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Diabetes mellitus and the risk of ovarian cancer: a systematic review and meta-analysis of cohort and case–control studies

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ABSTRACT

Objective Emerging evidence from observational studies (cohort and case–control studies) suggests that a history of diabetes mellitus (DM) has been linked to increased risk of ovarian cancer (OC), but the association between them remains inconclusive. The aim of this systematic review and meta-analysis of observational studies was to clarify this association.

Design Systematic review and meta-analysis.

Methods We searched PubMed, Embase and the Cochrane library databases published from the inception through 9 April 2020 without language restriction. Observational studies that evaluated the correlation between DM and the incidence of OC were included in our study. Relative risk (RR) with 95% CI was pooled by use of a random-effects model.

Results A total of 36 epidemiological articles, including 9 case–control and 27 cohort studies, were finally enrolled, consisting of 14,496 incident cases of OC. Synthesised RRs of developing OC by history of DM were 1.20 (95% CI=1.10 to 1.31) for all eligible studies, 1.08 (95% CI=0.77 to 1.53) for case–control studies and 1.22 (95% CI=1.11 to 1.33) for cohort studies. The above-mentioned positive association persisted across most of subgroup analyses, whereas it was not significant among studies from North American and European countries, level of unadjusted, and patients with low-quality and gestational DM group. The cumulative meta-analysis and sensitivity analysis showed pooled effect was stable and reliable, and no apparent publication bias was identified in this study.

Conclusions Our study found weaker but still association between DM and OC risk. However, further well-designed prospective studies that control for potential confounders are warranted.

INTRODUCTION

Diabetes mellitus (DM), characterised as hyperglycaemia, is a rock-ribbed and costly chronic ailment metabolic disease,1 divided into four different subtypes—type 1 DM (T1DM), type 2 DM (T2DM), gestational DM (GDM) and other specific categories of diabetes.2 The International Diabetes Federation report of 2017 has estimated that the number of DM will reach approximately 693 million (9.9%) by 2045, up over 1.5-fold from 451 million (8.4%) in 2017 among adults aged 18–99 years worldwide.3 That is, the number of DM will continue to rise due to the increasing ageing population and prevalence of rising obesity, recognised as a global public health issue challenge of the 21st century across the world.4,5

Ovarian cancer (OC), as a leading cause of death in women with gynaecological malignancy, is the fifth leading cause of carcinoma-related death in women, with a 5-year survival rate varying from 30% to 40%.6,7 The Global Cancer Observatory predicted that in 2018 there are 295,414 people with OC and the incidence of this disease worldwide increased by 47% in 2040 estimates (434,184).8 Furthermore, in the last 30 years, the cure rate for OC has barely budged.9

Too well known, the ovarian disease, which is located deep in the pelvic cavity, lacks early identifiable clinical symptoms, specific laboratory indicators as well as effective screening strategies, making early lesions difficult to detect.10 Therefore, the majority
of patients are already diagnosed in an advanced stage owing to the insidious onset of OC. Early identification and intervention is of vital significance in controlling cancer, especially for OC; unfortunately, few modifiable risk factors for this cancer are well documented such as smoking, hormonal replacement therapy and dietary factors. Besides, other immutable risk factors included age of menarche, age of natural menopause, endometriosis and so on.

In recent years, the causal relationship between DM and cancer risk has been widely concerned in cancer prevention research. Accumulating lines of evidence have demonstrated that DM is associated with greater risk of certain types of cancer at multiple sites, such as pancreatic, liver and endometrium cancer. Nonetheless, the relationship between DM and the observed excess risk of cancer may be a result of confounding factors such as age, obesity, physical activity and exogenous insulin therapy.

In recent decades, there are several epidemiological observational studies in this area since the first study investigating the association between DM and subsequent risk of OC in women was published. Several cohort and case–control studies have been reported that a history of DM is associated with an augmented risk of OC, however, other relevant studies found a negative significant association. Because obesity or high body mass index (BMI) has been regarded as a risk factor for both DM and OC, it remains unclear as to whether or not DM is associated with an increased OC risk on account of confounding by this factor. Studies in recent years have shown that DM may be closely related to OC, but epidemiological findings between them remain open to discussion.

