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Association between diabetes mellitus and subsequent ovarian cancer in women

A systematic review and meta-analysis of cohort studies

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Abstract

Epidemiologic studies have suggested that diabetes mellitus (DM) might be associated with risk of ovarian cancer; however, the results have been inconsistent. The aim of this study was to determine the relationship between DM and the incidence of ovarian cancer on the basis of cohort studies.

Relevant studies from PubMed, Embase, and the Cochrane Library until September 2016 were collected. The summary risk ratio (RR) was used as the effect measure in a random effects model. Sensitivity analysis, subgroup analysis, and calculation of publication bias were conducted.

Thirteen articles including 14 cohorts comprising a total of 3708, 313 women and reporting 5534 cases of ovarian cancer were included. The summary RR suggested that patients with DM had a higher risk of ovarian cancer than patients without DM (RR: 1.19; 95% confidence interval: 1.06–1.34; $P = .004$), and no evidence of publication bias was found. The subgroup analysis indicated a higher incidence of ovarian cancer in patients with DM in studies published after 2010, studies not conducted in Europe or the United States, studies that did not adjust for body mass index or smoking status, and studies with lower Newcastle–Ottawa Scale scores.

The present findings indicated that DM is a risk factor for ovarian cancer, and future large-scale epidemiologic studies should be performed to evaluate this relation in specific populations.

Abbreviations: BMI = body mass index, CI = confidence interval, DM = diabetes mellitus, RR = risk ratio.

Keywords: diabetes mellitus, meta-analysis, ovarian cancer, systematic review

1. Introduction

Ovarian cancer is the 5th leading cause of death among malignancies and accounting for approximately 240,000 cases and 150,000 deaths in 2012 worldwide.[1] Nearly 2/3 of cases are diagnosed in its advanced stages or unstaged and just 30% for 5-year survival rate for these patients.[2,3] The survival rates are poor, owing to the lack of effective screening strategies.[4] This emphasizes the need to focus on identifying risk factors, in order to reduce the risk of ovarian cancer. The associations among dietary flavonoids, flavonoid subclasses, bilateral salpingectomy, depression and anxiety, dietary fat and fatty acid, overweight, or obesity and the incidence of ovarian cancer have been evaluated in previous meta-analyses.[5–9] However, several other factors associations with the risk of ovarian cancer are not precisely understood and remain controversial.

Diabetes mellitus (DM) is a growing global pandemic affecting approximately 3.0% to 4.0% of adults worldwide.[10] Systematic reviews and meta-analyses have already evaluated the risk of cancer incidence at different sites.[11–15] A previous study indicated that women with DM have a moderately increased risk of developing ovarian cancer.[16] However, traditional case–control studies were included in the previous study, which are less strong than cohort studies, and the findings of stratified analyses were affected by differences in study design. Furthermore, whether this relation differs according to the characteristics of participants remains unclear.

Several prospective cohort studies that explored the relationship between DM and ovarian cancer risk have already been published.[17–29] Several studies suggested that DM is associated with an elevated risk of ovarian cancer,[19,28] whereas other studies showed no evidence for this association.[17,18,20–27,29] Clarifying any potential correlation between DM and ovarian cancer, which has not been definitively established, is particularly important in the general population. We therefore attempted a comprehensive examination of the available cohort studies to determine the association between DM and the incidence of ovarian cancer.

2. Materials and methods

2.1. Data sources, search strategy, and selection criteria

This study was conducted and reported according to the Meta-analysis of Observational Studies in Epidemiology protocol.[30] Any prospective observational study that examined the relationship between DM and ovarian cancer was eligible for inclusion in

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this review. The included articles were restricted to those published in English; however, there was no restriction on publication status (published, in press, or in progress). Electronic databases including PubMed, Embase, and the Cochrane Library were systematically searched by using the combination of the search terms (diabetes or DM or glucose) and (cancer, carcinoma, neoplasm, and tumor) and ovarian, with the deadline being September 2016. To identify unpublished studies or collect updated information in some of the included studies that could provide useful data, we contacted the authors, reviewed abstracts and presentations of recent major meetings, and searched for ongoing studies that were registered as completed but not yet published. Manual searches of reference lists from all the relevant articles were conducted to identify additional potential eligible studies. All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

