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Association between diabetes status and breast cancer in US adults: A cross-sectional study

Running title: Association between diabetes status and breast cancer

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 doi:10.20944/preprints202209.0481.v1

Abstract

Objectives: The purpose of this study was to determine whether breast cancer and diabetes status are related in adult Americans.

Methods: We conducted a cross-sectional study of 7,599 individuals from the National Health and Nutrition Examination Survey (NHANES). Diabetes was classified as type 2 diabetes and pre-diabetes. Both prediabetes and diabetes were diagnosed according to ADA 2014 guidelines. Multiple logistic regression analysis was used to explore the relationship between diabetes status and breast cancer.

Results: We found that prediabetes (OR = 0. 60, 95% CI:(0. 40, 0. 88), P= 0. 009613) and non−diabetes (OR = 0.05.3,95% CI: (0.34, 0.83), P = 0. 006014) were associated with a reduced risk of breast cancer in comparison to Type 2 diabetes (literature). Prediabetes in non-Hispanic blacks was associated with a reduced risk of breast cancer (OR=0. 55,95%CI:0. 40-0. 75, P<0. 001). Using two segmented linear regression models to fit the relationship between BMI and breast cancer, we found that the relationship between BMI and breast cancer was nonlinear, but there was a threshold effect. The threshold effect analysis found that BMI affcted breast cancer at an inflection point 26. 3 Kg/m2. Adjusted OR (95% CI) on both sides of the turning point was 1. 0799 (1. 0029, 1. 1629) and 0. 9873 (0. 9638, 1. 0115), respectively.

Conclusions: Diabetes status is associated with the risk of breast cancer development. Moreover, the risk of developing breast cancer steadily increased from nondiabetes to prediabetes and type 2 diabetes. In addition, the prevalence of breast cancer showed a gradual increase with increasing BMI up to 26. 3 Kg/m2 with the highest prevalence of breast cancer. There was an inverse U-shaped relationship between BMI and the breast cancer prevalence.

Keywords: diabetes status, prediabetes, type 2 diabetes, breast cancer, NHANES

INTRODUCTION

There are more than 40 million cases of breast cancer in women worldwide and it is the second most common cancer among women in the United States [1, 2]. The American Cancer Society indicates that approximately 42,000 women will die from breast cancer in 2020, with 276,000 newly diagnosed cases [3]. Breast cancer affects women of all ages. However, the incidence of breast cancer increases with age, with a peak incidence at 45-64 years [4]. There are many factors associated with the risk of breast cancer [5,6]. The prevalence of diabetes is increasing at an alarming rate and has become one of the most serious public health problems in the world. Diabetes is also considered to be the most common endocrine disease. The American Diabetes Association (ADA) shows that diabetes is the fourth leading cause of death in United States [7].

There is a growing recognition that diabetes mellitus (DM) and breast cancer (BC) occur together in the same patient population with high mortality rates [8]. Overall survival and disease-specific survival are significantly worse in diabetic BC patients compared to non-diabetic BC patients, suggesting a correlation between DM2 and cancer progression [9].

Hardefeldt et al. showed that diabetes mellitus is an independent risk factor for breast cancer [10]. According to the results of a meta-analysis, women with diabetes had a 23% higher risk of future breast cancer than women without diabetes [11]. A meta-analysis showed that women with diabetes had a significantly higher risk (~20%) of breast cancer than those without diabetes [12]. DM2 and hyperinsulinemia were independently associated with postmenopausal breast cancer [13]. In addition, a growing body of data suggests that diabetes and its complications adversely affect cancer treatment [14] and increase mortality [15], thereby affecting the prognosis of breast cancer patients[16,17].

Patients with prediabetes have higher than normal blood glucose levels, but not high enough to be considered as type 2 diabetes (DM2); however, this is often seen as a warning sign. Pre-diabetes is characterized by impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or an HbA1c of 39 mmol/mol (5.7%) to 46 mmol/mol (6.4%) [18]. The significance of prediabetes (pre-DM) lies in the risk associated with progression to DM2, which is disproportionately higher at the upper end of the prediabetes range and in the combined presence of IFG and IGT [18]. Prediabetes and DM2 are parts of a continuum of spectrum that share pathophysiology and are associated with typical phenotypes including obesity, hypertension (HTN) and dyslipidemia (DLP) [19]. Few studies have examined the impact of diabetes on breast cancer. Therefore, the aim of this study was to investigate the relationship between diabetes status and breast cancer in United States adults.

