Research Article

Cancer Epidemiology, Biomarkers & Prevention

Diabetes and Overall Survival among Breast Cancer Patients in the U.S. Military Health System

Stephanie Shao[1], Abegail A. Gill[1], Shelia H. Zahm[2], Ismail Jatoi[3], Craig D. Shriver[1,4,5], Katherine A. McGlynn[2], and Kangmin Zhu[1,5]

Abstract

Background: Although research suggests that type II diabetes mellitus (DM-2) is associated with overall and breast cancer–specific decreased survival, most prior studies of breast cancer survival investigated the effect of preexisting DM-2 without assessing the effect of DM-2 diagnosed at or after breast cancer diagnosis. This study examined the relationship between DM-2 diagnosed before and after breast cancer diagnosis and overall survival.

Methods: This study uses linked Department of Defense cancer registry and medical claims data from 9,398 women diagnosed with breast cancer between 1998 and 2007. Cox proportional hazards models were used to assess the association between DM-2 and overall survival.

Results: Our analyses showed that women with DM-2 diagnosed before breast cancer diagnosis tended to have a higher risk of mortality compared with women without diabetes [HR = 1.17; 95% confidence interval (CI), 0.95–1.44] after adjustment for potential confounders. Similarly, patients diagnosed with DM-2 at or after breast cancer diagnosis had increased mortality compared with women without DM-2 (HR = 1.39; 95% CI, 1.16–1.66). The similar tendency was also observed among most subgroups when results were stratified by race, menopausal status, obesity, tumor hormone receptor status, and stage.

Conclusions: Using data from a health system that provides universal health care to its beneficiaries, this study showed an increased risk of death associated with DM-2, regardless of whether it was diagnosed before or at/after breast cancer diagnosis.

Impact: These results suggest the potential effects of factors independent of the timing of DM-2 clinical diagnosis on the association of DM-2 with overall survival. *Cancer Epidemiol Biomarkers Prev; 27(1); 50–57. ©2017 AACR.*

Introduction

In the United States, breast cancer remains the second most common cause of cancer-specific mortality among women (1). Although the 5-year relative survival rate for women with breast cancer was approximately 91% during 2005 to 2011 (1), some studies suggest that certain comorbid conditions, like diabetes, may negatively impact prognosis (2, 3).

As of 2012, approximately 9.3% of the U.S. population was diagnosed with diabetes (4). There are two main types of diabetes (type I and type II), with type II accounting for 95% of all clinical diagnoses (4). The association between diabetes (primarily type II) and breast cancer survival has been inconsistent in the literature (5), but most studies have found that it is associated with decreased overall survival (6–14) and breast cancer–specific survival (11, 14–17). A prospective cohort of one million U.S. adults reported a 2-fold increased risk of all-cause mortality and a 16% increased risk of breast cancer–specific mortality among persons with diabetes (10). In a large case–control study, diabetes was significantly associated with an elevated risk of all-cause mortality, with greater risk among those who were obese (6). However, some studies have reported no association between diabetes and overall survival (5) or breast cancer–specific survival (8, 12).

Most previous studies examined the association between breast cancer survival and diabetes diagnosed prior to breast cancer (5, 6, 8, 9, 11, 14, 18–20). In a large cohort study of stage I–III breast cancer patients from MD Anderson Cancer Center (Houston, TX), those with preexisting diabetes had a higher risk of all-cause mortality [HR = 1.39; 95% confidence interval (CI), 1.10–1.77; ref. 8]. In another study based on SEER-Medicare data, women diagnosed with diabetes prior to breast cancer diagnosis had a higher all-cause mortality compared with women without diabetes (20). In a meta-analysis of 17 studies, preexisting diabetics were shown to have a 50% higher all-cause mortality than those without diabetes (21). To the best of our knowledge, the association between diabetes diagnosed at or after breast cancer diagnosis and survival has not been studied. Diabetes detected at or following breast cancer diagnosis may differ from diabetes diagnosed prior to breast cancer diagnosis in the severity of the disease, potential effects on breast cancer treatment, and therefore, survival. As shown in a study based on the data from seven state cancer registries in the United States (22), diabetes severity is related to lower guideline-concordant chemotherapy and lower guideline concordance for locoregional treatment, although the association may vary

[1]John P. Murtha Cancer Center at Walter Reed National Military Medical Center, Bethesda, Maryland. [2]Division of Cancer Epidemiology and Genetics, NCI, Bethesda, Maryland. [3]The University of Texas Health Science Center at San Antonio, San Antonio, Texas. [4]General Surgery Service, Walter Reed National Military Medical Center, Bethesda, Maryland. [5]Uniformed Services University, Bethesda, Maryland.

Corresponding Author: Kangmin Zhu, Walter Reed National Military Medical Center, 11300 Rockville Pike, Suite 1120, Rockville, MD 20852. Phone: 301-816-4786; Fax: 301-881-7197; E-mail: kzhu@murthacancercenter.org

doi: 10.1158/1055-9965.EPI-17-0439

by age. Diabetes can increase the risk of wound infection after surgery (23), which may delay the initiation of adjuvant chemotherapy and thereby potentially result in worse outcomes (24). Such effects may be more likely for more severe diabetes. In addition, antidiabetic treatment of preexisting diabetes itself may affect breast cancer survival (25), and it is possible that diabetes may result from breast cancer treatment (26). Thus, an examination of the relationship between diabetes and survival by timing of diabetes may help better understand the basis of the association. For example, if breast cancer–specific mortality is increased among patients with diabetes reported before breast cancer diagnosis but not at/after, it may suggest that influences of diabetes on breast cancer treatment may be more possible because the former tends to have more severe form of the disease. On the other hand, if all-cause mortality is increased irrespective of timing of the diagnosis of diabetes, it may suggest that factors related to diabetes itself may be more influential.