After the literature search, the selected studies were independently reviewed by 2 of the authors, and a group discussion settled any inconsistencies until a consensus was reached. A study was eligible for inclusion if the following criteria were met: the study had a prospective cohort design; the study investigated the association between DM and the risk of ovarian cancer; and the study reported an effect estimate (risk ratio [RR], hazard ratio, or odds ratio) and 95% confidence intervals (CIs) for comparisons of DM and non-DM participants. We excluded all retrospective case–control studies owing to various confounding factors that could bias the results. We included the latest outcomes if there were cases of overlapping reports.

2.2. Data extraction and quality assessment

The data extraction and quality assessment processes were conducted independently by 2 of the authors. Any discrepancy was resolved through a discussion or by consulting the corresponding author. Information was extracted from the included studies and recorded in electronic Excel sheets. Data were extracted on the basis of the first author, publication year, country, sample size, mean age at baseline, body mass index (BMI), number of ovarian cancer cases, follow-up duration, and adjusted factors. For studies that reported several multivariable adjusted effect estimates, we selected the maximally adjusted estimates for potential confounders. The quality of the included studies was appraised by using the Newcastle–Ottawa scale (NOS).[31] This scale was categorized into 3 groups of items: selection (representativeness of the exposed cohort; selection of the nonexposed cohort; ascertainment of DM; demonstration that ovarian cancer was not present at start of study; 4 points), comparability (comparability on the basis of the design or analysis; 2 points), and outcome (assessment of outcome; adequate follow-up duration; adequate follow-up rate; 3 points), with a total of 9 points. In this review, studies with a total of score of 8 or 9 were considered to be of high quality.

2.3. Statistical analysis

We examined the relationship between DM and the risk of ovarian cancer on the basis of the effect estimate (RR, hazard ratio, or odds ratio) and its 95% CI published in each study. The random effects model was used for data pooling of DM versus non-DM participants.[32] The heterogeneity was tested by using the Q statistics and I^2 test. I^2 values of <25%, 25% to 50%, 50% to 75%, and >75% were considered to indicate no, low, moderate, and high heterogeneity, respectively. $P < .05$ or $I^2 >$ 50% was deemed to denote a significant heterogeneity.[33,34] Subgroup analyses were conducted for ovarian cancer incidence on the basis of publication year, country, mean age, follow-up duration, adjusted BMI, adjusted smoking status, and study quality. The P values for heterogeneity between subgroups were calculated by using the χ^2 test.[35] Sensitivity analysis was conducted by removing a single study from the overall analysis to evaluate the impact of an individual study.[36] Visual inspections of funnel plots for ovarian cancer were conducted. The Egger[37] and Begg[38] tests were employed to statistically assess publication bias for ovarian cancer. All reported P values were 2-sided, and P values $< .05$ were considered statistically significant for all included studies. Statistical analyses were performed by using STATA software (version 10.0; Stata Corporation, College Station, TX).

3. Results

Among the 2042 studies that were identified through searching PubMed, Embase, and the Cochrane library, 1984 duplicates (n = 1152) and irrelevant (n = 832) records were first excluded. Fifty-eight full-text studies were assessed for eligibility. Furthermore, 9 studies with a case–control design, 13 studies showing insufficient data, and 23 epidemiology studies on other risk factors were excluded. Finally, 13 studies including 14 cohorts were included for qualitative synthesis. The selection process is presented in Fig. 1.

