RESEARCH ARTICLE

Association Between Gestational Diabetes Mellitus and Subsequent Risk of Cancer: a Systematic Review of Epidemiological Studies

Gui-Xian Tong, Jing Cheng, Jing Chai, Qing-Qing Geng, Peng-Lai Chen, Xin-Rong Shen, Han Liang, De-Bin Wang*

Abstract

Purpose: This study aimed at summarizing epidemiological evidence of the association between gestational diabetes mellitus (GDM) and subsequent risk of cancer. Materials and Methods: We searched Medline, Embase, Cancer Lit and CINAHL for epidemiological studies published by February 1, 2014 examining the risk of cancer in patients with history of GDM using highly inclusive algorithms. Information about first author, year of publication, country of study, study design, cancer sites, sample sizes, attained age of subjects and methods used for determining GDM status were extracted by two researchers and Stata version 11.0 was used to perform the meta-analysis and estimate the pooled effects. Results: A total of 9 articles documented 5 cohort and 4 case-control studies containing 10,630 cancer cases and 14,608 women with a history of GDM were included in this review. Taken together, the pooled odds ratio (OR) between GDM and breast cancer risk was 1.01 (0.87-1.17); yet the same pooled ORs of case-control and cohort studies were 0.87 (0.71-1.06) and 1.25 (1.00-1.56) respectively. There are indications that GDM is strongly associated with higher risk of pancreatic cancer (HR=8.68) and hematologic malignancies (HR=4.53), but no relationships were detected between GDM and other types of cancer. Conclusions: Although GDM increases the risk of certain types of cancer, these results should be interpreted with caution because of some methodological flaws. The issue merits added investigation and coordinated efforts between researchers, antenatal clinics and cancer treatment and registration agencies to help attain better understanding.

Keywords: Gestational diabetes mellitus - cancer - epidemiological - systematic review

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Introduction

Cancer has become one of the most important threats to human health and life all over the world. GLOBOCAN 2008 reported that there were 12.7 million new cancer cases and 7.6 million cancer deaths worldwide (Ferlay et al., 2010). It is estimated that, annual new cases and deaths of the disease will rise to 15 million and 10 million respectively in 2020 (Parkin et al., 2005). Although the pathogenesis of diabetes mellitus (DM) and cancer were not fully understood, there were some speculations about associations between them during the late 19th century. The unexpectedly high prevalence of hyperglycemia among cancer patients led investigators to suggest the use of blood glucose measurements as a new screening or diagnostic method for cancer (Kessler, 1971). Rising prevalence of DM and the high cancer morbidity warrant a careful consideration of the potential effects of this preventable risk factor. In the early 20th century, much evidence has accumulated on the possible interactions between DM and cancer (Wolf et al., 2005; Larsson et al., 2007; Chodick et al., 2011; Hardefeldt et al., 2012). Compared with women, men have somewhat higher risk of both cancer and DM. However, several studies on the relationship between DM and cancer have shown that among subjects with DM, women are at higher risk of cancer (Chodick et al., 2011). Pregnancy is known as a significantly critical time in relation to women’s subsequent health conditions, especially cancer (Kelsey et al., 1993; Russo et al., 2005). Although the biological mechanisms underlying the role of pregnancy in cancer etiology are still unclear (Sivaraman et al., 2002; Schedin, 2006), a role for pregnancy hormones (e.g., progesterone, androgens, estrogens, human chorionic gonadotropin) had been put forward by several hypotheses (Russo et al., 1994; Russo et al., 2005; Schedin, 2006). Given that it is unrealistic to examine the hormonal levels of women during the period between the beginning of pregnancy...
and diagnosis of cancer (Hoover et al., 2001), insight into this pathogenesis may be achieved by investigating the association between cancer and certain pregnancy characteristics which may be related with pregnancy hormonal levels (e.g., neonatal metabolic disturbances, fetal macrosomia, fetal growth, multiple births) instead (Troisi et al., 1998; Innes et al., 2004; Cnattingius et al., 2005; Nechuta et al., 2010).