Previous studies have been conducted in populations in which accessibility to health care may vary. Access to health care has been found to influence the detection and diagnosis of diabetes, its management, treatment, and overall survival (27–30). Access to health care could potentially not only increase the likelihood of diabetes detection and diagnosis (due to better blood glucose monitoring), but also possibly decrease the risk of diabetes (due to the implementation of better preventive measures, such as exercise and improved diet). Thus, when diabetics and nondiabetics are compared in the general population, the identified difference in mortality may partially result from differential detection or diagnosis of diabetes and other socioeconomic factors related to access to care. Research in an equal access system can reduce these potential effects and provide information to assess the relationship between diabetes and cancer. The Military Health System (MHS) of the U.S. Department of Defense (DoD) is an equal access system, providing its beneficiaries with health care at little or no charge. The objective of this study was to examine the relationship between timing of type II diabetes (DM-2) and overall survival among breast cancer patients in the MHS.

Materials and Methods

Data source

This study was based on the linked data from the DoD's Central Cancer Registry (CCR) and the MHS Data Repository (MDR). The linked data include cancer patients diagnosed between 1998 and 2007 who received health care through the DoD health care program, including active duty members, retirees, National Guard and Reserve members, and dependents. The CCR contains demographic, tumor characteristic, cancer treatment, and vital status data that are abstracted from the records of patients diagnosed and/or treated at military treatment facilities (MTF). The data are reviewed and edited according to North America Association of Central Cancer Registries guidelines. The MDR data contain administrative and medical care records for inpatient and outpatient services that are either provided directly at MTFs (direct care) or paid for by the DoD at civilian facilities (indirect care). The MDR data include clinical diagnoses, diagnostic procedures, prescription medications, treatment, and vital status.

The data linkage project was reviewed and approved by the Institutional Review Boards of the Walter Reed National Military Medical Center, Tricare Management Activity, and the National Institutes of Health Office of Human Subjects Research.

Study subjects

Women with histologically confirmed, first primary, malignant breast cancer (ICD-0-3 codes C500-C506 and C508-C509) diagnosed between 1998 and 2007 were eligible for the study ($n = 9{,}944$). They were followed up until December 31, 2008. Women with type I diabetes ($n = 536$), under 20 years of age ($n = 1$), and/or with missing survival information ($n = 9$) were excluded.

Study variables

Medical conditions were identified in the MDR. Women were classified as having type II diabetes (DM-2) if they had ICD-9 diagnoses codes 250.x0, 250.x2, 357.2, 362.0, and 366.41 in at least one inpatient record, or at least three outpatient records (31, 32). Other medical conditions included in the analyses were obesity, heart disease, kidney disease, chronic obstructive pulmonary disease (COPD), stroke, and hypertension. These conditions were considered to be present if codes were identified in one or more inpatient or three or more outpatient records.

Pathologic breast cancer features obtained from CCR included AJCC tumor stage (I through IV, unknown), histologic grade, and hormone receptor status. Histologic grade was classified on the basis of level of differentiation (well differentiated, moderately differentiated, poorly differentiated, and unknown). Estrogen receptor (ER) and progesterone receptor (PR) statuses were categorized into five groups (ER^+/PR^+, ER^-/PR^-, ER^+/PR^-, or ER^-/PR^+, unknown).

Medical care and recurrence variables included breast cancer treatment (surgery, chemotherapy, radiotherapy, and hormone therapy), diabetes treatment (insulin, insulin secretagogue, and metformin), surveillance mammography, and recurrence. Receipt of breast cancer surgery, chemotherapy, and radiotherapy was determined by combining data from CCR and MDR and was considered "yes" if therapy occurred within 3 months postdiagnosis. Hormone therapy information was obtained from CCR. Information on diabetes-specific treatment and surveillance mammography was obtained from MDR. Use of diabetes medications, which may be related to cancer survival (33, 34), was considered "yes" if one or more prescriptions were documented and filled. Surveillance mammography was a variable for women with a breast or breasts left after surgery, including those who underwent breast conserving surgery and received a bilateral mammogram, or those who underwent a unilateral mastectomy and received a unilateral mammogram. It was categorized as "yes" if it was identified 6 months or more after a previous mammogram among women. If a mammogram was received 2 months prior to a diagnosis of a breast mass or other breast symptom, it might be diagnostic and thus was not considered as surveillance procedures (35). Recurrence was defined on the basis of the CCR definition and supplemented with information obtained from MDR (36).

Demographic characteristics were obtained from CCR with missing values supplemented from MDR. Demographic variables included age at diagnosis, race/ethnicity, marital status, active duty status, service branch of the active duty member/sponsor,

rank of the active duty member/sponsor, and insurance plan (TRICARE Prime, an HMO-like component, TRICARE Standard, and TRICARE Extra).