The main objectives of this study were: 1) to understand the weighted distribution of the diabetes status characteristics in the study population; 2) to determine the correlation between diabetes status (nondiabetes, prediabetes, T2DM) and breast cancer; 3) to determine the relationship between race and breast cancer; 4) to determine the relationship between BMI and breast cancer. All analyses were based on data from the National Health and Nutrition Examination Survey (NHANES) from 2011-2016.

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MATERIALS AND METHODS

Data Source

NHANES is a publicly available, cross-sectional, population-based survey administered by the Centers for Disease Control and Prevention (CDC) designed to assess the health and nutritional status of the civilian, noninstitutional population of United States through interviews, physical examinations, and laboratory tests. NHANES data are released on a 2-year cycle and use a multistage probability sampling design and weights to produce, at each cycle, a nationally representative sample[20]. The NHANES program is reviewed annually by the National Center for Health Statistics Ethics Review Committee [21].

Study Population

The data for this study were obtained from the 2011-2016 survey cycle [22]. This is information on all variables used to determine type 2 diabetes and its determinants in recent years. This study included a total of 15151 women in three cycles from 2011 to 2016, excluding 5242 women with unclear or missing diabetes diagnosis, 545 women diagnosed with other cancers, 1730 women with unknown cancer diagnoses, and 35 women under 20 years of age diagnosed with diabetes. Finally, 7,599 participants were included in the study (Figure 1). Multiple interpolation was used for missing data.

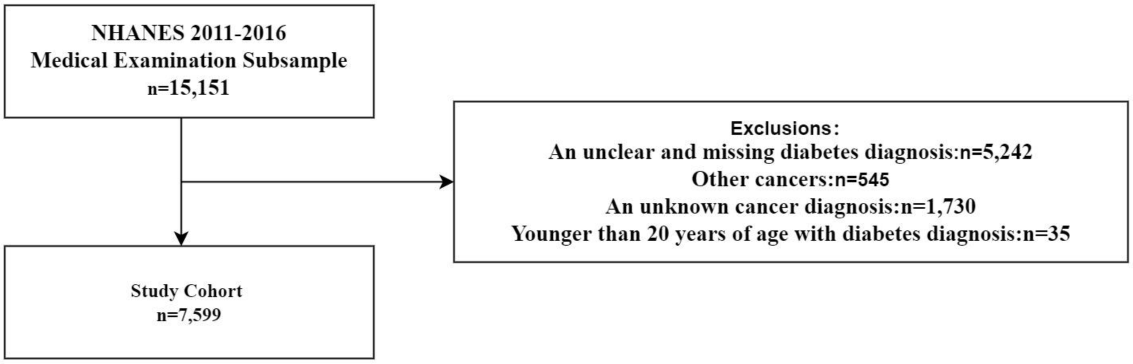

Figure 1.

Diagnostic criteria for diabetes and prediabetes

The diagnostic criteria for diabetes and prediabetes are shown in Table 1. Diagnostic criteria for diabetes and prediabetes are shown in the table, and the population included in the study had to meet the diagnostic criteria or have a clear diagnosis of diabetes in NHANES.

Table 1

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Criteria for the diagnosis of diabetes

Criteria for the diagnosis of diabetes:
FPG≥126mg/dL（7.0mmol/L）.Fasting is defined as no caloric intake for at least8h.*
OR
2-hPG≥200mg/dL（11.1mmol/L during OGTT.The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C≥6.5%（48m mol/mol）.The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay*.
OR
In a patient with classic Symptoms of hyperglycemia or hyperglycemic crisis,a random plasma glucose ≥200mg/dl（11.1mmol/L）.

