CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF

PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2658560

Available online at: http://www.iajps.com *Research Article*

RELATIONSHIP BETWEEN FEMALE HORMONAL AND MENSTRUAL FACTORS AND PANCREATIC CANCER: A META-ANALYSIS OF OBSERVATIONAL STUDIES

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Article Received: February 2019 **Accepted:** March 2019 **Published:** April 2019

Abstract:

The objective of this study was to assess the relationship between female hormone and menstrual factors and pancreatic cancer (PC) through a meta-analysis of observational studies.

We undertook a systematic literature search up through PubMed and EMBASE databases. Combined relative risks (RRs) were estimated by random-effects models. Subgroup analysis was performed by study design, source of control, and geographic regions. Sensitivity analyses and publication bias were utilized to evaluate the robustness of our results.

A total of 27 case–control and cohort studies were retrieved for this meta-analysis. No significant associations were observed between the risk of PC and age at menarche (RR=0.94, 95% confidence interval [CI] 0.83–1.07), age at menopause (RR=0.98, 95% CI 0.85–1.13), hysterectomy (RR=0.97, 95% CI 0.84–1.11), oophorectomy (RR=1.02, 95% CI 0.82–1.26), hormone replacement therapy (RR=0.97, 95% CI 0.87–1.08), and oral contraceptives (RR=1.09, 95% CI 0.96–1.23).

This meta-analysis of observational studies does not support the hypothesis that exogenous hormone use and menstrual factors are associated with PC.

Keywords: *Female Hormonal Factors; Menstrual Factors; Pancreatic Cancer; Cohort Study.*

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Please cite this article in press Mahwish Majeed et al., ***Relationship Between Female Hormonal And Menstrual Factors And Pancreatic Cancer: A Meta-Analysis Of Observational Studies.,*** *Indo Am. J. P. Sci, 2019; 06(04).*

INTRODUCTION:

Pancreatic cancer (PC) represents the fourth most common cause of cancer mortality. The primary causes are poorly understood. Although cigarette smoking, obesity, a history of diabetes mellitus (DM), a history of pancreatitis, and not belonging to the O blood group have been shown to be risk factors for PC, they may only account for a small number of cases. Therefore, the question of what additional risk factors might influence the development of PC remains open.

A number of findings suggest that a cause and effect relationship may exist between PC risk and sex hormones. First, the incidence of PC is approximately 30% to 50% higher in men than in women. Second, biological experiments have confirmed the presence of steroid hormone receptors and sex-steroid biosynthetic enzymes in both normal and cancerous human pancreatic tissue. Third, exogenous estrogens can inhibit the development of PC in animal models. On the contrary, testosterone has been shown to strongly promote growth in experimental PCs. Fourth, the results of previous meta-analyses showed that parity (number of birth) is associated with a decreased risk of PC. Finally, obesity, one of the well-established risk factors for PC, provides a leading source of endogenous estrogen exposure in postmenopausal women. Therefore, these have raised interest in some exposures related with female hormones in the development of PC. Over the last 2 decades, many studies have examined hormonal and menstrual factors in relation to PC risk. However, findings regarding the association between hormonal and menstrual factors and PC risk have conflicted with each other. Thus, we tested the hypothesis that exogenous hormone use and menstrual factors are associated with PC by conducting a meta-analysis of case–control and cohort studies.

METHODS:

Selection Criteria:

We used the following inclusion criteria: the article described a case–control or cohort study that evaluated the relationship between hormonal and menstrual factors and PC risk; the article presented relative risk (RR) (ie, odds ratios [ORs], hazard ratios [HRs]) with corresponding 95% confidence intervals [CIs] or standard errors (SEs), or sufficient data to estimate them); if >1 article involving the same subjects was published, only the most informative study was included; reviews, meta-analyses, case reports, and conference abstracts were excluded.