Statistical analysis

We first described the distributions of demographics, comorbid conditions, tumor features, surveillance, and treatment by timing of DM-2 diagnosis. We then used Cox proportional hazards models to assess the association between DM-2 (before or at/after breast cancer diagnosis) and overall survival with adjustment for potential confounding factors. Survival time was calculated as the time interval beginning at the date of breast cancer diagnosis through the date of death, date of last contact, or study end (truncated at December 31, 2008). DM-2 status before breast cancer diagnosis was defined as a dichotomized variable (no/yes) based on whether DM-2 was identified prior to breast cancer diagnosis. In regard to DM-2 diagnosed at/after breast cancer, we define it as a time-dependent variable to minimize the potential impact of immortal time bias (37), in which only those who survive to the point of exposure (diabetes at/after breast cancer for this study) could have the chance to be exposed, therefore biasing the survival results in favor of the exposed group. A potential confounder was defined if it was associated with both DM-2 and survival and was not an intervening variable between DM-2 and survival. The identified potential confounding variables included age at diagnosis, race, marital status, rank of active duty member/sponsor, benefit type, tumor grade, obesity, coronary heart disease, chronic obstructive pulmonary disease, stroke, kidney disease, ER/PR status, and chemotherapy. Although tumor stage did not meet the confounder criteria, this variable was adjusted for due to its complex effects and association with prognosis. We repeated Cox model analyses with stratification by race, menopausal status, obesity, ER/PR status, and tumor stage. Information on menopausal status was not available; therefore, age at diagnosis (<50 and ≥50 years) was used as a proxy variable based on the average age of natural menopause (38). The proportional hazards assumption was tested for Cox model analyses, and no violations of model assumptions were found.

All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC). All tests of significance were two-tailed and performed at $\alpha = 0.05$.

Results

Among 9,398 study women, 1,594 had DM-2 (17%). Table 1 shows the distributions of demographic factors and other medical conditions by timing of DM-2 diagnosis. Compared with women without DM-2, those with DM-2 diagnosed both before and at/after breast cancer diagnosis were less likely to be white, active-duty members, and holders of nonprime TRICARE insurance ($P < 0.01$, all variables). Although both DM-2 groups were older than the nondiabetic group ($P < 0.01$), women diagnosed before breast cancer tended to be oldest. Women with DM-2 diagnosed before breast cancer were also more likely to be enlisted service members than the other two groups ($P < 0.01$). Despite timing of diagnosis, women with DM-2 tended to have a higher frequency of obesity, coronary heart disease, kidney disease, COPD, stroke, and hypertension than nondiabetics ($P < 0.01$, all variables).

Table 2 shows the distributions of treatment, surveillance, and tumor characteristics by timing of DM-2 diagnosis. Women with DM-2 diagnosed before breast cancer diagnosis were more likely to have well-differentiated tumors ($P = 0.03$) and less likely to have radiation treatment ($P = 0.04$), chemotherapy ($P < 0.01$), and recurrence of the disease ($P = 0.01$) than the other two groups. Although the proportions of women who received metformin, insulin, or insulin secretagogue were negligible in the nondiabetic group, they were higher in women with DM-2 diagnosed before breast cancer than those diagnosed at/after the disease ($P < 0.01$, all variables). There were no significant differences in tumor stage between the groups ($P = 0.59$).

The median follow-up time after breast cancer diagnosis was 5.7 years. During follow-up, 16.9% of women with DM-2 and 13.9% of women without DM-2 died. After adjusting for potential confounders, women diagnosed with DM-2 before breast cancer tended to have an increased risk of mortality compared with women without DM-2 (HR = 1.17; 95% CI, 0.95–1.44; Table 3). Women diagnosed with DM-2 at/after breast cancer had higher mortality than women without the disease (HR = 1.39; 95% CI, 1.16–1.66).

Table 4 shows the results of multivariate analyses stratified by demographic, tumor, or obesity variables. Among women diagnosed with DM-2 both before and at/after breast cancer, the tendency of increased mortality was seen across most subgroups stratified by race, menopausal status, or obesity, although not significant for most of them due to smaller numbers of women within those subgroups. Similar findings were observed when data were stratified by tumor hormone receptor status or stage.

Discussion

This study showed a modest increased risk of death associated with DM-2, regardless of whether it was diagnosed before or at/after breast cancer diagnosis. This association tended to exist in most subgroups when results were stratified by race, age, obesity status, tumor stage, or tumor hormone receptor status, although it was not significant in many strata due to smaller sample sizes.

Most previous studies examined diagnosis of DM-2 prior to breast cancer. Although the results of these studies were not consistent (5), most found an increase in all-cause mortality with preexisting DM-2 (6, 8, 9, 18–20). Our results on DM-2 diagnosed before breast cancer diagnosis, although marginally significant, support these findings. This may be attributable to differences in the receipt of cancer treatment and the effects of diabetes on overall survival.

As a result of diabetes and its complications, breast cancer patients with DM-2 may be less likely to receive breast cancer treatments such as adjuvant chemotherapy or radiotherapy (20, 39, 40). Research has reported that physicians may use chemotherapy less frequently or aggressively to treat breast cancer patients with DM-2 due to an increase in hospitalization for chemotherapy toxicity as well as an increase in breast cancer–specific mortality (20). Less receipt of radiation treatment among diabetics compared with nondiabetics has been reported in the literature (40). These were also demonstrated in our study, in which women with DM-2 diagnosed before breast cancer were less likely to receive chemotherapy and

Table 1. Demographic and health characteristics of women diagnosed with breast cancer from 1998 to 2008 in the Military Health System, by diabetes status ($N = 9,398$)

