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Association between hysterectomy and ovarian carcinoma: a systematic review and meta-analysis

Azadeh Yousefnezhad[1#], Seyedeh Reyhaneh Yousefi Sharami[2#], Elham Saffarieh[3*], Fahimeh Nokhostin[4*]

[1]Department of Obstetrics and Gynecology, Tehran University of Medical Sciences, Tehran, Iran
[2]Cancer and Immunology Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran
[3]Abnormal Uterine Bleeding Research Center, Semnan University of Medical Sciences, Semnan, Iran
[4]Department of Obstetrics and Gynecology, Faculty of Medicine, Shahid Sadughi University of Medical Sciences, Yazd, Iran
[#]Both authors contributed equally.

***Correspondence to**
Fahimeh Nokhostin, Email: fahimeh.nokhostin@yahoo.com; and Elham Saffarieh, Email: eli_saffarieh@yahoo.com

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Abstract

Introduction: Ovarian carcinoma is one of the deadliest of the reproductive system cancers, with research results regarding the relationship between hysterectomy and ovarian carcinoma conflicting. For this reason, this study aimed to evaluate the association between hysterectomy and ovarian carcinoma through a systematic review and meta-analysis.

Materials and Methods: This study searched ProQuest, Embase, PubMed, Web of Science, Cochrane databases, and Google Scholar search engines until September 23, 2024. STATA 14 software was used for data analysis, and tests were significant at P<0.05.

Results: In the 29 studies reviewed, no statistically significant association was observed between hysterectomy and ovarian carcinoma (OR: 1; 95% CI: 0.91, 1.11). However, tubal ligation was found to reduce the risk of ovarian carcinoma (OR: 0.72; 95% CI: 0.67, 0.78). No significant correlation was detected between hysterectomy and serous (OR: 1.02; 95% CI: 0.94, 1.12) or endometrioid (OR: 0.92; 95% CI: 0.63, 1.36) subtypes. Nonetheless, hysterectomy was associated with a decreased risk of mucinous (OR: 0.74; 95% CI: 0.57, 0.98) and clear cell carcinoma (OR: 0.49; 95% CI: 0.32, 0.75). On the other hand, there was no notable link between hysterectomy and ovarian carcinoma recognized in cohort studies (HR: 1.01; 95% CI: 0.79, 1.29) or case-control studies (OR: 1.01; 95% CI: 0.91, 1.12). This finding also applied to women younger than sixty years old (OR: 1; 95%CI: 0.71, 1.40), as well as those older than sixty years of age (OR: 0.83; 95%CI: 0.55, 1.26). In countries like the Netherlands, Italy, Sweden, and Finland, there were fewer cases of ovarian carcinoma among women who have had a hysterectomy. However, in Taiwan, it seemed that undergoing this procedure was associated with an increased risk of developing the disease.

Conclusion: Hysterectomy reduced the risk of mucvinous and clear cell carcinoma and reduced the risk of ovarian carcinoma in the Netherlands, Italy, Sweden and Finland. Tubal ligation also reduced the risk of ovarian cancer.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD4202459588) and Research Registry (UIN: reviewregistry1893) website.

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Introduction

Ovarian carcinoma is rare but one of the deadliest cancers of the reproductive system (1). Approximately 95% of ovarian cancers are epithelial in origin, and they are primarily classified into five main types of serous, endometrioid, clear cell, and mucinous ovarian carcinoma (2). Nearly 70% of cases of epithelial ovarian carcinoma are diagnosed at advanced stages (3,4), making it the deadliest cancer in women. In 2024, an estimated 19 680 new cases of ovarian carcinoma will occur in the United States, and 12 740 people will die from the disease. The five-year survival rate for those diagnosed is 50.9% (1).

Non-modifiable risk factors for ovarian carcinoma include older age (5), genetics (6), family history (7), history of previous cancers (8), and late menopause (9). Infertility (10), hormone replacement therapy (11), smoking (12), and a high-fat diet (13) are modifiable risk factors. In addition, endometriosis increases the risk of ovarian carcinoma (14).

One of the most common major surgeries for women worldwide is hysterectomy (15,16). A common surgical method for benign conditions is hysterectomy with ovarian preservation (17,18). The prevailing hypothesis was that hysterectomy prevents carcinogens from ascending through the reproductive tract and damaging the ovaries (19). Nevertheless, observational studies on this topic have yielded different results. Hysterectomy has been shown to protect

Key point

In the 29 studies reviewed, hysterectomy reduced the risk of mucvinous and clear cell carcinoma and reduced the risk of ovarian cancer in the Netherlands, Italy, Sweden and Finland. Tubal ligation also reduced the risk of ovarian carcinoma.

women from ovarian carcinoma in some studies (20,21) and to increase the risk of ovarian carcinoma in others (22,23). Some even showed no significant link between hysterectomy and ovarian carcinoma (24,25). Additionally, the previous meta-analysis reviewed only case-control studies (26), whereas the current meta-analysis included case-control and cohort studies. For this reason, the present study was carried out to examine the relationship between hysterectomy and ovarian carcinoma using a systematic review and meta-analysis.