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization ；2-h PG， 2-h plasma glucose."In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Criteria defining prediabetes*

Criteria defining prediabetes:
FPG 100mg/dL（5.6mmol/L）to 125mg/dL（6.9mmol/L） （IFG）
OR
2-h PG duringg75-gOGTT 140mg/dL（7.8mmol/L）to 199mg/dL（11.0mmol/L）（IGT）
OR
A1C 5.7-6.4%（39-47mmol/mol）

FPG, fasting plasma glucose;IFG, impaired fasting glucose; IGT, impaired glucose tolerance ；OGTT, oral glucose tolerance test ；2-h PG， 2-h plasma glucose.* For all three tests, the risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at the higher end of the range.

Statistical analysis

To determine the correlation between type 2 diabetes status and breast cancer in adults, a multivariate logistic regression model was developed in which the above covariates were adjusted for potential confounding variables. Continuous variables were expressed as mean ± SD, which included BMI, cholesterol, creatinine, serum glucose, tricarbaminol, serum cotinine, estradiol, glycohemoglobin, age of onset of menarche, age at the last menstrual period and times of pregnancies. Categorical variables were expressed as percentages or frequencies, which included age, race, level of education, marital status, history of pregnancy and breast cancer. Stratified analysis and smoothed curve fitting were used to test the association between type 2 diabetes and breast cancer based on age, race, body mass index, education level, serum creatinine, cholesterol, triglycerides, glycoprotein, serum cotinine, estradiol, marital status, glucose, and reproductive health. The statistical software packages R (http://www. R-project. org) was used for stastical analyses. Statistical significance was considered when the P value was < 0. 05.

RESULTS

Characteristics of the participants

Table 2 describes the weighted characteristic of the study sample. Our study included 7,779 participants subclassified according to NHANES. Participants were divided into three groups: type 2 diabetes, prediabetes, and nondiabetes. Among the participants, the proportions of type 2 diabetes, prediabetes, and nondiabetes were 17. 16% (n = 1,335), 31. 74% (n = 2,469), and 48. 79% (n = 3,795) respectively. In terms of race, the proportions of Mexican Americans, white and black were 17. 43, 32. 92, and 19. 34%, respectively. In terms of age, nondiabetes had the largest population of 2529 (66. 640 %) with an age less than or equal to 45. However, prediabetes had the largest population of 1688 (68. 368%) being younger than 45 years. The majority of the population included in this study was non-diabetic, with rates of 494 (13. 017%), 428 (11. (38 278%), 1471. 762%), 759 (20. 000%), and 643 (16. 943%) for Mexican Americans, other Hispanics, non-Hispanic whites, non-Hispanic blacks, and other races, respectively. Among breast cancers, the largest proportion of patients with prodromal diabetes was 81 (3. 281%). More detailed results are given in Table 2.

Table 2 Weighted characteristic of study sample

	Type 2 diabetes	Prediabetes	Non-diabetes	P-value
N	1335	2469	3795	
Body mass index (kg/m^2)	33.556 ± 8.259	30.948 ± 7.868	27.696 ± 6.865	<0.001
Cholesterol (mmol/L)	4.995 ± 1.227	5.195 ± 1.055	4.932 ± 1.018	<0.001
Creatinine (umol/L)	77.994 ± 46.251	68.772 ± 36.638	65.326 ± 24.726	<0.001
Serum glucose (mmol/L)	8.433 ± 4.246	5.420 ± 0.770	4.913 ± 0.695	<0.001
Triglycerides (mmol/L)	2.118 ± 2.318	1.618 ± 1.089	1.331 ± 0.955	<0.001

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Serum Cotinine (ng/mL)	34.874 ± 104.414	42.641 ± 111.436	38.821 ± 100.767	0.094
Estradiol (pg/mL)	38.958 ± 365.299	55.830 ± 328.953	151.202 ± 822.626	<0.001
Glycohemoglobin (%)	7.334 ± 1.877	5.739 ± 0.330	5.224 ± 0.277	<0.001
Age when first menstrual period occurred	12.682 ± 1.984	12.790 ± 1.909	12.726 ± 1.748	0.229
Age at last menstrual period	44.833 ± 8.410	45.451 ± 8.046	43.546 ± 9.378	<0.001
How many times have been pregnant	3.981 ± 2.334	3.417 ± 1.900	3.157 ± 1.947	<0.001
Age (years)				<0.001
≤45	217 (16.255%)	781 (31.632%)	2529 (66.640%)	
>45	1118 (83.745%)	1688 (68.368%)	1266 (33.360%)	
Race				<0.001
Mexican American	235 (17.603%)	343 (13.892%)	494 (13.017%)	
Other Hispanic	187 (14.007%)	292 (11.827%)	428 (11.278%)	
Non-Hispanic White	354 (26.517%)	837 (33.900%)	1471 (38.762%)	
Non-Hispanic Black	385 (28.839%)	619 (25.071%)	759 (20.000%)	
Other Race - Including Multi-Racial	174 (13.034%)	378 (15.310%)	643 (16.943%)	
Education level				<0.001
Less than 9th grade	247 (18.516%)	276 (11.188%)	216 (5.695%)	