	Diabetes			
Characteristics	**No ($n = 7,804$) *n* (%)**	**Yes before dx ($n = 792$) *n* (%)**	**Yes after dx ($n = 802$) *n* (%)**	***P***
Age at diagnosis, years				<0.001
20–39	1,055 (13.5)	12 (1.5)	42 (5.2)	
40–49	2,066 (26.5)	80 (10.1)	132 (16.5)	
50–59	1,984 (25.4)	225 (28.4)	232 (28.9)	
60–69	1,651 (21.2)	268 (33.8)	256 (31.9)	
70–79	786 (10.1)	163 (20.6)	110 (13.7)	
80+	262 (3.4)	44 (5.6)	30 (3.7)	
Race				<0.001
White	5,773 (74.0)	515 (65.0)	558 (69.6)	
Black	1,104 (14.2)	142 (17.9)	134 (16.7)	
Asian/Pacific Islander	702 (9.0)	114 (14.4)	94 (11.7)	
American Indian/Alaska Native	15 (0.2)	3 (0.4)	4 (0.5)	
Unknown	210 (2.7)	18 (2.3)	12 (1.5)	
Ethnicity				0.655
Non-Hispanic	6,790 (87.0)	690 (87.1)	699 (87.2)	
Hispanic	368 (4.7)	45 (5.7)	38 (4.7)	
Unknown	646 (8.3)	57 (7.2)	65 (8.1)	
Marital status at diagnosis				<0.001
Married	6,202 (79.5)	601 (75.9)	642 (80.1)	
Never married	200 (2.6)	9 (1.1)	10 (1.3)	
Separated	61 (0.8)	5 (0.6)	8 (1.0)	
Divorced	268 (3.4)	20 (2.5)	24 (3.0)	
Widowed	842 (10.8)	139 (17.6)	102 (12.7)	
Unknown	231 (3.0)	18 (2.3)	16 (2.0)	
Active duty status at diagnosis				<0.001
No	7,317 (93.8)	785 (99.1)	781 (97.4)	
Yes	487 (6.2)	7 (0.9)	21 (2.6)	
Service branch at diagnosis[a]				0.046
Army	2,636 (33.8)	305 (38.5)	280 (34.9)	
Air Force	2,111 (27.1)	177 (22.4)	196 (24.4)	
Marines	1,387 (17.8)	136 (17.2)	147 (18.3)	
Navy	1,299 (16.7)	128 (16.2)	145 (18.1)	
Other	371 (4.8)	46 (5.8)	34 (4.2)	
Rank[b]				<0.001
Enlisted	3,778 (48.4)	553 (69.8)	360 (44.9)	
Officer	1,933 (24.8)	151 (19.1)	120 (15.0)	
Other	63 (0.8)	5 (0.6)	2 (0.3)	
Unknown	2,030 (26.0)	83 (10.5)	320 (39.9)	
Benefit type at diagnosis				<0.001
TRICARE prime	1,826 (23.4)	340 (42.9)	261 (32.5)	
TRICARE nonprime	4,883 (62.6)	374 (47.2)	388 (48.4)	
Unknown	1,095 (14.0)	78 (10.0)	153 (19.1)	
Obesity				<0.001
No	6,153 (78.8)	433 (54.7)	500 (62.3)	
Yes	1,651 (21.2)	359 (45.3)	302 (37.7)	
Coronary heart disease				<0.001
No	7,014 (89.9)	592 (74.8)	623 (77.7)	
Yes	790 (10.1)	200 (25.3)	179 (22.3)	
Kidney disease				<0.001
No	6,789 (87.0)	609 (76.9)	626 (78.1)	
Yes	1,015 (13.0)	183 (23.1)	176 (22.0)	
Chronic obstructive pulmonary disease				<0.001
No	7,012 (89.9)	669 (84.5)	646 (80.6)	
Yes	792 (10.2)	123 (15.5)	156 (19.5)	
Stroke				<0.001
No	7,587 (97.2)	743 (93.8)	754 (94.0)	
Yes	217 (2.8)	49 (6.2)	48 (6.0)	
Hypertension				<0.001
No	3,581 (45.9)	58 (7.3)	100 (12.5)	
Yes	4,223 (54.1)	734 (92.7)	702 (87.5)	

Abbreviation: dx, diagnosis.

[a]Service branch or rank of active duty member or sponsor of family member.

Table 2. Treatment, surveillance, and tumor characteristics of women diagnosed with breast cancer from 1998 to 2008 in the Military Health System, by diabetes status ($N = 9{,}398$)

	Diabetes			
Characteristics	**No ($n = 7{,}804$) *n* (%)**	**Yes before dx ($n = 792$) *n* (%)**	**Yes after dx ($n = 802$) *n* (%)**	***P***
Tumor stage				0.587
Stage I	3,720 (47.7)	391 (49.4)	356 (44.4)	
Stage II	2,849 (36.5)	284 (35.9)	319 (39.8)	
Stage III	798 (10.2)	78 (9.9)	88 (11.0)	
Stage IV	242 (3.1)	21 (2.7)	20 (2.5)	
Unknown	195 (2.5)	18 (2.3)	19 (2.4)	
Tumor grade				0.032
Well differentiated	1,586 (20.3)	192 (24.2)	152 (19.0)	
Moderately differentiated	2,778 (35.6)	293 (37.0)	289 (36.0)	
Poorly differentiated	2,505 (32.1)	217 (27.4)	252 (31.4)	
Unknown	935 (12.0)	90 (11.4)	109 (13.6)	
Hormone receptor status				0.318
ER^+/PR^+	4,166 (53.4)	453 (57.2)	428 (53.4)	
ER^-/PR^-	1,541 (19.8)	142 (17.9)	143 (17.8)	
ER^+/PR^- or ER^-/PR^+	856 (11.0)	85 (10.7)	96 (12.0)	
Unknown	1,241 (15.9)	112 (14.2)	135 (16.8)	
Surgery				0.2
No	1,980 (25.4)	192 (24.2)	224 (27.9)	
Yes	5,824 (74.6)	600 (75.8)	578 (72.1)	
Radiation				0.042
No	3,144 (40.3)	355 (44.8)	333 (41.5)	
Yes	4,660 (59.7)	437 (55.2)	469 (58.5)	
Chemotherapy				<0.001
No	2,915 (37.4)	381 (48.1)	317 (39.5)	
Yes	4,889 (62.7)	411 (51.9)	485 (60.5)	
Hormone therapy[a]				0.309
No	1,916 (38.2)	221 (41.1)	199 (38.0)	
Yes	2,813 (56.0)	280 (52.0)	287 (54.8)	
Unknown	293 (5.8)	37 (6.9)	38 (7.3)	
Surveillance mammography				0.544
No	3,691 (47.3)	390 (49.2)	386 (48.1)	
Yes	4,113 (52.7)	402 (50.8)	416 (51.9)	
Metformin[b]				<0.001
No	4,274 (97.7)	178 (30.3)	140 (44.6)	
Yes	103 (2.4)	410 (69.7)	174 (55.4)	
Insulin[b]				<0.001
No	4,278 (97.7)	470 (79.9)	267 (85.0)	
Yes	99 (2.3)	118 (20.1)	47 (15.0)	
Insulin secretagogue[b]				<0.001
No	4,364 (99.7)	346 (58.8)	243 (77.4)	
Yes	13 (0.3)	242 (41.2)	71 (22.6)	
Recurrence				0.01
No	6,241 (80.0)	666 (84.1)	630 (78.6)	
Yes	1,563 (20.0)	126 (15.9)	172 (21.5)	

