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Gestational diabetes and the risk of breast cancer among women in the Jerusalem Perinatal Study

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Abstract Gestational diabetes is becoming increasingly common; it is important to determine how it relates to future risk of disease. We investigated the relation of gestational diabetes to breast cancer in 37,926 women who had one or more live births in 1964–1976 for whom information had been collected on complications of pregnancy. In this cohort there were 1,626 cases of breast cancer reported to the Israel Cancer Registry before January 1, 2005 and 410 cases of gestational diabetes recorded from birth records. There were 29 cases of breast cancer among women diagnosed with gestational diabetes. Using Cox proportional hazards models to control for age and birth order at the first observed birth and other characteristics, we found that the incidence of breast cancer was increased among women diagnosed with gestational diabetes (relative rate = 1.5, 95% confidence interval 1.0–2.1). This effect was seen only among women 50 years and older (relative rate 1.7, 95% confidence interval 1.1–2.5) but not among women <50 (relative rate = 1.0, 95% confidence interval 0.5–2.1). The findings suggest that gestational diabetes may be an important early marker of breast cancer risk among post-menopausal women, but these results need to be confirmed in future studies.

Keywords Gestational diabetes · Breast cancer · Diabetes · Jerusalem Perinatal Study

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Background

During pregnancy women become progressively more insulin resistant because of an increase in weight and release of placental hormones [1]. Most women secrete enough insulin to compensate for the increased resistance though some do not and develop gestational diabetes. Common risk factors for gestational diabetes include family history of diabetes in a first degree relative, obesity and ethnicity [1]. In the U.S., the prevalence of gestational diabetes is approximately 7% [2] though it varies by ethnic group. It is more common among African-Americans, Hispanics and Native Americans than among non-Hispanic Whites [3–6]. The prevalence of gestational diabetes appears to be increasing [7, 8]. Other than an increased risk of Type 2 diabetes in the mother, the health sequelae of gestational diabetes are largely unknown [2].

Though Type 2 diabetes has been frequently studied as a risk factor for breast cancer (reviewed in Wolf, 2005 [9]), few studies have examined gestational diabetes and breast cancer [10, 11]. We investigated the relation between gestational diabetes and breast cancer in a large prospective cohort study of parents and their offspring born in 1964–1976.

Methods

We made use of an ongoing cohort study based on offspring born in Jerusalem in 1964–1976 and their parents, with follow up of all until the present. The study has been previously described [12, 13]. Briefly, in 1964–1976, the Jerusalem Perinatal Study surveyed all 92,408 births in a defined geographic area. Data on obstetric information were copied from the labor ward log at the time of birth using separate rubrics in the printed forms which allowed for a record of maternal ''diabetes'' (presumed to be insulin-dependent juvenile diabetes) and ''pre-diabetes'', corresponding, approximately, to gestational diabetes. In that era, pregnant women were screened for glycosuria at each antenatal visit; if found positive they would be referred for an oral glucose tolerance test. The present analysis focuses on the mothers of 84,781 offspring born in the three largest obstetric units in which active surveillance of maternal and obstetric conditions took place.

Using the national identity (ID) numbers that are assigned to citizens of Israel, 40,898 women (94.2%) were successfully traced in 2005 and vital status determined through linkage with Israel's National Population Registry. The traced ID numbers were then linked to the Israel Cancer Registry, which ascertains cancer cases through active surveillance of all pathology departments, hospital admissions and death certificates. This registry, established in 1961, is considered to be 94.2% complete for breast cancer [14]. Names, ID numbers and other identifying information were removed from the file which was analyzed collaboratively in New York and Jerusalem. The study was approved by the Institutional Review Boards at both Columbia University in New York and Hadassah-Hebrew University Hospital in Jerusalem