Table 1 summarizes the general characteristics of the included studies. Of the 13 included studies, 5 were conducted in Europe,[17,20–22,27] 2 were conducted in the United States or Canada,[18,24] and the remaining 6 were conducted in Asia.[19,23,25,26,28,29] The number of participants ranged from 11,686 to 1,152,122, with a total of 3,708,313 women. The mean age of participants ranged from 44.0 to 62.6 years, and the follow-up duration ranged from 3.5 to 15.0 years. The NOS score of the included studies ranged from 6 to 8, with 5 studies being of high quality and the remaining 8 studies being of low

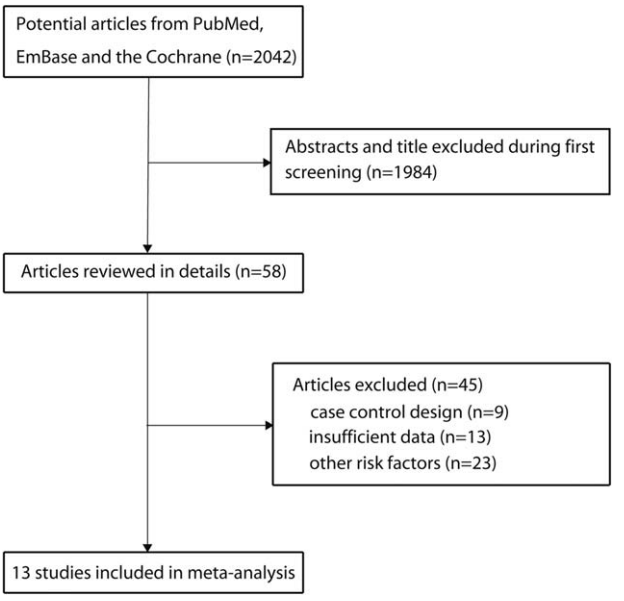

Figure 1. Study selection process.

Table 1

Baseline characteristic of studies included.

Author	Publication years	Country	Sample size	Mean age at baseline, y	BMI, kg/m^2	Number of ovarian cancer cases	Follow-up duration, y	Adjusted factors	NOS score
Rapp[22]	2006	Austria	77,228	43.0	NA	99	8.6	Age, smoking status, occupational group, and BMI	7
Inoue[23]	2006	Japan	51,223	51.8	NA	74	10.7	Age at baseline, study area, history of cerebrovascular disease, history of ischemic heart disease, smoking, ethanol intake, BMI, leisure-time physical activity, green vegetable intake, and coffee intake	8
Khan[26]	2006	Japan	33,503	NA	NA	30	8.0	Age, BMI, smoking, and drinking	8
Stattin[17]	2007	Sweden	33,293	46.1	25.3	90	8.3	Age, calendar year, and smoking	8
Chodick[19]	2010	Israel	47,682	61.6	NA	88	8.0	Age, region, SES, use of healthcare services a year prior to index date, BMI, and history of cardiovascular diseases	7
Wotton[20]	2011	England	11,686	>30.0	NA	45	NA	Age in 5-year bands, time period in single calendar years, and district of residence	7
Lambe[21]	2011	Sweden	230,737	46.4	23.9	783	11.7	Age, fasting status, parity, age at birth of first child	6
Johnson[24]	2011	Canada	169,012	60.7	NA	295	4.3	Age, SES, number of physician visits, and year of diagnosis	7
Bjørge[27]	2011	Austria, Norway and Sweden	287,320	44.0	NA	128	11.0	Age, cohort, smoking, and BMI	8
Gapstur[18]	2012	US	63,440	62.2	NA	524	15.0	Age, race, education, and postmenopausal hormone use, and BMI	8
Lo[25]	2012	China	912,447	60.5	NA	948	3.5	Age, residence, hypertension, hyperlipidemia	7
Chen[29]	2014	China	638,620	61.0	NA	935	9.0	Age, geographic area, urbanization status, Charlson score, history of endometriosis, cardiovascular disease, pelvic inflammatory disease, chronic liver disease, rheumatic disease, and frequency of medical visit	6
Dankner[28]	2016	Israel	1,152,122	NA	NA	1,495	11.0	Age, ethnicity, and SES	7

BMI = body mass index, NA = not available, NOS = Newcastle–Ottawa scale, SES = socioeconomic status.

quality (Table 1). Overall, 5 studies had a score of 8, 6 studies had a score of 7, and the remaining 2 studies had a score of 6.