Abbreviation: dx, diagnosis.

[a]Restricted to women who are hormone receptor positive.

[b]Pharmacy detail was available in our data from 2002 onward; therefore, information on diabetes medications was restricted to women diagnosed with breast cancer between 2002 and 2008.

radiotherapy than women without DM-2. However, chemotherapy as a potential confounder was adjusted for in the analysis, and thus, the potential effects that treatment may have on survival were reduced. Nevertheless, we cannot exclude the possibility that treatment regimen (intensity, type, timing, frequency, or duration of chemotherapy as well as other cancer treatments) may have differed between women with and without DM-2. Such differences could be associated with increased mortality risk.

As all-cause mortality was the study outcome, DM-2 and other related medical conditions may have affected the outcome. Hyperglycemia, a serious problem for many individuals with DM-2,

Table 3. Multivariate analysis for diabetes in relation to survival among 9,398 Department of Defense beneficiaries with breast cancer, 1998–2008

	Number of patients		
Diabetes status	**Alive**	**Dead**	**HR (95% CI)[a]**
No	6,716	1,088	1.00 (reference)
Yes - Before breast cancer diagnosis	679	113	1.17 (0.95–1.44)
Yes - At/after breast cancer diagnosis	646	156	1.39 (1.16–1.66)

[a]HR and 95% CIs adjusted for age at diagnosis, race, marital status at diagnosis, rank of active duty member or sponsor of family members, beneficiary type at diagnosis, grade, obesity, coronary heart disease, chronic obstructive pulmonary disease, stroke, kidney disease, hormone receptor status, chemotherapy, and tumor stage.

Table 4. Multivariate analysis assessing the effect of diabetes status on survival among 9,398 Department of Defense beneficiaries with breast cancer by race, menopausal status, hormone receptor status, and tumor stage

		Number of patients		
Strata	**Diabetes**	**Alive**	**Dead**	**HR (95% CI)[a]**
Race[b]				
White	No	4,948	825	1.00 (Reference)
	Yes: before BC dx	435	80	1.26 (0.99–1.60)
	At/after BC dx	452	106	1.23 (0.99–1.53)
Black	No	919	185	1.00 (Reference)
	Yes: before BC dx	120	22	1.19 (0.71–1.98)
	At/after BC dx	101	33	2.05 (1.36–3.07)
Asian/Pacific Islander	No	637	65	1.00 (Reference)
	Yes: before BC dx	104	10	0.60 (0.24–1.50)
	At/after BC dx	79	15	1.51 (0.76–2.99)
Menopausal status				
<50 years	No	2,769	352	1.00 (Reference)
	Yes: before BC dx	82	10	1.84 (0.95–3.58)
	At/after BC dx	138	36	2.49 (1.71–3.62)
≥50 years	No	3,947	736	1.00 (Reference)
	Yes: before BC dx	597	103	1.29 (1.03–1.62)
	At/after BC dx	508	120	1.38 (1.12–1.70)
Obese				
No	No	5,214	939	1.00 (Reference)
	Yes: before BC dx	365	68	1.20 (0.91–1.55)
	At/after BC dx	384	116	1.63 (1.33–2.01)
Yes	No	1,502	149	1.00 (Reference)
	Yes: before BC dx	314	45	1.35 (0.92–1.99)
	At/after BC dx	262	40	1.22 (0.83–1.82)
Hormone receptor status				
ER^+/PR^+	No	3,739	427	1.00 (Reference)
	Yes: before BC dx	405	48	1.47 (1.07–2.03)
	At/after BC dx	363	65	1.42 (1.07–1.89)
ER^-/PR^-	No	1,245	296	1.00 (Reference)
	Yes: before BC dx	110	32	1.48 (0.98–2.23)
	At/after BC dx	101	42	1.70 (1.17–2.46)
ER^+/PR^- or ER^-/PR^+	No	722	134	1.00 (Reference)
	Yes: before BC dx	74	11	1.03 (0.53–1.99)
	At/after BC dx	82	14	0.96 (0.52–1.78)
Unknown	No	1,010	231	1.00 (Reference)
	Yes: before BC dx	90	22	0.73 (0.45–1.20)
	At/after BC dx	100	35	2.07 (1.40–3.05)
Tumor stage				
Stage I	No	3,436	284	1.00 (Reference)
	Yes: before BC dx	363	28	1.09 (0.72–1.64)
	At/after BC dx	312	44	1.11 (0.79–1.57)
Stage II	No	2,471	378	1.00 (Reference)
	Yes: before BC dx	248	36	1.23 (0.85–1.77)
	At/after BC dx	254	65	1.94 (1.47–2.58)
Stage III	No	585	213	1.00 (Reference)
	Yes: before BC dx	51	27	1.43 (0.88–2.31)
	At/after BC dx	59	29	1.65 (1.07–2.54)
Stage IV	No	71	171	1.00 (Reference)
	Yes: before BC dx	4	17	1.99 (1.05–3.77)
	At/after BC dx	6	14	1.61 (0.86–3.03)
Unknown stage	No	153	42	1.00 (Reference)
	Yes: before BC dx	13	5	1.50 (0.41–5.43)
	At/after BC dx	15	4	2.47 (0.58–10.45)