In view of these conflicting results, we decided to update a meta-analysis of case–control and cohort studies to clarify whether there is an association between DM and OC risk in women.

METHODS

This meta-analysis was performed and reported based on the Meta-analysis Of Observational Studies in Epidemiology protocol checklist and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (online supplemental file 1).

Patient and public involvement

Since our meta-analysis is based on previous published researches, patient and public involvement is not required.

Search strategy and selection criteria

Online databases, such as PubMed, Embase and the Cochrane library databases, were searched from the inception to 9 April 2020 for observational studies. The inclusion criteria were as follows: (1) original observational studies (cohort and case–control studies), (2) evaluating the association between DM and OC risk, (3) the risk estimates were reported, (4) human population, (5) without language restriction. The Medical Subject Headings keywords were as follows: “diabetes mellitus”, “diabetes mellitus, type 1”, “diabetes mellitus, type 2”, “diabetes, gestational”, “ovarian neoplasms”, “ovarian cancer”, “cohort studies”, “case-control studies”. A comprehensive search strategy was provided in online supplemental file 2. In addition, we searched the potentially eligible bibliographies of relevant articles for the purpose of completeness. The exclusion criteria in this meta-analysis were: randomised controlled trial, case reports, letters, reviews or animals studies.

First, these two authors excluded duplicates via a reference manager. Second, the two authors read the title and abstract to further screen the eligible studies. Finally, we included the studies by reviewing the full text. Any disagreements were solved by means of discussion.

Data extraction

Data were extracted by one author (LW), and then checked by a second investigator (LZ). The main extracted information is described in tables 1 and 2. The association between DM and OC was the primary outcome of interest of our study.

Assessment of study quality

The Newcastle–Ottawa Scale (NOS) score was employed to evaluate the study quality of observational studies (cohort and case–control studies), with a maximum score of 9, of which 0–3, 4–6 and 7–9 scores were considered as low, fair and high quality, respectively.

Assessment of risk of bias

All selected literature was subjected to a sensitivity analysis to explore the robustness of the pooled effects.

Statistical analysis

The effect estimates of original studies were five measures of association, including relative risk (RR), standardised incidence ratio, incidence rate ratio, HR and OR. Given that the frequency of OC is relatively low, the last four measures were considered to yield approximately equal estimates to that of the RR. Therefore, we reported all pooled results as RR with 95% CI.

The statistical heterogeneity was measured by χ² (threshold p=0.10) and quantified by the I² statistic. The publication bias was also appraised using the funnel plot, Begg’s and Egger’s test. We prefer to choose the random-effects model to analyse all data due to the conservativeness of the analysed results. The statistical analyses were performed with the Stata V.12.0 software (StataCorp, College Station, Texas, USA). All statistical analyses were two-sided with an α level of 0.05.