All of the included studies reported the relationship between DM and ovarian cancer incidence. The summary result is shown in Fig. 2, and we noted that women with DM had a higher risk of developing ovarian cancer when compared with non-DM participants (RR: 1.19; 95% CI: 1.06–1.34; $P = .004$; Fig. 2), and a significant heterogeneity was observed ($I^2 = 43.8\%$; $P = .040$). As a result, a sensitivity analysis was conducted, and after each study was sequentially excluded from the pooled analysis, the conclusion was not affected by the exclusion of any specific study (Table 2).

Q-test for the analysis showed a value of $P < .05$ for ovarian cancer. Therefore, we conducted subgroup analyses to minimize the heterogeneity among the included studies and evaluate this relationship in specific subsets (Table 3). Overall, we noted that women with DM had an elevated risk of ovarian cancer in studies published after 2010 (RR: 1.18; 95% CI: 1.04–1.34; $P = .010$), studies not conducted in Europe or the United States (RR: 1.26; 95% CI: 1.06–1.50; $P = .008$), studies that did not adjust for BMI (RR: 1.15; 95% CI: 1.04–1.27; $P = .007$) or smoking status (RR: 1.20; 95% CI: 1.05–1.35; $P = .005$), and studies with lower NOS scores (RR: 1.22; 95% CI: 1.07–1.38; $P = .003$). No other significant difference was observed between the presence and absence of DM for ovarian cancer based on predefined factors.

A review of the funnel plots could not rule out the potential for publication bias for ovarian cancer (Fig. 3). The Egger and Begg test results showed no evidence of publication bias (P value for Egger = .378; P value for Begg = .381).

4. Discussion

The purpose of the present meta-analysis was to determine the correlates of DM and the incidence of ovarian cancer. Thirteen cohort studies that included 3,708,313 women were identified. The results showed that DM is associated with an increased risk of ovarian cancer. The findings of sensitivity analysis were consistent with the overall analysis. This result will help in better defining the risk factors of ovarian cancer, and could help physicians in evaluating the risk score of the general population.

The impact factor for the incidence of ovarian cancer has already been reported in previous meta-analyses. Hua et al[5] reported that consumption of dietary flavonoids and their subtypes (isoflavones, flavonols) has a protective effect against ovarian cancer (reduces the risk of ovarian cancer); however, flavone consumption had no such effect. Yoon et al[6] found that removal of the fallopian tubes is an effective approach to protect against ovarian cancer risk in the general population. Liu et al[9] indicated that a high body weight might have a harmful impact on the risk of ovarian cancer, especially for premenopausal women with severe obesity. However, the impact of other chronic diseases such as DM was not confirmed. Few prospective cohort studies have confirmed the relationship between DM and ovarian cancer. Chodick et al[19] conducted a retrospective cohort study and found that DM increased the ovarian cancer risk by 139% after an average of 8 years follow-up. Dankner et al[28] indicated that DM posed an increased risk of ovarian cancer, with the RRs being particularly elevated during the first year after the diabetes diagnosis; however, their study had a shorter follow-up duration of between 1 and 2 years. These 2 cohort studies were specifically