Abbreviations: BC, breast cancer; dx, diagnosis.

[a]HR and 95% CIs adjusting for age at diagnosis, race, marital status at diagnosis, rank of active duty member/sponsor, beneficiary type at diagnosis, date of first visit, obesity, coronary heart disease, chronic obstructive pulmonary disease, stroke, hypertension, hormone receptor status, chemotherapy, and tumor stage. Missing pharmacy data for diabetes medications were adjusted as the missing category in the models. Stratified variables were not included in stratified analyses.

[b]Models stratified by American Indian/Alaska Native and unknown race had too few deaths to converge; therefore, data were not presented.

may play a role in the decreased survival among women diagnosed with DM-2. Increased blood glucose levels have been found to increase cancer mortality (41–43), with survival decreasing as glycemic control decreases. In addition, patients with DM-2 in the current study were about twice as likely to have obesity, coronary heart disease, kidney disease, COPD, stroke, and hypertension, which can increase the risk of death. These medical conditions were adjusted for in the models. Nonetheless, repeated analysis without these conditions did not change the HR estimates substantially, suggesting the possible effects of factors other than these medical conditions on the identified association between diabetes and overall survival.

We assessed the independent effects of DM-2 diagnosed at or after breast cancer diagnosis with the hypothesis that DM-2 diagnosed at or after breast cancer may be a more indolent or less severe form of the disease than DM-2 diagnosed before breast cancer diagnosis. This hypothesis is based on the fact that DM-2 diagnosed at or after breast cancer diagnosis is detected as a result of medical examination for cancer diagnosis or medical surveillance for cancer care and has shorter duration of disease. Therefore, it may be less likely to affect breast cancer treatment. Lower severity of DM-2 diagnosed after breast cancer diagnosis was demonstrated in our study: Patients with DM-2 diagnosed at or after breast cancer diagnosis were less likely to receive diabetes treatment than those diagnosed before breast cancer. It is possible that DM-2 diagnosed at/after breast cancer diagnosis might not influence breast cancer treatment decisions as heavily. Our data showed that patients with DM-2 diagnosed at/after breast cancer diagnosis were more likely to receive radiation treatment and chemotherapy than those with DM-2 diagnosed before breast cancer. The proportions of breast cancer treatment among the former were close to those among patients without DM-2. Although the hypothesis on DM-2 severity and possible effects on breast cancer treatment is tenable as shown in our data, our analysis did not display significant differences in survival between patients with DM-2 diagnosed at/after and before breast cancer diagnosis. The overall mortality was also higher among DM-2 patients diagnosed at/after breast cancer diagnosis, being similar to those with DM-2 diagnosed before breast cancer. Therefore, factors other than diabetes severity and breast cancer treatment might account for a higher mortality among DM-2 patients despite timing at diagnosis.

Limitations in this study included possible misclassification of DM-2 status because of lack of data on diabetes diagnoses prior to 1998. However, such misclassification was likely limited as individuals with diabetes would continue to receive antidiabetic therapy, which would be captured in their records after 1998. In addition, such misclassification was likely to occur only for DM-2 diagnosed before breast cancer because the initial year for breast cancer diagnosis was 1998. This misclassification might dilute rather than overestimate the association between DM-2 and survival. Second, we cannot exclude residual confounding by the frequency, intensity, timing, and duration of breast cancer treatment, as mentioned above. Third, overadjustment or underadjustment for confounders may be possible. We adjusted for obesity and other comorbidities in our multivariate models. The relationship between diabetes and obesity and other comorbidities is complex. We do not exclude the possibility that a comorbid condition is on the causal pathway between diabetes and mortality, and thus, our multivariate results were overadjusted. However, the HR estimates remained similar after we removed these comorbidities from the multivariate models. On the other hand, there is a possibility that we underadjusted for potential confounders as we did not have data on variables such as physical activity, dietary intake, and smoking, which may be associated with both diabetes and survival (44–46). Finally, there might be incomplete information and inaccurate coding in our data that are typical in medical records data. Nonetheless, the extent of these limitations might not be substantial enough to change the results.

In summary, our findings indicate that breast cancer patients with DM-2 are at a higher risk of mortality despite timing at diagnosis, compared with those without DM-2. Further research into these findings is warranted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Army, Department of Defense, National Cancer Institute, nor the U.S. government. Nothing in the presentation implies any federal/Department of Defense endorsement.