Prespecified subgroup analyses were carried out to identify the sources of heterogeneity between studies in accordance with the study design (case–control vs cohort studies), DM types (T1DM vs T2DM vs GDM), duration of follow-up (<10 years vs ≥10 years), level of adjustment (unadjusted vs adjusted and BMI adjusted vs BMI unadjusted), study quality (NOS ≥7 vs <7 points) and geographical areas (North America vs Europe vs Asia vs Oceania). Subsequently, a cumulative
| Study ID           | Country or region | Study period   | Follow-up duration (years) | Population | Age (years) | No of subjects | No of OC cases | Population setting | NOS score |
|--------------------|-------------------|----------------|-----------------------------|------------|-------------|----------------|----------------|--------------------|-----------|
| Weiderpass et al   | Sweden            | 1965–1994      | 5.7                         | Type 2 DM  | 66.4        | 141 627        | 337            | PBR                | 8         |
| Zendehdel et al    | Sweden            | 1965–1999      | 15.0                        | Type 1 DM  | 17.3        | 143 323        | 9              | PBR                | 7         |
| Swerdlow et al     | UK                | 1972–2003      | 18.0                        | Type 1 DM  | <30         | 110 473        | 16             | PBR                | 7         |
| Swerdlow et al     | UK                | 1972–2003      | 18.0                        | Type 2 DM  | 30–49       | 21 222         | 6              | PBR                | 7         |
| Inoue et al        | Japan             | 1990–2003      | 10.7                        | Type 2 DM  | 51.8        | 51 223         | 74             | PBR                | 8         |
| Khan et al         | Japan             | 1988–1997      | 7.6                         | Type 2 DM  | 40–79       | 33 503         | 29             | PBR and HBR        | 7         |
| Hemminki et al     | Sweden            | 1964–2007      | 15.0                        | Type 2 DM  | 39–75       | 24 827         | 192            | PBR and HBR        | 7         |
| Chodick et al      | Israel            | 2000–2008      | 8.0                         | Type 2 DM  | 62          | 47 682         | 88             | PBR                | 7         |
| Shu et al          | Japan             | 1964–2006      | 17.0                        | Type 1 DM  | 12.3        | 11 290         | 9              | PBR and HBR        | 8         |
| Wotton et al       | Southern England  | 1963–1998      | —                           | Type 2 DM  | >30         | 132 271        | 37             | PBR and HBR        | 7         |
| Wotton et al       | Southern England  | 1999–2008      | —                           | Type 2 DM  | >30         | 90 427         | 8              | PBR and HBR        | 7         |
| Johnson et al      | Canada            | 1994–2006      | 4.4                         | Type 2 DM  | 60.7        | 169 012        | 295            | PBR                | 7         |
| Lambe et al        | Sweden            | 1985–1996      | 11.7                        | Type 2 DM  | 46.6        | 230 737        | 536            | PBR                | 8         |
| Gapstur et al      | USA               | 1992–2007      | —                           | Type 2 DM  | 62.28       | 63 440         | 524            | PBR                | 7         |
| Lo et al           | Taiwan            | 1996–2009      | 3.5                         | Type 2 DM  | 60.45       | 912 447        | 948            | PBR                | 7         |
| Chen et al         | Taiwan            | 2000–2008      | >9.0                        | Type 2 DM  | 61.09       | 638 618        | 935            | PBR                | 9         |
| Hsu et al          | Taiwan            | 2000–2008      | 6.2                         | Type 1 DM  | 49.2        | 7752           | 7              | PBR                | 7         |
| Harding et al      | Australia         | 1997–2008      | 12.0                        | Type 1 DM  | 27.4        | 38 644         | 38             | PBR                | 7         |
| Harding et al      | Australia         | 1997–2008      | 5.8                         | Type 2 DM  | 60.4        | 408 426        | 792            | PBR                | 7         |
| Dankner et al      | Israel            | 2002–2012      | 11.0                        | Type 2 DM  | 46.63       | 1 152 122      | 1495           | PBR                | 8         |
| Carstensen et al   | Multicountries    | 1972–2014      | —                           | Type 1 DM  | <40         | —              | 252            | PBR                | 7         |
| Fuchs et al        | Israel            | 1988–2013      | 12.0                        | GDM        | 28.45       | 104 715        | 56             | PB                 | 7         |
| Ballotari et al    | Italy             | 2010–2013      | 4.0                         | Type 2 DM  | 47          | 195 930        | 160            | PBR                | 6         |
| Han et al          | Korean            | 2002–2015      | 10.0                        | GDM        | 27.33       | 102 900        | 1148           | PB                 | 8         |
| He et al           | China             | 2003–2014      | —                           | Type 2 DM  | 63.7        | 14 193         | 24             | PB                 | 7         |
| Bao et al          | Swedish           | 1998–2014      | —                           | Type 2 DM  | 62.57       | 25 154         | 57             | Twin               | 6         |
| Saarela et al      | Finland           | 1988–2014      | 10.5                        | Type 2 DM  | —           | 223 602        | 977            | PBR                | 6         |
| Linkeviciute-Ulinskiene et al | Lithuania 2000–2012 6.8 Type 2 DM 64.0 | 78 823 | 249 | PBR | 7 |
| Peng et al         | Taiwan            | 2000–2013      | 6.8                         | GDM        | 28.97       | 990 572        | 1196           | PB                 | 7         |
| Pace et al         | Canada            | 1990–2007      | 13.1                        | GDM        | —           | 68 588         | 56             | PB                 | 7         |

DM, diabetes mellitus; GDM, gestational DM; HBR, hospital-based registry; NOS, Newcastle–Ottawa Scale; OC, ovarian cancer; PB, population-based; PBR, population-based registry.
meta-analysis for the association between DM and the risk of OC was performed to detect the accumulated effects of DM on OC risk based on the publication year.