9-11th grade	215 (16.117%)	313 (12.687%)	400 (10.546%)	
High school graduate/GED or equivalent	313 (23.463%)	512 (20.754%)	734 (19.351%)	
Some college or AA degree AA degree	375 (28.111%)	774 (31.374%)	1307 (34.458%)	
College graduate or above	184 (13.793%)	592 (23.997%)	1136 (29.950%)	
Marital status				<0.001
Married	588 (44.078%)	1177 (47.690%)	1777 (46.849%)	
Widowed	274 (20.540%)	296 (11.994%)	202 (5.326%)	
Divorced	185 (13.868%)	367 (14.870%)	384 (10.124%)	
Separated	72 (5.397%)	110 (4.457%)	129 (3.401%)	
Never married	160 (11.994%)	348 (14.100%)	933 (24.598%)	
Living with partner	55 (4.123%)	170 (6.888%)	368 (9.702%)	
Ever been pregnant				<0.001
no	119 (9.925%)	250 (11.395%)	772 (23.323%)	
yes	1080 (90.075%)	1944 (88.605%)	2538 (76.677%)	
Breast cancer				<0.001
no	1257 (94.157%)	2388 (96.719%)	3730 (98.287%)	
yes	78 (5.843%)	81 (3.281%)	65 (1.713%)	

Mean ± SD for continuous variables: P value was calculated by weighted linear regression model.% for categorical variables: P value was calculated by weighted chi-square test.

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Associations between diabetes status and breast cancer

Table 3 shows the results of multiple logistic regression analysis of the association between diabetes status and breast cancer. Model 1: adjusted for: None. Model 2:Adjusted for age, race, body mass index. Model 3: Adjusted for age, race, body mass index, educational level, serum creatinine, cholesterol, triglycerides, glycohemoglobin, serum cotinine, estradiol, marital status, serum glucose, and reproductive health. From Model 3, we found that prediabetes (OR = 0. 60, 95%CI: (0. 40, 0. 88), P=0.009613) and non-diabetes (OR = 0.03, 95% CI: (0. 34, 0. 83) , P=0. 006014) were associated with a reduced risk of breast cancer. The results are shown in details in Table 3.

Table 3 Associations between diabetes status and breast cancer.

	Model 1 OR (95% CI, P)	Model 2 OR (95% CI, P)	Model 3 OR (95% CI, P)
Type 2 diabetes	Reference	Reference	Reference
Prediabetes	0.55 (0.40, 0.75) <0.001	0.61 (0.44, 0.84) 0.002662	0.60 (0.40, 0.88) 0.009613
Non- diabetes	0.28 (0.20, 0.39) <0.001	0.55 (0.39, 0.80) 0.001444	0.53 (0.34, 0.83) 0.006014

Model 1: adjust for: None
Model 2: age, race, body mass index were adjusted.
Model 3: age, race, body mass index, educational level, serum creatinine, cholesterol, triglycerides, glycohemoglobin, serum cotinine, estradiol, marital status, serum glucose and reproductive health were adjusted.

Associations between race and breast cancer

Table 4 shows the results of multiple logistic regression analysis testing the relationship between race and breast cancer. Model 1: adjust for: None. Model 2: Adjusted for age, race, and body mass index. Model 3: Adjusted for age, body mass index, educational level, serum creatinine, cholesterol, triglycerides, glycohemoglobin, serum cotinine, estradiol, marital status, serum glucose and reproductive health. From Model 3, we found prediabetes (OR = 0. 30, 95%CI: 0. 12-0. 74, P= 0. 0092) and non-diabetes(OR=0. 21, 95%CI: 0. 07-0. 69, P= 0. 0097) in non-Hispanic black were associated with a lower risk of breast cancer (OR = 0.25% CI: 0.20-0. 75, P<0. 001). The results are shown in Table 4.