Materials and Methods

Protocol study

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) (27) was conducted for the design of this systematic review and meta-analysis, and the study protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) and Research Registry websites.

PICO components

- Population: Association between hysterectomy and ovarian carcinoma.
- Exposure/Intervention: Hysterectomy.
- Comparison: General population.
- Outcomes: The association between hysterectomy and ovarian carcinoma is the primary outcome. Secondary outcomes include the relationship between hysterectomy and serous, endometrioid, mucinous, and clear cell carcinoma and between tubal ligation and ovarian cancer.

Search strategy

The databases searched using the keywords 'Ovarian Neoplasms,' 'Ovary Cancer,' 'Ovarian Cancer,' 'Hysterectomy,' and 'Hysterectomies' and their Medical Subject Headings (MeSH) equivalents were ProQuest, Embase, PubMed, Web of Science, Cochrane, and Google Scholar up to September 23, 2024. No geographic limitations were applied to studies published from 2000 to 2024. For advanced searches, keywords were combined using (AND, OR) operators, and for manual searches, the reference lists of selected studies were reviewed. The search strategy for the Web of Science database is provided as follows:

Ovarian Neoplasms OR Ovary Cancer OR Ovarian Cancer (Title) AND Hysterectomy OR Hysterectomies (Title)

Inclusion criteria

Studies that examined the association between hysterectomy and ovarian carcinoma.

Exclusion criteria

- Duplicate studies
- Case reports
- Studies investigating the effects of hysterectomy combined with other factors (e.g., hormone therapy) on ovarian carcinoma
- Review articles
- Letters to the editor
- Conference proceedings
- Studies of poor quality
- Studies with unavailable full texts
- Studies lacking necessary data for analysis

Qualitative assessment

Two authors used the Newcastle Ottawa Scale (NOS) checklist to assess the studies. Each question could receive a maximum of one star, with the comparison question being allowed two stars. Therefore, the lowest possible score was zero (poorest quality), and the highest score was ten (highest quality) (28).

Data extraction

The following information was extracted from each study: author's name, type of study, mean age, location of study, sample size, study period, association between hysterectomy and ovarian carcinoma, associations with serous, endometrioid, mucinous, and clear cell carcinoma (along with their confidence intervals), study duration, and other relevant data. This work was performed by two authors.

Statistical analysis

Logarithms of hazard ratios (HR) and odds ratios (OR) were conducted, and the studies were combined. Study heterogeneity was assessed using the I^2 index. Due to the high level of heterogeneity, a random-effects model was used. Subgroup analysis was performed to assess the association between hysterectomy and ovarian carcinoma based on age, study type, and location variables. Additional analyses were conducted using meta-regression and publication bias tests. Data analysis was carried out using STATA 14 software, with statistical significance set at $P < 0.05$.

Results

Study selection: A total of 1202 studies were found through database and Google Scholar searches. Of these, 702 were duplicates and were excluded. After screening, 500 studies proceeded to the next stage. Based on the abstracts, 86 studies were excluded for incomplete information or lack of access to full texts. Full texts of 414 studies were reviewed, with 94 studies being excluded due to a lack of essential data for analysis. Of the remaining 320 studies, 291 were excluded based on other exclusion criteria,

leaving 29 studies for the meta-analysis (Figure 1).

In this meta-analysis, 29 observational studies were reviewed, comprising 21 case-control studies and 8 cohort studies. Details of these studies are provided in Table 1.

Overall, there was no statistically significant association between hysterectomy and ovarian carcinoma (OR: 1; 95% CI: 0.91, 1.11) (Figure 2).

Subgroup analysis also showed no statistically significant association between hysterectomy and ovarian cancer in cohort studies (HR: 1.01; 95% CI: 0.79, 1.29) or case-control studies (OR: 1.01; 95% CI: 0.91, 1.12) (Figure 3).

Moreover, there was not any noticeable link between removal of the uterus and ovarian cancer in females less than 60 years old (OR: 1; 95% CI: 0.71, 1.40) or those who are aged more than or equal to 60 (OR: 0.83; 95% CI: 0.55, 1.26) (Figure 4).

Analysis of geography: As shown in Table 2, a lower risk of ovarian cancer was linked with hysterectomy in countries such as the Netherlands, Italy, Sweden, and Finland. However, no concrete statistical link between them could be observed in places like the USA, Australia, Albania, China, Denmark, England, Wales and Northern Ireland. On a different note, Taiwan showed an increased risk of ovarian carcinoma due to hysterectomy.

Tubal ligation: Figure 5 shows that tubal ligation was associated with a reduced risk of ovarian carcinoma (OR: 0.72; 95% CI: 0.67, 0.78).

