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EPIDEMIOLOGY

Type 2 diabetes as a predictor of survival among breast cancer patients: the multiethnic cohort

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Abstract

Purpose The purpose of the study was to investigate the association of type 2 diabetes (T2D) with survival of breast cancer (BC) patients across five ethnic groups within the Multiethnic Cohort study.

Methods Between recruitment in 1993–1996 and 2013, 7570 incident BC cases were identified through SEER cancer registries in Hawaii and California. T2D diagnosed before BC was ascertained in 1013 women from self-reports and confirmed by administrative data sources. Covariate information was collected by questionnaire. Cox regression analysis with age as the time metric and BMI as time-varying exposure was applied to estimate hazard ratios (HR) and 95% confidence intervals (CI) for BC-specific and all-cause survival while adjusting for known prognostic factors.

Results In total, 2119 all-cause and 730 BC-specific deaths were recorded with corresponding 5-year survival rates of 86 and 93%. T2D was not a significant predictor of BC-specific survival (HR 0.84; 95% CI 0.65–1.09), but mortality was 36% lower for those with < 7 years of T2D than a longer history of T2D. On the other hand, all-cause mortality was higher in women with T2D (HR 1.23; 95% CI 1.08–1.40), especially in women with T2D of ≥ 7 years duration (HR 1.27; 95% CI 1.07–1.49). In women receiving none or either chemotherapy or radiation but not both, T2D predicted higher all-cause mortality ($P_{interaction} = 0.004$). Variations in the association of T2D with mortality across ethnic groups were small.

Conclusions T2D was associated with higher all-cause but not BC-specific mortality among women with BC in the Multiethnic Cohort study. However, T2D affected survival in cases who did not receive both radiation and chemotherapy.

Keywords Breast neoplasms · Ethnic groups · Type 2 diabetes · Obesity · Survival

Introduction

The population living with two or more chronic conditions is growing worldwide. As of 2012, one in four adults in the U.S. had two or more chronic conditions [1]. Type 2 diabetes (T2D) is one major chronic disease that is a part of this trend [2]. Several previous studies have shown that the presence of T2D reduces the survival for women with breast cancer (BC), the most common cancer in females [3–6]. Studies among racially diverse populations are sparse. Evidence of differential associations by ethnic groups largely comes from The California Breast Cancer Survivorship Consortium (CBCSC) which includes whites, African Americans, Latinas, and Asian Americans [7], two studies of African American women [8, 9], and one of Latinas [10]. The investigation of ethnic differences is important due to the higher prevalence of obesity and T2D in minority populations [11, 12] and ethnic/racial disparities in BC survival [13]. Pre-existing conditions, such as T2D, may partly account for worse BC survival among minority women [14, 15]. The CBCSC showed a 48% (95% CI 1.18–1.87) higher BC-specific mortality among BC cases with a self-reported history of T2D, with a similar mortality increase across whites, Latinas, African Americans, and Asian Americans, as well as body mass index (BMI) categories [7]. In a meta-analysis [4], the survival for women with T2D in Asia did

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not differ from that for women in Europe and America. We hypothesized that the presence of T2D at the time of a BC diagnosis shortens survival among BC participants of the Multiethnic Cohort (MEC). Using MEC data allowed us to more adequately assess T2D status over the course of follow-up, compared to previous studies, because of the multiple sources of diagnostic information both from questionnaires and administrative data.

Materials and methods

Study participants

The design and implementation of the MEC study have been described in detail elsewhere [16]. Briefly, residents in Hawaii and California (primarily Los Angeles County) entered the cohort from 1993 to 1996 by completing a 26-page, self-administered mail questionnaire. The population-based sampling frames included drivers' license records in both states, supplemented with voter registration lists in Hawaii and Health Care Financing Administration (Medicare) files in California. Of the more than 215,000 cohort members aged 45–75 years at cohort entry, 118,869 were women. The majority of the cohort was composed of five ethnic groups: white, African American, Native Hawaiian, Japanese American, and Latino. The Institutional Review Boards at the University of Hawaii and the University of Southern California approved the study protocol.