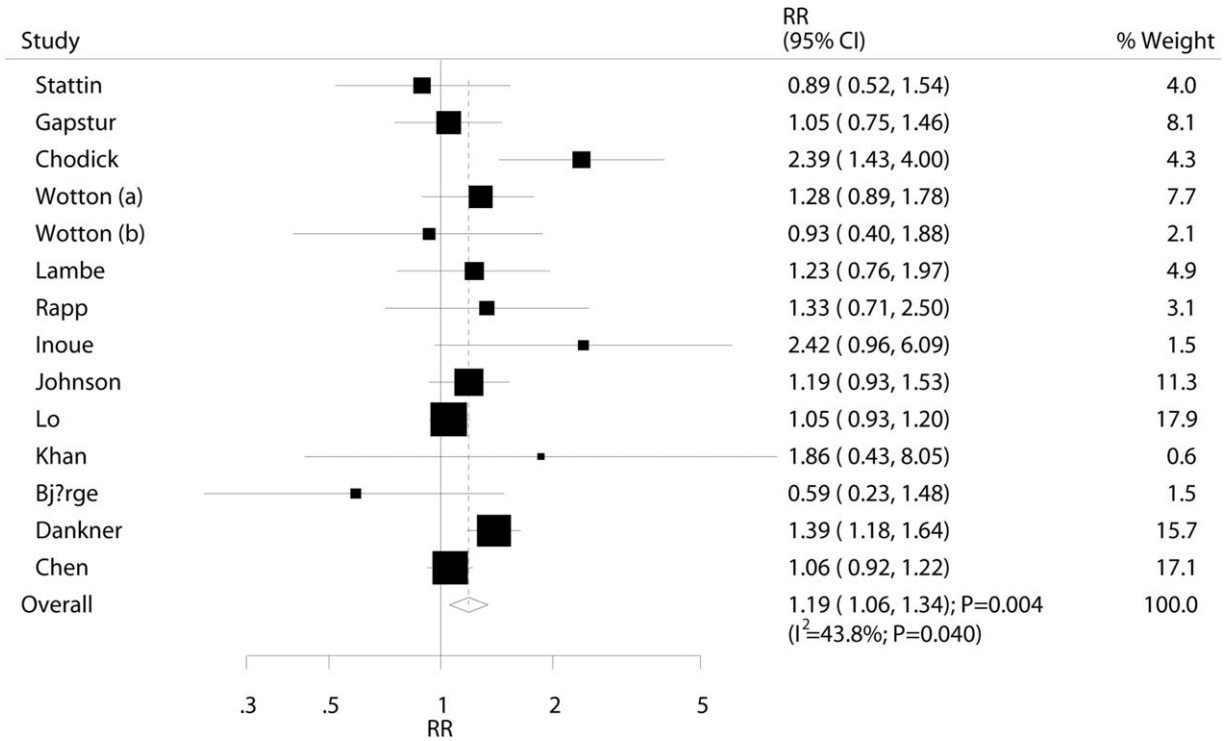

Figure 2. Association between diabetes mellitus and the risk of ovarian cancer. CI = confidence interval, RR = risk ratio.

conducted in Israel. The increased risk of ovarian cancer could be due to perturbations in insulin, insulin-like growth factors, gonadotropin, and steroid hormone metabolism, which could affect cell proliferation.[39,40] Furthermore, DM might play an important role in endometrioid cell histologic subtypes.

The subgroup analyses suggested that DM had a harmful impact on ovarian cancer in studies not conducted in Europe or the United States. The reason for this could be that the prevalence of DM was higher in Asia, and the diagnosis of DM took a longer time than in Western countries. In studies that did not adjust for BMI or smoking status, a significant difference was found between the presence and absence of DM for ovarian cancer, which might have biased the true correlates of DM and ovarian cancer. Progesterone and leptin may be potential endocrine mediators of the risk of ovarian cancer, and obesity was associated with the levels of insulin, androgens, and free insulin-like growth factor-I, which play an important role in the risk of ovarian cancer.[40,41] Furthermore, Faber et al[42] suggested that current smokers had an increased risk of developing invasive mucinous and borderline mucinous ovarian tumors, and former smokers also have an increased risk of developing borderline serous ovarian tumors. In addition, we noted DM was associated with higher incidence of ovarian cancer if the study published after 2010. The reason for this could be mostly included studies published after 2010 (9/13). The relationship between DM and ovarian cancer in study published before 2010 was available in

Table 2

Sensitivity analysis for ovarian cancer incidence.

Excluding study	RR	95%CI	*P*	Heterogeneity (I^2)	Q statistic
Rapp[22]	1.19	1.05–1.34	.007	47.7	0.028
Inoue[23]	1.17	1.05–1.32	.006	41.9	0.056
Khan[26]	1.19	1.05–1.34	.006	47.2	0.030
Stattin[17]	1.20	1.07–1.36	.003	46.1	0.035
Chodick[19]	1.15	1.04–1.26	.004	21.4	0.227
Wotton (a)[20]	1.18	1.04–1.35	.010	47.3	0.030
Wotton (b)[20]	1.20	1.06–1.35	.004	47.5	0.029
Lambe[21]	1.19	1.05–1.35	.007	48.0	0.027
Johnson[24]	1.19	1.04–1.36	.010	48.0	0.027
Bjørge[27]	1.20	1.07–1.35	.002	43.2	0.048
Gapstur[18]	1.21	1.06–1.37	.005	47.4	0.029
Lo[25]	1.22	1.07–1.40	.004	40.5	0.064
Chen[29]	1.22	1.06–1.40	.005	43.7	0.046
Dankner[28]	1.14	1.02–1.29	.024	29.6	0.148

CI = confidence interval, RR = risk ratio.

