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Association between pelvic inflammatory disease and risk of ovarian carcinoma; a systematic review and meta-analysis of observational studies

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Abstract

Introduction: Ovarian carcinoma is among the leading causes of cancer deaths due to its asymptomatic growth. Hence, identifying factors affecting ovarian carcinoma incidence is of great significance. Accordingly, the present study examined the association between pelvic inflammatory disease (PID) and ovarian carcinoma.

Materials and Methods: The PRISMA checklist was used to design the current systematic review and meta-analysis. Databases, including ProQuest, PubMed, Web of Science, Cochrane, and Google Scholar Search Engine, were used without a time limit until September 8, 2024. Data was analyzed using the STATA 14 software, and tests with *P* values lower than 0.05 ($P < 0.05$) were considered statistically significant.

Results: A total of 20 studies (13 cohort and seven case-control) conducted from 1995 to 2024 were combined, and the total number of patients with PID in the studies was 754268. Results revealed that PID increased ovarian carcinoma risk (HR: 1.33, 95% CI: 1.19, 1.48) and number of PID episodes (2) increased the risk of ovarian neoplasm (HR: 1.42, 95% CI: 1.10, 1.83). However, there was no statistically significant relationship between the number of PID episodes (1) (HR: 1.09, 95% CI: 0.98, 1.22) and number of PID episodes (≥3) (HR: 1.39, 95% CI: 0.54, 3.58) and the risk of ovarian carcinoma. PID increased the risk of ovarian carcinoma in age groups 20 to 29 (HR: 1.44, 95% CI: 1.31, 1.59), 30 to 39 (HR: 1.43, 95% CI: 1.04, 1.97), 40 to 49 (HR: 1.37, 95% CI: 1.16, 1.63), and 50 to 59 (HR: 1.39, 95% CI: 1.07, 1.81). Furthermore, PID raised the risk of serous carcinoma (HR: 1.36, 95% CI: 1.09, 1.69). Nevertheless, there was no statistically significant relationship between PID and the risk of endometrioid (HR: 0.87, 95% CI: 0.65, 1.18), mucinous (HR: 1.06, 95% CI: 0.89, 1.26), and clear cell carcinoma (HR: 1.05, 95% CI: 0.66, 1.66).

Conclusion: Pelvic inflammatory disease increases the risk of ovarian carcinoma and serous carcinoma. Taiwanese patients with PID aged 20 to 39 had higher rates of exposure to ovarian carcinoma than other patients.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42024590681) and Research Registry (UIN: reviewregistry1885) website.

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Introduction

Sexually transmitted infections cause pelvic inflammatory disease (PID) and affect different areas of the upper female reproductive system, including the uterus, ovaries, fallopian tubes, and other pelvic and even abdominal organs(1). According to the estimates, 20 percent of women in Western countries experience PID during their lives (2). Annually, about 800 000 women undergo treatments in the United States due to PID (3).

Pelvic inflammatory disease leads to various adverse consequences, including infertility and ovarian cancer (4,5). The 'inflammation' hypothesis proposal is suggested as ovarian carcinoma is associated with conditions and events related to inflammation and recovery (i.e., ovulation, endometriosis) (6). Ovarian carcinoma is the third most common cancer and the most lethal malignancy of the female reproductive system (7). The mean age of patients at the time of ovarian carcinoma diagnosis in most developed countries is approximately 63, and ovarian cancer is more common in older women than younger women (8,9).

Ovarian carcinoma has a high mortality rate due to the asymptomatic tumor growth and delayed onset of symptoms, as it cannot be diagnosed in most patients until they experience manifestations including back pain, fatigue, constipation, abdominal discomfort, feeling full after eating, and urinary symptoms (10,11). Despite the

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Key point

In our A total of 20 studies (13 cohort and seven case-control) conducted from 1995 to 2024 were combined, and the total number of patients with pelvic inflammatory disease (PID) in the studies was 754268. We found, PID increases the risk of ovarian carcinoma and serous carcinoma. Taiwanese patients with PID aged 20 to 39 had higher rates of exposure to ovarian carcinoma than other patients.

advances in screening technologies and surgical and chemotherapy methods, most ovarian cancer cases are diagnosed at advanced stages (12). Hence, identifying factors related to the incidence of ovarian cancer is of great significance.

Researchers demonstrated in various studies that there was no significant relationship between PID and ovarian cancer incidence (13,14). On the other hand, some of the authors believed that PID is a significant risk factor for ovarian carcinoma (15,16). Considering the inconsistency of the results of previous studies, the present study was conducted using the systematic review method and meta-analysis to investigate the association between PID and ovarian carcinoma and present a general and updated statistical report.