Women diagnosed with in situ and invasive BC were identified through linkages with the Los Angeles County Cancer Surveillance Program, the State of California Cancer Registry, and the statewide Hawaii Tumor Registry. These tumor registries participate in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and provide data on tumor characteristics, i.e., stage, histology, estrogen receptor (ER) and progesterone receptor (PR), and first course of treatment, including surgery, chemotherapy and/or radiotherapy within 6 months after diagnosis. Information on recurrence or comorbidities is not collected by the tumor registries. Linkage with the California and Hawaii death certificate files and the National Death Index provided information on vital status and date and causes of death. Complete case and death ascertainment was available up to December 31, 2013. Women among the five ethnic groups without previous BC (self-reported or registry-linked) at the time of cohort entry and subsequently diagnosed with invasive BC during follow-up were eligible for the present analysis ($n = 7757$). We excluded women with missing values for stage of disease at diagnosis ($N = 87$) and BMI ($N = 100$), providing an analytical cohort of 7570 female BC cases.

Data collection

The baseline questionnaire (QX1) captured information on demographic factors, anthropometric measures, prior medical conditions, reproductive history and use of hormone therapy (HT), family history of BC, lifestyle behaviors, and an extensive diet history [16]. The presence of a comorbidity was defined as a self-reported history of hypertension, heart attack, angina, or stroke in QX1. In 1999–2002, a 4-page follow-up survey (QX2) was completed by 84% of the cohort and in 2003–2007, the full baseline questionnaire (QX3) was returned again by 50% of the cohort.

T2D status

T2D status was determined based on self-reports from the 3 questionnaires (QX1–QX3), specifically in response to the question "Has your doctor ever told you that you had diabetes?", and confirmed by administrative data obtained through linkages with 3 data sources: Medicare claims [17], health insurance plans in Hawaii [18], and hospital discharge diagnosis data in California [19]. When records from all 3 data sources were considered, 83% of T2D self-reports in the full cohort were confirmed by at least one administrative data source. Of the 1103 women with T2D confirmed by at least one administrative data source, only the 1013 women whose T2D was detected before BC were classified as T2D cases [20]. We calculated T2D duration as the time between a first report of T2D (questionnaire or administrative data) and BC diagnosis.

Statistical methods

Demographic information, tumor characteristics, and BC treatment were compared between participants with and without T2D using means and frequency distributions. To explore ethnic differences, we evaluated 5-year survival rates, T2D prevalence, obesity, and BC treatment across the five ethnic groups. Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CI) were estimated using Cox proportional hazards regression. Age was used as the time metric in the analyses. Follow-up time started at the age of BC diagnosis and ended at time of death or end of follow-up (12/31/2013). In the BC-specific models, women who died of other causes were censored at time of death. Models were adjusted for known predictors of survival, i.e., ethnicity (whites as reference group), BMI at QX1–QX3 (< 22.5, 22.5–24.9, 25.0–29.9, ≥ 30 kg/m^2), age at BC diagnosis (50–59, 60–69, ≥ 70 years), SEER summary stage (in situ, local, regional, distant), surgery (conserving, mastectomy, none, unknown), radiotherapy (yes, no, unknown),

chemotherapy (yes, no, unknown), and hormonal therapy (yes, no, unknown). Also, the following covariates as reported at cohort entry were included in all models: family history of BC (yes, no, unknown), educational status (≤ 12, 13–15, ≥ 16 years), menopausal status (pre, post, unknown), postmenopausal hormone therapy (none, estrogen only, combined), smoking status at cohort entry (never, former, current, unknown), physical activity (< 30 min or ≥ 30 min daily moderate/vigorous activity), alcohol intake (< 1 drink/month, < 1 drink/day, ≥ 1 drink/day), non-steroidal anti-inflammatory drugs (NSAID) use (yes, no, unknown), and cardiovascular comorbidity (CVD). Differential associations by ethnicity, stage of disease at diagnosis, chemotherapy and/or radiation treatment, ER/PR, BMI (< 25 vs. ≥25 kg/m^2), and comorbidity status were examined through subgroup analyses. To understand the joint association of BMI and T2D status, a four-level variable was created (BMI < 25 or ≥ 25 kg/m^2 and T2D presence) and modeled by Cox regression. Effect modification by ethnic group was evaluated based on multiplicative interactions using global Wald tests of the cross-product terms between ethnic group and the BMI/T2D variable. SAS version 9.4 (SAS Insitute Inc., Cary, NC) was used for all analyses with a two-sided *P* value of < 0.05 considered to be statistically significant.