Search Strategy:

A systematic search of the PubMed and EMBASE databases (up to July 10, 2014) was performed without language limitations. We identified articles using the follows search terms: (“pancreatic cancer” OR “pancreatic neoplasms” OR “pancreatic tumors” OR “pancreatic adenocarcinoma”) AND (“hormone” OR “exogenous hormones” OR “exogenous hormones use” OR “hormone replacement therapy” OR “menopausal hormone therapy” OR “estrogen replacement therapy” OR “menopausal hormone use” OR “oral contraceptives” OR “reproductive factors” OR “reproductive history” OR “menstrual factors” OR “age at menarche” OR “menarche” OR “menstruation” OR “menopause” OR “age at menopause” OR “gravidity” OR “pregnancy” OR “breastfeeding” OR “miscarriage” OR “abortion” OR “fertility” OR “birth” OR “age at first birth” OR “climacteric” OR “parity” OR “ovariectomy” OR “oophorectomy” OR “hysterectomy”) AND (“risk” OR “risk factors” OR “risk assessment”). We also manually examined the references of relevant studies or reviews that assessed the association between menstrual factors and the risk of PC to identify additional studies.

Data Extraction:

Two reviewers (B.T. and J.L.) independently extracted the following data from each eligible study: last name of the first author, year of publication, country, study period/follow-up years, study design, cases/cohort size (ie, controls), exposure variables, measurement of exposure, and RRs with corresponding 95% CIs or SEs, and raw data. Risk estimates that were adjusted for the maximum number of confounders were utilized in this meta-analysis; when these were unavailable, the raw data were used.

Statistical Analysis:

RR was used to measure of the association between hormonal and menstrual factors and PC risk. ORs and HRs were deemed equivalent to RRs because the prevalence of PC is rare. When publication bias was detected by Egger test, the Duval and Tweedie nonparametric trim-and-fill procedure was used to further evaluate the robustness of our results. All statistical analyses were conducted using STATA software, version 12.0 (STATA Corporation, College Station, TX).

RESULTS:

Features of the Study

Figure1 shows the process used for the literature

search and study selection. A total of 441 publications were identified from databases. Seven studies were additionally identified from the references of other relevant studies. To begin with, 122 duplicate records were excluded. Next, we reviewed the titles and abstracts, and 285 articles were further removed. Finally, 41 articles with full-text were assessed for eligibility. Of these 41 articles, 14 were further excluded because they provided insufficient data, 46 were reviews or meta-analysis involved parity, and had overlapping data.

