HHS Public Access

Author manuscript

Cancer Causes Control. Author manuscript; available in PMC 2022 December 19.

Published in final edited form as:

Cancer Causes Control. 2018 August ; 29(8): 731–736. doi:10.1007/s10552-018-1048-6.

Gestational diabetes, type II diabetes, and mammographic breast density in a U.S. racially diverse population screened for breast cancer

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Abstract

Purpose—Type II diabetes mellitus (T2DM) has consistently been associated with an increased risk of breast cancer, but the association of gestational diabetes mellitus (GDM) with breast cancer is less clear. T2DM and GDM may influence breast cancer risk through mammographic breast density, a strong risk factor for breast cancer. We examined whether T2DM and GDM are associated with higher mammographic breast density in a largely racial/ethnic minority sample.

Methods—We collected digital mammograms, anthropometric measures, and interview data from 511 racially diverse women recruited during screening mammography appointments between 2012 and 2016 (mean age 51 years; 70% Hispanic). We examined the associations of self-reported GDM, T2DM, and medication use (metformin and insulin) with mammographic breast density, measured as percent and area of dense tissue using Cumulus software.

Results—In multivariable linear regression models, history of T2DM and/or GDM and length of time since diagnosis were not associated with percent density or dense breast area, either before or after adjustment for current BMI. Use of metformin in diabetic women was associated with lower percent density ($\beta = -5.73$, 95% CI −10.27, −1.19), only before adjusting for BMI. These associations were not modified by menopausal status.

Conclusions—Our results do not support associations between T2DM and/or GDM and higher amount of mammographically dense breast tissue, suggesting that the mechanism linking diabetes with breast cancer risk may not include mammographic breast density in midlife.

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Conflict of interest

The authors declare that they have no potential conflict of interest.

Keywords

Diabetes; Gestational diabetes; Mammographic breast density; Breast cancer; Metabolic syndrome; Hispanic

Introduction

In the U.S., the prevalence of type II diabetes mellitus (T2DM) and gestational diabetes mellitus (GDM) among adult women is 11% and 9%, respectively, and varies by racial/ethnic group with higher occurrence in Hispanic and black women [1, 2]. T2DM has been consistently associated with an increased risk of breast cancer, with a meta-analysis showing a 27% increased relative risk that is attenuated to 13% after adjusting for body mass index (BMI) [3]. GDM, which confers a sevenfold increased risk of T2DM 5–10 years after delivery, resembles T2DM in terms of metabolic and hormonal milieu, and thus may increase breast cancer risk via similar pathways [2, 4]. However, previous epidemiologic studies have produced mixed results on the association between GDM and breast cancer risk [4], and only a few studies have simultaneously considered T2DM and GDM [5, 6].

The speculated biological mechanisms relating diabetes to breast cancer involve changes in growth and sex hormones that promote cellular proliferation in the breast. As such, diabetes may be similarly associated with mammographic breast density (MBD), a measure of amount of dense (fibro-glandular) breast tissue on a mammogram and one of the strongest risk factors for breast cancer [7]. MBD has been shown to change in response to hormone replacement and selective estrogen receptor modulator (SERM) therapies (e.g., tamoxifen), and these changes have been associated with subsequent breast cancer risk, making MBD a potentially useful target for altering breast cancer risk from modifiable risk factors [8–11]. Understanding whether other risk factors for breast cancer operate via MBD can provide important information for designing breast cancer prevention studies. Only a few studies to date have investigated the associations between T2DM and MBD, and results have been inconclusive [12–16]. Here, we expand this limited research by examining the associations of T2DM, GDM, and length of time since diagnosis in relation to MBD in a racially diverse sample.

Methods

We obtained in-person interview data, height and weight measurements, and digital mammograms from 534 women during screening mammography appointments in 2012–2016 (age range 40–64 years) [17]. We excluded participants who had missing mammograms ($n = 5$), breast implants ($n = 9$), history of breast of cancer ($n = 2$), and type 1 diabetes ($n = 7$), yielding a final sample of 511 women.

