Polycystic ovarian syndrome and risk of breast, endometrial, and ovarian cancer: a systemic review and meta-analysis

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disease affecting the reproductive age women. Objective: To investigate the relationship between PCOS and breast, ovarian, and endometrial cancer. Search Strategy: Systematic search of PubMed, EMBASE using keywords 'PCOS', 'ovarian cancer', 'breast cancer' and 'endometrial cancer'. Selection Criteria: The study providing the relative risk (RR) in the cohort study, odds risk(OR) in the case-control study, and 95%confidence interval (95%CI) were included. The single-case report and the non-English study were excluded. Data Collection and Analysis: This meta-analysis was performed by calculating RR, OR and 95%CI using random-effect models. Main Result: A total of 21 studies (8 cohort studies,13 case-control studies) involving 3831083 participants fulfilled the inclusion criteria. Based on the results of cohort studies and case-control studies, the prevalence of breast cancer among PCOS and non-PCOS women was not significant increased, the RR and OR were 0.959 (95%CI, 0.806-1.112) and 0.991 (95%CI, 0.626-1.35), respectively. Evidence from case-control studies showed that PCOS did not increase the risk of endometrial and ovarian cancer, the summary ORs of case-control studies were 1.288 (95%CI,0.763-1.814) and 1.219 (95%CI, 0.816-1.623). The risk of endometrial and ovarian cancer was significantly increased based on cohort studies, the overall RRs of cohort studies were 2.542 (95%CI, 1.755-3.328) and 1.818 (95%CI, 1.222-2.414). Conclusion: The meta-analysis demonstrate that PCOS will not increase the risk of breast cancer. Evidence from the cohort studies suggests that PCOS significantly increases the risk of endometrial and ovarian cancer, although the case-control studies did not.

Introduction

Polycystic ovarian syndrome(PCOS) is now one of the most common endocrine disturbance, affecting 8%-13% women of reproductive age[1]. Referring to Rotterdam criteria which had been commonly recognized the basis of the diagnosis of PCOS by most clinicians and researchers, PCOS is a syndrome of ovarian dysfunction along with the cardinal features hyperandrogenism and polycystic ovary(PCO)morphology[2]. In recent decades, concern has mounted regarding the damage of PCOS to other body systems. Studies have suggested that the prevalence of cardiovascular risk factors, insulin resistance/diabetes and/or uterine pathology appears to be increased in women with polycystic ovarian syndrome (PCOS)[3] and it can even affect Health-related quality of life (HRQoL)[4]. However, among those long-term malignant consequences, estimates of the association between PCOS and cancer were still controversial. The earliest report was about the relationship between PCOS and endometrial cancer, which was published in 1949[5]. The first meta-analysis about the association between PCOS and cancer risk[6] has found that women with PCOS were at an increased risk of endometrial cancer but the risk of ovarian and breast cancer was not significantly increased. However, studies report conflicting findings about whether PCOS increases the risk of gynecological cancer. Reliable estimates of the relationship between PCOS and gynecological cancer are important for public heath, which can inform medical workers to improve the diagnosis and treatment strategies. Therefore, we conduct the present

meta-analysis of cohort and case-control studies to qualify the association between PCOS and gynecological cancer.

Methods

Literature search

Two authors independently identified the cohort and case-control studies on PubMed, JAMA, the Lancet and EMBASE. The potential eligible studies, which related to PCOS (or polycystic ovarian syndrome) and the risk of cancer (or neoplasm, or carcinoma) were collected. In addition, the references cited in relevant original papers and review articles were scrutinized as the further pertinent studies.

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Study selection

Studies were initially included in this meta-analysis if it met the following criteria: 1) the study was a cohort or case-control study that compared the prevalence of cancer of women with and without PCOS; 2) the eligible literatures also needed to provide the inclusion criteria of the experimental and control groups, the data source; 3) the affect values and 95% confidence intervals should be reported. In addition, the relevant data such as region, sample size in each group should be revealed.

Articles written in non-English languages, non-human experiments and single case reports would be excluded.

Data collection and Quality assessment

Two authors extracted the following data from each article independently: year, region, cancer site, PCOS diagnostic criteria, design, the age of participates, sample size, the effect value, and adjustment.