Statistical analyses

Included in the analysis are all first, primary in-situ and invasive breast cancers as defined by the International Classification of Diseases for Oncology, 3rd edition diagnosed through December 31, 2004 (ICD-O C50; fifth digit morphology codes 2 and 3). We used Cox proportional hazards models to estimate the relative rate (hazard ratio) of breast cancer in mothers with and without gestational diabetes in any pregnancy during the study period (1964–1976) using the PHREG procedure available in SAS 9.0 (SAS Institute Inc, Cary, North Carolina). Proportional hazards assumptions were tested using log-negative log plots and by testing each variable as a time-dependent variable constructed from its product with the length of follow-up. Women were followed from date of the first observed birth in 1964–1976 until death, date of diagnosis of any cancer or until the end of follow-up December 31, 2004. Since proportional hazard assumptions were not met based on the log-negative log plots, we examined whether there were differences in risk associated with gestational diabetes based on age of diagnosis of breast cancer (<50 and ≥50) to approximate menopausal age [15]. Unless otherwise stated categories of missing data in other variables (most affected less than 1% of women) were included in the referent category. Other variables considered for inclusion in the model were a series of binary variables (coded as 1 if present versus 0 if absent) for other birth complications such as preeclampsia, congenital malformations in any observed birth, at least one high birth weight (4,000+ g) or low birth weight (<2,500 g) offspring in any observed birth, social class (based on husband's occupation), religion (Jewish, non-Jewish), education (≤ 8 years, >8 years), ethnic origin based on the woman's father's place of birth (Israel, other West Asia, North Africa and Europe (includes the Americas, sub-Saharan Africa, New Zealand and Australia)); there was no information on place of birth for the woman's mother. There were 1,584 women with missing information on education, however these women were similar to women who received ≤ 8 years of education and were therefore included in that group. Models were constructed to include confounders (>10% change in the estimate of relative rate) and those characteristics, which were significantly associated with breast cancer. Since confounding by these variables was minimal, only those characteristics that were significantly associated with breast cancer risk were included in the final models. The results are presented as relative rates (RR) with 95% confidence intervals.

Numbers and exclusions

Of the 40,898 women traced, 37,980 (92.9%) gave birth in one of the three hospitals where information was obtained on diabetes. Untraced women were similar in age at first observed birth, more often unmarried and more likely to be of European ancestry. Among women who were successfully traced, the incidence of breast cancer was not significantly related to hospital of birth. The prevalence of a diagnosis of gestational diabetes in any observed birth was 0.4% in the untraced women, compared to 1.0% among women who were traced. We excluded 41 women diagnosed with cancer prior to their first observed birth in the study. Another 13 women who were diagnosed with gestational diabetes in one observed pregnancy and with Type 1 diabetes in another were excluded; among these women there was one case of diagnosed breast cancer.

Results

Of the 37,926 women who were both successfully traced and had delivered in one of the three major hospitals, 410 were diagnosed with gestational diabetes in one or more pregnancies in 1964–1976. By December 31, 2004 the median length of follow-up was 34 years and the median age of the surviving women in the cohort was 59 (range 43–94). There were 1,506 women diagnosed with invasive breast cancer, and 120 with in-situ disease. The median age at diagnosis was 52 (range 23–76). The 5-year survival rate of the cases was 81.8%.

Table 1 compares the characteristics of women with and without gestational diabetes. Those with gestational diabetes were older at entrance into the study, more likely to be of European origin and middle social class than women without diabetes. Pregnancy complications such as pre-eclampsia were also more common among women with gestational diabetes. Women with gestational diabetes were more likely to have given birth to low and high birth weight offspring and to have offspring with congenital malformations.

Characteristics of the cohort that were significantly associated with breast cancer are shown in Table 2. Women of North African and other West Asian ancestry were at reduced risk of breast cancer compared to those of European ancestry. Women born in Israel were 40% more likely to develop breast cancer than immigrant women. Compared to women in the highest social class, women in the lowest social class were at reduced risk of breast cancer. As would be expected, higher parity (4 or more births compared to 1 birth) at first observed birth was associated with a greatly reduced risk of breast cancer.

Table 3 shows an estimate of the relative rate of breast cancer in women who were diagnosed with gestational diabetes compared with other women. Breast cancer was increased one and half times after gestational diabetes (relative rate (RR) 1.5, 95% confidence interval (CI) 1.0–2.1). Adjusting for birth order at first observed birth and other variables did not appreciably alter the crude estimate.