Authors' Contributions

Conception and design: A.A. Gill, C.D. Shriver, K. Zhu
Development of methodology: A.A. Gill, K. Zhu
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K. Zhu
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S. Shao, S.H. Zahm, K.A. McGlynn, K. Zhu
Writing, review, and/or revision of the manuscript: S. Shao, A.A. Gill, S.H. Zahm, I. Jatoi, K.A. McGlynn, K. Zhu
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.A. Gill, C.D. Shriver
Study supervision: C.D. Shriver, K. Zhu

Acknowledgments

The authors thank the following individuals and institutes for their contributions to or support for the original data linkage project: Guy J. Garnett, David E. Radune, and Dr. Aliza Fink of ICF Macro; Wendy Funk, Julie Anne Mutersbaugh, Linda Cottrell, and Laura Hopkins of Kennel and Associates, Inc.; Kim Frazier, Dr. Elder Granger, and Dr. Thomas V. Williams of TMA; Annette Anderson, Dr. Patrice Robinson, and Dr. Chris Owner of the Armed Forces Institute of Pathology; Dr. Joseph F. Fraumeni Jr, Dr. Robert N. Hoover, Dr. Susan S. Devesa, and Gloria Gridley of the NCI; Dr. Lindsey Enewold, Dr. John Potter, Raul Parra, Anna Smith, Fiona Renalds, William Mahr, Hongyu Wu, Dr. Larry Maxwell, Miguel Buddle, and Virginia Van Horn of the United States Military Cancer Institute. The authors also thank Dr. Jie Lin for her help in conducting supplementary statistical analysis. This project was supported by the John P. Murtha Cancer Center, Walter Reed National Military Medical Center via the Uniformed Services University of the Health Sciences under the auspices of the Henry M. Jackson Foundation for the Advancement of Military Medicine and by the intramural research program of the NCI. The original data linkage was supported by the United States Military Cancer Institute and Division of Cancer Epidemiology and Genetics, NCI.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received June 1, 2017; revised July 26, 2017; accepted October 9, 2017; published OnlineFirst November 2, 2017.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7–30.
2. Louwman WJ, Janssen-Heijnen ML, Houterman S, Voogd AC, van der Sangen MJ, Nieuwenhuijzen GA, et al. Less extensive treatment and inferior