The literature quality was evaluated by Newcastle Ottawa Scale(NOS)[7]. The NOS evaluates 8 items in the case-control study and the cohort study respectively, including Selection, Comparability, Exposure or Outcome, with a total score of 9 stars. If the study satisfied the evaluation score at 7 points or above, the quality of the literature was thought to be high; if the research evaluation score ranged 4–6, the quality of the literature was medium; and if the score was$<$ 4, the literature quality was considered low.

Data analysis

Relative risk (RR) and odds risk (OR) estimates of the association between PCOS and gynecological cancer were calculated by pooling the study specific estimates using random-effects. Based on OR estimates obtained from the case-control studies and RR from the cohort studies. The data analysis of the case-control and cohort studies were conducted separately. The pooled ORs and RRs were calculated by STATA 15.1.

The heterogeneity between studies was quantitatively determined by I^2 test. If the I^2 was lower than 50%, which indicated the heterogeneity was low, we would apply the fixed-effect model for the result. If I^2>50% which indicated the significant heterogeneity between studies was exist, the source of heterogeneity will be further analyzed, and the random-effect model will be adopted.

Result

Study inclusion and basic characteristic of studies

We initially identified 8050 references, 7938 through searching the websites and database and 112 from the reference list. By reading the title and abstract of the literature, 6630 literatures were not related to this theme and 858 duplicates were excluded. After viewing the specific content of these studies, 21 articles involving a total of 3831083 participants were include in this meta-analysis: 13 case-control[8-21] studies and 8 cohort studies[13, 22-28]. The complete details of the search strategy were given in Figure1. The characteristic of studies: year, region, PCOS diagnostic criteria, age, measurement and cancer site was shown in Table 1.

Quality assessment

The literature quality was evaluated by Newcastle Ottawa Scale(NOS). The Newcastle Ottawa score components for the 13 case-control studies and 8 cohort studies was shown in Table 2 and Table 3 respectively.

Data analysis

Seven cohort studies (RR=0.959; 95%CI,0.806-1.112) and four case-control (OR,0.991; 95%CI,0.626-1.356) studies compared the prevalence of breast cancer among PCOS and non-PCOS women. As shown in Table 5 and Table 6, there was no significant association of PCOS with breast cancer. Five case-control studies investigating the association between endometrial cancer and PCOS, as shown in Table 7, demonstrated that there was no statistically significant association of PCOS and endometrial cancer (OR=1.219; 95%CI,0.816-1.623), while in six cohort studies, as shown in Table 8, women with PCOS were at significant increased risk of endometrial cancer (RR=2.542; 95%CI,1.755-3.328). The sensitivity analysis was performed that excluded the trial which had a greater weight in the result of the case-control (Zucchetto: 73.02%) and the cohort study (Brinton: 51.16%) and the results remained unchanged. The OR in the sensitivity analysis of the case-control study was 1.609 (95%CI,0.597-2.621, I^2=37.3%), the RR of the cohort study obtained from the sensitivity analysis was 2.542 (95%CI,1.755-3.328, I^2=0.0%). Four case-control studies compared the prevalence of ovarian cancer of PCOS and non-PCOS women. As shown in Table 9, we did not find a significant association between PCOS and ovarian cancer (OR=1.219; 95%CI,0.816-1.623), while in six cohort studies, as shown in Table 10, there was a statistically significant association between PCOS and ovarian cancer (RR=1.818; 95%CI,1.222-2.414). The sensitivity analysis excluded the trial with high weight of the case-control study (Harris: 54.77%) and demonstrated that the result was not affected by the individual study. The OR obtained from the sensitivity analysis of the case-control study was 1.291 (95%CI,0.691-1.891, I^2=0.0%).

Heterogeneity was examined within case-control studies and cohort studies. No significant heterogeneity was found among case-control (I^2=11.7%, p=0.334) and cohort studies (I^2=0.0%, p=0.523) which investigated the association between breast cancer and PCOS. The analysis did not show significant heterogeneity in case-control studies (I^2=24.7%, p=0.257) and cohort studies (I^2=0.0%, p=0.515) which compared the prevalence of endometrial cancer of PCOS and non-PCOS women. No significant heterogeneity was observed in case-control studies (I^2=0.0%, p=0.705) and cohort studies (I^2=0.0%, p=0.965), which investigated the association between PCOS and ovarian cancer.