We used self-reported data on history of T2DM diagnosis, and diabetes medication use and type (metformin, insulin, and other where specified). We asked parous women to report whether they had been diagnosed with gestational diabetes during any of their pregnancies, and to report the age at their first diagnosis. Participants were categorized as having a history GDM if they reported GDM in at least one pregnancy. We categorized nulliparous women

with parous women who never experienced GDM during any of their pregnancies, but we also repeated our analysis of GDM and MBD excluding nulliparous women. If history of GDM was reported, time since GDM was defined as the difference between interview date and the date of the first onset of GDM. To examine the potential joint effect of T2DM and GDM, we categorized participants as having both conditions, T2DM only, GDM only, and neither condition. We used a standardized protocol and Cumulus software, previously described [17], to assess percent density (dense area/breast area × 100) and area of dense tissue (dense area).

Statistical analysis

Using linear regression models, we separately examined the associations of T2DM, GDM, and presence of both conditions with percent density and dense area. In addition to age and race/ethnicity as a priori confounders, we considered and included in multivariable analyses variables that were associated with diabetes and percent density or dense area at $p < 0.10$, and altered the coefficient of the association between T2DM and GDM with either measures of MBD by ≥ 10%. These variables included menopausal status and educational attainment. We first fit a model that included all of these variables along with each measure of diabetes. In the final model, we also adjusted for current BMI given that BMI is strongly correlated with mammographic density and diabetes. Effect modification of the diabetes-MBD associations by menopausal status was examined through stratification (premenopausal vs. postmenopausal), and by including cross-product terms in multivariable models. All tests were 2-sided, and statistical analyses were performed using SAS 9.4 software (SAS Institute, Gary, NC).

Results

Distributions of sample characteristics by T2DM status are presented in Table 1. A majority of the study samples were Hispanic (70.1%) and non-Hispanic black (15.9%). Approximately 12.7% of women reported a history of T2DM with a mean age at diagnosis of 44.7 years. Over two-thirds of women with T2DM (69.2%) used metformin as a method of controlling T2DM. Of 450 parous women, 10.4% reported at least one diagnosis of GDM; the average age of first GDM onset was 30.4 years. About 3.1% of women had both T2DM and GDM. On average, women with T2DM were older relative to non-diabetic women (54.9 vs. 50.5 years), and more likely to be postmenopausal, less educated, overweight or obese, and current or former smokers.

Table 2 presents the results of multivariable models for the associations between T2DM and GDM variables and mammographic density, initially adjusting for age, race/ethnicity, menopausal status, and education (model 1), followed by further adjustment for current BMI (model 2). Diagnosis of T2DM, time since T2DM diagnosis, and insulin use were not associated with either percent density or dense area. Metformin use among women with T2DM was associated with an average 5.7% (95% CI: − 10.27, 1.19) lower percent density in model 1 as compared with the group without T2DM; this association was significantly attenuated after adjusting for BMI (model 2). There were no significant differences in percent density between non-diabetic women and diabetic women who did not use

metformin or any differences in dense area by metformin use. GDM alone, in combination with T2DM, and time since GDM diagnosis were not significantly associated with percent density and dense area. We observed the same overall results when we restricted our analysis of GDM to parous women. We did not find support for effect modification of any associations by menopausal status, tested through inclusion of cross-product terms between diabetes measures and menopausal status and through stratified analysis by menopausal status (data not shown).

Discussion

In a racially diverse sample of midlife women, GDM and T2DM diagnoses, separately and together, were not associated with significant differences in MBD. Our results with respect to T2DM are consistent with three prior studies that also used continuous measures of MBD [14–16], but differ from two other studies that used categorical measures of MBD [12, 13] and found lower MBD in women diagnosed with T2DM. As no prior studies have examined the association between GDM and MBD, more research is necessary to confirm our results. We did not observe different associations by menopausal status, which is consistent with results from one prior study [12], but another study reported stronger inverse associations between T2DM and MBD in pre- than in postmenopausal women [13].