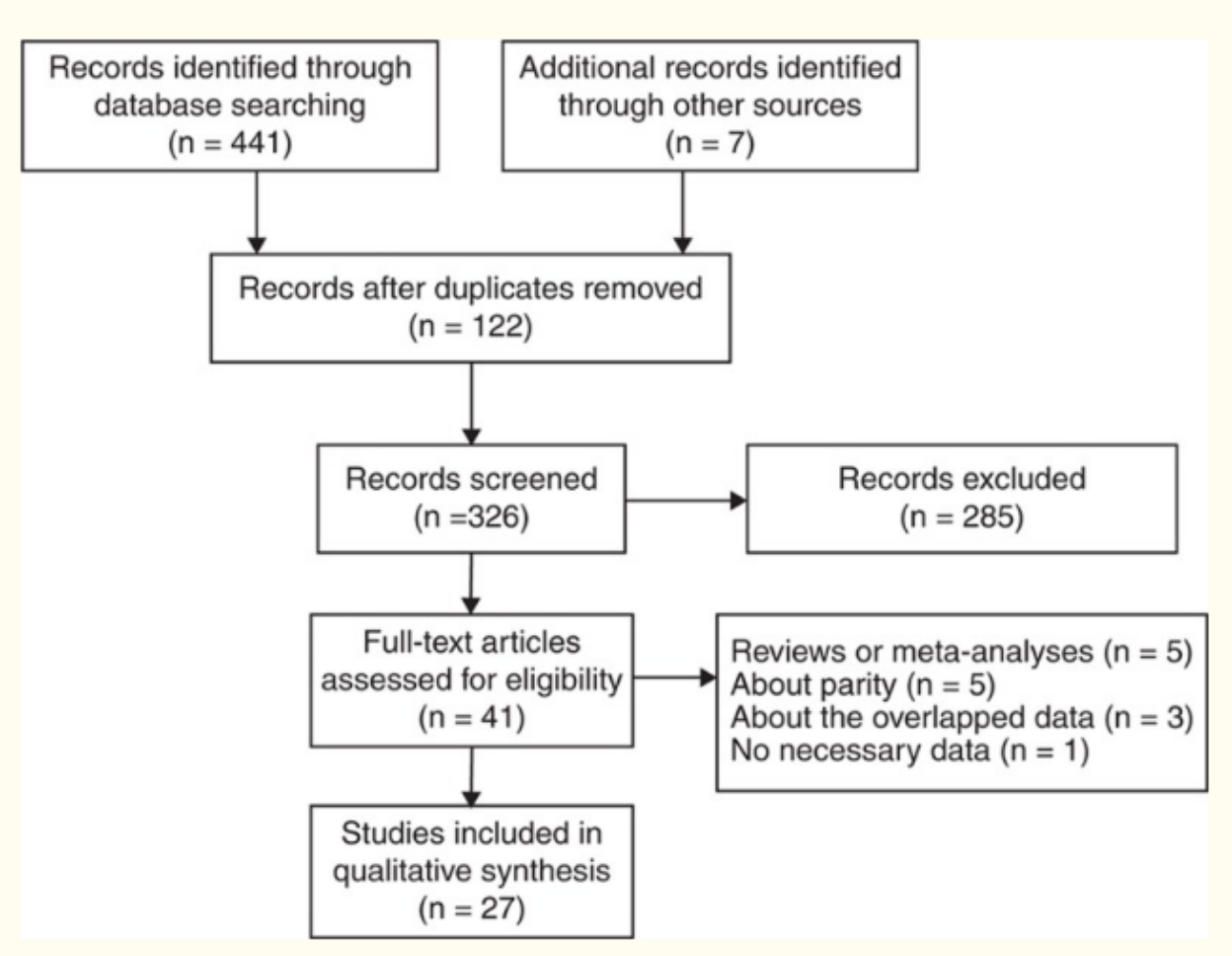