There was no significant association between hysterectomy and serous (OR: 1.02; 95% CI: 0.94, 1.12) or endometrioid (OR: 0.92; 95% CI: 0.63, 1.36) ovarian carcinoma (Figures 6 and 7). However, hysterectomy significantly reduced the risk of mucinous (OR: 0.74; 95% CI: 0.57, 0.98) and clear cell carcinoma (OR: 0.49; 95% CI: 0.32, 0.75) (Figures 8 and 9).

Meta-regression: Meta-regression analysis indicated no significant association between the "association between hysterectomy and ovarian carcinoma" and the publication year of studies ($P = 0.066$; Figure 10).

Publication bias: No evidence of publication bias was found ($P = 0.719$), and the source search was comprehensive and unbiased (Figure 11).

Discussion

No statistically significant association was found between hysterectomy and ovarian carcinoma, but tubal ligation was associated with a 28% reduction in the risk of ovarian

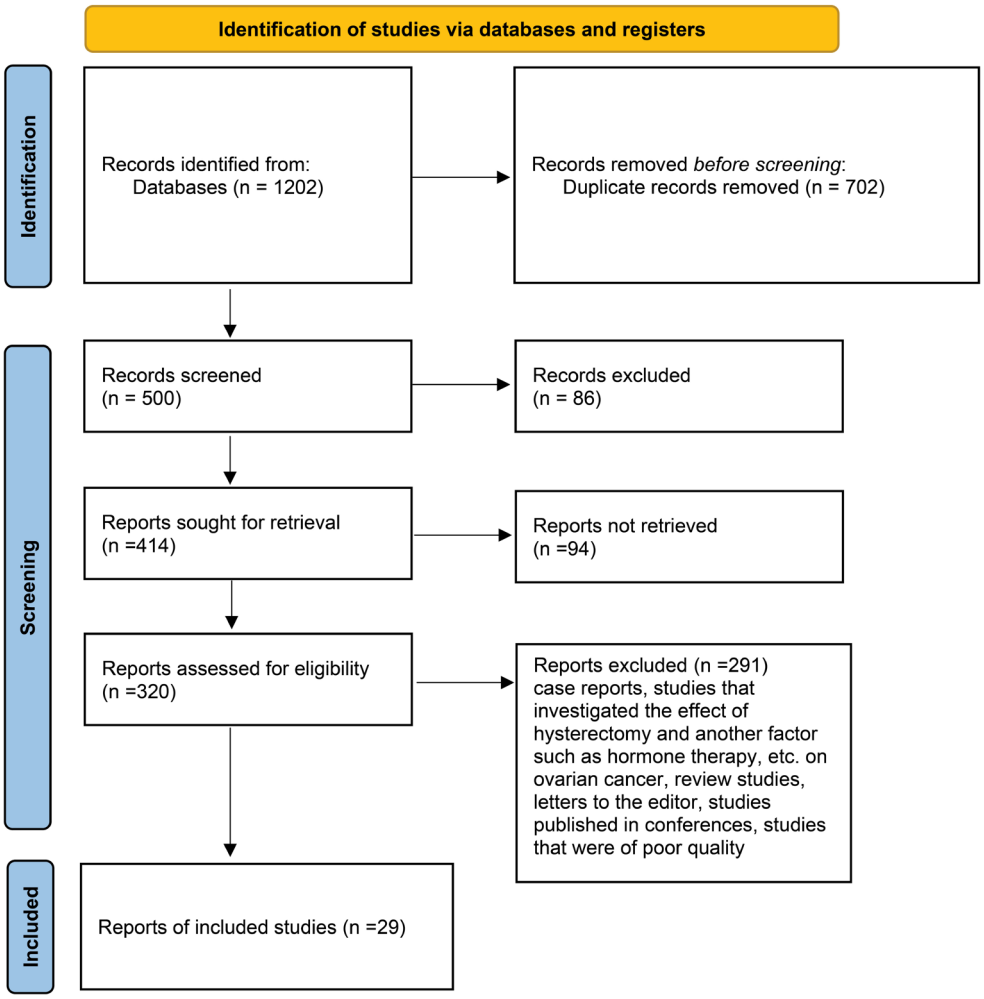

Figure 1. PRISMA flowchart of the study selection.