As the prevalence of obesity and DM grows, gestational diabetes mellitus (GDM), which is defined as diabetes diagnosed during pregnancy that is not clearly overt diabetes, is becoming more common (American Diabetes Association, 2013). The situation of GDM varied across countries with the prevalence ranged from 2.2% to 12.9% (Kalra et al., 2013; Bardenheier et al., 2013; Rajput et al., 2013; Arora et al., 2013; Mwanri et al., 2014; Ignell et al., 2014; Jesmin et al., 2014; Liao et al., 2014). GDM is associated with adverse pregnancy outcomes, including stillbirth, neonatal metabolic disturbances, fetal macrosomia and other related problems (O’Sullivan et al., 1966). Women with GDM are more likely to develop DM in the years following pregnancy (Kim et al., 2002; Damm, 2009; Coustan, 2013; Vanalhruaii et al., 2013).

Recent years witnessed some epidemiological studies investigating the relationship between GDM and cancer. Yet the results were inconsistent. This study aims at investigating the relationship between GDM and cancer.

Materials and Methods

Data sources and search strategy
We utilized two approaches to locate as many relevant papers as possible. First, we searched the literatures in Medline, Embase, Cancer Lit and CINAHL available by February 1, 2014 using the following search terms “(gestational diabetes or GDM) AND (cancer or oncology or tumor or tumour or neoplasm* or carcinoma or malignant*)”. Second, we searched the references of relevant review papers for additional articles.

Inclusion criteria
The inclusion criteria were: 1) articles written in English; 2) epidemiological studies investigating the relationships between GDM and cancer and 3) studies using cohort or case-control designs.

Data extraction and analysis
Descriptive data about the included studies were extracted from the articles identified using a data-extracting form, including first author, year of publication, country of study, study design, cancer sites, sample sizes, attained age of subjects (the age of subjects when they were studied) and methods used for determining GDM status. All data extraction was performed by two researchers independently and discrepancies were solved by consensus. Statistical analysis software Stata version 11.0 was used to perform meta-analysis and estimate the pooled effects. Odds ratios (ORs) and relative risks (RRs) with 95% confidence intervals (CIs) were calculated using the random effects model.

Results

Studies included
We retrieved 727 articles from Medline, Embase, Cancer Lit and CINAHL, from which 710 were excluded on the basis of title and abstract. Eleven out of the remaining 17 articles were excluded via full-text evaluation including 6 articles investigating the relation between DM (rather than GDM) and cancer, 3 related review articles and 2 articles with irrelevant contents. After combining with 3 studies from reference lists, finally 9 studies met the inclusion criteria and included in this review (Figure 1).

The 9 articles documented 5 cohort and 4 case-control studies containing 10630 cancer cases and 14608 women with history of GDM from 5 countries including United

<table>
<thead>
<tr>
<th>First author, Location &amp; year</th>
<th>Design</th>
<th>Cancer site</th>
<th>Cancer patients/ Controls</th>
<th>Attained age of subjects (years)</th>
<th>Methods used for determining GDM status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troisi 1998 United States</td>
<td>Case-control</td>
<td>Breast</td>
<td>1235/1163</td>
<td>20-44</td>
<td>Self-report</td>
</tr>
<tr>
<td>Lawlor 2004 Britain</td>
<td>Case-control</td>
<td>Breast</td>
<td>147/3690</td>
<td>60-79 (mean age=68.9)</td>
<td>Self-report</td>
</tr>
<tr>
<td>Dawson 2004 Scotland</td>
<td>Cohort</td>
<td>Various sites</td>
<td>34/719</td>
<td>NG</td>
<td>Self-report</td>
</tr>
<tr>
<td>Cnattingius 2005 Sweden</td>
<td>Cohort</td>
<td>Breast</td>
<td>2216/311803</td>
<td>95%&lt;50</td>
<td>Sweden Birth Register</td>
</tr>
<tr>
<td>Perrin 2007 Israel</td>
<td>Cohort</td>
<td>Pancreas</td>
<td>54/37872</td>
<td>43-94 (median age=59)</td>
<td>OGTT</td>
</tr>
<tr>
<td>Rollison 2008 United States</td>
<td>Case-control</td>
<td>Breast</td>
<td>2324/2523</td>
<td>&lt;25-79</td>
<td>Self-report</td>
</tr>
<tr>
<td>Perrin 2008 Israel</td>
<td>Cohort</td>
<td>Breast</td>
<td>1626/36300</td>
<td>43-94 (median age=59)</td>
<td>OGTT</td>
</tr>
<tr>
<td>Sella 2011 Israel</td>
<td>Cohort</td>
<td>Various sites</td>
<td>2034/183281</td>
<td>15-50 (mean age=30.7)</td>
<td>GCT and OGTT</td>
</tr>
<tr>
<td>Brasky 2013 United States</td>
<td>Case-control</td>
<td>Breast</td>
<td>960/1852</td>
<td>Mean age=58.2</td>
<td>Self-report</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of Studies