Results

Of the 7570 in situ and invasive BC cases, 1013 had pre-existing T2D before their BC diagnosis (Table 1) with an average T2D duration of 8.5 ± 5.3 years. The mean ages of participants at cohort entry, T2D diagnosis, and BC diagnosis were 59.8, 62.0, and 69.0 years, respectively. By the end of 2013, 2119 all-cause deaths and 730 BC-specific deaths were recorded with higher mortality among women with than without T2D (40 vs. 26%); the 5-year survival rates differed accordingly (79 and 87%, respectively). On the other hand, the number of BC-specific deaths and the 5-year survival rates were similar by T2D status. Japanese Americans constituted the largest group of patients (31%), followed by whites (24%), African Americans (19%), Latinos (16%), and Native Hawaiians (10%). Multiple comorbidities (≥ 2) were more common among women with than without T2D (44% vs. 5%, respectively). There was little difference in stage at diagnosis and tumor characteristics between women by T2D status.

Women with T2D (Table 2) did not experience greater BC-specific mortality (HR 0.84; 95% CI 0.65–1.09) than those without T2D, while all-cause mortality was significantly elevated (HR 1.23; 95% CI 1.08–1.40). BC-specific mortality was lower by 36% (95% CI 0.46–0.80) among the 452 women with < 7 years T2D duration compared to those without T2D, whereas there was no BC-specific

Table 1 Characteristics of breast cancer cases in the multiethnic cohort study

Characteristic	All patients	History of type 2 diabetes	
		Yes	No
N	7570	1013	6557
Deaths, *n* (%)			
All-cause	2119 (28)	406 (40)	1713 (26)
Breast cancer-specific	730 (10)	94 (9)	730 (10)
5-year survival[a], %			
All-cause	85.8	79.1	86.8
Breast cancer-specific	93.0	92.5	93.1
Age at cohort entry, years	59.8 (8.4)	60.5 (8.0)	59.1 (8.5)
Age at diabetes diagnosis, years	N/A	62.0 (7.8)	N/A
Age at breast cancer diagnosis, years	69.0 (9.3)	70.5 (8.5)	68.7 (9.4)
BMI, kg/m^2	26.8 (5.7)	30.3 (6.2)	26.2 (5.4)
BMI, kg/m^2, *n* (%)			
< 22.5	1691 (22)	79 (8)	1612 (25)
22.5–< 25	1610 (21)	101 (10)	1509 (23)
25–< 30	2490 (33)	357 (35)	2133 (32)
≥ 30.0	1779 (24)	476 (47)	1303 (20)
Ethnicity, *n* (%)			
White	1836 (24)	131 (13)	1705 (26)
African American	1421 (19)	239 (23)	1182 (18)
Native Hawaiian	736 (10)	127 (13)	609 (9)
Japanese American	2366 (31)	283 (28)	2083 (32)
Latina	1211 (16)	233 (23)	978 (15)
Comorbidity, *n* (%)			
None	4261 (56)	191 (19)	4070 (62)
1	2561 (34)	372 (37)	2189 (33)
2+	748 (10)	450 (44)	298 (5)
Hormone receptor, *n* (%)			
ER + PR+	3951 (52)	528 (51)	3423 (52)
ER−PR−	980 (13)	126 (12)	854 (13)
ER + PR−/ER−PR+	847 (11)	103 (10)	744 (11)
Missing	1725 (24)	256 (27)	1536 (24)
SEER stage, *n* (%)			
In situ	1500 (20)	178 (18)	1322 (20)
Local	4319 (57)	580 (57)	3739 (57)
Regional	1558 (21)	231 (23)	1327 (20)
Distant	193 (2)	24 (2)	169 (3)
Tumor grade			
1–2	4569 (60)	590 (58)	3979 (61)
3–4	2141 (28)	316 (31)	1825 (28)
Missing	860 (12)	107 (11)	753 (11)
Tumor size (cm)			
< 2	4473 (59)	574 (57)	3899 (60)
2–5	2072 (28)	295 (29)	1777 (27)
> 5	409 (5)	62 (6)	347 (5)
Missing	616 (8)	82 (8)	534 (8)
Surgery, *n* (%)	7291 (96)	973 (96)	6318 (96)