RESULTS

Search results and study characteristics

The details on the study-selection procedure are shown in figure 1. As of 9 April 2020, our search strategy initially identified 543 records and 36 citations met criteria for final inclusion after screening. These 36 publications published between 1985 and 2020, which included 9 case–control and 27 cohort studies, were eligible for final analysis, with 14,496 incident cases of OC in this meta-analysis.

Among these included studies, 6 studies evaluated the relation between T1DM and risk of OC, 28 studies investigated the relationship between T2DM and OC risk, and the remaining 4 studies assessed this association between GDM and OC risk as well. With regard to geographical location, 1 study originated from Oceania, 1 in Europe and Oceania, 6 in North America, 14 in Europe and 14 studies from Asia. The follow-up period of cohort studies

| Study ID | Country or region | Study period | Population | Age (years) | No of cases/controls | Population setting | NOS score |
|----------|-------------------|--------------|------------|-------------|----------------------|--------------------|-----------|
| O’Mara et al71 | USA | 1957–1965 | Type 2 DM | 30–89 | 328/2342 | HB | 5 |
| Adler et al72 | USA | 1975–1987 | Type 2 DM | 51.98 | 595/1587 | PBR | 5 |
| Parazzini et al73 | Italy | 1983–1991 | Type 2 DM | 52.52 | 971/2758 | HB | 5 |
| Mori et al74 | Japan | 1994–1996 | Type 2 DM | 54.24 | 89/323 | PB | 7 |
| Kuriki et al75 | Japan | 1988–2000 | Type 2 DM | 57.57 | 218/33,569 | PBR and HBR | 6 |
| Reis and Kizilkaya Beji76 | Turkey | 2002–2003 | Type 2 DM | 51.0 | 217/1050 | HB | 6 |
| Attner et al76 | Sweden | 1998–2007 | Type 2 DM | — | 289/2207 | PBR | 7 |
| Bosetti et al77 | Italy | 1991–2009 | Type 2 DM | 56.70 | 1031/2411 | HB | 5 |
| Ruiz et al78 | USA | 2003–2008 | Type 2 DM | 57.5 | 208/224 | HB | 5 |

DM, diabetes mellitus; HB, hospital-based; HBR, hospital-based registry; NOS, Newcastle–Ottawa Scale; PB, population-based; PBR, population-based registry.
varied, ranging from 3.5 to 18.0 years. Studies were heterogeneous regarding age, ranging from 12.3 to 89 years. The case–control studies comprised 3946 OC cases and 46,471 controls.

The main characteristics of included studies are given in tables 1 and 2.

Assessment of study quality
The NOS quality stars ranged between 5 and 9, and the average score was 6.3 for case–control and 7.19 for cohort studies (online supplemental file 3). Two (22.22%) case–control and 24 (88.89%) cohort studies were regarded as high quality (NOS ≥ 7 points).

The sensitivity analysis suggested no single study had significant influence on the summarised RR, which revealed the stability of pooled estimate (online supplemental file 4). No obvious evidence of publication bias was detected by inspection of the funnel plot and statistical tests (Begg’s test, p=0.246; Egger’s test, p=0.132; online supplemental file 4).

Synthesis of primary outcome
All 36 studies reported the association between DM and OC risk, and the combined RR was 1.20 (95% CI=1.10 to 1.31), with substantial statistical heterogeneity among these studies (X²=152.43, p=0.000; I²=75.1%; figure 2).