Table 3

Subgroup analysis.

Group	Number of studies	RR and 95%CI	*P*	Heterogeneity, %	*P* value for heterogeneity	*P* value for heterogeneity between subgroups
Publication year						
2010 or after	9	1.18 (1.04–1.34)	.010	53.1	.024	.675
Before 2010	4	1.29 (.84–1.99)	.239	20.8	.285	
Country						
Europe or USA	6	1.10 (.92–1.32)	.287	0.0	.696	.609
Other	7	1.26 (1.06–1.50)	.008	68.4	.004	
Mean age						
60 years or greater	5	1.15 (.98–1.34)	.086	59.8	.041	.043
<60 years	5	1.14 (.81–1.62)	.444	28.6	.231	
Follow-up duration						
10 years or greater	5	1.24 (.97–1.58)	.086	40.9	.148	.106
<10 years	7	1.15 (.99–1.34)	.068	47.0	.079	
Adjusted BMI						
Yes	6	1.41 (.93–2.15)	.107	57.1	.040	.210
No	7	1.15 (1.04–1.27)	.007	29.3	.195	
Adjusted smoking						
Yes	5	1.16 (.75–1.80)	.504	32.5	.205	.894
No	8	1.20 (1.05–1.35)	.005	53.5	.028	
Study quality						
8 or 9	5	1.07 (.75–1.52)	.707	28.0	.235	.465
<8	8	1.22 (1.07–1.38)	.003	53.1	.030	

BMI = body mass index, CI = confidence interval, RR = risk ratio.

few studies, and the follow-up, number of participants were lower than study published after 2010, which always acquired broad CIs, that is, no statistically significant difference. In this study, we intended to conduct a stratified analysis based on these factors; however, data in each subset were not available. In addition, for several other subpopulations, the findings might be unstable owing to the smaller number of included studies. We therefore provided relative results and a synthetic review.

The present meta-analysis has some limitations. First, a language bias may exist in the selection of studies published only in English. Second, the types of DM and ovarian cancer were not available, which could have introduced confounder biases. Third, the heterogeneity among included studies was relatively high, and the heterogeneity in subgroup analysis was also higher. Fourth, the relationship between DM and ovarian cancer in specific subpopulations was not available. Finally, the adjusted models, which might play an important role in the development of ovarian cancer, differed among the included studies.

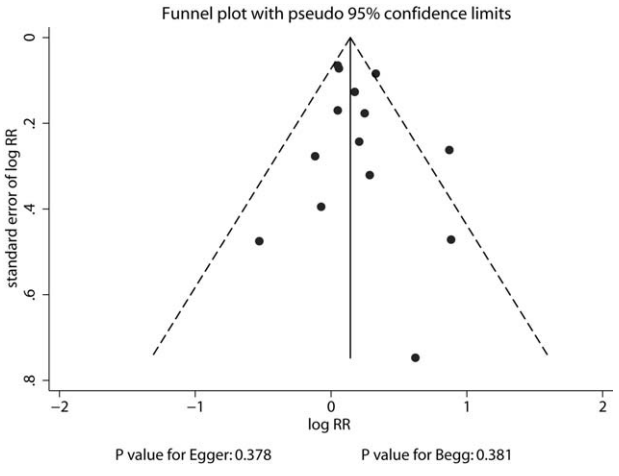

Figure 3. Funnel plot for ovarian cancer.

5. Conclusions

The present meta-analysis demonstrated that women with DM had an increased risk of developing ovarian cancer, especially among Asians. To lower the risk of ovarian cancer, any potential risk factors need to be investigated, in order to allow early diagnosis and treatment. Additional epidemiologic studies about this relationship in specific populations need to be further conducted.

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