Publication bias was not reported because the number of trials was less than 10 for each comparison part.

Discussion

Main findings

PCOS is one of the most common endocrine disturbance of the reproductive-age women, causing anovulatory infertility, hirsutism, and hyperandrogenism. PCOS is a systematic disease which can increase the risk of cardiovascular disease[29], and cause dyslipidemia[30]. Women with PCOS are observed having a higher prevalence of autoimmune thyroid disease[31].

This meta-analysis of 13 case-control and 8 cohort studies involving 3831083 participants demonstrates that women with PCOS are not at a significantly increased risk of breast cancer. Results of case-control studies show that PCOS do not increase the risk of endometrial cancer and ovarian cancer, while the results of cohort studies show a statistically increased risk of endometrial and ovarian cancer within women with PCOS. The present analysis building on recent works demonstrate a controversial result among the case-control study and the cohort study. Several reasons are considered for the differences. The prospective cohort study is following the natural development of disease, while the case-control study is aiming to investigate the previous exposure factors. It is important to recognize that in the case-control study, the data synthesize are almost exclusively derived from self-report inventories that varied substantially in their sensitivity and specificity for diagnosing PCOS. However, the ascertainment of exposure in the cohort study is mainly from secure record and structured interview which indicate the diagnostic criteria of PCOS, which can make the result more available. According to the "Evidence Pyramid" of the new nine-level evidence grading system,

the evidence level of the cohort study is higher than that of the case-control study. The cohort study is more suitable for the investigation of risk factor of disease with a higher incidence, such as PCOS with a prevalence of 6%-8%. Therefore, the evidence from cohort studies is considered having higher value and reliability in this meta-analysis.

Strengths and Limitations

This meta-analysis has several strengths. Our meta-analysis include comprehensive coverage of the case-control study and cohort study with large sample size, which significantly increased the statistical power to detect potential associations. Careful appraisal of study quality and comprehensive analysis for the comparison of cancer risk among PCOS and non-PCOS women.

It must be recognized that this meta-analysis has some possible limitations. First, 12 of 13 case-control studies included rely on self-report measures of PCOS diagnosis. The self-report of the included studies may have introduced bias to the present results. For instance, women with gynecological cancer may be more likely to recall the gynecological diseases they have been diagnosed, such as PCOS. Second, the data are derived from studies that have different designs and screening instruments. The substantial heterogeneity among the studies remained largely unexplained by the variables inspected. Third, the current analysis does not combine case-control and cohort studies, which makes the number of articles in each section is less than 10, which limited the investigation of publication bias. Fourth, the analysis demonstrates that several studies have a greater weight which means the analysis might have been dominated by a single study. The stability of the results can be significantly influenced. The sensitivity analysis excluded the study with high weight is performed and the result remains unchanged. Last, the characteristic and the sources of participants are different. For example, the group from hospital can be different from the group from community in some characteristics, which may have introduced bias to the results.

Interpretation

The results of this meta-analysis and the previous meta-analysis show some differences. The meta-analysis in 2014 which included in 11 studies suggested that women of all ages with PCOS are at an increased risk of endometrial cancer (OR, 2.79; 95% CI, 1.31–5.95, P, 0.008) but the risk of ovarian and breast cancer (OR, 1.41; 95% CI, 0.93–2.15, P, 0.11 and OR, 0.95; 95% CI, 0.64–1.39, P, 0.78, respectively) was not significantly increased overall. The meta-analysis investigating the relationship between PCOS and breast cancer demonstrated that PCOS no does increase the risk of breast cancer. The OR in case-control studies was 0.87 (95% CI, 0.44 to 1.31) and that of cohort studies was estimated 1.18 (95% CI, 0.93 to 1.43).

This meta-analysis demonstrate that PCOS will not increase the risk of breast cancer. Evidence from the cohort studies suggests that PCOS significantly increases the risk of endometrial and ovarian cancer, although the case-control studies did not. In the current analysis, the point estimate regarding the association of PCOS with the risk of endometrial and ovarian cancer is increased, but it just reaches statistical significance in the cohort study and does not reach statistical significance in the case-control study. These results suggest the possibility of a significant association of PCOS with increased risk of endometrial and ovarian cancer, but the current analysis may have lacked statistical power to show this association. The results of our study may provide practical and valuable clues for the poor prognosis of PCOS and promote the progress in the field of the prevention, diagnosis and treatment of PCOS.