Table 4 Associations between race and breast cancer.

	Model 1	**Model 2**	**Model 3**
	OR (95% CI, P)	OR (95% CI, P)	OR (95% CI, P)
Mexican American			
Type 2 diabetes	Reference	Reference	Reference
Prediabetes	0.54 (0.21, 1.38) 0.1976	0.74 (0.28, 1.93) 0.5352	1.01 (0.28, 3.69) 0.9886

Non- diabetes	0.18 (0.06, 0.59) 0.0045	0.69 (0.20, 2.36) 0.5531	1.08 (0.23, 5.18) 0.9233
Other Hispanic			
Type 2 diabetes	Reference	Reference	Reference
Prediabetes	0.43 (0.18, 1.02) 0.0545	0.47 (0.20, 1.14) 0.0949	0.43 (0.15, 1.22) 0.1121
Non- diabetes	0.29 (0.12, 0.68) 0.0049	0.52 (0.21, 1.33) 0.1726	0.47 (0.15, 1.50) 0.2010
Non-Hispanic White			
Type 2 diabetes	Reference	Reference	Reference
Prediabetes	0.61 (0.38, 0.99) 0.0460	0.70 (0.43, 1.15) 0.1623	0.88 (0.48, 1.60) 0.6798
Non- diabetes	0.31 (0.19, 0.50) <0.0001	0.63 (0.38, 1.06) 0.0836	0.80 (0.41, 1.56) 0.5099
Non-Hispanic Black			
Type 2 diabetes	Reference	Reference	Reference
Prediabetes	0.39 (0.18, 0.85) 0.0169	0.49 (0.22, 1.06) 0.0703	0.30 (0.12, 0.74) 0.0092
Non- diabetes	0.20 (0.08, 0.49) 0.0004	0.48 (0.19, 1.22) 0.1238	0.21 (0.07, 0.69) 0.0097
Other Race			
Type 2 diabetes	Reference	Reference	Reference
Prediabetes	0.45 (0.17, 1.22) 0.1151	0.53 (0.19, 1.46) 0.2189	0.39 (0.11, 1.45) 0.1616
Non- diabetes	0.13 (0.04, 0.44) 0.0010	0.34 (0.10, 1.19) 0.0910	0.25 (0.05, 1.28) 0.0958

Model 1: adjust for: None

Model 2: age, race, body mass index were adjusted.

Model 3: age, body mass index, educational level, serum creatinine, cholesterol, triglycerides, glycohemoglobin, serum cotinine, estradiol, marital status, serum glucose and reproductive health were adjusted.

Analysis of the effect of BMI threshold on female breast cancer using a two-part linear regression model

We fitted the relationship between BMI and breast cancer using a two-piece linear regression model is shown in Table 5. The value of the log-likelihood ratio test was 0. 037,

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and the inflection point determined by two segmented linear regression was 26. 3Kg/m2. There was a non-linear relationship between BMI and breast cancer. The inflection point for BMI was 26.3 kg/m2. To the left side of the inflection point (< 26.3 kg/m2), BMI was positively associated with Breast cancer (OR =1.0799; 95% CI 1.0029, 1.1629). On the right side of the inflection point (＞ 26.3 kg/m2), BMI was not associated with Breast cancer (OR = 0.9873; 95% CI −0.9638, 1.0115). Although these results are all consistent with a lower risk of breast cancer to the right side of the inflection point, a statistically significant association between breast cancer and BMI was lacking. Results are detailed in Table 5 and Figure 2.

Table 5 Threshold effect analysis of BMI on breast cancer in female using the two piecewise linear regression model.