Table 1. A summary of the information of the reviewed articles

First author, year	Index	Country	Design	Duration of study	Sample size in hysterectomy group	Mean age in hysterectomy group	Sample size in compare group	Mean age in compare group	Association between hysterectomy and ovarian carcinoma		
									OR /HR	Low limit	Up limit
Ring LL, 2023 (25)	OR	Denmark	Case-control	1998–2016	6738	40–79	101070	40–79	0.99	0.91	1.09
Khoja L, 2022 (22)	OR	USA	Case-control	1992-2010	5350	≥50	7544	≥50	1.19	1.09	1.31
Darelius A, 2021, ovarian cancer type 1 (20)	OR	Sweden	Case-control	between 2008 and 2014	1033	60.5	10027	60.3	0.71	0.51	0.98
Darelius A, 2021(20)	OR	Sweden	Case-control	between 2008 and 2014	3007	65.3	29073	65.1	0.77	0.65	0.92
Peres LC, 2018, Non-Hispanic (29)	OR	USA	Case-control	NR	8918	≥18	13619	≥18	1.13	1.05	1.22
Peres LC, 2018, Hispanic (29)	OR	USA	Case-control	NR	433	≥18	533	≥18	1.41	0.94	2.12
Peres LC, 2018, Black (29)	OR	USA	Case-control	NR	911	≥18	1233	≥18	1.64	1.34	2.02
Peres LC, 2018, Asian/Pacific Islander (29)	OR	USA	Case-control	NR	1233	≥18	765	≥18	1.42	0.95	2.12
Peres LC, 2017 (21)	OR	USA	Case-control	Dec 1, 2010, to Dec 31, 2015	614	20-79	743	20-79	0.66	0.47	0.92
Ruiz MP, 201 6(23)	OR	USA	Case-control	between 2003 and 2008	208	62	224	53	3.6	2.1	6.2
Le ND, 2014 (24)	OR	USA	Case-control	between Jan 2001 and Dec 2007	608	20-79	335	20-79	0.83	0.6	1.16
Pajenga E, 2013 (30)	OR	Albania	Case-control	from 1 Jan 2000 through 31 Dec 2005	283	48	1019	48	0.59	0.41	1.39
Merritt MA, 2013, ovarian cancer type 1 (31)	OR	USA	Case-control	from 1992 to 2008	358	54.34	2100	52.3	0.71	0.45	1.13
Merritt MA, 2013, ovarian cancer type 2 (31)	OR	USA	Case-control	from 1992 to 2008	1108	54.34	2100	52.3	1.16	0.89	1.51
Rice MS, 2013 (32)	OR	USA	Case-control	1978-2008	2265	52.3	2333	52.3	1.09	0.83	1.42
Pasalich M, 2013 (33)	OR	China	Case-control	between 2006 and 2008	500	59	500	59.7	0.86	0.46	1.62
Faber MT, 2013 (34)	OR	Denmark	Case-control	Between Jan 1995 and May 1999	554	35–79	1564	35–79	1.55	1.15	2.08
Koskela-Niska V, 2013 (35)	OR	Finland	Case-control	1995–2007	3958	≥50	11325	≥50	0.71	0.61	0.82
Ness RB, 2011 (36)	OR	USA	Case-control	between Feb 2003 and Nov 2008	900	≥25	1800	≥25	1.24	0.99	1.53
Moorman PG, 2009,african americans(37)	OR	USA	Case-control	between 1999 and 2008	143	20-74	189	20-74	1.07	0.61	1.87

Table 1. Continued

First author, year	Index	Country	Design	Duration of study	Sample size in hysterectomy group	Mean age in hysterectomy group	Sample size in compare group	Mean age in compare group	Association between hysterectomy and ovarian carcinoma		
									OR /HR	Low limit	Up limit
Moorman PG, 2009, Whites (37)	OR	USA	Case-control	between 1999 and 2008	943	20-74	868	20-74	1.22	0.97	1.54
Chiaffarino F, 2005 (38)	OR	Italy	Case-control	between Jan 1992 and September 1999	1031	56	2411	56	0.6	0.4	0.9
Modugno F, 2004 (14)	OR	USA	Case-control	from 1993 through 2001	2098	20-69	2953	20-69	0.99	0.83	1.18
Mills PK, 2004 (39)	OR	USA	Case-control	Jan 2000 to Dec 2001	256	56.6	1122	55	1.14	0.8	1.64
Riman T, 2002 (40)	OR	Sweden	Case-control	Between 1993 and 1995	655	62.4	3899	63.4	0.71	0.47	1.06
Modugno F, 2001 (41)	OR	USA	Case-control	from 1994 to 1998	767	51.36	1367	49.45	0.73	0.55	1.02
Beard CM, 2000 (42)	OR	USA	Case-control	1975–1991	129	60	103	60	0.5	0.2	0.96
Tekle H, 2024 (43)	HR	USA	Cohort	2003-2009	NR	NR	NR	NR	1.29	0.95	1.74
Taylor JA, 2022 (44)	HR	England, Wales and Northern Ireland	Cohort	between 2001 and 2005	NR	NR	NR	NR	0.98	0.85	1.14
Dixon-Suen SC, 2019 (45)	HR	Australia	Cohort	1970-2015	NR	NR	NR	NR	0.98	0.85	1.11
Harnod T, 2019 (46)	HR	Taiwan	Cohort	2000 to 2013	181151	45	953744	45	3.88	2.55	5.89
Falconer H, 2015 (47)	HR	Sweden	Cohort	between 1973 and 2009	NR	NR	NR	NR	0.79	0.7	0.88
Rice MS, 2014 (48)	HR	USA	Cohort	1976-1989	NR	NR	NR	NR	0.8	0.66	0.97
Stewart LM, 2013 (49)	HR	Australia	Cohort	1982–2002	NR	NR	NR	NR	0.55	0.13	2.32
Braem MG, 2010 (50)	HR	Netherlands	Cohort	1986–2002	375	62	NR	NR	0.49	0.34	0.72

NR: Not reported; HR: Hazard ratio; OR: Odds ratio.