Materials and Methods

The present systematic review and meta-analysis utilized Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) (17), and its protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) website.

Search strategy

The databases ProQuest, PubMed, Web of Science, Cochrane, and Google Scholar Search Engine were searched using keywords Pelvic Inflammatory Disease, Adnexitis, Ovarian Neoplasms, Ovary cancer, and their Medical Subject Headings (MeSH) equivalents without a time limit until September 8, 2024. The keywords were combined using operators 'AND' and 'OR,' and an advanced search was conducted. The references of the primary studies were examined using a manual search. The search strategy of the database Web of Science was as follows: Pelvic Inflammatory Disease OR Adnexitis (All Fields) AND Ovarian Neoplasms OR Ovary Cancer (All Fields).

PECO components

- Population: Studies examining the association between PID and the risk of ovarian carcinoma.
- Exposure: PID.
- Comparison: Individuals without PID.
- Outcomes: The risk of ovarian carcinoma.

Inclusion and exclusion criteria

Studies that examined the relationship between PID and the risk of ovarian carcinoma entered the meta-analysis. Duplicate studies, studies that were not observational, those without sufficient data for analysis, low-quality studies, case report studies, studies published at conferences, and those without accessible full texts were removed.

Quality assessment

Two authors evaluated the studies using the Newcastle-Ottawa Scale. Each question received a maximum of one star, and only the question regarding the comparison could receive two stars using the checklist. Accordingly, the lowest score was zero (i.e., lowest quality), and the highest score was 10 (i.e., highest quality). Score six was considered the cutoff point for the present study (18).

Data extraction

Two authors independently conducted the data extraction step. From each study, information including the author's name, indicator, type of study, country of origin, publication year, number of samples, and the relationship between PID and the risk of diseases such as ovarian neoplasm, serous carcinoma, endometrioid, mucinous, and clear cell carcinoma was extracted. The extracted data were entered into SPSS 20 software.

Statistical analysis

Logarithms of hazard ratio (HR), odds ratio (OR), and relative risk (RR) indicators were used for data analysis, and the studies were combined. The heterogeneity of the studies was examined using Cochran's Q test and I^2 indicator. Considering the moderate heterogeneity of the studies, the random effects model was conducted (I^2= 65.4%). Subgroup analysis was used to investigate the association between PID and the risk of ovarian carcinoma based on the variables study type, age, and country of origin. Meta-regression, publication bias, and sensitivity analyses were conducted for further examination. Data was analyzed using the STATA 14 software, and tests with P values lower than 0.05 ($P < 0.05$) were considered statistically significant.

Results

A total of 253 studies were found by searching the sources; among these, 91 were duplicates and were removed from the study. Then, 162 articles entered the next step, and after examining the information presented in their abstracts, 33 studies were excluded because their full texts were not accessible or because they lacked the required data for analysis. From the remaining 92 studies, 72 were removed due to other exclusion criteria, and eventually, 20 articles remained (Figure 1).

The present meta-analysis combined the results of 20 studies (13 cohort and 7 case-control studies). The studies were published from 1995 to 2024 and covered three decades. The total number of patients in the PID group was 754 268 (Table 1).