Table 4 compares estimates of the relative rate of breast cancer before and after age 50 to approximate menopausal status. Women diagnosed with gestational diabetes showed a marked increase in risk after age 50 (RR 1.7, 95% CI 1.1–2.5), but were not at increased risk of breast cancer before that age. We also examined age 50 as a time-dependent variable and had similar results (data not shown). We were unable to determine in these data whether the effect was truly an age effect or a latency effect. Inclusion of the thirteen women excluded because they were diagnosed with both gestational diabetes and insulin dependent diabetes did not alter the results. There were no cases of in-situ disease among women with gestational diabetes. For invasive breast cancer the RR associated with gestational diabetes was 1.6 (95% CI 1.1–2.4) adjusted for age and birth order at first observed pregnancy, ethnic origin, social class, education and immigration status.

Discussion

This study found that the incidence of breast cancer was moderately higher in women who had gestational diabetes in any observed birth. This effect was seen among women diagnosed with breast cancer aged 50 years and older but not among women diagnosed before age 50. Two other studies have investigated the effects of gestational diabetes or glucose intolerance during pregnancy and risk of breast cancer [10, 11]. In a small prospective study measures of glucose intolerance were assessed among women without known diabetes in relation to breast cancer risk. The risk of breast cancer was increased across all quartiles of fasting plasma glucose levels relative to the lowest quartile [10]. An earlier study, which investigated gestational diabetes and breast cancer found that there was a slight non-significant decrease in risk <5 years since the last pregnancy, while there was a small non-significant increase in risk more than 5 years after the last pregnancy [11]. We could not compare our finding of a relation between gestational diabetes and the risk of breast cancer among older women but not younger women to these studies, as the results were not stratified by menopausal status [10, 11].

The mechanism by which gestational diabetes leads to an increased incidence of breast cancer in this study is not clear. Gestational diabetes is often accompanied by a beta-cell defect leading to an insufficient insulin response to serum glucose levels, resulting in hyperglycemia [1]. Hyperglycemia causes increased oxidative stress and results in the generation of reactive oxygen species (ROS) [16]. It has been reported that individuals with insulin and non-insulin dependent diabetes generate more ROS and had greater oxidative damage to DNA than controls [17] which might result in mutations to DNA repair genes, oncogenes and others.

A diagnosis of gestational diabetes may be an early marker of risk for breast cancer since the conversion rate of gestational diabetes to Type 2 diabetes ranges from 2.6% to 70%, depending on the length of follow-up [18]. Diabetes has been linked to an increased risk of breast cancer in some [19–24] but not all studies [25–28]. The effect seen here among older women but not younger women might plausibly be related to the increased prevalence of Type 2 diabetes among older compared to younger women. In several studies, which examined diabetes and risk of breast cancer and considered the effects by age or menopausal

Table 1 Percent distribution of women with and without a history of gestational diabetes by selected characteristics

Characteristics	Gestational Diabetes		*P*-value
	–	+	
Number of women	37,516	410	
Percent	100.0	100.0	
Age at first observed birth			
<25	47.2	32.4	<0.0001
25–29	28.0	29.3	
30–34	14.5	23.4	
35+	10.3	14.9	
Birth order at first observed birth			
1	62.6	60.0	0.5
2–3	21.7	21.5	
4+	16.7	18.5	
Birth place of woman			
Born in Israel	46.8	47.8	0.7
Born abroad	53.2	52.2	
Ethnic ancestry			
Israel	14.6	11.5	0.05
Other West Asia	28.3	27.6	
North Africa	21.5	19.5	
Europe Etc.	35.5	41.4	
Social class			
Low	30.8	25.6	0.03
Middle	37.2	42.7	
High	32.0	31.7	
Education (years)			
≤ 8	33.7	34.2	0.8
>8	66.3	65.9	
Preeclampsia			
No	97.2	87.8	<0.0001
Yes	2.8	12.2	
Offspring ≥4000 g at birth			
No	88.7	73.7	<0.0001
Yes	11.3	26.3	
Offspring <2500 g at birth			
No	89.0	80.0	<0.0001
Yes	11.0	20.0	
Offspring with congenital malformations			
No	92.5	88.3	0.001
Yes	7.5	11.7	

status it was found that the diabetes was associated with an increased risk of breast cancer among older women but not younger women [19–21, 24].