Table 1 (continued)

Characteristic	All patients	History of type 2 diabetes	
		Yes	No
Chemotherapy, *n* (%)	1606 (21)	209 (21)	1397 (21)
Radiotherapy, *n* (%)	3626 (48)	430 (43)	3196 (49)

BMI Body Mass Index, *ER* estrogen receptor, *PR* progesterone receptor

Unless specified, means (standard deviation) presented; percentages may not add to 100 because of rounding

[a]Product-limit estimate for 5-year survival

mortality difference for the 561 women with longer T2D duration. On the other hand, all-cause mortality was only elevated with T2D in women with ≥ 7 years of known T2D (HR 1.27; 95% CI 1.07–1.49). An interaction term of BMI (< 25 vs. ≥ 25 kg/m^2) with T2D was significant for BC-specific ($P_{interaction} = 0.02$) but not all-cause mortality ($P_{interaction} = 0.25$). The presence of T2D predicted significantly lower BC-specific mortality in women of BMI < 25 kg/m^2 (HR 0.34; 95% CI 0.14–0.79) but not in those with BMIs ≥ 25 kg/m^2. In contrast, T2D was associated with elevated all-cause mortality in women with BMIs ≥ 25 kg/m^2 (HR 1.29; 95% CI 1.12–1.50) but not among those with a BMI < 25 kg/m^2.

Significant heterogeneity in mortality (Table 2) as predicted by T2D status was observed for stage at diagnosis ($P_{interaction} = 0.03$ BC-specific and $P_{interaction} < 0.01$ all-cause) and treatment ($P_{interaction} < 0.01$ all-cause), while there was limited evidence of heterogeneity by ER/PR or comorbidity status. Although not statistically significant, a pattern of elevated BC-specific and all-cause mortality was observed in women with a distant stage. The HRs were significantly elevated for all-cause mortality in women with localized disease (HR 1.53; 95% CI 1.28–1.83) and women who had not received chemotherapy or radiation (HR 1.33; 95% CI 1.11–1.59) or either of the two treatments (HR 1.24; 95% CI 1.00–1.54).

Considerable differences in the frequency of pre-existing T2D were seen across ethnic groups (Table 3) with 19% of Latinas, 17% of African Americans and Native Hawaiians, 12% of Japanese Americans, and 7% of whites. African

Table 2 Breast cancer-specific and all-cause survival among MEC participants with T2D versus no T2D

Characteristic	Category	Breast cancer mortality			All-cause mortality		
		HR	95% CI	HR	HR	95% CI	HR
T2D	All cases	0.84	0.65	1.09	1.23	1.08	1.40
	< 7 years T2D	0.64	0.46	0.80	1.10	0.94	1.28
	≥ 7 years T2D	1.22	0.89	1.66	1.27	1.07	1.49
Stage of disease at diagnosis	In situ	0.40	0.11	1.44	0.86	0.58	1.28
	Localized	0.88	0.57	1.36	1.53	1.28	1.83
	Regional	0.78	0.51	1.13	1.00	0.78	1.30
	Distant	1.50	0.73	3.07	1.55	0.82	2.93
	$P_{Interaction}$	*0.03*			*< 0.0001*		
ER/PR status	ER+/PR+	0.70	0.46	1.06	1.31	1.07	1.59
	ER−/PR−	1.04	0.63	1.72	1.18	0.85	1.85
	Discordant	0.96	0.46	2.04	1.35	0.88	2.07
	$P_{Interaction}$	*0.52*			*0.86*		
Chemotherapy/radiation	None	0.69	0.46	1.03	1.33	1.11	1.59
	Either	1.04	0.70	1.55	1.24	1.00	1.54
	Both	0.73	0.37	1.45	0.85	0.53	1.38
	$P_{Interaction}$	*0.97*			*0.004*		
Body Mass Index (kg/m^2)	< 25	0.34	0.14	0.79	1.08	0.80	1.46
	≥ 25	0.95	0.72	1.25	1.29	1.12	1.50
	$P_{Interaction}$	*0.02*			*0.32*		
Comorbidity	None	0.83	0.46	1.49	1.28	0.94	1.73
	1+	0.81	0.54	1.20	1.12	0.91	1.37
	$P_{Interaction}$	*0.90*			*0.59*		