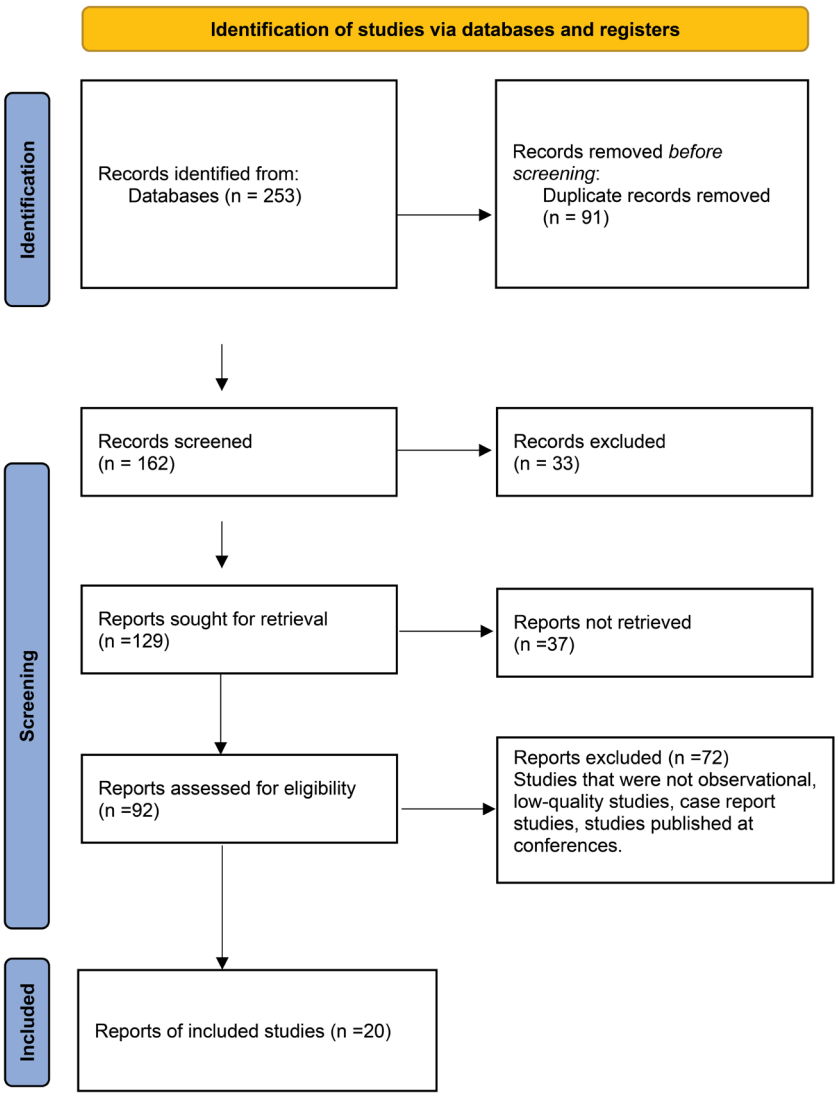

Figure 1. PRISMA Flowchart of the study selection.

Figure 2 demonstrates that, generally, PID increases the risk of ovarian carcinoma (HR: 1.33, 95% CI: 1.19, 1.48).

There was no statistically significant relationship between number of PID episodes (1) (HR: 1.09, 95% CI: 0.98, 1.22) and the number of PID episodes (≥3) (HR: 1.39, 95% CI: 0.54, 3.58) and ovarian cancer. However, number of PID episodes (2) increased the risk of ovarian cancer (HR: 1.42, 95% CI: 1.10, 1.83).

Subgroup analysis indicated that there was no statistically significant relationship between PID and ovarian cancer risk in countries Italy (HR: 0.70, 95% CI: 0.39, 1.26), Denmark (HR: 1.08, 95% CI: 0.83, 1.4), United States (HR: 1.38, 95% CI: 0.94, 2.04), and Canada (HR: 1.67, 95% CI: 0.88, 3.19). However, in Taiwan (HR: 1.51, 95% CI: 1.21, 1.88), Australia (HR: 1.38, 95% CI: 1.08, 1.77), and Sweden (HR: 1.43, 95% CI: 1.31, 1.55), PID was a risk factor for ovarian neoplasm (Figure 3).

As Figure 4 shows, there was no significant relationship between PID and ovarian carcinoma in case-control studies (HR: 1.17, 95% CI: 0.94, 1.45). In cohort studies, however, PID increased the risk of ovarian cancer (HR: 1.42, 95% CI: 1.25, 1.61).

Figure 5 demonstrates that in the age groups 20 to 29 (HR: 1.44, 95% CI: 1.31, 1.59), 30 to 39 (HR: 1.43, 95% CI: 1.04, 1.97), 40 to 49 (HR: 1.37, 95% CI: 1.16, 1.63), and 50 to 59 (HR: 1.39, 95% CI: 1.07, 1.81), PID increased the risk of ovarian carcinoma, and the age group 20 to 29 was considered a high-risk group.

Examining secondary consequences showed that PID increased the risk of serous carcinoma (HR: 1.36, 95% CI: 1.09, 1.69) (Figure 6). However, there was no statistically significant association between PID and the risk of endometrioid (HR: 0.87, 95% CI: 0.65, 1.18), mucinous (HR: 1.06, 95% CI: 0.89, 1.26), and clear cell carcinoma (HR: 1.05, 95% CI: 0.66, 1.66) (Figures 7 to 9).