The results of subgroup analysis
When stratified by study design subtypes, a statistically significant effect of DM on OC risk was observed in cohort studies (RR, 1.22; 95% CI=1.11 to 1.33), however, the case–control studies found no relationship between

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Figure 2  Meta-analysis of the association between DM and the risk of OC. DM, diabetes mellitus; ES, effect size; OC, ovarian cancer.
DM and the incidence of OC in spite of a positive trend (RR, 1.08; 95% CI=0.77 to 1.53). In the analysis stratified according to DM types, a positive significant association was noted in both T1DM (RR, 1.44; 95% CI=1.06 to 1.95) and T2DM group (RR, 1.17; 95% CI=1.06 to 1.30), but not in GDM group (RR, 1.14; 95% CI=0.90 to 1.43).

A subgroup analysis was conducted considering the level of adjustment, the summary of RR in adjusted studies (RR, 1.23; 95% CI=1.10 to 1.37) was more marked than in unadjusted studies (RR, 1.13; 95% CI=0.98 to 1.31). Both BMI-adjusted (RR, 1.37; 95% CI=1.16 to 1.62) and BMI-unadjusted (RR, 1.12; 95% CI=1.03 to 1.22) analyses were associated with an augmented risk of OC. In further analysis by the length of follow-up, women who experienced a long period of follow-up, that is, ≥10 years (RR, 1.33; 95% CI=1.09 to 1.63) were more likely to have a higher risk of OC than those who had less than 10 years (RR, 1.14; 95% CI=1.01 to 1.29).

In a subgroup analysis by continent, DM was significantly positively correlated with increased OC risk among studies conducted in Asia (RR, 1.43; 95% CI=1.20 to 1.71) and Oceania (RR, 1.24; 95% CI=1.16 to 1.32) except for European (RR, 1.15; 95% CI=0.99 to 1.35) and North American (RR, 0.94; 95% CI=0.73 to 1.21) studies. The RR was 1.24 (95% CI=1.12 to 1.36) for high-quality studies with significant difference and 1.07 (95% CI=0.85 to 1.35) for non-high-quality studies without statistical significance (online supplemental file 4).

The results of subgroup analyses are shown in table 3.

**Cumulative meta-analysis**

Although there is no association between DM and the risk of OC before Shu et al 38 (cumulative RR, 1.32; 95% CI=1.00 to 1.74), subsequent studies after this study show a consistently positive association (cumulative RR, 1.32; 95% CI=1.01 to 1.71; figure 3).

**DISCUSSION**

Our systematic review and meta-analysis of 27 cohort and 9 case–control studies evaluated the association between DM and the incidence of OC, and suggested that women with DM had a 20% elevated risk of OC as compared with those without a history of DM. Similar positive finding was observed when we analysed by cohort studies; however, no meaningful difference was noted when pooled by the case–control studies. Since there is inherent nature of recall and select bias in case–control study, certain biases might lead to inaccurate reporting of causal relationship. 30

A subgroup meta-analysis based on DM types indicated that the risk of OC in T1DM group (44%) is higher than in T2DM group (17%), while no significant association is found in GDM group. That may explain the excess risk in populations with T1DM that persons with T1DM usually require exogenous insulin treatment for the purpose of regulating blood glucose level, 36 and those who are treated with insulin appear to be at higher risk to develop cancer. 37 On the other hand, due to the limited numbers of eligible studies and sample sizes, the result obtained from GDM group should be interpreted with caution. In addition, owing to an increased risk of cancer with age, the length of follow-up for patients with GDM might be too short to detect cancers in young women. 38

The positive link was even more prominent arresting in studies that adjusted for covariates (ie, age, obesity, hypertension, reproductive history, smoking or alcohol) than those for unadjusted covariates analysis. Similarly, compared with subjects without BMI adjusted, the significant relationship between DM and OC also still existed and became stronger in BMI-adjustment studies. These two suggested DM is a potential independent risk factor for the development of OC.