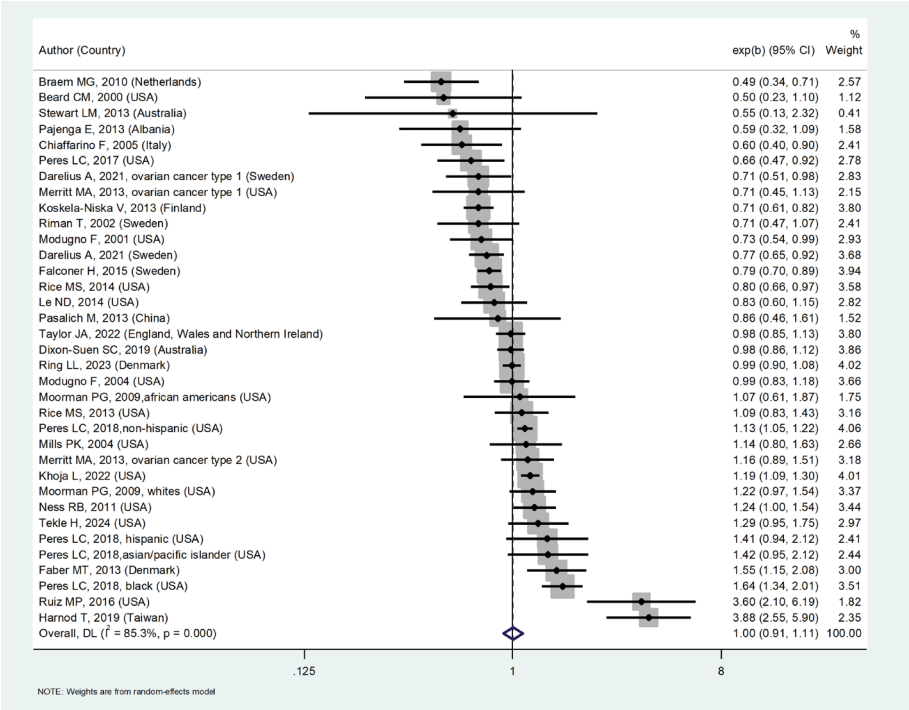

Figure 2. Forest plot showing the association between hysterectomy and ovarian carcinoma

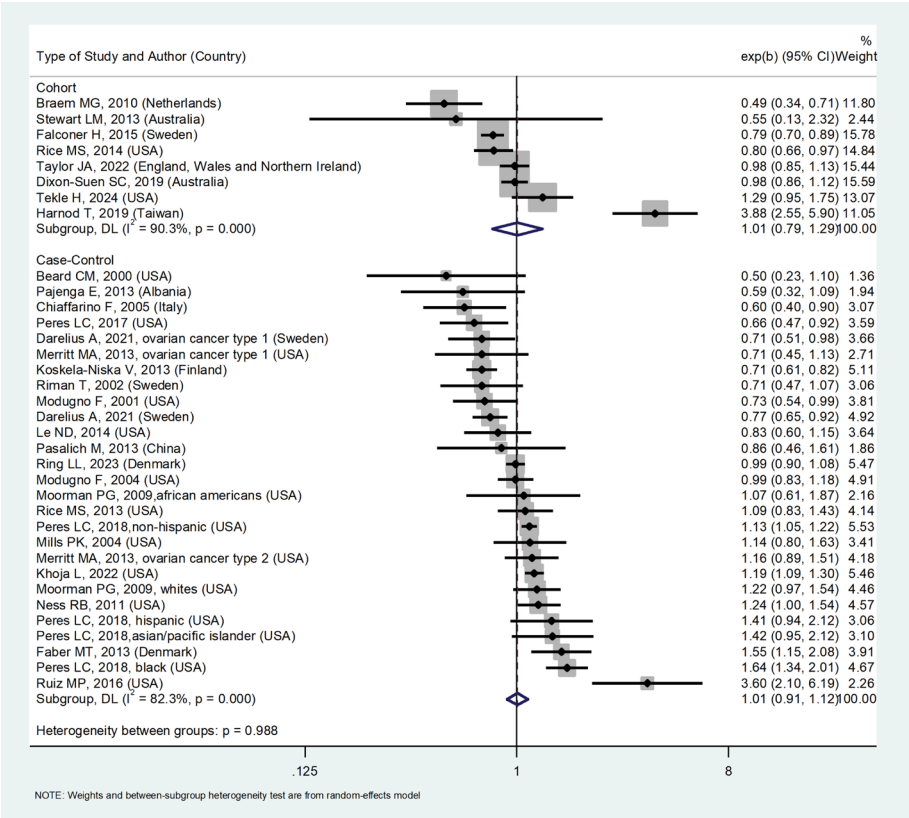

Figure 3. Forest plot showing the association between hysterectomy and ovarian carcinoma by design.