Several pathways have been proposed by which Type 2 diabetes might lead to development of breast cancer. In response to increased insulin resistance associated with diabetes, hyperinsulimia may result [29]. Insulin receptors are present in both normal and tumor breast tissue; the binding of insulin to its receptors initiates a cascade of mechanisms, which promote cell cycle progression in breast cancer cells [9]. Hyperinsulemia is also associated with low levels of sex hormone binding globulin (SHBG), which leads to an increase in the bioavailability of estradiol [9]. Insulin at high levels binds to the insulin-like growth factor I (IGF1) receptor [30] and down-regulates the IGF binding protein 1, (IGFBP1) [31], thus the amount of bioavailable IGF-1 could increase. Other conditions and disorders that are associated with insulin resistance include

Table 2 The association between selected characteristics and breast cancer risk

Characteristic	Breast Cancer		Age adj. RR	95% CI	*P*-value
	– (n = 36,300)	+ (n = 1,626)			
Birthplace of woman					
Born Abroad	19,360	809	1		
Born in Israel	16,940	817	1.4	1.2–1.5	<0.0001
Ethnic origin					
Europe	12,855	649	1		
Israel	5,294	245	0.9	0.8–1.0	0.1
Other West Asia	10,277	464	0.8	0.7–0.9	0.0001
North Africa	7,874	268	0.6	0.5–0.7	<0.0001
Social class					
High	11,575	575	1		
Middle	13,511	611	0.9	0.8–1.0	0.03
Low	11,214	440	0.6	0.6–0.7	<0.0001
Education (years)					
≤ 8	12,292	482	1		
>8	24,008	1,144	1.7	1.5–1.9	<0.0001
Birth order at first observed birth					
1 (ref)	22,727	895	1		
2–3	7,504	492	1.0	0.9–1.1	0.8
4+	6,069	239	0.4	0.3–0.5	<0.0001

Table 3 The association between gestational diabetes and breast cancer adjusted for age and other variables

Gestational diabetes	Breast cancer		Age-adjusted RR	95% CI	RR[a]	95% CI	RR[b]	95% CI	*P*-value
	–	+							
–	35,919	1,597	1		1		1		
+	381	29	1.6	1.1–2.3	1.5	1.0–2.1	1.5	1.0–2.1	0.03

[a] Adjusted for age and birth order at a first observed birth

[b] Adjusted for age and birth order at first observed birth, social class, ethnic origin, education and immigration status

Table 4 The association between gestational diabetes and breast cancer by age

Age at diagnosis	Gestational diabetes	Breast cancer[a]		RR[b]	95% CI	*P*-value
		–	+			
<50	–	36,879	637	1		
	+	403	7	1.0	0.5–2.1	1
≥50	–	33,591	960	1		
	+	374	22	1.7	1.1–2.5	0.01

[a] For women <50 who developed cancer, the term for breast cancer in the model was set to zero for women 50 years and older when calculating the relative rate of breast cancer after a diagnosis of gestational diabetes therefore the total sample remains 37,926. For women ≥50, women who were diagnosed with cancer prior to age 50 or were <50 at the end of follow-up or death were deleted which is why the total sample size for that stratum is only 34, 947

[b] Adjusted for age and birth order at first observed birth, social class, ethnic origin, education and immigration status

the metabolic syndrome and obesity [32]. Obesity, particularly central obesity [33] and postmenopausal weight gain [34] have also been linked to risk of breast cancer. Advantages of our study were its prospective design, long follow-up and complete obstetric history on all births. The data on gestational diabetes were taken from medical records and the data on breast cancer were derived from a national registry; neither ascertainment could be biased vis-

à-vis the other. Furthermore, the association was unaltered in analyses that considered social class, religion, ethnicity, or immigration status, or by the offsprings' sex, birth weight, presence of malformations and other obstetrical complications. We also did not have information on height and weight at different time points and were therefore unable to consider prepregnant BMI or BMI at age of diagnosis or end of follow-up.