Breast cancer	Adjusted OR (95% CI)
Fitting by the standard linear model	1.0035 (0.9866, 1.0208)
Fitting by the two-piecewise linear model	
Inflection point	26.3
Body mass index (kg/m²) < 26.3 (kg/m²)	1.0799 (1.0029, 1.1629)
Body mass index (kg/m²) ＞26.3 (kg/m²)	0.9873 (0.9638, 1.0115)
Log likelihood ratio	0.037

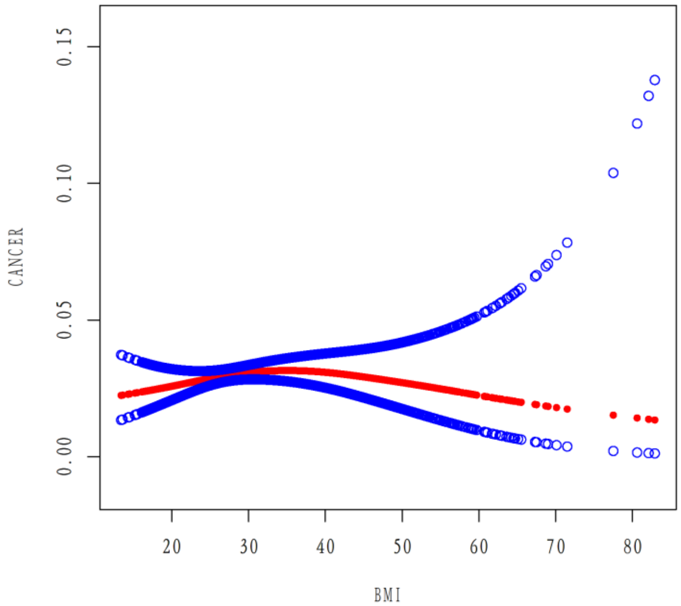

Figure 2.

 doi:10.20944/preprints202209.0481.v1

Associations between Age and Breast Cancer

The relationship between age and breast cancer was found using multiple linear regression and curve fitting analysis. There was a linear relationship between age and breast cancer (OR=1. 0799,95%CI:1. 0688-1. 0912, P=<0. 0001). The results are detailed in Figure 3.

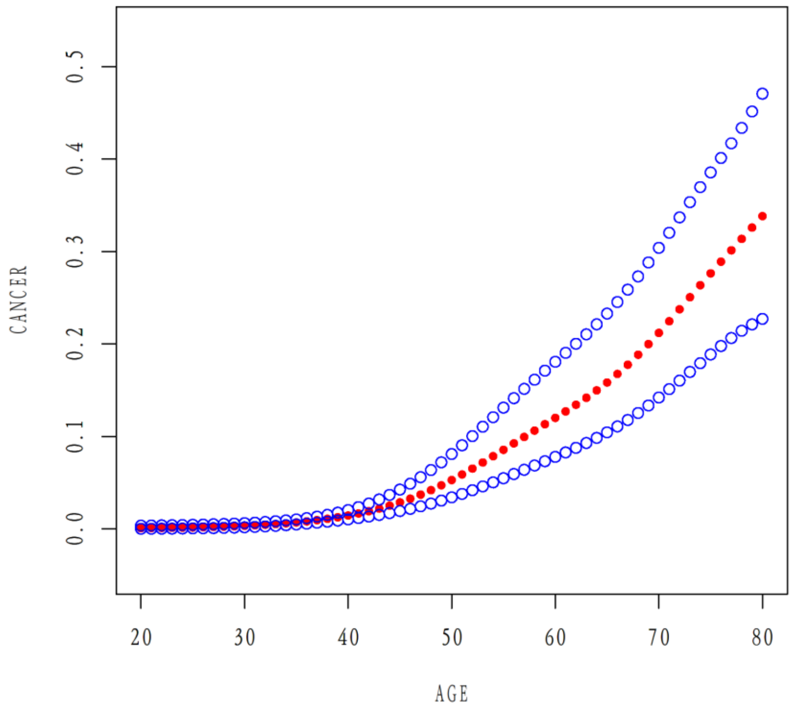

Figure 3.

DISCUSSION

Breast cancer is the most common cancer which affects women around the world [6]. According to the American Breast Cancer website (http://www.breastcancer.org/symptoms/understand_bc/statistics)[23], approximately 12% of American women have breast cancer, which raises a major public health topic. Multiple factors contribute to the development of breast cancer, including but not limited to age, estrogen, genetic factors, and obesity [24]. Many studies have explored the relationship between diabetes and breast cancer[25,26]. Rehman et al. showed that women with diabetes had poorer survival rates after breast cancer diagnosis than women without diabetes [27], while Park et al. showed that type 2 diabetes (T2D) was associated with an increased risk of developing breast cancer [28]. However, previous literature had also reported that type 2

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diabetes is unlikely to cause breast cancer or prostate cancer [29]. Therefore, the relationship between diabetes and breast cancer remains controversial and requires further investigation. In the absence of consensus, the aim of this study was to examine the relationship between diabetes and breast cancer in the American population.