In keeping with finding, women with DM had a less risk of OC during the early follow-up period (<10 years) than during the late follow-up duration (≥10 years). Owing that OC occurs mostly in middle-aged and elderly women, therefore, women who enjoyed a long-term follow-up are more susceptible to OC compared with those who had a short follow-up period. 39 Subgroup analysis on geographical areas, the Asian and Oceania studies, yielded similar positive results as the aforementioned analyses apart from European and North American studies, which is consistent with a previous

### Table 3 Summary risk estimates of the subgroup analysis results of DM and OC risk

| Subgroup          | Studies (n) | RR (95% CI) | I² (%) | P value |
|-------------------|-------------|-------------|--------|---------|
| Total             | 36          | 1.20 (1.10 to 1.31) | 75.1   | 0.000   |
| Study design      |             |             |        |         |
| Case–control      | 9           | 1.08 (0.77 to 1.53) | 71.1   | 0.001   |
| Cohort            | 27          | 1.22 (1.11 to 1.33) | 76.7   | 0.000   |
| DM types          |             |             |        |         |
| Type 1 DM        | 6           | 1.44 (1.06 to 1.95) | 67.2   | 0.009   |
| Type 2 DM        | 28          | 1.17 (1.06 to 1.30) | 78.5   | 0.000   |
| GDM               | 4           | 1.14 (0.90 to 1.43) | 31.5   | 0.224   |
| Geographical location |           |             |        |         |
| North America    | 6           | 0.94 (0.73 to 1.21) | 53.9   | 0.054   |
| Europe           | 14          | 1.15 (0.99 to 1.35) | 81.3   | 0.000   |
| Asia             | 14          | 1.43 (1.20 to 1.71) | 69.5   | 0.000   |
| Oceania          | 1           | 1.24 (1.16 to 1.32) | 0.00   | 0.486   |
| Follow-up        |             |             |        |         |
| <10 years        | 11          | 1.14 (1.01 to 1.29) | 77.0   | 0.000   |
| ≥10 years        | 12          | 1.33 (1.09 to 1.63) | 84.8   | 0.000   |
| Level of adjustment |           |             |        |         |
| No               | 8           | 1.13 (0.98 to 1.31) | 85.0   | 0.000   |
| Yes              | 28          | 1.23 (1.10 to 1.37) | 63.9   | 0.000   |
| BMI              |             |             |        |         |
| Yes              | 13          | 1.37 (1.16 to 1.62) | 53.5   | 0.011   |
| No               | 23          | 1.12 (1.03 to 1.22) | 69.9   | 0.000   |
| Study quality    |             |             |        |         |
| NOS <7           | 10          | 1.07 (0.85 to 1.35) | 66.7   | 0.001   |
| NOS ≥7           | 26          | 1.24 (1.12 to 1.36) | 74.2   | 0.000   |

BMI, body mass index; DM, diabetes mellitus; GDM, gestational DM; NOS, Newcastle–Ottawa Scale; OC, ovarian cancer; RR, relative risk.
meta-analysis described by Zhang et al. Geographical variation in the incidence of OC in women worldwide might explain such heterogeneity. The significant association was consistent in high-quality studies (NOS ≥7 points) except for non-high-quality studies (NOS <7 points).

To our knowledge, only three previous meta-analyses were published in this field. In 2013, Lee et al. performed a first meta-analysis with 7 case-control and 11 cohort studies, and supported that patients with DM have a 17% increased risk of OC compared with patients without DM. A subsequent meta-analysis carried out by Wang et al. in 2017 with 14 cohort studies exposed that DM is associated with a 19% raised risk of OC, which was further confirmed by a meta-analysis with 15 cohort studies (32%) later the same year. Our results, in accordance with these relevant studies, suggested that DM is correlated with a 20% increased risk of OC, and a significant positive association between them was observed in cohort studies (22%) but not in case-control studies (8%). Furthermore, the result of cumulative meta-analysis showed that it is not until in Shu et al. that aforementioned positive result first appeared and the association tended to be stable thereafter.

The underlying carcinogenesis effect of DM to ovary was not completely uncovered at present, but several plausible mechanisms have been postulated to explain the links between them. Previous studies have shown that the neoplastic process has been considered to influence by DM through these mechanisms, mainly including hyperglycaemia, hyperinsulinaemia and chronic inflammation. Because of a prolonged exposure to inflammation and hyperglycaemic condition, the reiterant lesion and repair cycles which are associated with incessant ovulation process could be slowed down, thus, resulting in an underlying risk of

![Figure 3](cumulative-meta-analysis.png) Cumulative meta-analysis of the association between DM and risk of OC. DM, diabetes mellitus; ES, effect size; OC, ovarian cancer.
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