We additionally examined and found no differences in MBD by the length of time since diagnoses of T2DM and GDM and use of insulin or metformin to control T2DM. The few prior studies considering these associations have yielded mixed results [14, 15]. No significant differences in MBD by length of time since diabetes diagnosis were reported in one study [14], while a suggestive lower MBD in women with more long-standing diabetes (10 years or longer) relative to women with more recent diagnosis (< 5 years) was noted in another study [15]. Two studies have investigated diabetes medication use and MBD associations. There were no effects of the use of insulin or pills on mean percent density among diabetic women in one study, majority of whom were of African American and Hispanic backgrounds [15]. In another study conducted in Denmark, use of insulin and metformin were, respectively, associated with higher and lower odds of having mixed/dense breasts in both premenopausal and postmenopausal women [12]. The direction of these associations were consistent with the purported opposite biological effects of insulin as promoting and metformin as reducing cell growth and circulating estrogen levels [18–20]. We also found some support for an inverse association between metformin use among women with T2DM and percent density. However, a lack of a similar association with dense area and the significant reduction in the association between metformin use and percent density after adjusting for BMI in our study point to the possibility that metformin may exert an influence on mammographic density through reducing body and breast fatness or size. Additional research to follow up on these intriguing findings, and more broadly on whether control of diabetes through medications with differing physiological and cellular changes, can provide important mechanistic insight into the effect of diabetes on breast cancer risk, and reconcile the mixed results with respect to MBD.

One limitation of the research in this area, including our study, is reliance on self-reported data on diabetes diagnosis and related variables. While physician diagnosis of chronic

diseases has shown high validity [21], self-reported medication, GDM diagnosis, and time of diagnosis may have more limited accuracy. Thus, errors in these exposure variables, which are likely to be non-differential with respect to the MBD measures, may have contributed to the null results in our study and majority of prior studies. The small sample size may have also lowered the statistical power and our ability to detect small differences in MBD. However, prior studies that used similar measures of MBD as used in our study had smaller sample sizes (range n = 191–476) [12–16]. While we report on the first investigation of GDM and MBD, lack of detailed data precluded a more in-depth analysis of GDM diagnosis, including the number of pregnancies with GDM, which may be more relevant to risk [6].

The strengths of our study include the use of physical measures of BMI and highly reproducible measures of MBD, lowering the possibility of confounding by body size and errors in the outcome of our analysis. Our study sample, predominately comprised black and Hispanic women, also extends the generalizability of research in this area to two racial/ethnic groups with the highest prevalence of diabetes in the US [1]. Majority of prior studies examining the association between diabetes and breast cancer have predominately been in samples of non-Hispanic white women, a racial group with the highest incidence of breast cancer in the US. Reproductive factors such as parity and age at first birth have been proposed as possible reasons behind differences in breast cancer incidence rates between non-Hispanic white women and racial/ethnic minority women. Our null findings in the relationship between T2DM and MBD, one of the strongest risk factors for breast cancer, may be possibly due to a reduced underlying risk in this population. In our study sample, only 10% of women were nulliparous and women on average, had two children, were 25 years old at first birth, and 5% were former or current hormone replacement therapy users.

In conclusion, we found no association between GDM and/or T2DM diagnoses and MBD among a racially diverse cohort of women, but observed suggestive evidence for lower percent density with the use of antidiabetic medication, metformin. While more research is needed to expand this limited literature, the evidence to date points to null or inverse associations between diabetes and MBD, suggesting that MBD is unlikely to be a pathway linking diabetes with increased breast cancer risk.

Funding

This work was supported by grants from the National Cancer Institute [K07 CA151777] and the Susan G. Komen Breast Cancer Foundation [KG110331].