Meta-regression indicated that there was no statistically significant relationship between the effect of PID on the risk of ovarian cancer, the publication year of the articles

Table 1. Characteristics of observational studies

Author, year	Index	Country	Design	Duration of study	Total number in PID group	Mean age in PID group (year)	Total number in compare group	Mean age in compare group (year)	Relationship between PID and ovarian carcinoma		
									Risk	Low limit	Up limit
Jonsson S, 2024 (16)	OR	Sweden	Case-control	between 1999 and 2020	15072	43.3	141322	41.8	1.39	1.17	1.66
Lo HW, 2022 (15)	HR	Taiwan	Cohort	between Jan 1, 2000 and Dec 31, 2015	130852	34.56	NR	NR	2.11	1.52	2.92
Falconer H, 2021 (19)	HR	Sweden	Cohort	between 1973 and 2010	93242	29.1	NR	NR	1.44	1.31	1.59
Chang CY, 2021 (20)	HR	Taiwan	Cohort	2000 till 2012	64925	35.43	129850	35.38	1.49	1.21	1.84
Huang JY, 2021 (14)	HR	Taiwan	Cohort	between 1 Jan 2002 and 31 Dec 2014	114726	NR	135236	NR	1.17	0.87	1.56
Huang CY, 2020 (13)	HR	Taiwan	Cohort	between 2001 and 2010	11620	≥20	NR	NR	0.76	0.3	1.92
Stewart LM, 2018 (21)	HR	Australia	Cohort	1945-2014	454	54.4	NR	NR	1.47	1.04	2.07
Park HK, 2018 (22)	OR	USA	Case-control	between Dec 1, 2010 and Dec 31, 2015	600	58.1	752	55	1.33	0.82	2.16
Rasmussen CB, 2017 (23)	HR	Denmark	Cohort	1978-2012	81281	30.51	1318929	29.5	1.05	0.92	1.2
Shen CC, 2016 (24)	HR	Taiwan	Cohort	Jan 1st, 2000 and Dec 31st, 2002	32268	34.48	32268	34.48	1.33	0.78	2.27
Rasmussen CB, 2016 (25)	HR	Denmark	Cohort	1978-2012	81263	NR	NR	NR	1.39	1.19	1.61
McAlpine JN, 2014 (26)	OR	Canada	Cohort	between Jan 1, 1981, and Dec 31, 2012	888	≥20	552	≥20	5.56	0.52	59.4
Rasmussen CB, 2013 (27)	OR	Denmark	Case-control	between Jan 1995 and May 1999	554	35–79	1564	35–79	0.83	0.65	1.05
Stewart LM, 2013 (28)	HR	Australia	Cohort	1982–2002	21646	46	NR	NR	1.02	0.42	2.43
Lin HW, 2011 (5)	HR	Taiwan	Cohort	between Jan 1, 2004, and Dec 31, 2005	67936	13-65	135872	13-65	1.92	1.27	2.92
Wu AH, 2009 (29)	RR	USA	Case-control	1998 to 2002	609	18-74	688	18-74	1.48	0.78	2.82
Merritt MA, 2008 (30)	OR	Australia	Case-control	between Jan 2002 and Jun 2005	1576	18–79	1509	18–79	1.15	0.85	1.57
Parazzini F, 1996 (31)	RR	Italy	Case-control	between 1983-1991	971	54	2758	52	0.7	0.4	1.3
Risch HA, 1995(32)	OR	Canada	Case-control	1989-1992	450	57.2	564	57.5	1.53	1.1	2.13
Stewart LM, 2020 (33)	HR	Australia	Cohort	between 1 Jan 1980 and 30 Jun 2014	33335	52	NR	NR	1.95	1.22	3.1

NR: Not reported; OR: Odds ratio; RR: Risk Ratio; HR: Hazard Ratio; PID: Pelvic inflammatory disease.

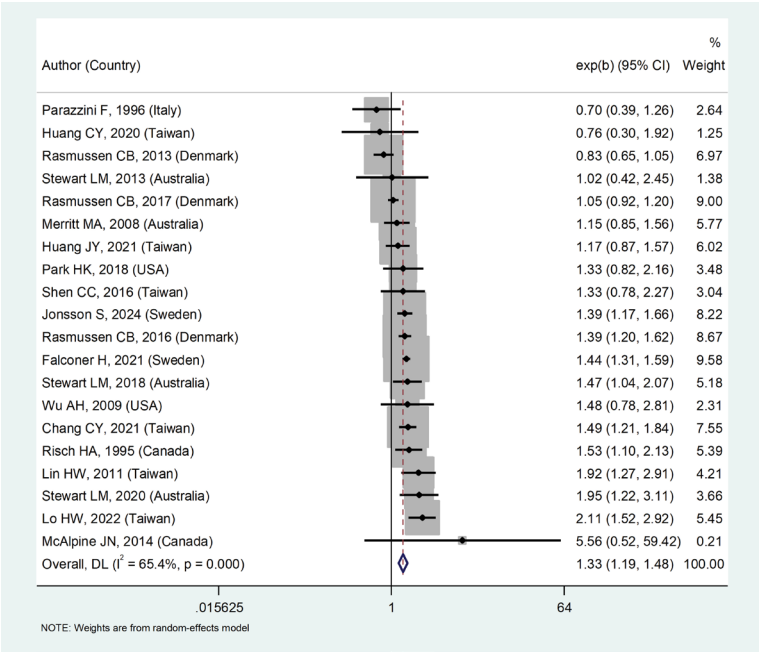

Figure 2. Forest plot showing the associations between pelvic inflammatory disease and the risk of ovarian carcinoma.

