SHORT COMMUNICATION

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Gestational diabetes mellitus may be associated with increased risk of breast cancer

Yong-Moon Mark Park[1], Katie M O'Brien[2], Shanshan Zhao[2], Clarice R Weinberg[2], Donna D Baird[1] and Dale P Sandler*[,1]

[1]*Epidemiology Branch, Division of Intramural Research, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC 27709, USA and* [2]*Biostatistics & Computational Biology Branch, Division of Intramural Research, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC 27709, USA*

Background: Although a positive association between type 2 diabetes and breast cancer has been reported, an association with gestational diabetes mellitus (GDM) is less clear.

Methods: The Sister Study enroled 50 884 women aged 35–74 years, from 2003 through 2009. Cox proportional hazards models were used to estimate breast cancer risk in relation to GDM.

Results: Ever having GDM was not associated with breast cancer overall (hazards ratio (HR) = 1.10, 95% confidence interval (CI) = 0.88–1.36), but there was a suggestive association between ever having a GDM pregnancy and oestrogen receptor (ER) - negative breast cancer (HR = 1.73, 95% CI = 0.98–3.06). However, having 2 or more GDM pregnancies was associated with overall breast cancer risk 1.68 (95% CI = 1.15–2.44) and with ER-positive breast cancer (HR = 1.81, 95% CI = 1.10–2.98), which was supported by sensitivity analyses. Results were similar when analyses were stratified by whether or not type 2 diabetes had developed after GDM.

Conclusions: Women with multiple GDM pregnancies had a higher incidence of breast cancer, suggesting that such women could benefit from increased surveillance for breast cancer.

Gestational diabetes mellitus (GDM) is associated with adverse pregnancy outcomes (Agha-Jaffar *et al*, 2016) and long-term adverse health conditions, including type 2 diabetes (Bellamy *et al*, 2009), metabolic syndrome (Xu *et al*, 2014), cardiovascular diseases (Li *et al*, 2014) and some cancers (Tong *et al*, 2014). GDM is characterised by insulin resistance and glucose intolerance that may persist after delivery. Chronic health outcomes associated with GDM could be due to persistent beta-cell dysfunction and impaired insulin sensitivity with onset during the reproductive years (Catalano, 2010). Although a positive association between type 2 diabetes and breast cancer has been reported (Hardefeldt *et al*, 2012), an association with GDM is less clear (Tong *et al*, 2014). In addition, since recurrent GDM is a potent predictor of type 2 diabetes, perhaps due to exposure to multiple episodes of insulin resistance (Bottalico, 2007), we hypothesised that multiple GDM pregnancies would be associated with increased risk of breast cancer. The objective of this study was to investigate the association between GDM and breast cancer risk.

MATERIALS AND METHODS

The Sister Study is a nationwide prospective cohort study investigating environmental and genetic risk factors for breast cancer (Weinberg *et al*, 2007). Enrolment targeting 35–74-year olds during 2003–2009 accrued 50 884 breast-cancer-free sisters of

*Correspondence: Dr DP Sandler; E-mail: sandler@niehs.nih.gov

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women diagnosed with breast cancer. Incident breast cancer cases included in this analysis were ascertained until 14 August 2015 (Data release 5.0). Characteristics of participants, including history of GDM and diabetes mellitus, were obtained using telephone interviews completed at baseline. Incident breast cancers were subsequently reported on annual health updates (response rates > 92%). Self-reported incident breast cancers were verified by medical records when available (81% of cases at the time of this data release). Agreement between self-reports and medical records was high (99.5%), so self-reported diagnoses were included when records were not obtained. Participants were questioned about each pregnancy to ascertain whether they had had pregnancy-related diabetes or an abnormal glucose tolerance test during the pregnancy. Participants with diabetes prior to their pregnancy were not considered GDM cases and were excluded from the analysis ($n = 187$). For the present analysis, we included parous women ($n = 41\,640$) and excluded those who had incomplete information for GDM or diabetes, or who had reported a history of any cancer except non-melanoma skin cancer at baseline ($n = 2255$). The remaining 39 198 women contributed 291 150 person-years of follow-up.