References

1. Centers for Disease Control and Prevention (2017) National Diabetes Statistics Report, 2017. Centers for Disease Control and Prevention, US Department of Health and Human Services, Atlanta
2. DeSisto CL, Kim SY, Sharma AJ (2014) Prevalence estimates of gestational diabetes mellitus in the United States, pregnancy risk assessment monitoring system (prams), 2007–2010. Prev Chronic Dis 11:130415
3. Boyle P, Boniol M, Koechlin A et al. (2012) Diabetes and breast cancer risk: a meta-analysis. Br J Cancer 107(9):1608–1617 [PubMed: 22996614]

4. Tong G-X, Cheng J, Chai J et al. (2014) Association between gestational diabetes mellitus and subsequent risk of cancer: a systematic review of epidemiological studies. Asian Pac J Cancer Prev 15(10):4265–4269 [PubMed: 24935382]
5. Powe CE, Tobias DK, Michels KB et al. (2017) History of gestational diabetes mellitus and risk of incident invasive breast cancer among parous women in the Nurses' Health Study II prospective cohort. Cancer Epidemiol Biomarkers Prev 26(3):321–327 [PubMed: 27729356]
6. Park Y-MM, O'Brien KM, Zhao S, Weinberg CR, Baird DD, Sandler DP (2017) Gestational diabetes mellitus may be associated with increased risk of breast cancer. Br J Cancer 116(7):960–963 [PubMed: 28208154]
7. Boyd NF, Guo H, Martin LJ et al. (2007) Mammographic density and the risk and detection of breast cancer. N Engl J Med 356(3):227–236 [PubMed: 17229950]
8. van Duijnhoven FJB, Peeters PHM, Warren RML et al. (2007) Postmenopausal hormone therapy and changes in mammographic density. J Clin Oncol 25(11):1323–1328 [PubMed: 17312333]
9. Li J, Humphreys K, Eriksson L, Edgren G, Czene K, Hall P (2013) Mammographic density reduction is a prognostic marker of response to adjuvant tamoxifen therapy in postmenopausal patients with breast cancer. J Clin Oncol 31(18):2249–2256 [PubMed: 23610119]
10. Cuzick J, Warwick J, Pinney E et al. (2011) Tamoxifen-induced reduction in mammographic density and breast cancer risk reduction: a nested case-control study. JNCI J Natl Cancer Inst 103(9):744–752 [PubMed: 21483019]
11. Byrne C, Ursin G, Martin CF et al. (2017) Mammographic density change with estrogen and progestin therapy and breast cancer risk. JNCI J Natl Cancer Inst 109(9):djx001
12. Buschard K, Thomassen K, Lynge E et al. (2017) Diabetes, diabetes treatment, and mammographic density in Danish Diet, Cancer, and Health cohort. Cancer Causes Control 28(1):13–21 [PubMed: 27832382]
13. Roubidoux MA, Kaur JS, Griffith KA et al. (2003) Correlates of mammogram density in Southwestern Native-American women. Cancer Epidemiol Biomarkers Prev 12(6):552–558 [PubMed: 12815002]
14. Sellers TA, Jensen LE, Vierkant RA et al. (2007) Association of diabetes with mammographic breast density and breast cancer in the Minnesota breast cancer family study. Cancer Causes Control 18(5):505–515 [PubMed: 17437179]
15. Sanderson M, O'Hara H, Foderingham N et al. (2015) Type 2 diabetes and mammographic breast density among underserved women. Cancer Causes Control 26(2):303–309 [PubMed: 25421380]
16. Tehranifar P, Reynolds D, Fan X et al. (2014) Multiple metabolic risk factors and mammographic breast density. Ann Epidemiol 24(6):479–483 [PubMed: 24698111]
17. Tehranifar P, Protacio A, Schmitt KM et al. (2015) The metabolic syndrome and mammographic breast density in a racially diverse and predominantly immigrant sample of women. Cancer Causes Control 26(10):1393–1403 [PubMed: 26169301]
18. Chappell J, Leitner JW, Solomon S, Golovchenko I, Goalstone ML, Draznin B (2001) Effect of insulin on cell cycle progression in MCF-7 breast cancer cells. Direct and potentiating influence. J Biol Chem 276(41):38023–38028 [PubMed: 11500498]
19. Gunter MJ, Hoover DR, Yu H et al. (2009) Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. JNCI J Natl Cancer Inst 101(1):48–60 [PubMed: 19116382]
20. Campagnoli C, Berrino F, Venturelli E et al. (2013) Metformin decreases circulating androgen and estrogen levels in nondiabetic women with breast cancer. Clin Breast Cancer 13(6):433–438 [PubMed: 24267731]
21. Jackson JM, DeFor TA, Crain AL et al. (2014) Validity of diabetes self-reports in the Women's Health Initiative. Menopause 21(8):861–868 [PubMed: 24496083]