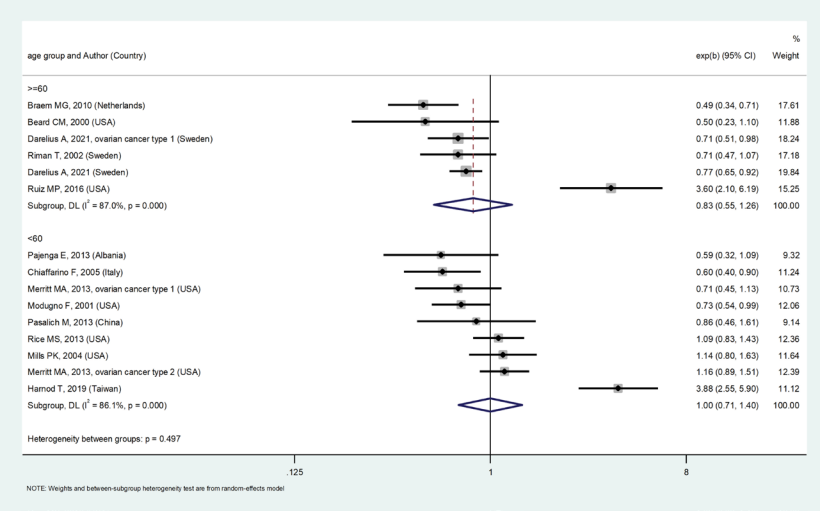

Figure 4. Forest plot showing the association between hysterectomy and ovarian carcinoma by mean age.

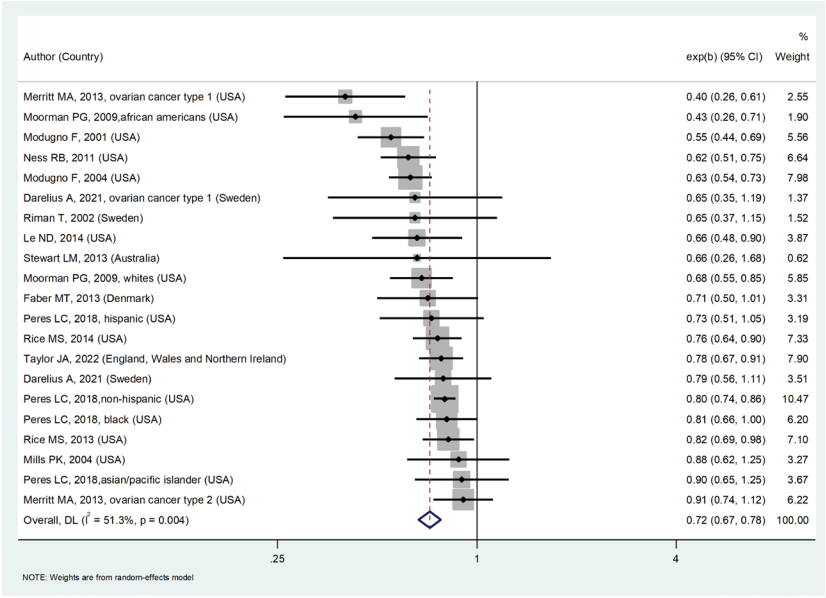

Figure 5. Forest plot showing the association between tubal ligation and ovarian carcinoma.

carcinoma. In the subtypes of ovarian carcinoma studied, hysterectomy was not significantly associated with serous or endometrioid cancers. However, it did reduce the risk of mucinous carcinoma by 26% and clear cell carcinoma by 51%. Geographically, hysterectomy was associated with a reduction in risk

In a meta-analysis conducted by Huo et al on 18 case-control studies, the results showed no significant association between hysterectomy and ovarian carcinoma (OR: 0.97, 95% CI: 0.83, 1.12). No significant associations were found between serous and mucinous types. However, protective effects for invasive endometrioid/clear cell carcinomas were observed following hysterectomy (OR: 0.70, 95% CI: 0.51, 0.94) (26). The current meta-analysis included 21 case-control studies and 8 cohort studies; therefore, the total number of studies and the overall sample size are larger in this meta-analysis and thus more generalizable.

In a meta-analysis that Jordan and others carried out on observational studies, it was discovered that hysterectomy could lessen the risk of ovarian cancer (RR: 0.81, 95% CI: 0.72, 0.92) (51). However, in general terms, this particular meta-analysis did not show any notable relationship between hysterectomy and ovarian cancer. As a result, our findings are not in line with these findings. However, it should be pointed out that the previous meta-analysis only included case-control studies, whereas the present one incorporates both cohort and case-control studies. The reason for this difference might be due to the variation in the results of the two investigations.