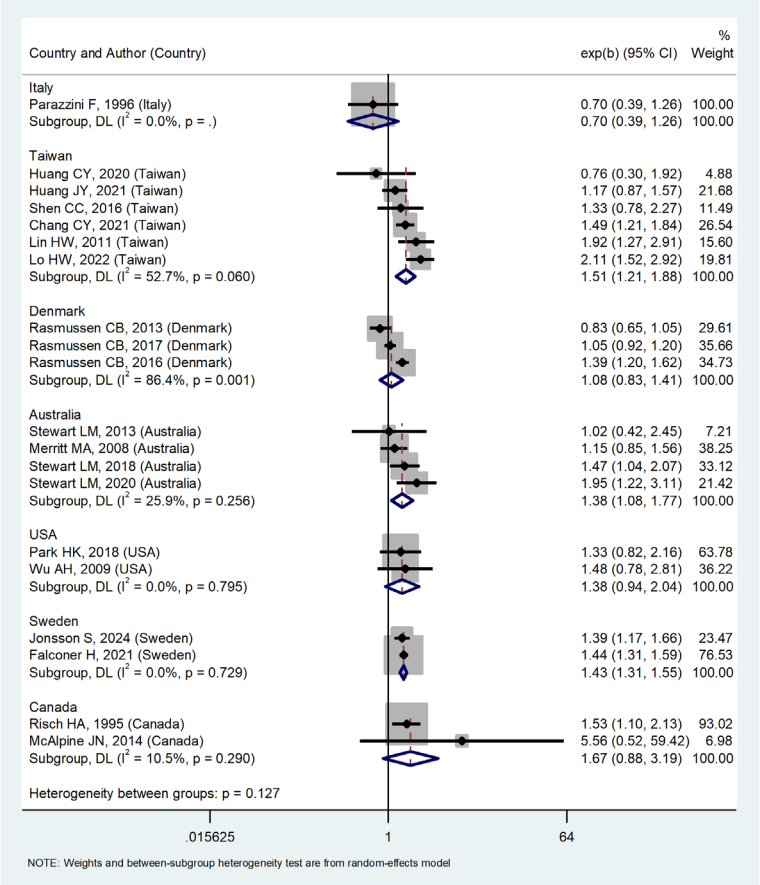

Figure 3. Forest plot showing the associations between pelvic inflammatory disease and the risk of ovarian carcinoma by country.

(P = 0.277), and the number of patients in the PID group (0.167) (Figures 10 and 11).

Furthermore, there was no publication bias in the resource search stage, and the searches were conducted thoroughly (P = 0.902). Sensitivity analysis showed that studies Lo et al (15) and Rasmussen et al (27) had the highest impact on the final result of the present meta-analysis (Figures 12 and 13).

Discussion

Results revealed that PID increased the risk of ovarian carcinoma (33%) and serous carcinoma (36%), and number of PID episodes (2) increased the risk of ovarian carcinoma (42%).PID increased the risk of ovarian cancer in age groups 20 to 29 (44%), 30 to 39 (43%), 40 to 49 (37%), and 50 to 59 (39%). However, there was no statistically significant relationship between PID and the risk of endometrioid, mucinous, or clear cell carcinoma.

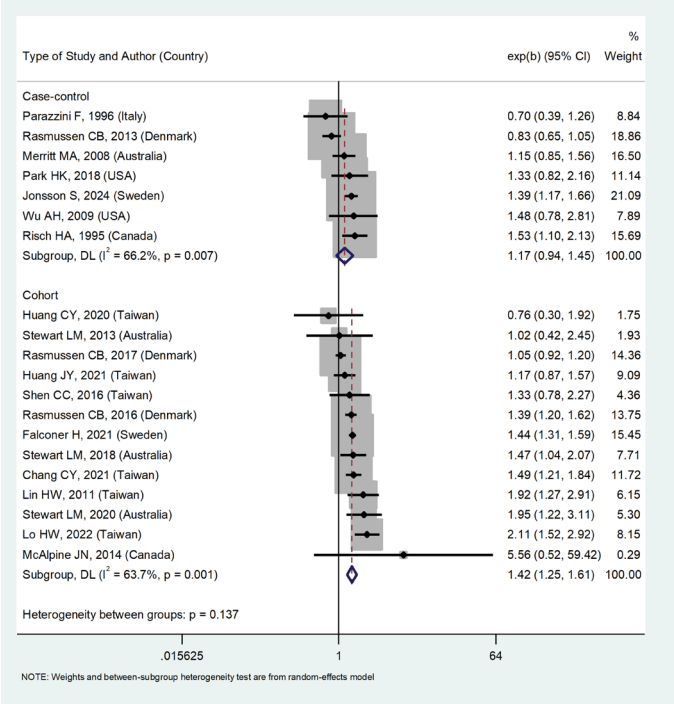

Figure 4. Forest plot showing the associations between pelvic inflammatory disease and the risk of ovarian carcinoma by study design.