Conclusion

By combining data from multiple studies, this meta-analysis found that PCOS was not associated with increased risk for breast cancer. In case-control studies, the result demonstrated that PCOS did not increase the risk of endometrial and ovarian cancer, while in cohort studies, women with PCOS were at significantly increased risk of endometrial and ovarian cancer. Future research is needed to evaluate the associations of PCOS and gynecological cancer. However, the results of this analysis prompt public-health workers to take active measures to prevent, diagnose and treat PCOS.

Disclosure of interests

The author has no conflicts of interest

Contribution to authorship

Daxi Wang conceived and designed the study. Wang, Zhaoxun Li and Wenyuan Lu performed the literature search, data extraction and data analysis. Wang, Li, Lu and Shiyi Cao wrote the manuscript.

Details of ethics approval

All analysis were based on previous published studies, thus no ethical approval and patient consent are required.

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Supporting Information

Supporting Information may be found in the online version of this article.

Figure1 Flow diagram selection and inclusion process

Table 1 Characteristic of included studies

Table 2 Quality assessment of the case-control study using the Newcastle-Ottawa scale.

Table 3 Quality assessment of the cohort study using the Newcastle-Ottawa scale.

Table 5 The forest plot of breast cancer in women with PCOS compared with controls in case-control studies.

Table 6 The forest plot of breast cancer in women with PCOS compared with controls in cohort studies.

Table 7 The forest plot of endometrial cancer in women with PCOS compared with controls in case-control studies

Table 8 The forest plot of endometrial cancer in women with PCOS compared with controls in cohort studies

Table 9 The forest plot of ovarian cancer in women with PCOS compared with controls in case-control studies.

Table10 The forest plot of ovarian cancer in women with PCOS compared with controls in cohort studies.

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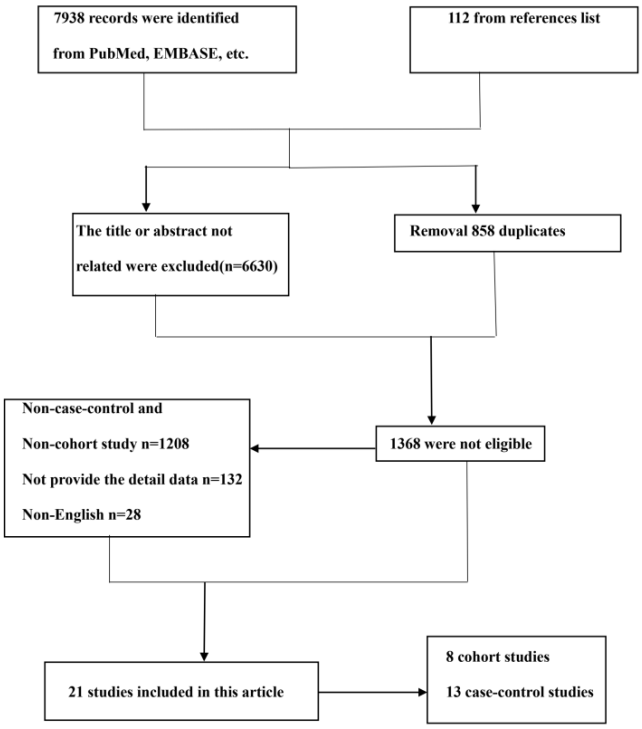

Figure1. Flow diagram selection and inclusion process

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Table 2 Quality assessment using the Newcastle-Ottawa scale (for case-control study).docx available at https://authorea.com/users/333512/articles/459721-polycystic-ovarian-syndrome-and-risk-of-breast-endometrial-and-ovarian-cancer-a-systemic-review-and-meta-analysis

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Table 3 Quality assessment using the Newcastle for the cohort study.docx available at https://authorea.com/users/333512/articles/459721-polycystic-ovarian-syndrome-and-risk-of-breast-endometrial-and-ovarian-cancer-a-systemic-review-and-meta-analysis