We used multivariable Cox proportional hazards models to assess hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between GDM and invasive breast cancer, with adjustment for race/ethnicity, 10-year birth cohorts, educational attainment, age at first birth, age at menarche, relative weight at age 10, BMI at 30–39 years old and physical activity (metabolic equivalent hours/week) in their childhood and teens. Age was used as the time-scale. Women with *in situ* breast cancer were censored at the time of diagnosis in analyses of invasive breast cancer. Potential effect modification by menopause status (pre- and postmenopause) was evaluated by adjusting for menopause as a time-varying covariate; likelihood ratio tests were used to test for effect modification. In addition, potential effect modification by birth cohort due to changes in diagnostic criteria and/or changes in treatments for GDM over time (Mestman, 2002) was evaluated by testing for interaction between GDM and a categorical variable based on 10-year birth cohorts, using a likelihood ratio test. Case-only analysis (Martinez *et al*, 2010) was applied to evaluate whether the association between GDM and breast cancer differed according to oestrogen receptor (ER) expression. To explore whether type 2 diabetes might mediate the association between GDM and risk of breast cancer, we stratified the Cox model by type 2 diabetes status at baseline, allowing the baseline hazard during follow-up to be different for those who reported that they had or had not developed type 2 diabetes between their first GDM pregnancy and baseline. Statistical significance was evaluated with two-sided tests, with $\alpha = 0.05$. SAS 9.3 software (SAS Institute Inc., Cary, NC, USA) was used throughout.

RESULTS

Among the study subjects, 4.2% had at least one pregnancy with GDM and 0.9% had multiple GDM pregnancies. Women with two or more pregnancies with GDM were more likely to report being heavier than their peers in childhood, to have been obese at 30–39 years old and at baseline, to have had pregnancy complications, and to have subsequently been diagnosed with diabetes mellitus (Table 1).

A total of 2141 women developed incident breast cancer during a mean follow-up of 7.4 years (1609 invasive and 532 *in situ* cancers). While ever having a pregnancy with GDM was not associated with breast cancer risk overall, GDM was marginally associated with an increased risk of ER-negative invasive breast cancer (covariate-adjusted HR = 1.73, 95% CI: 0.98–3.06). Compared with women without GDM, women who had experienced multiple GDM pregnancies had increased risk of total and invasive breast cancer (HR = 1.68, 95% CI: 1.15–2.44; HR = 1.72, 95% CI: 1.11–2.65, respectively; Table 2). This association was seen in both premenopausal and postmenopausal breast cancer (Supplementary Table 1). Multiple episodes of GDM were also associated with ER-positive breast cancer (HR = 1.81, 95% CI: 1.10–2.98). An association between GDM and ER-negative breast cancer was apparent among women with a single GDM pregnancy (HR = 1.88, 95% CI: 1.02–3.47), but the HR for ER-negative breast cancer and multiple pregnancies could not be estimated due to small numbers (Table 2). When we restricted analysis to women who had two full-term pregnancies, to address potential bias due to selective fertility (for example, if women with a GDM-related pregnancy complication chose not to have a subsequent pregnancy) and differential opportunity for exposure, the estimated associations between GDM and breast cancer were more pronounced (Supplementary Table 2). When we included women who reported borderline GDM, which may represent a history of subclinical glucose intolerance, the association between multiple GDM pregnancies and risk of breast cancer persisted, although the effect estimates were attenuated (data not shown). There was no evident effect modification by time-varying menopause status and no evidence for interaction between GDM and birth cohort.

When we stratified the Cox regression model on type 2 diabetes at baseline, the results were not materially changed (Supplementary Table 3). When we excluded women who reported subsequent type 2 diabetes, the overall results were not materially different from the main analysis (data not shown). Furthermore, inclusion of body mass index and waist circumference at baseline (no one was pregnant at baseline, by design) in the multivariable models also did not materially change the results (data not shown).