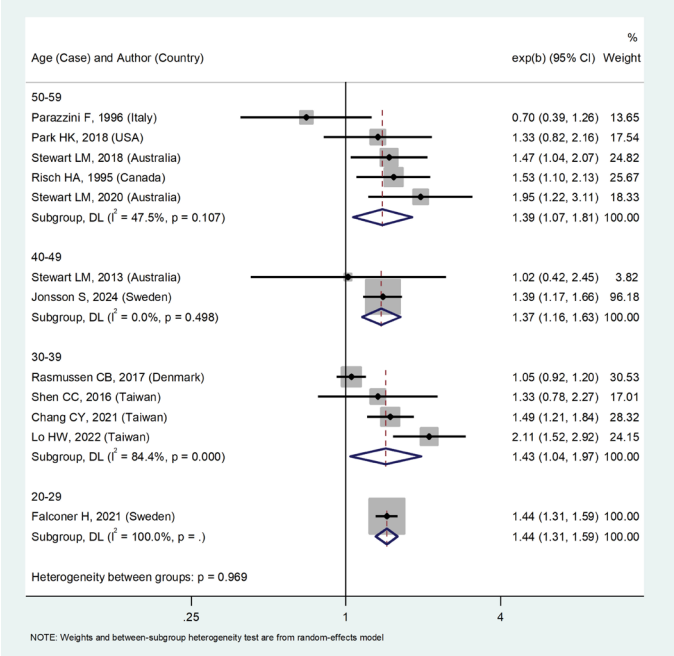

Figure 5. Forest plot showing the associations between pelvic inflammatory disease and the risk of ovarian carcinoma by age group.

According to the results of a meta-analysis by Piao et al, PID was associated with an increase in the risk of ovarian carcinoma (HR 1.18, 95% CI: 1.13 to 1.22) (34). In another meta-analysis by Zhou et al on 13 observational studies, PID increased the risk of ovarian cancer (RR: 1.24, 95% CI: 1.06, 1.44) (35). The results of a systematic review by Ingerslev et al on seven studies indicated a potentially significant relationship between PID and ovarian neoplasm (36). The results of these studies were consistent with the present study, indicating that PID was

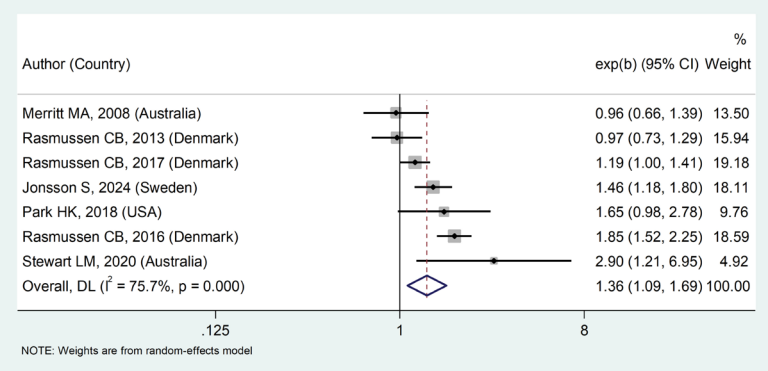

Figure 6. Forest plot showing the associations between pelvic inflammatory disease and the risk of serous carcinoma.

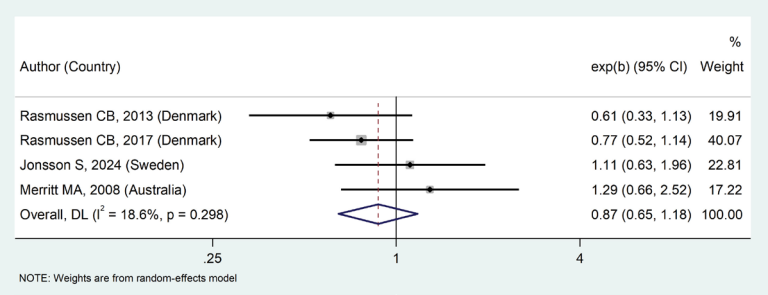

Figure 7. Forest plot showing the associations between pelvic inflammatory disease and the risk of endometrioid.

