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 becuase 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

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 unreality to examine the hormonal levels of women during the period between the beginning of pregnancy

Center for Health Management, School of Health Services Management, Anhui Medical University , Hefei, China &Equal contributors
For correspondence: dbwang@vip.sina.com

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; Vanlalhruaii 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 summarizing these evidence and tries to produce some preliminary pooled interpretations.

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 malignan*)". 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
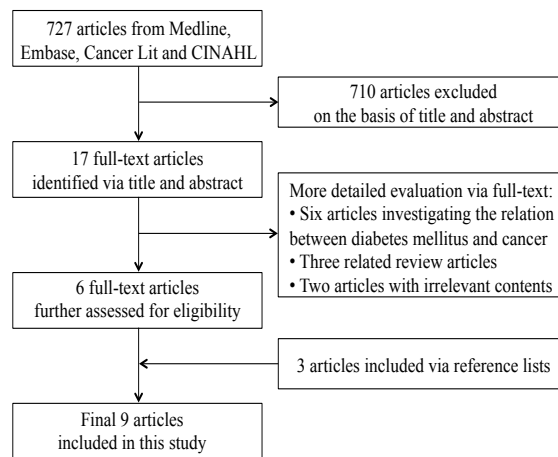
Figure 1. Article Retrieval and Selection

Table 1. Characteristics of Studies

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

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

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States (n=3), Israel (n=3), Britain (n=1), Scotland (n=1) and Sweden (n=1). The sample size of the studies ranged from 753 to 314019 and the mean/median attained age of subjects ranged from 30.7 to 68.9. The relationship between GDM and breast cancer was most frequently studied (n=6), followed by multi-site cancers (n=2) and pancreas cancer (n=1). Methods used for determining GDM status were inconsistent across studies, in which 5 studies were via self-report, 3 by oral glucose tolerance test (OGTT)/glucose challenge test (GCT) and 1 from Sweden Birth Register. Summary characteristics of included studies are presented in Table 1.

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 (I^2 =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 et al. (2007) carried out a large cohort study of 37926

Israeli women. After having followed for 28-40 years, they found 5 new pancreatic cancer cases in women with GDM history and 49 without the history; the hazard ratio (HR) of GDM history was 7.1 (2.8-18.0) after adjusted for age at first observed birth and birth weight. Similar result was also observed in a recent cohort of 185315 women by Sella et al (2011). After average follow-up period of 5.19 years, they revealed an adjusted HR of GDM history versus non-GDM history as 7.06 (1.69-29.45). When combined together, the pooled RR of the 2 researches was 8.68 (4.00-18.83) (Figure3). Sella and colleagues' study also reported statistically significant association between GDM and hematologic malignancies in women with 5 or more years of follow-up (HR=4.53, 95%CI: 1.81-11.31). No relationship was detected between GDM and other types of cancer including cancer of stomach, colorectal, genital organs, thyroid gland etc.

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 over-nutrition diet) during pregnancy (Chodick et al., 2011). Evidences regarding the associations between cancer and other pregnancy characteristics were documented in previous reviews. Nechuta et al. (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
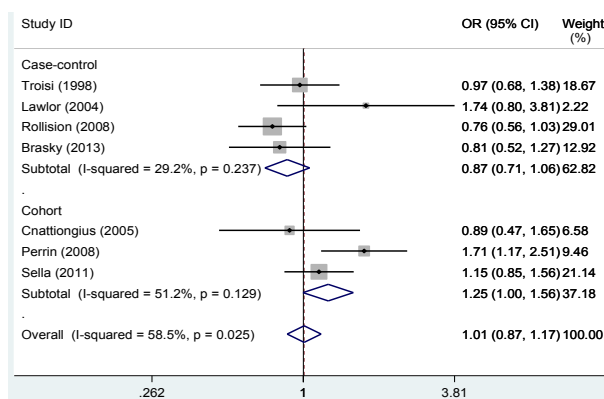

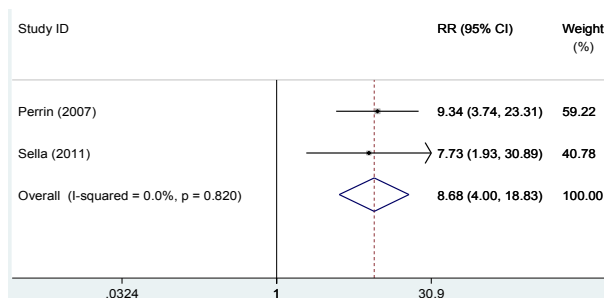**Figure 2. Forest Plot of ORs between GDM and Breast Cancer**

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

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 observable malignancies 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 women 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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