Table 1

Sample characteristics by type II diabetes mellitus status, $n = 511$

Characteristic	Total sample	With T2DM ($n = 65$)	Without T2DM ($n = 446$)
Age in years, mean (SD)	51.1 (5.8)	54.9 (3.9)	50.5 (5.9)
Race/ethnicity, *n* (%)			
Non-Hispanic White	56 (11.0)	4 (6.2)	52 (11.7)
Non-Hispanic Black	81 (15.9)	14 (21.5)	67 (15.0)
Hispanic	358 (70.1)	46 (70.1)	312 (70.0)
Asian	16 (3.1)	1 (1.5)	15 (3.4)
Education, *n* (%)			
Less than high school	108 (21.1)	28 (43.1)	80 (18.0)
High school graduate	118 (23.2)	16 (24.6)	102 (22.9)
Some college	120 (23.5)	12 (18.5)	108 (24.3)
Bachelor's or higher degree	164 (32.2)	9 (13.8)	155 (34.8)
BMI kg/m^2, mean (SD)	30.0 (5.7)	33.8 (6.9)	29.4 (5.3)
BMI kg/m^2, *n* (%)			
< 25.0	97 (19.0)	6 (9.2)	91 (20.5)
25.0–29.9	185 (36.3)	14 (21.5)	171 (38.4)
30.0–34.9	142 (27.8)	20 (30.8)	122 (27.4)
≥ 35.0	86 (16.9)	25 (38.5)	61 (13.7)
Menarche, mean (SD)	12.7 (1.8)	12.5 (2.0)	12.8 (1.7)
Partiy (n = 446), mean (SD)	2.1 (1.4)	2.2 (1.5)	2.1 (1.4)
Age at first birth ($n = 466$), mean (SD)	25.2 (6.6)	23.3 (5.3)	25.5 (6.7)
Menopausal status, *n* (%)			
Premenopausal/perimenopausal	240 (47.0)	12 (18.5)	228 (51.1)
Postmenopausal	271 (53.0)	53 (81.5)	218 (48.9)
Hormone replacement therapy, *n* (%)			
Never	482 (94.7)	60 (92.3)	422 (95.0)
Former user	16 (3.1)	3 (4.6)	14 (3.2)
Current user	11 (2.2)	2 (3.1)	8 (1.8)
Alcohol consumption per week, *n* (%)			
Never or former drinker	269 (53.0)	42 (65.6)	227 (51.2)
< 3 Servings, current drinker	146 (28.8)	12 (18.8)	134 (30.3)
3–7 Servings, current drinker	55 (10.9)	8 (12.5)	47 (10.6)
> 7 Servings, current drinker	37 (7.3)	2 (3.1)	35 (7.9)
Smoking status, *n* (%)			
Never	359 (70.8)	36 (56.2)	323 (72.9)
Former	98 (19.3)	17 (26.6)	81 (18.3)
Current	50 (9.9)	11 (17.2)	39 (8.8)
GDM ever, *n* (%)			
No	464 (90.8)	49 (75.4)	415 (93.0)
Yes	47 (9.2)	16 (24.6)	31 (7.0)