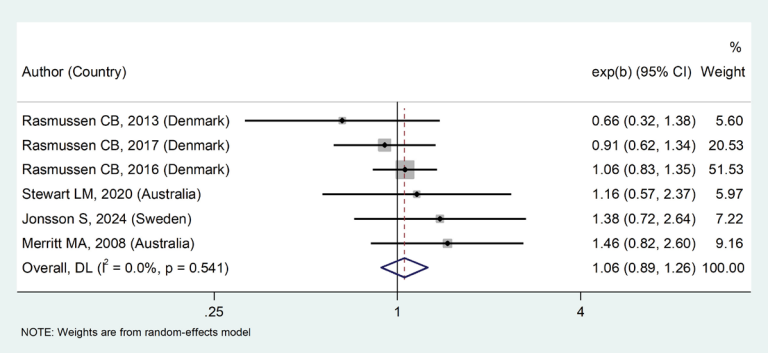

Figure 8. Forest plot showing the associations between pelvic inflammatory disease and the risk of mucinous.

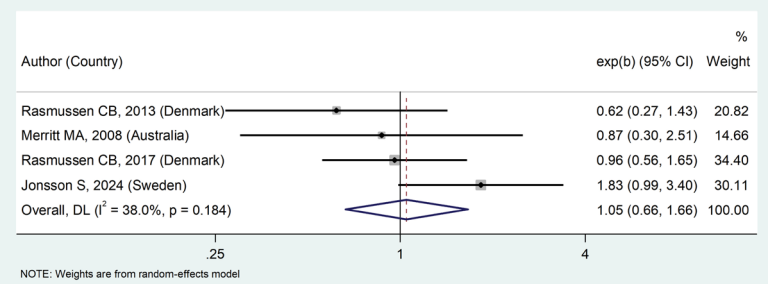

Figure 9. Forest plot showing the associations between pelvic inflammatory disease and the risk of clear cell carcinoma.

a risk factor for ovarian carcinoma.

A cohort study by Falconer et al investigating the relationship between PID and subsequent salpingectomy and the risk of ovarian carcinoma indicated a significant relationship between PID and ovarian cancer (HR: 1.44, 95% CI: 1.31, 1.59) (19). Based on the findings of a cohort study by Lo et al, the risk of ovarian cancer in female patients with endometriosis followed by PID was higher than those who only had PID (HR: 8.07, 95% CI: 4.53, 14.37) (15). The results of these studies were consistent with the present study, as in our study, the combination of the results of cohort studies showed that PID was a risk factor leading to an increased risk of ovarian cancer.

In a meta-analysis of 13 case-control studies by Rasmussen et al, there was no significant relationship between PID and ovarian carcinoma risk (OR: 0.99, 95% CI: 0.83, 1.19) (37). This study was consistent with the present meta-analysis, as no significant relationship was reported between PID and the risk of ovarian cancer in case-control studies.

In a case-control study by Jonsson et al aimed at examining the relationship between PID and the risk of epithelial ovarian carcinoma, findings demonstrated that PID was associated with an increase in the risk of epithelial ovarian carcinoma (OR: 1.39, 95% CI: 1.17, 1.66) (16). This study was inconsistent with ours because the present meta-analysis showed no significant relationship between PID and ovarian cancer in case-control studies. However, it must be noted that the former study merely examined epithelial ovarian carcinoma, while the current study investigated every form of ovarian carcinomas.

Results of a retrospective cohort study by Yang et al investigating the risk of endometrial cancer in female patients with PID demonstrated that the risk of endometrial cancer in the PID group was 1.79 times higher (HR: 1.79, 95% CI: 1.25, 2.56) than the group without PID (38). The study was inconsistent with the present study, as we concluded that PID did not affect the risk of endometrioid. The difference between the type of studies and the number of samples in the present study and Yang et al may be among the causes of the discrepancies between the two studies.