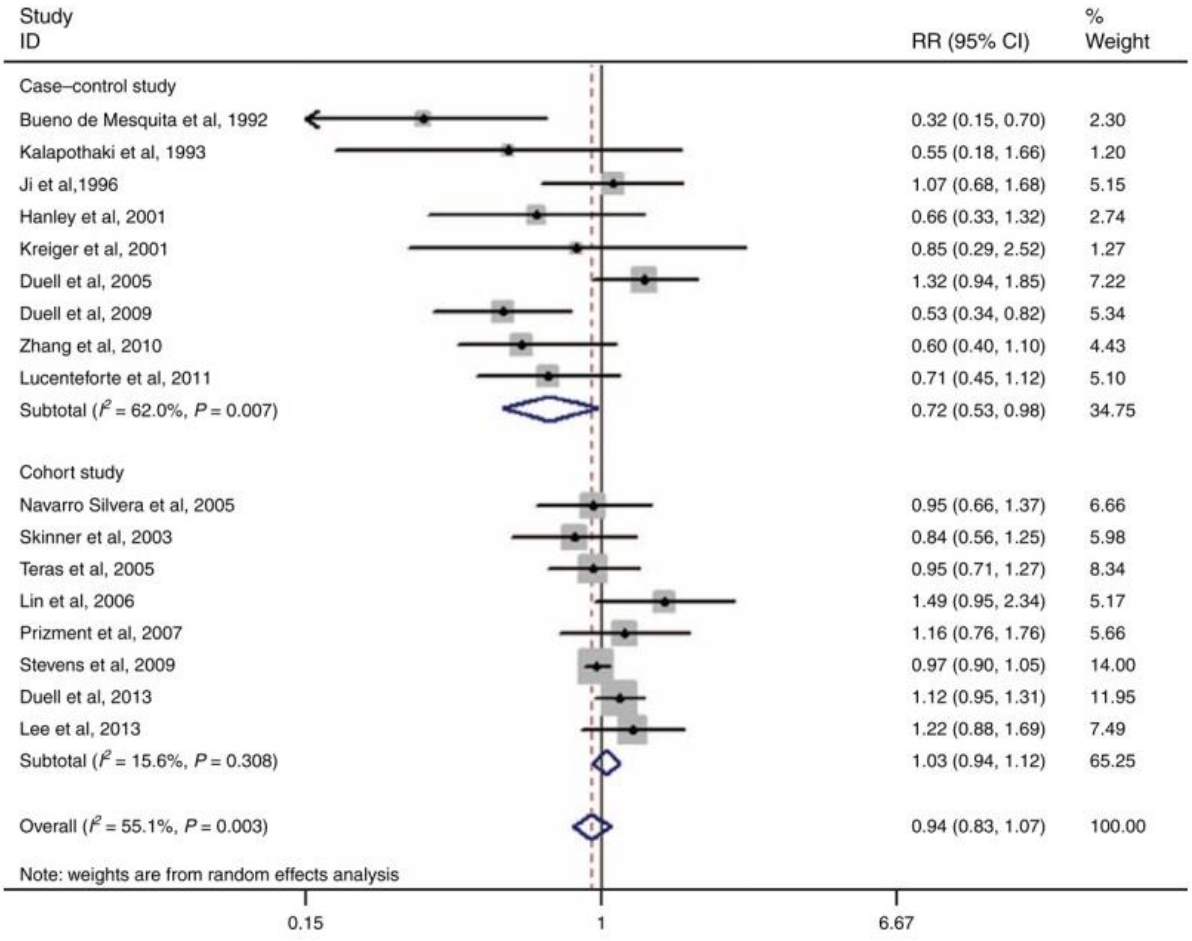