Another meta-analysis of the same type as the one above is provided by Rice et al, who report a reduced risk for

Table 2. Association between hysterectomy and ovarian carcinoma by countries

Countries	OR	Low limit	Up limit	I^2 (%)	*P* value
Netherlands	0.49	0.34	0.71	0	-
USA	1.10	0.99	1.22	76	0.000
Australia	0.98	0.85	1.11	0	0.434
Albania	0.59	0.32	1.02	0	-
Italy	0.60	0.40	0.90	0	-
Sweden	0.77	0.71	0.85	0	0.904
Finland	0.71	0.61	0.82	0	-
China	0.86	0.46	1.61	0	-
England, wales and north Ireland	0.98	0.85	1.13	0	-
Denmark	1.21	0.78	1.87	87.6	0.005
Taiwan	3.88	2.55	5.90	0	-

ovarian cancer in tubal ligation and hysterectomy (52). Wang et al reported in a meta-analysis that endometriosis increases the risk of epithelial ovarian cancer, and tubal ligation decreases the risk of epithelial ovarian cancer but not hysterectomy (53). As with these previous studies, the meta-analysis also found tubal ligation to be a protective factor against ovarian cancer.

According to the results of Luo et al 's meta-analysis, the risk of colorectal cancer was associated with hysterectomy and oophorectomy (54). A meta-analysis by Fabiani et al also found an association between hysterectomy and thyroid cancer risk (55). In a study by Luo et al to investigate the relationship between hysterectomy and oophorectomy and the risk of renal cell cancer, they found that hysterectomy, whether or not oophorectomy, was associated with increased risk of renal cell carcinoma

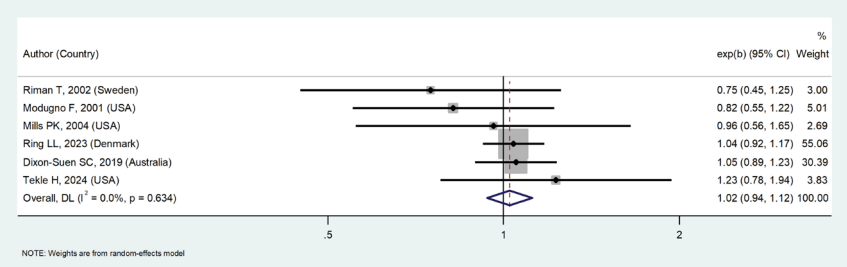

Figure 6. Forest plot showing the association between hysterectomy and serous.

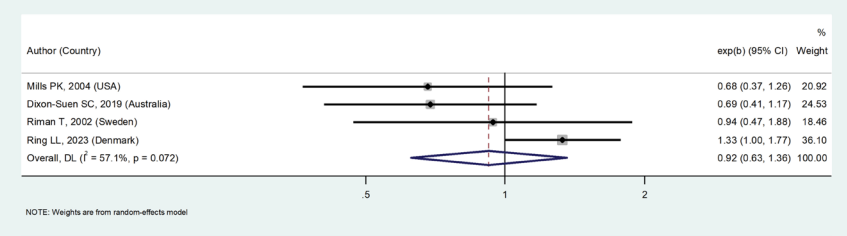

Figure 7. Forest plot showing the association between hysterectomy and endometrioid

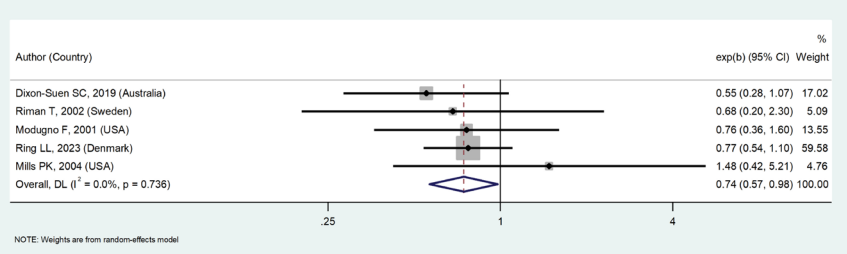

Figure 8. Forest plot showing the association between hysterectomy and mucinous

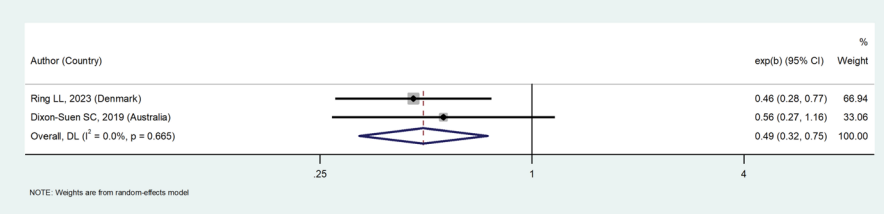

Figure 9. Forest plot showing the association between hysterectomy and clear cell carcinoma.