In a meta-analysis by Ye et al examining the relationship between PID and the risk of endometriosis, findings indicated that PID was related to an increase in the risk of endometriosis (OR: 2.70, 95% CI: 1.87, 3.90) (39). Based on the results of a cohort study by Hsu et al investigating the risk of colorectal cancer in female patients with PID, the hazard ratio of colorectal cancer during a follow-up period of five years for patients with PID compared

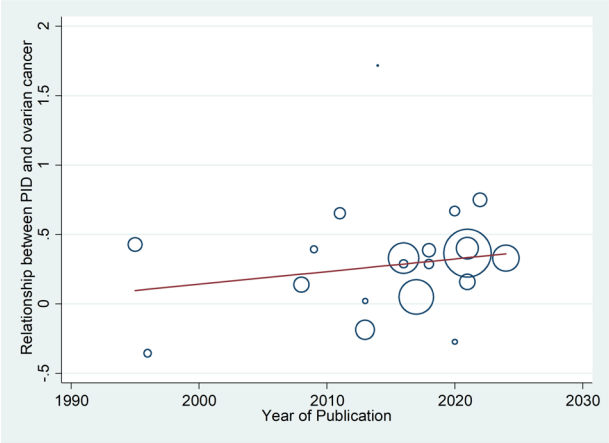

Figure 10. Meta-regression of the associations between PID and the risk of ovarian carcinoma with year of publication.

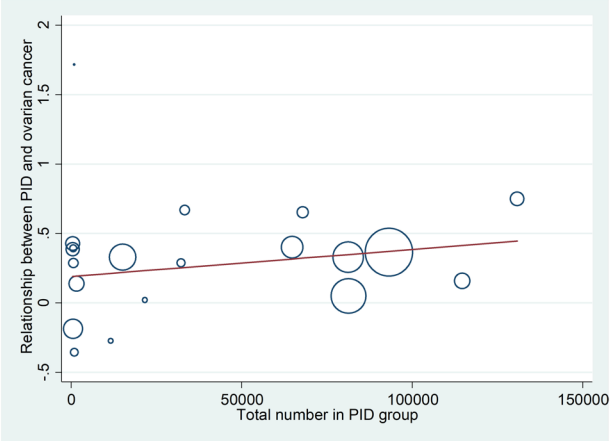

Figure 11. Meta-regression of the associations between PID and the risk of ovarian carcinoma with total number in PID group

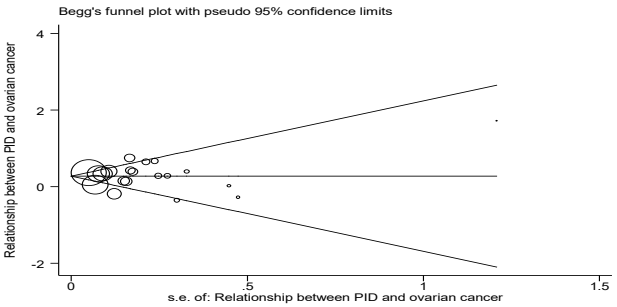

Figure 12. Diagram of publication bias.

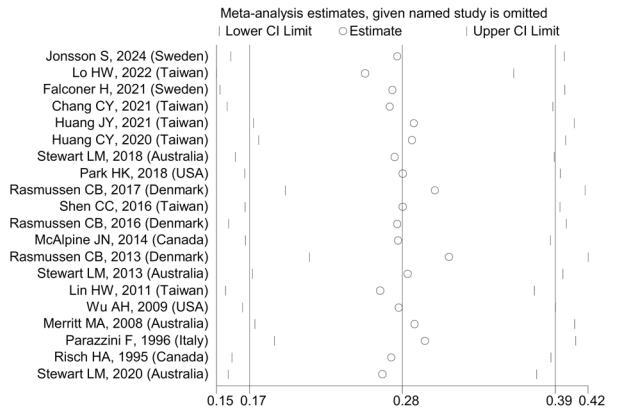

Figure 13. Diagram of sensitivity analysis

to the women of the control group was (HR: 2, 95% CI: 1.30, 3.08) (40). These studies confirmed the results of the current study, as in the present study, we concluded that PID is an aggravating factor for cancer incidence.

Limitations of the study

Some studies did not specify the number of women in the comparison group; hence, the total number of women in the comparison group was unclear. Merely one study was conducted on patients aged 20 to 29. The examined studies did not mention the duration of PID; accordingly, we did not conduct any subgroup analysis based on the duration of the disease.

Conclusion

Pelvic inflammatory disease increases the risk of ovarian carcinoma and serous carcinoma. Furthermore, Taiwanese patients with PID aged 20 to 39 were at higher risk of ovarian neoplasm than other patients. Generally, it is recommended to screen women aged 20 to 39 for PID, and controlling PID in them will help take a preventive step to stop ovarian carcinoma incidence.

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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, and Fahimeh Nokhostin.
Project administration: Elham Saffarieh and Fahimeh Nokhostin.
Resources: Elham Saffarieh, Azadeh Yousefnezhad and Fahimeh Nokhostin.
Supervision: Azadeh Yousefnezhad, Seyedeh Reyhaneh Yousefi Sharami.
Validation: All authors.
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 (ID: CRD42024590681) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1885). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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