hysterectomy with BSO tended to have a higher prevalence of comorbidities, for example, diabetes mellitus and hypertension at baseline, than women who had no surgery[29] or hysterectomy alone.[2] It is possible that not adjusting for comorbidities confounded some of the associations, in particular, the strongest associations with mortality,[2] colorectal cancer,[2] and dementia,[39] which were not adjusted for comorbidities or other lifestyle factors.

Detection bias, misclassification bias, and informative censoring might have influenced some of the results. Detection bias could occur as women with a previous history of surgery (hysterectomy with or without BSO) might seek more medical attention than women with no surgery. Thus, it is likely that detection bias affected the results more when comparison was made against no surgery, for example, in studying the associations with cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidemia)[29,32,34,36] or neuropsychiatric outcomes,[29,38,39] in which the evidence was available only compared with no surgery. Misclassification of the surgery type could have happened when surgery was self-reported, for example, in the Nurses' Health Study,[19,52] the Women's Health Initiative,[23,30,33] and the Cancer Prevention Study II.[19] Although most likely it was a nondifferential misclassification, it could have reduced the power of these studies to detect associations with cardiovascular outcomes, hip fracture, cancer, and all-cause mortality. Finally, survival analysis applied in most of the studies assumes noninformative censoring. Nevertheless, it is possible that censoring because of death was informative.

Comparison against hysterectomy alone or no surgery

There is evidence suggesting that hysterectomy on its own is associated with premature ovarian failure.[3,4] In a cohort study, Moorman et al[3] compared the incidence of ovarian failure between women with hysterectomy alone and women with intact uteri. Ovarian failure was defined by follicle-stimulating hormone (FSH) levels of $\geq$40 IU/L. Hysterectomy alone was associated with almost 2 times the risk of ovarian failure (HR, 1.92; 95% CI, 1.29–2.96).[3] Another prospective cohort study showed that women with hysterectomy alone reach menopause (defined by FSH level) 4 years earlier than women with no hysterectomy.[4] Therefore, it is expected that the studied associations would be stronger when the comparison is against no surgery. For example, studies on the association with diabetes mellitus reported a increased risk of diabetes mellitus when hysterectomy with BSO was compared with no surgery, but not when compared with hysterectomy alone.[32,34] Finally, for the association with bone health, compared with no surgery,

hysterectomy with BSO was associated with increased risk of osteoporosis. Conversely, there was no association in the meta-analysis for the effect of hysterectomy with BSO vs hysterectomy alone and hip fracture. In addition, when the comparison was made against no surgery, it is possible that some of the associations were confounded by the indication for the hysterectomy. For instance, in the association with thyroid cancer, both hysterectomy with BSO and hysterectomy alone were associated with an increased risk of thyroid cancer. However, even without hysterectomy, uterine fibroids (the most common indication for hysterectomy) was associated with increased risk thyroid cancer.[28] The key clinical question when the ovaries are removed at the time of hysterectomy is the association with the long-term outcomes against hysterectomy alone. These estimates would be more appropriate for counseling women who are having hysterectomy, as these women would be more concerned about the extra risk caused by removing the ovaries as well.

Heterogeneity between the studies

For most of the outcomes, the meta-analysis of the age-unstratified estimates showed evidence of substantial heterogeneity. In contrast, in most of the age-stratified meta-analyses performed, there was no evidence of substantial heterogeneity between the studies. There was substantial heterogeneity between studies in colorectal cancer (age at surgery <45 years), CVD (age at surgery <50 years), and thyroid cancer meta-analyses, and this was addressed by excluding the outlier studies in each analysis. In the colorectal cancer (age at surgery <45 years) meta-analysis, the outlier study, which reported the strongest association, was Mytton et al,[2] which was a retrospective cohort study using routinely collected data. The study did not control for a range of variables that were adjusted for in the other studies, for example, body mass index (BMI), physical activity, or alcohol intake. In the CVD (age at surgery <50 years) meta-analysis, the outlier study was Jacoby et al.[23] Unlike the other 2 studies included in the CVD meta-analysis, Jacoby et al[23] did not find evidence for association. The study had the shortest follow-up time and was the only study comparing the association against hysterectomy. For the thyroid cancer meta-analysis, the strongest association was reported by Guenego et al.[28] The analysis adjusted for multiple covariates that could confound the association, for example, age, smoking status, history of thyroid disease, and BMI. All the studies included in the thyroid cancer meta-analysis had a long follow-up of more than 20 years.

In addition, there was substantial heterogeneity in the anxiety and all-cause mortality (age at surgery <50 years) meta-analyses. Only 2 studies were included in the meta-analysis for the association with anxiety.[29,38] Both studies were on women from the 2 independent Mayo Clinic cohorts. However, the method of ascertainment of the outcome was different. The study that showed the strongest association ascertained the diagnosis of anxiety via telephone interviews and the other retrieved the diagnosis from medical records. Not all patients with anxiety seek medical help; hence, fewer cases could be identified from medical records, and this could have limited the power of the study to detect possible association. For all-cause mortality, we repeated the meta-analysis after the exclusion of the outlier studies, but heterogeneity between the studies remained substantial. The study[2] that reported the strongest positive association did not adjust for lifestyle covariates, such as BMI, physical activity, or alcohol intake, whereas the study that reported a protective association[18] had the shortest follow-up time (5 years).

Recently, there has been an increased interest in bilateral risk-reducing salpingectomy as a method of preventing ovarian cancer. This is based on the hypothesis that most high-grade serous ovarian tumors arise originally from the fallopian tubes.[53,54] However, bilateral salpingectomy provides less protection compared with BSO,[6] as salpingectomy compared with no surgery is associated with an approximate 30% risk reduction in ovarian cancer,[6] whereas salpingo-oophorectomy is associated with more than 80% risk reduction. Salpingectomy alone would not affect estrogen production and thus may mitigate the long-term outcomes associated with premenopausal oophorectomy identified in the current review. However, additional studies are required to assess the long-term outcomes of salpingectomy and the balance of harms and benefits of salpingo-oophorectomy at the time of hysterectomy.

Conclusion and implications

Hysterectomy with BSO at any age reduced the risk of ovarian cancer, and hysterectomy with BSO at a young age was associated with a reduced risk of breast cancer. Nevertheless, this risk reduction should be balanced against the possible increase in the risk of CVD, colorectal cancer, and all-cause mortality in young women. HRT after hysterectomy with BSO is expected to mitigate the adverse effects of premature estrogen deprivation but more evidence on the efficacy of HRT is needed.

Furthermore, more studies with better adjustment for confounders are needed to ascertain the associations with CVD, neuropsychiatric outcomes, osteoporosis, and all-cause mortality. ■

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