Hazard ratios (HR) and 95% CIs were obtained by Cox regression adjusted for age at BC diagnosis, BMI (time-varying), ethnicity, education, menopausal status, postmenopausal hormone treatment, family history of BC, smoking status, physical activity, alcohol intake, comorbidity, NSAID use, surgery, radiotherapy, chemotherapy, hormonal therapy, and stage of disease at diagnosis

Table 3 Characteristics of the study population and mortality related to T2D by ethnic/racial group

Characteristic	Category	White	African American	Native Hawaiian	Japanese American	Latina
Number		1836	1421	736	2366	1211
Age at BC dx (years)		68.7	70.0	65.7	69.4	69.2
T2D diagnosis (%)	Yes	7.1	16.8	17.3	12.0	19.2
BMI status (%)	Overweight	30.1	37.2	32.7	28.4	40.4
	Obese	19.7	39.6	40.1	8.5	29.5
Stage at diagnosis (%)	In situ	16.7	20.3	16.4	23.1	19.7
	Localized	59.4	51.6	56.5	60.2	54.1
	Regional	21.0	24.2	24.7	15.2	23.8
	Distant	2.9	3.9	2.3	1.5	2.5
Chemotherapy (%)	Yes	21	21	27	19	22
Radiation (%)	Yes	50	25	59	56	38
5-year survival (%)	All	84.9	77.7	87.1	91.8	84.0
	BC	93.3	87.5	93.8	96.4	91.7
T2D as predictor (HR)	All	1.40	1.42	0.97	0.94	1.43
(95% CI)		(1.03, 1.91)	(1.11, 1.80)	(0.66, 1.42)	(0.68, 1.30)	(1.06, 1.94)
T2D as predictor (HR)	BC	0.45	1.19	0.41	0.59	1.01
(95% CI)		(0.18, 1.10)	(0.79, 1.80)	(0.18, 0.94)	(0.27, 1.27)	(0.59, 1.72)

Hazard ratios (HR) and 95% CIs were obtained by Cox regression adjusted for age at BC diagnosis, BMI (time-varying), ethnicity, education, menopausal status, postmenopausal hormone treatment, family history of BC, smoking status, physical activity, alcohol intake, comorbidity, NSAID use, surgery, radiotherapy, chemotherapy, hormonal therapy, and stage of disease at diagnosis

All-cause all-cause mortality, *BC* breast cancer-specific mortality

Americans and Native Hawaiians had the highest prevalence of obesity/overweight (40%), followed by Latinos (30%), whites (20%), and Japanese Americans (9%). Five-year survival rates for all-cause and BC-specific mortality were lowest for African Americans (78% and 88%) and highest for Japanese Americans (92% and 96%). Although the interaction terms of T2D with ethnicity were not significant ($P_{\text{interaction}} = 0.38$ and 0.32) for all-cause or BC-specific mortality, some ethnic differences were present. All-cause mortality related to T2D was higher among whites (HR 1.40; 95% CI 1.03–1.91), African Americans (HR 1.42; 95% CI 1.11–1.80), and Latinos (HR 1.43; 95% CI 1.06–1.94), but not in Japanese Americans or Native Hawaiians. For BC-specific mortality, pre-existing T2D was inversely associated in Native Hawaiians (HR 0.41; 95% CI 0.18–0.94) and null among the other groups.