(56). In a retrospective cohort study by Wilson et al on 839,332 women from the population of Western Australia, a hysterectomy was associated with an increased risk of thyroid cancer and a decreased risk of breast cancer (57). In a cohort study by Altman et al in Sweden, hysterectomy was associated with increased risk of thyroid and brain cancers (58). These studies showed that hysterectomy is a risk factor for colorectal, thyroid, brain cancers, and renal cell carcinoma. The results of the aforementioned studies also showed that hysterectomy was a risk factor for ovarian cancer, and this evidence was found in the current meta analysis in Taiwan. It may be that race is an important and influential factor.

Meanwhile, the cohort study by Woolcott et al, including 68,065 women, found no association between hysterectomy and breast cancer risk (RR: 0.98, 95% CI: 0.86, 1.11) (59). This study aligns with the current analysis, suggesting that hysterectomy is generally not associated with ovarian or breast cancer.

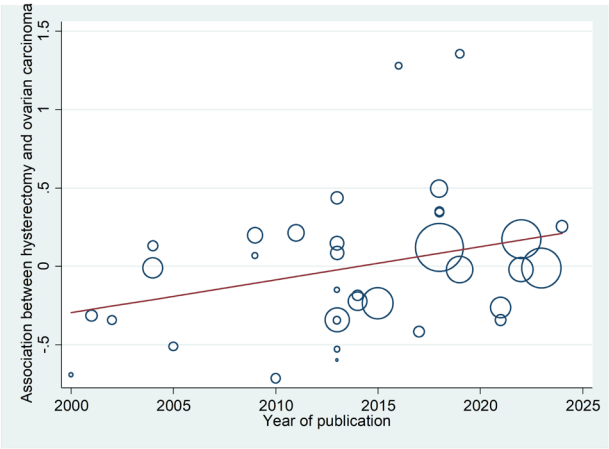

Figure 10. Meta-regression plot of the association between hysterectomy and ovarian carcinoma with year of publication.

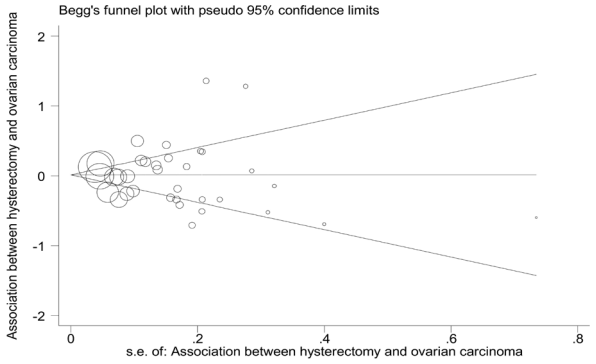

Figure 11. Chart of Publication bias.

Conclusion

Although no significant overall association was found between hysterectomy and ovarian cancer, women who underwent hysterectomy had a reduced risk of mucinous and clear cell carcinoma compared to those who did not. Additionally, tubal ligation was associated with a decreased risk of ovarian cancer. Given the limitations of this study, future researchers are encouraged to address these constraints and explore other aspects of the relationship between hysterectomy and ovarian cancer.

Limitations of the study

Very few studies mentioned patient ethnicity or ovarian cancer type (type 1 or type 2), precluding subgroup analysis based on these variables. Most studies reported women's mean age in multi-decade ranges, preventing age-based subgroup analysis for some studies that did not fit into either category (<60 and ≥60 years).

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Authors' contribution

Conceptualization: Elham Saffarieh, Fahimeh Nokhostin and Seyedeh Reyhaneh Yousefi Sharami.
Data curation: Fahimeh Nokhostin.
Formal analysis: Fahimeh Nokhostin.
Funding acquisition: Elham Saffarieh and Seyedeh Reyhaneh Yousefi Sharami.
Investigation: Elham Saffarieh.
Methodology: Azadeh Yousefnezhad, Elham Saffarieh, and Fahimeh Nokhostin.
Project administration: Elham Saffarieh and Fahimeh Nokhostin.
Resources: Elham Saffarieh, Azadeh Yousefnezhad and Fahimeh Nokhostin.
Supervision: Azadeh Yousefnezhad, Seyedeh Reyhaneh Yousefi Sharmi
Validation: Elham Saffarieh, Fahimeh Nokhostin, Azadeh Yousefnezhad, and Seyedeh Reyhaneh Yousefi Sharmi.
Visualization: Elham Saffarieh and Seyedeh Reyhaneh Yousefi Sharami.
Writing-original draft: Seyedeh Reyhaneh Yousefi Sharami.

Writing-review and editing: Elham Saffarieh, Azadeh Yousefnezhad and Fahimeh Nokhostin.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website with (ID: CRD4202459588) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1893). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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