prognosis for breast cancer patient with comorbidity: a population-based study. Eur J Cancer 2005;41:779–85.
3. Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JW. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 2001;285:885–92.
4. Centers for Disease Control and Prevention. National diabetes statistics report, 2014. Atlanta, GA: Centers for Disease Control and Prevention; 2014.
5. Du W, Simon MS. Racial disparities in treatment and survival of women with stage I-III breast cancer at a large academic medical center in metropolitan Detroit. Breast Cancer Res Treat 2005;91:243–8.
6. Cleveland RJ, North KE, Stevens J, Teitelbaum SL, Neugut AI, Gammon MD. The association of diabetes with breast cancer incidence and mortality in the Long Island Breast Cancer Study Project. Cancer Causes Control 2012;23:1193–203.
7. Griffiths RI, Danese MD, Gleeson ML, Valderas JM. Epidemiology and outcomes of previously undiagnosed diabetes in older women with breast cancer: an observational cohort study based on SEER-Medicare. BMC Cancer 2012;12:613.
8. Jiralerspong S, Kim ES, Dong W, Feng L, Hortobagyi GN, Giordano SH. Obesity, diabetes, and survival outcomes in a large cohort of early-stage breast cancer patients. Ann Oncol 2013;24:2506–14.
9. Lipscombe LL, Goodwin PJ, Zinman B, McLaughlin JR, Hux JE. The impact of diabetes on survival following breast cancer. Breast Cancer Res Treat 2008;109:389–95.
10. Campbell PT, Newton CC, Patel AV, Jacobs EJ, Gapstur SM. Diabetes and cause-specific mortality in a prospective cohort of one million U.S. adults. Diabetes Care 2012;35:1835–44.
11. Gold HT, Makarem N, Nicholson JM, Parekh N. Treatment and outcomes in diabetic breast cancer patients. Breast Cancer Res Treat 2014; 143:551–70.
12. Luo J, Virnig B, Hendryx M, Wen S, Chelebowski R, Chen C, et al. Diabetes, diabetes treatment and breast cancer prognosis. Breast Cancer Res Treat 2014;148:153–62.
13. Yeh HC, Platz EA, Wang NY, Visvanathan K, Helzlsouer KJ, Brancati FL. A prospective study of the associations between treated diabetes and cancer outcomes. Diabetes Care 2012;35:113–8.
14. Wu AH, Kurian AW, Kwan ML, John EM, Lu Y, Keegan TH, et al. Diabetes and other comorbidities in breast cancer survival by race/ethnicity: the California Breast Cancer Survivorship Consortium (CBCSC). Cancer Epidemiol Biomarkers Prev 2015;24:361–8.
15. Minicozzi P, Berrino F, Sebastiani F, Falcini F, Vattiato R, Cioccoloni F, et al. High fasting blood glucose and obesity significantly and independently increase risk of breast cancer death in hormone receptor-positive disease. Eur J Cancer 2013;49:3881–8.
16. Coughlin SS, Calle EE, Teras LR, Petrelli J, Thun MJ. Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. Am J Epidemiol 2004;159:1160–7.
17. De Bruijn KM, Arends LR, Hansen BE, Leeflang S, Ruiter R, van Eijck CH. Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer. Br J Surg 2013;100:1421–9.
18. Peairs KS, Barone BB, Snyder CF, Yeh HC, Stein KB, Derr RL, et al. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. J Clin Oncol 2011;29:40–6.
19. Yerrabothala S, Shaaban H, Capo G, Maroules M, Debari VA. The impact of diabetes mellitus on breast cancer outcomes: a single center retrospective study. Pathol Oncol Res 2014;20:209–14.
20. Srokowski TP, Fang S, Hortobagyi GN, Giordano SH. Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. J Clin Oncol 2009;27:2170–6.
21. Zhao XB, Ren GS. Diabetes mellitus and prognosis in women with breast cancer: a systematic review and meta-analysis. Medicine 2016;95:e5602.
22. Sabatino SA, Thompson TD, Wu XC, Fleming ST, Kimmick GG, Trentham-Dietz A, et al. The influence of diabetes severity on receipt of guideline-concordant treatment for breast cancer. Breast Cancer Res Treat 2014;146: 199–209.
23. Martin ET, Kaye KS, Knott C, Nguyen H, Santarossa M, Evans R, et al. Diabetes and risk of surgical site infection: a systematic review and meta-analysis. Infect Control Hosp Epidemiol 2016;37:88–99.
24. Chavez-MacGregor M, Clarke CA, Lichtensztajn DY, Giordano SH. Delayed initiation of adjuvant chemotherapy among patients with breast cancer. JAMA Oncol 2016;2:322–9.
25. Ferroni P, Riondino S, Buonomo O, Palmirotta R, Guadagni F, Roselli M. Type 2 diabetes and breast cancer: the interplay between impaired glucose metabolism and oxidant stress. Oxid Med Cell Longev 2015;2015:183928.
26. Lipscombe LL, Chan WW, Yun L, Austin PC, Anderson GM, Rochon PA. Incidence of diabetes among postmenopausal breast cancer survivors. Diabetologia 2013;56:476–83.
27. Zhang X, Geiss LS, Cheng YJ, Beckles GL, Gregg EW, Kahn HS. The missed patient with diabetes: how access to health care affects the detection of diabetes. Diabetes Care 2008;31:1748–53.
28. Nelson KM, Chapko MK, Reiber G, Boyko EJ. The association between health insurance coverage and diabetes care; data from the 2000 Behavioral Risk Factor Surveillance System. Health Serv Res 2005;40:361–72.
29. Vest BM, Kahn LS, Danzo A, Tumiel-Berhalter L, Schuster RC, Karl R, et al. Diabetes self-management in a low-income population: impacts of social support and relationships with the health care system. Chronic Illn 2013;9:145–55.
30. Ward E, Halpern M, Schrag N, Cokkinides V, DeSantis C, Bandi P, et al. Association of insurance with cancer care utilization and outcomes. CA Cancer J Clin 2008;58:9–31.
31. Chen WW, Shao YY, Shau WY, Lin ZZ, Lu YS, Chen HM, et al. The impact of diabetes mellitus on prognosis of early breast cancer in Asia. Oncologist 2012;17:485–91.
32. Gill KS, Muntner P, Lafayette RA, Petersen J, Fink JC, Gilbertson DT, et al. Red blood cell transfusion use in patients with chronic kidney disease. Nephrol Dial Transplant 2013;28:1504–15.
33. Col NF, Ochs L, Springmann V, Aragaki AK, Chlebowski RT. Metformin and breast cancer risk: a meta-analysis and critical literature review. Breast Cancer Res Treat 2012;135:639–46.
34. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009;52:1766–77.
35. Enewold L, McGlynn KA, Zahm SH, Jatoi I, Anderson WF, Gill AA, et al. Surveillance mammography among female Department of Defense beneficiaries: a study by race and ethnicity. Cancer 2013;119:3531–8.
36. Cheng L, Swartz MD, Zhao H, Kapadia AS, Lai D, Rowan PJ, et al. Hazard of recurrence among women after primary breast cancer treatment–a 10-year follow-up using data from SEER-Medicare. Cancer Epidemiol Biomarkers Prev 2012;21:800–9.
37. Shariff SZ, Cuerden MS, Jain AK, Garg AX. The secret of immortal time bias in epidemiologic studies. J Am Soc Nephrol 2008;19:841–3.
38. Thomas F, Renaud F, Benefice E, de Meeus T, Guegan JF. International variability of ages at menarche and menopause: patterns and main determinants. Hum Biol 2001;73:271–90.
39. van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercksen MW, Coebergh JW, Haak HR. Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. Int J Cancer 2007;120:1986–92.
40. Luo J, Hendryx M, Virnig B, Wen S, Chlebowski R, Chen C, et al. Pre-existing diabetes and breast cancer prognosis among elderly women. Br J Cancer 2015;113:827–32.
41. Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829–41.
42. Saydah SH, Loria CM, Eberhardt MS, Brancati FL. Abnormal glucose tolerance and the risk of cancer death in the United States. Am J Epidemiol 2003;157:1092–100.
43. Erickson K, Patterson RE, Flatt SW, Natarajan L, Parker BA, Heath DD, et al. Clinically defined type 2 diabetes mellitus and prognosis in early-stage breast cancer. J Clin Oncol 2011;29:54–60.
44. Goodwin PJ, Ambrosone CB, Hong CC. Modifiable lifestyle factors and breast cancer outcomes: current controversies and research recommendations. Adv Exp Med Biol 2015;862:177–92.
45. Berube S, Lemieux J, Moore L, Maunsell E, Brisson J. Smoking at time of diagnosis and breast cancer-specific survival: new findings and systematic review with meta-analysis. Breast Cancer Res 2014;16:R42.
46. Zhu B, Wu X, Wang X, Zheng Q, Sun G. The association between passive smoking and type 2 diabetes: a meta-analysis. Asia Pac J Public Health 2014;26:226–37.