In models with combined BMI/T2D status (Fig. 1) and in comparison to patients with BMI < 25 kg/m^2 and no T2D, all-cause mortality was elevated for patients with both a BMI above 25 kg/m^2 and T2D (HR 1.39; 95% CI 1.19–1.62). On the other hand, BC-specific mortality was significantly lower for the small number of women ($n = 180$ and 6 BC-specific deaths) with BMI < 25 kg/m^2 and T2D (HR 0.36; 95% CI 0.16–0.81) but did not differ for patients with BMI ≥ 25 kg/m^2 with or without T2D (HR 1.03; 95% CI 0.77–1.38 and HR 1.08; 95% CI 0.90–1.29, respectively). The respective interaction terms of BMI/T2D status with ethnicity for all-cause and BC-specific mortality were 0.23 and 0.90 and the differences across groups were small. In the stratified models, the only statistically significant associations were seen in whites and African Americans in the BMI ≥ 25 kg/m^2 with T2D category while none of the other risk estimates for BC-specific mortality across ethnic groups were significant.

Discussion

In this multiethnic population, all-cause survival was reduced among BC patients with pre-existing T2D but this association was limited to whites, African Americans, and Latinas. On the other hand, T2D was not related to BC-specific survival except for an inverse association among Native Hawaiians. Duration of T2D modified the association; only BC patients with longer duration of T2D experienced adverse outcomes. Some effect modification by stage at diagnosis and treatment was apparent. Among patients with localized disease and among those who did not receive both chemotherapy and radiation, pre-existing T2D predicted worse survival.

The 23% higher all-cause mortality among BC patients with pre-existing T2D than those without agrees with numerous studies as summarized by three meta-analyses that found elevated 30–60% higher risks of mortality [3,