Characteristic	Total sample	With T2DM (*n* = 65)	Without T2DM (*n* = 446)
Age at first onset of GDM, mean (SD)	30.4 (6.6)	28.0 (4.0)	31.6 (7.4)
T2DM or GDM ever, *n* (%)			
Neither T2DM or GDM	415 (81.2)	–	–
T2DM only	49 (9.6)	–	–
GDM only	31 (6.1)	–	–
Both T2DM and GDM	16 (3.1)	–	–
Age at T2DM diagnosis, mean (SD)	—	44.7 (10.4)	–
Metformin ever use			
No	–	20 (30.8)	–
Yes	–	45 (69.2)	–
Insulin ever use			
No	–	51 (78.5)	–
Yes	–	11 (16.9)	–
Unknown	–	3 (4.6)	–
Percent density, mean (SD)	26.1 (15.5)	18.7 (12.0)	27.2 (15.7)
Dense area (cm^2), mean (SD)	47.6 (30.1)	46.3 (34.6)	47.8 (29.5)

SD standard deviation, *BMI* body mass index, *T2DM* type II diabetes, *GDM* gestational diabetes

Table 2

Linear regression coefficients (β) and 95% confidence intervals (CI) for the associations between diabetic conditions and mammographic density, n = 511

	Percent density				Dense area			
	Model 1		Model 2		Model 1		Model 2	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
T2DM								
No	Ref		Ref		Ref		Ref	
Yes	− 4.19	− 8.12, − 0.26	− 1.34	− 5.18, 2.50	3.58	− 4.46, 11.63	0.96	− 7.19, 9.11
Time since T2DM diagnosis								
No T2DM	Ref		Ref		Ref		Ref	
≤ 10 years	− 3.83	− 8.70, 1.04	− 1.51	− 6.21, 3.19	2.37	− 7.60, 12.34	0.21	− 9.77, 10.18
> 10 years	− 5.52	− 11.60, 0.56	− 2.32	− 8.21, 3.56	4.07	− 8.38, 16.53	1.09	− 11.40, 13.58
Metformin use								
Non-diabetic	Ref		Ref		Ref		Ref	
No Metformin use	− 0.60	− 7.19, 6.00	1.88	− 4.46, 8.23	7.41	− 6.11, 20.93	5.10	− 8.38, 18.58
Metformin use	− 5.73	− 10.27, − 1.19	− 2.74	− 7.16, 1.67	1.94	− 7.36, 11.24	− 0.84	− 10.23, 8.55
Insulin use								
Non-diabetic	Ref		Ref		Ref		Ref	
No insulin use	− 3.60	− 7.94, 0.74	− 0.95	− 5.17, 3.26	4.64	− 4.26, 13.53	2.12	− 6.83, 11.07
Insulin use	− 8.43	− 17.13, 0.26	− 4.62	− 13.00, 3.75	− 4.85	− 22.65, 12.94	− 8.48	− 26.25, 9.29
GDM								
Never	Ref	− 8.23, 0.42	Ref		Ref		Ref	
Ever	− 3.90		− 3.47	− 7.60, 0.65	− 1.20	− 10.05, 7.65	− 1.59	− 10.37, 7.18
Time since GDM diagnosis								
No GDM	Ref		Ref		Ref		Ref	
≤ 20 Years	1.82	− 7.26, 10.89	2.38	− 6.25, 11.02	9.98	− 8.51, 28.46	9.46	− 8.85, 27.77
> 20 Years	− 2.26	− 9.06, 4.54	− 1.91	− 8.38, 4.56	3.80	− 10.06, 17.66	3.48	− 10.25, 17.21
Ever T2DM or GDM diabetes								
No T2DM or GDM	Ref		Ref		Ref		Ref	
T2DM only	2.64	− 2.61, 7.89	1.89	− 3.12, 6.90	− 1.88	− 12.62, 8.86	− 1.23	− 11.89, 9.44
GDM only	− 0.67	− 7.29, 5.95	2.20	− 4.17, 8.56	4.80	− 8.75, 18.34	2.30	− 11.24, 15.84

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	Percent density				Dense area			
	Model 1		Model 2		Model 1		Model 2	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
T2DM and GDM	− 4.79	− 13.51, 3.93	− 4.56	− 12.87, 3.76	− 6.88	− 24.72, 10.96	− 7.09	− 24.78, 10.61

Model 1 adjusted for age, race/ethnicity, menopausal status, and educational attainment; *model 2* model 1 plus current BMI