Figure 1: Full Research Diagram

In total, 27 articles were included in the present analysis. All studies were published in English. The first study dated back to 1986. The latest article was published in 2018. Fourteen of 27 studies were case–control studies, the remainders were cohort studies. In 7 of case–control studies, controls were recruited randomly from hospitals in 3 studies; in the other 7, they were drawn from the general population. All studies were published in Western countries except 2 from Asia and 1 from Africa. Cases were ascertained by means of computerized record linkages to cancer registries, histopathology, and medical records (eg, health insurance records, death certificates, radiological images). Assessment tools to collect data on exposure variables consisted of interviewer-administered questionnaire, self-administered questionnaire, prescription registry, hospital records, and mass screening registry.

Overall Meta Analysis Results:

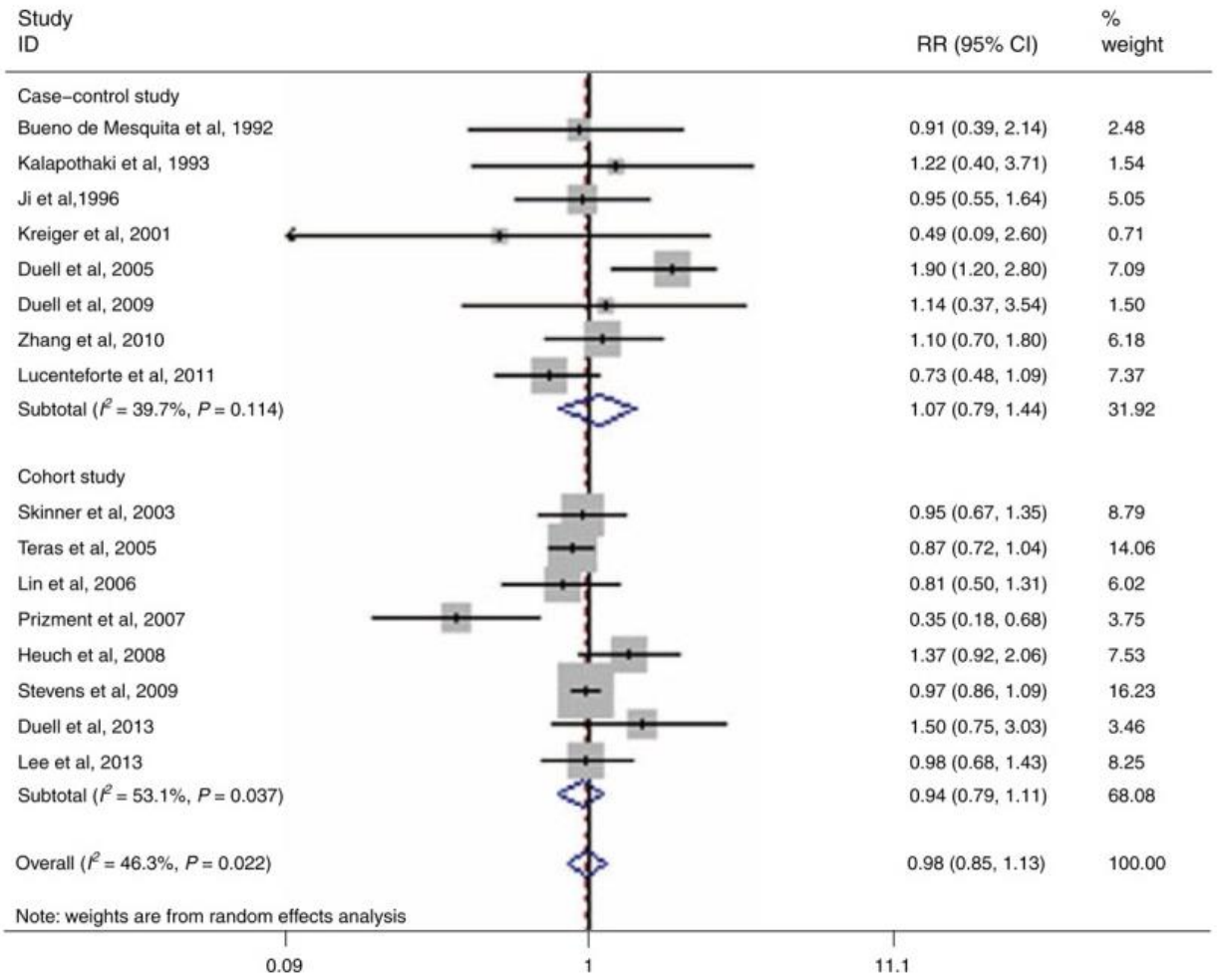


Late Versus Early Age at Menarche:

Seventeen studies have examined the association between age at menarche and PC risk.4,17–19,22–28,30,34–38 The pooled RR for the oldest age compared with the youngest age was 0.94 (95% CI 0.83–1.07, I2=55.1%, P_Q=0.003.