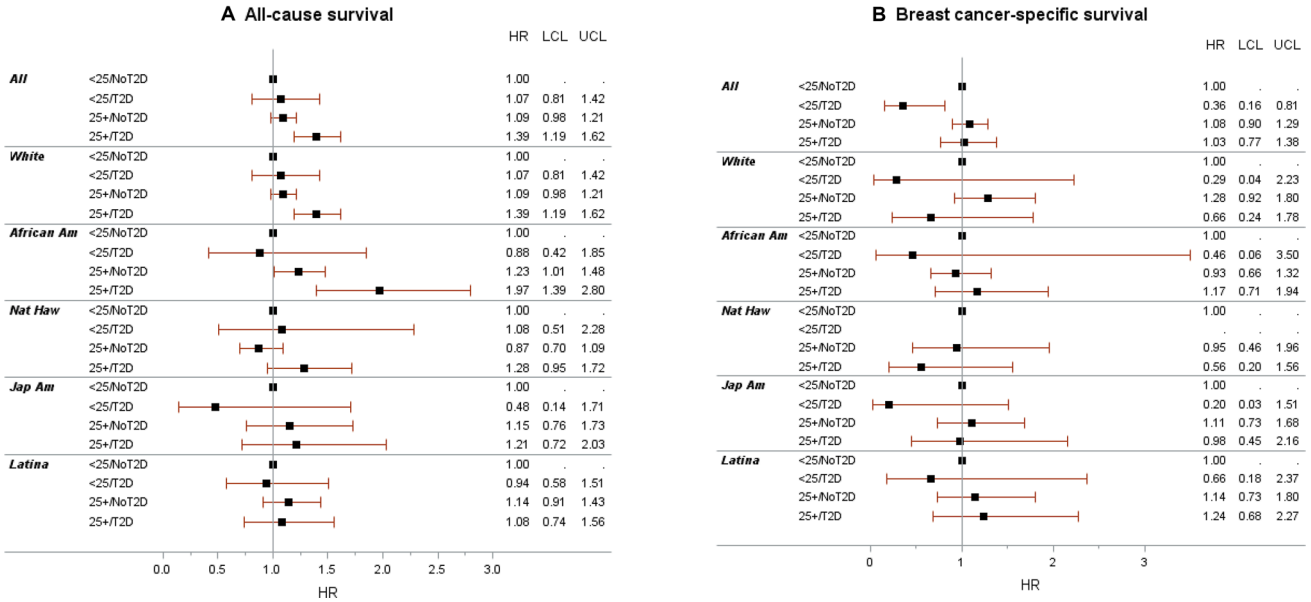

Fig. 1 Survival among women with breast cancer by combined BMI and T2D status, **a** all-cause survival; **b** breast cancer-specific survival. Hazard ratios (HR) and 95% CIs were obtained by Cox regression adjusted for age at BC diagnosis, ethnicity, smoking status, education, age at menarche, age at first live birth, number of children, menopausal status, hormone treatment family history of BC, total energy intake, physical activity, comorbidity, NSAID use, surgery, radiotherapy, chemotherapy, hormonal therapy, stage of disease at diagnosis. *<25* BMI < 25 kg/m^2; *25+* BMI ≥ 25 kg/m^2; *T2D* presence of diabetes at breast cancer diagnosis

4, 21]. Later studies reported HRs of all-cause mortality ranging from 1.26 (95% CI 1.06–1.48) [22] to 1.61 (95% CI 1.22–2.14) [10] and 1.75 (95% CI 1.50–2.05) [7]. Interestingly, a study among women with BC in the US military indicated that overall survival was negatively affected independent of the time of T2D diagnosis; mortality was twice as high for patients diagnosed with T2D after compared to before a BC diagnosis [5]. The finding of worse survival outcomes among BC patients with both obesity and T2D is similar to a small Italian study of 841 BC survivors, in which only the combined but not the individual presence of obesity and T2D predicted lower disease-free survival; all-cause survival was not affected in that study [6]. Our finding of an elevated all-cause mortality with localized tumors and longer T2D duration may be attributed to a higher risk of CVD, kidney disease, and other complications of T2D among BC survivors [23, 24]. The inverse associations between T2D and BC-specific mortality, i.e., for women with a BMI < 25 kg/m^2 and T2D (HR 0.36; 95% CI 0.16–0.81) and for Native Hawaiians (HR 0.41; 95% CI 0.18–0.94), may be chance findings due to the small number of women and deaths. Alternatively, these findings could be a result of regular contact with the health care system and earlier detection among T2D patients although many of the existing reports suggest lower not higher screening participation among women with chronic conditions [25].

The association between T2D and BC-specific mortality has been investigated less frequently and the results are inconsistent. Whereas some studies showed an increase in BC-specific mortality, e.g., the CBCSC study (HR 1.48; 95% CI 1.18–1.87) [7] and a case-control study of white and Latina patients (HR 1.63; 95% CI 1.08–2.47) [10], T2D did not predict BC-specific mortality in others [7, 22, 26, 27]. For example, the Women's Health Initiative, which included primarily white women and linked cases to Medicare claims from the date of diagnosis to death to identify T2D only, found a non-significant increase in risk of BC-specific mortality associated with T2D [22]. Also, the Danish Breast Cancer Cooperative Group did not detect higher risk of BC-specific mortality among women with T2D [27]. Differences across studies may be due to selection of BC cases by stage, differences in the prevalence of T2D, variations in duration and severity of T2D, changing case definitions over time, methods of T2D ascertainment, and availability of covariates.

The literature is limited on ethnic-specific findings. Little difference in all-cause mortality across ethnic groups was described among the US military BC patients [5]. For BC-specific mortality, one study in African Americans agrees with our null findings and Asian Americans [7], but others reported elevated mortality risks for African Americans (HR 1.86; 95% CI 1.20–2.89) [9], Latinas (HR 1.85; 95% CI 1.11–3.09) [10], and Whites (HR 1.22; 95% CI 1.13–1.30) [28]. Three studies reported higher all-cause mortality for African American women with HRs of 1.34 (95% CI 1.11–1.62) [8], 1.54 (95% CI 1.06–2.22) [7], and 1.54 (95%

CI 1.12–2.07) [9]. Two studies reported a higher all-cause mortality associated with pre-existing T2D for Latinos: HR 3.04 (95% CI 1.92–4.81) [7] and HR 1.64 (95% CI 1.14–2.38) [10]. One study reported higher all-cause mortality associated with T2D for Asian Americans (HR 1.92; 95% CI 1.31–2.84) [7], which contrasts with our null results. Again, differences in general health status, T2D treatment, or early detection and screening practices may be responsible for the conflicting findings.