Table 1. Characteristics of the Sister Study participants at baseline according to self-reported GDM status

Characteristic	Without GDM	With GDM	
No. of GDM	**0**	**1**	**⩾2**
No. of participants, *n* %	37 562 (95.8)	1283 (3.3)	353 (0.9)
Mean (s.d.)			
Age at baseline, year	56.1 (9.0)	51.6 (8.2)	51.2 (7.9)
BMI at baseline, kg m^{-2}	27.8 (6.0)	29.3 (7.3)	29.7 (6.8)
BMI at 30–39 years old, kg m^{-2}	23.2 (3.8)	24.6 (5.1)	25.0 (5.1)
Waist circumference at baseline, cm	86.4 (14.4)	89.7 (16.4)	91.3 (15.7)
Age at menarche, year	12.7 (1.5)	12.6 (1.5)	12.6 (1.7)
Age at first birth, year	24.6 (5.2)	26.4 (5.9)	25.8 (5.3)
Parity	2.4 (1.1)	2.5 (1.2)	2.8 (1.1)
Total MET-hours of physical activity, week at baseline	51.2 (31.2)	48.3 (31.4)	50.9 (30.5)
Total MET-hours of physical activity, week at childhood and teens	8.4 (15.5)	9.4 (16.7)	8.3 (13.9)
Proportion (%)			
Non-Hispanic white	83.6	77.0	72.5
Having ⩾ college degree	47.4	49.4	49.6
Relatively heavier at age 10	17.3	18.6	20.2
Postmenopausal at enrolment	68.2	47.7	49.0
Having ⩾ 2 first-degree family members with breast cancer	27.0	24.4	23.5
Having a mammogram within a year	81.2	78.3	76.5
Giving birth to a baby weighing more than 4 kg	15.6	24.7	29.1
History of gestational hypertension	7.1	18.6	20.4
History of pre-eclampsia or eclampsia	8.1	15.1	17.6
History of parental diabetes	34.6	47.7	52.7
Self-reported diabetes	5.6	16.5	22.3

Abbreviations: BMI = body mass index; GDM = gestational diabetes mellitus; MET = metabolic equivalent. Data are presented as mean (s.d.), or percentage (% within strata of GDM, except for total number of participants).

Table 2. HRs and 95% CIs for the association between GDM and breast cancer

	Ever having GDM pregnancy		Cumulative number of GDM pregnancy			
	No GDM	GDM	0	1	⩾2	*P*-trend
Person-years	279 284	11 866	279 284	9355	2511	
Total breast cancer						
No. of cases	2051	90	2051	61	29	
HR (95% CI)[a]	1 (ref)	1.10 (0.88–1.36)	1 (ref)	0.94 (0.73–1.22)	1.68 (1.15–2.44)	0.10
***In situ* breast cancer**						
No. of cases	495	17	495	10	7	
HR (95% CI)[a]	1 (ref)	0.78 (0.48–1.30)	1 (ref)	0.62 (0.33–1.17)	1.38 (0.62–3.10)	0.66
***Invasive* breast cancer**						
No. of cases	1540	69	1540	48	21	
HR (95% CI)[a]	1 (ref)	1.16 (0.91–1.49)	1 (ref)	1.02 (0.76–1.36)	1.72 (1.11–2.65)	0.06
ER+ invasive breast cancer						
No. of cases	1149	45	1149	29	16	
HR (95% CI)[a]	1 (ref)	1.03 (0.76–1.40)	1 (ref)	0.83 (0.57–1.20)	1.81 (1.10–2.98)	0.31
ER− invasive breast cancer						
No. of cases	200	13	200	11	2	
HR (95% CI)[a]	1 (ref)	1.73 (0.98–3.06)[b]	1 (ref)	1.88 (1.02–3.47)[b]	NA	0.12