Unlike many studies of diabetes, we were able to distinguish between women with Type 1 diabetes and those with gestational diabetes; however, we do not have an exact definition of diabetes and modern criteria for gestational diabetes mellitus were not applied in that era. It is possible that some women with gestational diabetes were negative for glycosuria test and were then not screened further with an oral glucose tolerance test. Therefore women could have been misdiagnosed as having normal glucose tolerance. Women could also have been misclassified if they were diagnosed with gestational diabetes in a pregnancy before 1964 or after 1976. In both instances, we would expect that misclassification by exposure status to be non-differential and bias our results to the null.

Gestational diabetes is a complicated disorder that confers an increased risk of diabetes in both the mother and offspring. Though our results need to be confirmed in future studies, the results suggest that gestational diabetes is an early marker of risk for breast cancer among older women. Since the prevalence of gestational diabetes is increasing [7, 8] it is important to clarify its relation to the risk of breast cancer.

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References

1. Buchanan TA, Xiang AH (2005) Gestational diabetes mellitus. J Clin Invest 115(3):485–491
2. Gestational diabetes mellitus. Diabetes Care (2003) 26 Suppl 1:S103–105
3. Green JR, Pawson IG, Schumacher LB, Perry J, Kretchmer N (1990) Glucose tolerance in pregnancy: ethnic variation and influence of body habitus. Am J Obstet Gynecol 163(1 Pt 1):86–92
4. Dooley SL, Metzger BE, Cho NH (1991) Gestational diabetes mellitus. Influence of race on disease prevalence and perinatal outcome in a U.S. population. Diabetes 40(Suppl 2):25–29
5. Berkowitz GS, Lapinski RH, Wein R, Lee D (1992) Race/ethnicity and other risk factors for gestational diabetes. Am J Epidemiol 135(9):965–973
6. Murphy NJ, Bulkow LR, Schraer CD, Lanier AP (1991) Prevalence of diabetes mellitus in pregnancy among Yup'ik Eskimos and Alaska Coastal Indians, 1987–1988. Arctic Med Res, Suppl:423–426
7. Thorpe LE, Berger D, Ellis JA, Bettegowda VR, Brown G, Matte T, Bassett M, Frieden TR (2005) Trends and racial/ethnic disparities in gestational diabetes among pregnant women in New York City, 1990–2001. Am J Public Health 95(9):1536–1539
8. Dabelea D, Snell-Bergeon JK, Hartsfield CL, Bischoff KJ, Hamman RF, McDuffie RS (2005) Increasing prevalence of gestational diabetes mellitus (GDM) over time and by birth cohort: Kaiser Permanente of Colorado GDM Screening Program. Diabetes Care 28(3):579–584
9. Wolf I, Sadetzki S, Catane R, Karasik A, Kaufman B (2005) Diabetes mellitus and breast cancer. Lancet Oncol 6(2):103–111
10. Dawson SI 2004 Long-term risk of malignant neoplasm associated with gestational glucose intolerance. Cancer 100(1):149–155
11. Troisi R, Weiss HA, Hoover RN, Potischman N, Swanson CA, Brogan DR, Coates RJ, Gammon MD, Malone KE, Daling JR et al 1998 Pregnancy characteristics and maternal risk of breast cancer. Epidemiology 9(6):641–647
12. Harlap S, Davies AM, Deutsch L, Calderon-Margalit R, Manor O, Paltiel O, Tiram E, Yanetz R, Perrin MC, Terry MB et al (2007) The Jerusalem Perinatal Study cohort, 1964–2005: methods and a review of the main results. Paediatr Perinat Epidemiol (in press)
13. Harlap S, Davies AM, Grover NB, Prywes R (1977) The Jerusalem Perinatal Study: the first decade 1964–1973. Isr J Med Sci 13:1073–1091
14. Investigation into the completeness for the Israel Cancer Registry. Methods and results. Publication 230. (In Hebrew). In: Israel Center for Disease Control 2003
15. Hosmer DW, Lemeshow S (1999) Applied survival analysis. John Wiley & Sons, Inc., New York
16. Niedowicz DM, Daleke DL (2005) The role of oxidative stress in diabetic complications. Cell Biochem Biophys 43:289–330
17. Dandona P, Thusu K, Cook S, Snyder B, Makowski J, Armstrong D, Nicotera T (1996) Oxidative damage to DNA in diabetes mellitus. The Lancet 347:444–445
18. Kim C, Newton KM, Knopp RH (2002) Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes Care 25(10):1862–1868
19. Michels KB, Solomon CG, Hu FB, Rosner BA, Hankinson SE, Colditz GA, Manson JE (2003) Type 2 diabetes and subsequent incidence of breast cancer in the Nurses' Health Study. Diabetes Care 26(6):1752–1758
20. Talamini R, Franceschi S, Favero A, Negri E, Parazzini F, La Vecchia C (1997) Selected medical conditions and risk of breast cancer. Br J Cancer 75(11):1699–1703
21. Weiderpass E, Gridley G, Persson I, Nyren O, Ekbom A, Adami HO (1997) Risk of endometrial and breast cancer in patients with diabetes mellitus. Int J Cancer 71(3):360–363
22. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM (2005) Fasting serum glucose level and cancer risk in Korean men and women. JAMA 293(2):194–202
23. Lipscombe LL, Goodwin PJ, Zinman B, McLaughlin JR, Hux JE (2006) Diabetes mellitus and breast cancer: a retrospective population-based cohort study. Breast Cancer Res Treat 98:349–356
24. Baron JA, Weiderpass E, Newcomb PA, Stampfer M, Titus-Ernstoff L, Egan KM, Greenberg ER (2001) Metabolic disorders and breast cancer risk (United States). Cancer Causes Control 12(10):875–880
25. Mink PJ, Shahar E, Rosamond WD, Alberg AJ, Folsom AR (2002) Serum insulin and glucose levels and breast cancer incidence: the atherosclerosis risk in communities study. Am J Epidemiol 156(4):349–352
26. Hjalgrim H, Frisch M, Ekbom A, Kyvik KO, Melbye M, Green A (1997) Cancer and diabetes-a follow-up study of two population-based cohorts of diabetic patients. J Intern Med 241(6):471–475
27. La Vecchia C, Negri E, Franceschi S, D'Avanzo B, Boyle P (1994) A case-control study of diabetes mellitus and cancer risk. Br J Cancer 70(5):950–953