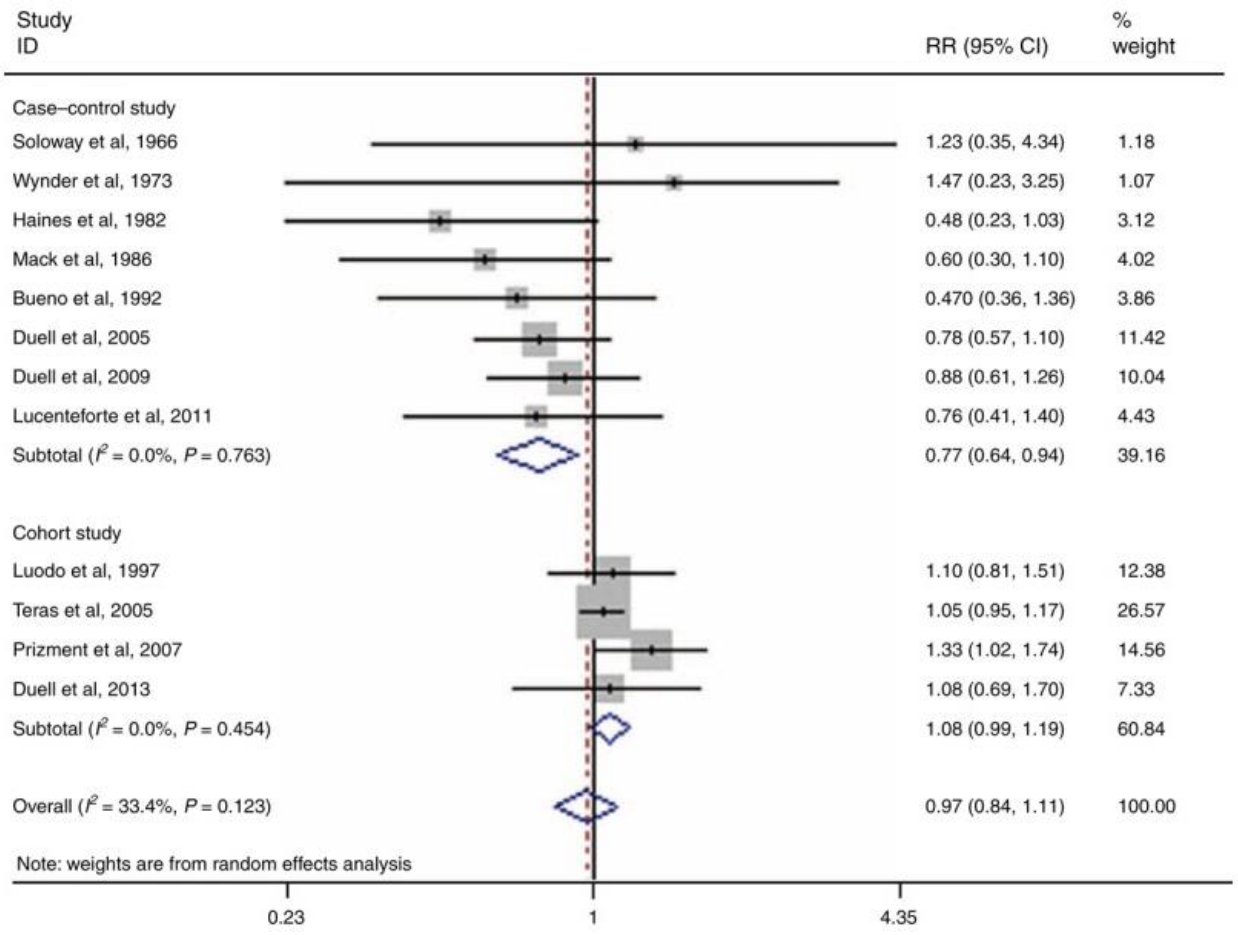
Late Versus Early Age at Menopause:

The effect of age at menopause on the risk of PC has been evaluated by 16 articles. The summary RR for the oldest age versus the youngest age was 0.98 (95% CI 0.85–1.13, I^2=46.3%, P_Q=0.022.



Ever Versus Never Hysterectomy:

Twelve reports have evaluated the correlation between hysterectomy and PC risk. The cumulative risk estimates for ever having had a hysterectomy versus never having had 1 was 0.97 (95% CI 0.84–1.11, I^2=33.4%, P_Q=0.123).



Results of Subgroup Analyses:

Subgroup analyses were performed according to study design (case–control vs cohort studies), source of control (population-based vs hospital-based case–control studies), and geographic regions (North America vs Europe vs Asia). For age at menopause, HRT, and oophorectomy, the overall results were not significantly influenced by geographic regions, study design, or source of control as mentioned. When subgroup analyses were conducted by study design, statistically significant associations between PC risk and age at menarche (RR=0.72, 95% CI 0.53–0.98) and hysterectomy (RR=0.77, 95% CI 0.64–0.94) were observed in case–control studies. However, these associations did not emerge in cohort studies. In further analysis by source of control, a decreased risk of significance was observed only for subjects who were from hospital-based case–control studies. For OC, a statistically marginal association was observed in cohort studies (RR=1.14, 95% CI 1.00–1.29).