NG, not given; GCT, glucose challenge test; OGTT, oral glucose tolerance test

Figure 1. Article Retrieval and Selection
GDM and breast cancer

As shown in Figure 2, 7 out of 9 researches investigated the risk of breast cancer associated with GDM were eligible for the conduct of meta-analysis. The ORs ranged from 0.76 to 1.74 with a pooled effect of 1.01 (0.87-1.17), and the heterogeneity was relatively high (I² = 58.5%). Subgroup analysis revealed pooled ORs of case-control and cohort studies as 0.87 (0.71-1.06) and 1.25 (1.00-1.56) respectively. Dawson et al’s study was not included in the meta-analysis due to inappropriate data type; their research aimed at probing long-term risk of malignant neoplasm associated with gestational glucose intolerance and concluded a positive dose-effect relation between subclinical glucose intolerance during pregnancy and malignant breast neoplasm risk (Dawson, 2004).

GDM and other types of cancer

Only a few studies have investigated the relationships between GDM and other types of cancer. Similar to DM, GDM seems to be related with pancreatic cancer. Perrin between GDM and other types of cancer. Similar to DM, GDM and other types of cancer

<table>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial (1998)</td>
<td>0.97 (0.88, 1.08)</td>
<td>18.67</td>
</tr>
<tr>
<td>Lavor (2004)</td>
<td>1.74 (0.80, 3.71)</td>
<td>22.2</td>
</tr>
<tr>
<td>Rollinson (2008)</td>
<td>0.76 (0.56, 1.03)</td>
<td>28.91</td>
</tr>
<tr>
<td>Brackx (2013)</td>
<td>1.81 (0.52, 6.71)</td>
<td>12.92</td>
</tr>
<tr>
<td>Subtotal (I-squared = 51.2%, p = 0.129)</td>
<td>0.87 (0.71, 1.06)</td>
<td>82.82</td>
</tr>
<tr>
<td>Cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crestoningiu (2000)</td>
<td>0.89 (0.47, 1.62)</td>
<td>5.58</td>
</tr>
<tr>
<td>Perrin (2008)</td>
<td>1.71 (1.17, 2.51)</td>
<td>9.46</td>
</tr>
<tr>
<td>Sella (2011)</td>
<td>1.15 (0.85, 1.56)</td>
<td>21.14</td>
</tr>
<tr>
<td>Subtotal (I-squared = 51.2%, p = 0.129)</td>
<td>1.25 (1.00, 1.56)</td>
<td>37.18</td>
</tr>
<tr>
<td>Overall (I-squared = 58.5%, p = 0.025)</td>
<td>1.01 (0.87, 1.17)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 2. Forest Plot of ORs between GDM and Breast Cancer

<table>
<thead>
<tr>
<th>Study ID</th>
<th>RR (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perrin (2007)</td>
<td>3.34 (1.74, 22.31)</td>
<td>59.22</td>
</tr>
<tr>
<td>Sella (2011)</td>
<td>7.13 (1.03, 49.89)</td>
<td>40.78</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.820)</td>
<td>8.68 (4.00, 18.83)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 3. Forest Plot of RRs between GDM and Pancreas Cancer