28. Weiss HA, Brinton LA, Potischman NA, Brogan D, Coates RJ, Gammon MD, Malone KE, Schoenberg JB (1999) Breast cancer risk in young women and history of selected medical conditions. Int J Epidemiol 28(5):816–823
29. Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, Dyer A (2000) Abnormal glucose metabolism and pancreatic cancer mortality. JAMA 283(19):2552–2558
30. Le Roith D (1997) Seminars in medicine of the Beth Israel Deaconess Medical Center. Insulin-like growth factors. N Engl J Med 336(9):633–640
31. Suikkari AM, Koivisto VA, Rutanen EM, Yki-Jarvinen H, Karonen SL, Seppala M (1988) Insulin regulates the serum levels of low molecular weight insulin-like growth factor-binding protein. J Clin Endocrinol Metab 66(2):266–272
32. Lorincz AM, Sukumar S (2006) Molecular links between obesity and breast cancer. Endocr Relat Cancer 13(2):279–292
33. Connolly BS, Barnett C, Vogt KN, Li T, Stone J, Boyd NF (2002) A meta-analysis of published literature on waist-to-hip ratio and risk of breast cancer. Nutr Cancer 44(2):127–138
34. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE (2006) Adult weight change and risk of postmenopausal breast cancer. JAMA 296(2):193–201