In this study, we analyzed the characterstics of the weighted distribution of the study population, compared the differences in various indicators among diabetic patients in different states, and found that the incidence of breast cancer differs in different populations. Also, we corrected for many relevant influences and used a weighted generalized sum model to explore the correlation between diabetes status and breast cancer incidence. Simultaneously, we performed a subgroup analysis of the study population to explore whether breast cancer incidence rates were the same between different populations in the United States.

Related studies have shown that obesity is a major risk factor for diabetes [30]. Ayoub revealed that Jordanian obese breast cancer patients have a higher risk of breast cancer recurrence and a lower survival rate compared to non-obese patients [31]. In this study, we fitted a smoothed curve for the relationship between BMI and breast cancer after adjusting for gender and age, and found the inflection point between BMI and breast cancer by threshold effect analysis.

The population in this study was divided into type 2 diabetes, prediabetes, and nondiabetic. Differences between groups were compared between the three groups for different factors. There was a significant difference in BMI among the three groups, with the highest BMI in patients with type 2 diabetes. As a result, a previous study confirms the findings [32]. Patients with type 2 diabetes had the lowest age at menarche, but the results were not statistically significant. The age at first menstruation was reported to be associated with a high risk of type 2 diabetes in China, [33], which is consistent with our study. Hormone changes may account for this. We also found statistically significant differences in age at last menstruation among the three groups and the earliest age at last menstruation in non-diabetic patients, which is consistent with a study in China that also showed that the later the menopause, the higher the sharing of diabetes [34]. We also found that non-diabetic patients were most prevalent in those under or equal to 45 years of age. The highest number of people with anterograde diabetes was found in those over 45 years of age.The study by Mordarska et al. showed that the prevalence of both type 2 diabetes and anterograde diabetes increased with age, which is consistent with our study.

In our study, we examined differences in diabetes status among five races/ethnicities (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and other races including multiracial). Non-Hispanic blacks had the highest prevalence of diabetes [385 (28. 839%)], followed by non-Hispanic whites [354 (26.51%)]. However, among prediabetes, non-HIspanic whites [837 (33.390%) had the highest prevalence, followed by non-Hispanic blacks [619 (23.571%)]. Possible reasons could be racial differences, different living environments and eating habits. However, the reason for the difference in prediabetic status between the two races is unclear and further studies are needed to find results. In terms of

 doi:10.20944/preprints202209.0481.v1

education, we found that the higher level of education, the more patients with type 2 diabetes and prediabetes. Our findings are consistent with a longitudinal study involving 9965 individuals that was designed to determine risk factors and prevalence of NCDs. This study found a higher prevalence of prediabetes and undiagnosed diabetes among low literacy, older adults, unemployed individuals, and homemakers [36]. By examining marital status, we found that the highest number of patients with type 2 diabetes and prediabetes were found in the married population, so we hypothesized that marital status may be associated with the prevalence of diabetes. Possible reasons for this are: in both sexes, age, marital status, education, employment, poor diet and leisure time are indirectly associated with prediabetes through cardiometabolic risk factors [37]. The rate of type 2 diabetes and prediabetes was much greater in those with a history of pregnancy than in those without a history of pregnancy. A possible reason for this is that the study population may include some individuals with a history of gestational diabetes mellitus (GDM). Ratner et al. showed that a previous history of GDM leads to a very high risk of postpartum diabetes, especially type 2 diabetes [38]. We also found statistically significant differences in the prevalence of different states of diabetes in different ethnic groups.