Our finding that T2D predicted lower survival only in women who had not received chemotherapy and/or radiation partially agrees with the elevated mortality for BC-specific and all-cause among women not receiving both treatments in the CBCSC study [7]. As has been shown previously, BC patients who receive chemotherapy and radiation may be healthier than those who do not and T2D patients may be less likely to receive the treatments due to their overall health status [21, 29]. For example, a Canadian study reported that BC patients with T2D were 7% less likely to receive chemotherapy and 3% less likely to be given radiation, but after controlling for comorbidities, no significant difference in all-cause mortality remained [29]. T2D patients may receive different services than women without. For example, the better BC outcomes in Native Hawaiian women with T2D may be a chance finding or due to regular health care and screening, which healthy women may not receive, leading to earlier stage at diagnosis and a better prognosis. However, the literature suggests the opposite, i.e., later stage at diagnosis among women with T2D. Among Canadian women, T2D was associated with more advanced BC even after accounting for mammogram screening [30]. Also, among Italian BC patients, women with obesity and/or T2D were more likely to be diagnosed at a later stage of disease than those with only one or no condition [6].

A number of biological mechanisms have been proposed for how T2D may affect survival of BC patients, including chronic inflammation, hyperinsulinemia and growth factors that may accelerate tumor growth and recurrence [31]. Therefore, women with T2D may develop more aggressive BC diagnosed at a later stage [30]. However, seeing that only all-cause mortality is affected by pre-existing T2D in the current analysis, the higher mortality in the women with T2D may strictly be a result of general poor health due to comorbid conditions that do not allow intensive BC treatment and lead to premature death from causes other than cancer.

One strength of our investigation is the unique ethnic diversity of the MEC, particularly with its large proportion of Japanese American and Native Hawaiian women, a population that has been relatively little studied. In contrast to some of the previous reports without BMI information, this MEC-based analysis had repeated measures of BMI and many other predictors of mortality available. Nevertheless, a number of limitations need to be acknowledged. BMI as an important predictor of mortality among BC patients [32, 33] was only assessed before BC diagnosis for many of the participants, not after when it may have changed. In particular, weight gain is commonly reported among BC patients as a result of cancer treatments [34]. As information on treatment of BC is recorded for first course (first 6 months after diagnosis) only in SEER registries and medication use is unknown for T2D, their potential contribution to survival could not be fully evaluated. Information on comorbid conditions was limited to cohort entry and diseases that developed later were not included in the models. Although T2D assessments from self-reports and administrative data are considered valid [35, 36], it is always possible that participants had never received the appropriate diagnostic tests or had not been covered by one of our administrative data sources leading to misclassification. Glucose, insulin, and HbA1C measurements would not only have allowed the detection of undiagnosed T2D cases but also the assessment of insulin resistance and the control of existing T2D. This may be important because hyperinsulinemia [31] or inadequate glycemic control may contribute to poorer survival as shown in several cohorts [37]. Finally, the duration of T2D before BC as estimated from self-reports and administrative data may be inaccurate because an exact date of diagnosis was not always known.

In conclusion, pre-existing T2D and the presence of overweight and/or obesity in combination with T2D status appear to predict a worse all-cause survival in this multiethnic population, but not all ethnic groups were affected to the same degree.

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Data availability The data underlying this study cannot be made publicly available because they contain patient identifying information. Data are available from the Multiethnic Cohort (MEC) study (http://www.uhcancercenter.org/research/the-multiethnic-cohort-study-mec/data-sharing-mec) for researchers who meet the criteria for access to confidential data. For details and to request application template please contact Gail Ichida, gichida@cc.hawaii.ed.

Compliance with ethical standards

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

Ethical approval The Multiethnic Study was approved by the Institutional Review Boards at the University of Hawaii and the University of Southern California and all aspects of the investigation complied with current rules for research involving Human Subjects.

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