Discussion

Although our meta-analysis did not reveal statistically significant relationship between GDM and the risk of breast cancer (the overall OR was 1.01; p<0.05), subgroup analysis showed moderate risk of GDM in cohort studies after stratified by study design (OR=1.25; 95%CI: 1.00-1.56). In addition, we also detected preliminary evidence that GDM was associated with pancreatic cancer (RR=8.68) and hematologic malignancies (HR=4.53). However, these results should be interpreted with caution for the following reasons: a) diagnosis of GDM cases differed across countries due to lack of international standard diagnosis criteria; b) over half of the studies gained information of GDM status via self-report, a method prone to various information biases; c) relatively small numbers of cancer cases observed, especially for some types of cancer (e.g., pancreatic cancer and hematologic malignancies), did not prevent chance-finding and d) inadequate data did not allow for rigorous analysis distinguishing associations with cancer due to GDM effect from that due to the presence of certain confounding risk factors (e.g., aging, physical inactivity, obesity and overweight) during pregnancy (Chodick et al., 2011). Evidences regarding the associations between cancer and other pregnancy characteristics were documented in previous reviews. Weyers (2010), for instance, performed a review exploring the interaction between pregnancy characteristics and maternal breast cancer risk. In their paper, multiple births was associated with about a 10-30% reduction in breast cancer risk; pregnancy-induced hypertension and/or preeclampsia protected against breast cancer by about 20-30%; and infant gender was not associated with breast cancer. In addition to breast cancer, several epidemiological studies also reported links between pregnancy characteristics and other types of cancer. These include: a) low age of first gestation increases the risk of cervical cancer (OR=13.1, 95%CI: 3.7-47.3) (Zhang et al., 2013); b) multiple births lower the risk of nonmucinous ovarian cancer (OR=0.71, 95%CI: 0.52-0.98) (Whiteman et al., 2000); c) preterm deliveries endanger women in (RR=2.3, 95%CI: 1.3-3.8) and low birth weight (RR=0.7; 95%CI:0.4-1.0) protects women
from developing epithelial ovarian cancer (Mucci et al., 2007) etc. The links between DM and cancer seem to be relatively clear. Liao et al. (2011) reported that DM was associated with a statistically significant 23% increased risk of breast cancer, especially in postmenopausal women (RR=1.25, 95%CI: 1.20-1.29). A meta-analysis of 23 studies (8 case-control studies, 15 cohort studies) revealed that DM was associated with an elevated risk of bladder cancer compared with non-DM (OR=1.68, 95%CI: 1.32-2.13) (Yang et al., 2013). There are also evidence that DM was associated with a higher risk of prostate cancer in Asians (unadjusted RR=2.82, 95%CI: 1.73-4.58; adjusted RR=1.31, 95%CI: 1.12-1.54) (Long et al., 2012).

The associations between GDM and cancer are still inconclusive. This is understandable for, on the one hand, retrospective studies are faced with paucity of relevant information and, on the other, the low prevalence of cancer and long time lag between GDM and observables make it prohibitive for most researchers to do prospective studies. Therefore, better understanding of the relationships between GDM and cancer depends heavily on coordinated efforts between all the key players. Firstly, providers of family planning, antenatal and gynecologic services should recognize the long-term implications of GDM, diagnose as many GDMs as possible using standardized methods and criteria and record data as accurate and complete as possible. Secondly, cancer diagnosis, treatment and registration should make it a standard procedure asking for and recoding GDM status and related information for every woman case. Thirdly, future researches should: a) collaborate closely with antenatal clinics, cancer treatment hospitals and registration agencies; b) have the vision and courage in doing long-term cohort/prospective studies and performing rigorous analysis with adequate attention being paid to potential confounding variables (e.g., aging, physical inactivity, obesity, over-nutrition diet, preterm deliveries, birth weight and multiple births).

Acknowledgements

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References