Sensitivity Analysis:

In the sensitivity analysis, one single study was excluded at a time to investigate the influence of individual study on the overall results. Sensitivity analysis demonstrated that the results of OC were not robust. When excluding the study conducted by Kreiger et al, an increased risk of borderline significance was found (RR=1.12, 95% CI 1.00–1.24). For other exposures, the results were not meaningfully changed (data not shown). In addition, we performed an alternative sensitivity analysis to investigate whether the overall results were influenced by potential confounders or not. All results were not significantly modified by smoking, body mass index (BMI), or diabetes except for OC. When we performed an analysis limited to those studies that provided risk estimates adjusted for smoking, BMI, and diabetes, a meaningful association between OC and PC risk was detected (RR=1.19, 95% CI 1.02–1.40).

DISCUSSION:

To our knowledge, this study is the first meta-analysis assessing the relationship between PC risk and hormonal and menstrual factors, and this meta-analysis included 14 case–control and 13 cohort studies involving >2,300,000 subjects. Findings from our meta-analysis revealed no significant associations between the risk of PC and age at menarche, age at menopause, hysterectomy, oophorectomy, HRT, and OC.

Hysterectomy is one of the most frequent gynecological procedures for women in developed countries. It has been estimated that approximately a third of women will have a hysterectomy in their lifetime. Having a good understanding of the consequences of this procedure is very important. In our meta-analysis, we found that 12 studies have addressed the relationship between hysterectomy and the risk of PC. The pooled results showed that hysterectomy was not correlated with the risk of PC. When subgroup analyses were performed according to study design, hysterectomy was inversely associated with PC risk in case–control studies; however, in cohort studies, this association did not emerge. In further analyses by source of control, the inverse association was observed in hospital-based case–control studies but not in population-based case–control studies. This discrepancy may be related with the limitations of hospital-based case–control studies. In hospital-based case–control studies, the likelihood of bias may be greater. Moreover, residual confounding was possible as 4/5 risk estimates in hospital-based case–control studies were not adjusted for any confounders.

Therefore, the true relationship between hysterectomy and PC risk may be overestimated or underestimated, and the results of case–control studies should be interpreted with caution. Assessment of partial versus total hysterectomy has been performed in a Finland cohort with 25,382 women. Luoto et al found a decreased risk for women with partial hysterectomy but an increased risk for women with total hysterectomy; however, these associations were not statistically significant. The significance of these findings is unclear. Therefore, the correlation between hysterectomy and the risk of PC requires further discussion.

Concerning the use of exogenous hormones, we found that HRTs were not significantly associated with the risk of PC, and that the association between HRT and PC risk was not significantly modified by study design, source of control, or the potential confounders (smoking, BMI, and diabetes). When an analysis was limited to subjects who were postmenopausal women, similar trend was detected. With regard to the OC use, the overall results showed no significant association between OC use and PC risk. However, in subgroup analysis by study design, an increased risk of borderline significance was associated with OC use, and the results from the previous 2 methods of sensitivity analysis showed that OC use may be correlated with PC risk.

CONCLUSION:

The relationship between reproductive factors and PC risk has been investigated by 2 meta-analyses. The meta-analysis of 11 prospective and 11 case–control studies that reported the summary RR for PC comparing the highest versus lowest parity was 0.86 (95% CI 0.73–1.02). However, significant inverse associations were observed in the studies that adjusted for cigarette smoking, BMI, and DM. In the latter meta-analysis of 10 cohort studies and 10 case–control studies with 8205 cases, Zhu et al distinguished the number of pregnancy from the number of parity and found ever-parous women were associated with a decreased risk of PC; there was no linear relationship between number of parity and risk of PC.

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