After adjusting for relevant covariates such as age, race and body mass index, we found a statistically significant difference between type 2 diabetes and pre-diabetes as risk factors for breast cancer. As diabetes progresses (from prediabetes to diabetes), the development of breast cancer is more closely related to the onset of diabetes. Hipp et al. showed that more than 25 million Americans in the United States have diabetes and more than 80 million have prediabetes. Thus, approximately one-third of Americans suffer from diabetes or prediabetes [39]. Many epidemiological studies have showned that type 2 diabetes is associated with an increased risk of breast cancer [40,41,42,43,44,45]. The main reason for this is that hyperglycemia and the inflammatory response of diabetes can lead to insulin resistance, thus forming insulin resistance. Insulin resistance associated with hyperinsulinemia and overexpression of insulin receptors (IRs) is closely related to the pathogenesis and treatment outcome of breast cancer [46]. However, this mechanism remains uncertain, and related studies suggest that the relationship between breast cancer and insulin resistance is controversial [47]. Therefore, the pathogenesis of diabetes and breast cancer needs to be further investigated.

In our study, after correcting for age and other relevant factors, we found that diabetes status associated with the occurrence of breast cancer in non-Hispanic blacks. Worldwide, both Hispanic and Asian populations have a higher prevalence of diabetes than European and African populations, both in their native environment and in their diaspora[48,49]. This conclusion was also reached in our study. These differences between racial or ethnic groups may raise from multiple factors, including genetics, epigenetics, lifestyles, and environment [50]. In other populations,there was no association found between diabetes status (type 2 diabetes and prediabetes) and breast cancer, after correction of associated factors. We found, in our study, that the number of breast cancer patients increased with the age of the female patients. Song et al. have demonstrated that age is a significant and well-established risk factor for breast cancer [51]. There is an association between age and breast cancer, and the

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median age of women who diagnosed with breast cancer in the United States is 62 years [52]. Altered hormone levels increase the incidence of breast cancer. The primary population of breast cancer is women between the ages of 40 and 60. This is because women in this age group are in a state of hormone disruption, indicating an increasing risk of breast cancer [53] .

A two-stage segmented linear regression model was used to analyze the threshold effect of BMI on breast cancer. It can be seen that the BMI of breast cancer patients showed an inverted U-shaped curves. After adjusting for age and other relevant factors, breast cancer showed a non-linear variation with BMI. The difference between the two models was statistically significant. From this we can conclude that overweight and obesity are associated with breast cancer. However, one study did not show a correlation between height, current BMI and weight change and the risk of developing breast cancer [54]. The main reason may be that these breast cancers are breast cancers associated with BRCA gene mutations. The leading cause of breast cancer is early mutation in the BRCA gene rather than obesity, but further studies are needed to confirm this. BMI may have different effects on breast cancer risk in premenopausal and postmenopausal women [55].

Strengths and Limitations. 1) This study had a large sample size and methodically organized; 2) NHANES is a multistage complex national survey whose methodology has remained constant; 3) The use of a sample frame that includes all U.S. counties enhances the generalizability of the results; 4) We also adjusted for many known potential confounders, including age, race, and educational level; 5) Despite adjusting for many potential confounders, additional unmeasured variables may contribute to the observed associations.

CONCLUSION

This analysis estimated the relationship between diabetes status and breast cancer in a nationally representative cohort in the United States. Breast cancer and diabetes are persistent problems in the United States. The fact that breast cancer and diabetes are strongly associated is becoming increasingly apparent. To better understand the relationship between breast cancer and diabetes status in American adults, future prospective studies with a large population are needed to confirm these preliminary findings. The risk of developing breast cancer increases steadily from nondiabetes to prediabetes and to type 2 diabetes.

DATA AVAILABILITY STATEMENT

In this study, publicly available datasets were analyzed. These data can be found here: https://wwwn. cdc. gov/nchs/nhanes/Default. aspx

ETHICS STATEMENT

The NHANES protocol is reviewed annually by the Ethics Review Board of the National Center for Health Statistics.

AUTHOR CONTRIBUTIONS

Conceptualization: Ziru Liu. Data curation and formal analysis: Pengcheng Hu. Writing: Original draft preparation: Xingyu Sun, Pengcheng Hu, Jialing Liu, Yulu Yan and Xiaozhu Liu. Writing: Review and Editing: Ziru Liu, Chenyu Sun, Vicky Yau, Muzi Meng and Scott Lowe. All authors contributed to the article and approved the submitted version.

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