Abbreviations: BMI = body mass index; CI = confidence interval; ER = oestrogen receptor; GDM = gestational diabetes mellitus; HR = hazard ratio; + = positive; − = negative.
[a]Adjusted for birth cohort (born in <1945, 1945 to <1955, 1955 to <1965 or ⩾1965), race or ethnicity (non-Hispanic white, non-Hispanic black, Hispanic and others), educational attainment (<high school, high school equivalent, some college or ⩾4-year degree), age at first birth (<21, 21 to <25, 25 to <29, 29 to <32 or ⩾32 years), age at menarche, relative weight at age 10 (lighter, same, heavier), BMI at 30–39 years old (<18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40 or ⩾40 kg m^{-2}) and physical activity (quintiles of metabolic equivalent hours/week) in their childhood and teens.
[b]HR was significantly different from ER+ breast cancer in case-only analysis.

DISCUSSION

To our knowledge, this is the first report of an association between multiple GDM pregnancies and increased risk of breast cancer. There was also an association between GDM and ER-negative breast cancer, but there were too few cases to evaluate risk related to the number of affected pregnancies.

Our findings have biological plausibility. Women with multiple GDM pregnancies have exhibited impaired glucose tolerance during pregnancy, and will tend to have had higher BMI, and greater weight gain during and between pregnancies (Schwartz *et al*, 2016) which might make them more vulnerable to chronic hyperinsulinemia and insulin resistance. Repeated episodes of GDM likely amplify these effects or serve as a marker for subclinical abnormalities in glucose metabolism (Bottalico, 2007). Resulting increases in bioactivity of insulin growth factors may have mitogenic and anti-apoptotic effects that could influence the remodelling of breast tissue late in pregnancy and contribute to the initiation and progression of breast cancer (Wolf *et al*, 2005; Ryu *et al*, 2014).

A previous meta-analysis (Tong *et al*, 2014) reported no association between ever having GDM and breast cancer, while inverse associations were reported for premenopausal women in two studies (Rollison *et al*, 2008; Bejaimal *et al*, 2016) and for both pre- and postmenopausal women in another study (Powe *et al*, 2016). However, the prior studies had limited ability to examine breast cancer subtypes, control for confounding (Bejaimal *et al*, 2016) or enrol appropriate controls (Rollison *et al*, 2008); none evaluated the role of multiple GDM pregnancies. Furthermore, our analysis that was restricted to women with exactly two full-term births should have served to minimise parity-based differential opportunity to develop GDM. In the present study, adjusting for subsequent type 2 diabetes did not change the risk estimates for the association between GDM and risk of breast cancer, and the association remained in analysis restricted to women who did not report subsequent clinical diabetes. However, our ability to address the possible mediation of this association through later onset diabetes was limited. We relied on self-report of diabetes rather than laboratory measurements of fasting blood glucose, so some women with diabetes will be misclassified. In addition, estimating an effect of clinical diabetes on breast cancer risk is challenging due to the common use of anti-diabetic medications that may have anti-neoplastic properties (Gonzalez-Angulo and Meric-Bernstam, 2010). GDM is likely a marker for women at risk for changes in glucose metabolism that could have implications for long-term disease risk. It might also be a marker for unknown risk factors for breast cancer that could not be accounted for in the present study.

A potential limitation is that history of GDM was based on self-report. However, agreement between self-report and medical records was 94% in another study (Powe *et al*, 2016). Strengths of the present study include the prospective design with high retention, large sample size, standardized data collection and comprehensive information on potential risk factors for breast cancer.

In summary, among parous women, a history of multiple episodes of GDM was associated with increased risk of breast cancer, suggesting that abnormal glucose metabolism might be aetiologically important for breast cancer and that history of multiple GDM pregnancies might be a marker for identifying women who are at increased risk of breast cancer and therefore should be screened more frequently.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Y-MMP and DPS contributed to the study concept and design. Y-MMP contributed to statistical analysis. Y-MMP drafted the manuscript. All authors contributed to interpretation of the data and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript. DPS is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. We are grateful to Drs Allen J Wilcox and Quaker E Harmon for critical review of this manuscript.

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