Timing of diabetes diagnosis and overall survival among breast cancer patients in the Military Health System

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Abstract

Purpose: While research suggests that type 2 diabetes (DM-2) is associated with overall and breast-cancer specific decreased survival, results have been inconsistent. Most prior studies of breast cancer survival have investigated the effect of pre-existing DM-2, without assessing the effect of DM-s diagnosed at or after breast cancer. This study aimed to examine the effect of DM-2, diagnosed before and after breast cancer, on breast cancer survival.

Methods: This study analyzed 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 survival.

Results: After adjustment for potential confounders, diabetes status (no/yes) was not associated with mortality risk (HR=1.00, 95% CI= 0.83, 1.20). However, when taking into consideration the timing of diabetes diagnosis relative to breast cancer diagnosis, women with pre-existing diabetes had a risk of mortality twice that of women without diabetes (HR=2.00, 95% CI 1.53-2.61) whereas women diagnosed with diabetes at or after breast cancer diagnosis had lower mortality than women without diabetes (HR= 0.81, 95% CI= 0.66-0.99). This association did not vary by demographics, obesity, or tumor characteristics.

Conclusion: Breast cancer patients who had pre-existing diabetes had increased mortality compared to those without diabetes. In contrast, women diagnosed with diabetes at or after breast cancer diagnosis had decreased mortality. These findings warrant further research confirmation.

Introduction

In the United States, breast cancer remains the second most common cause of cancer-specific mortality among women.[1] While the five-year relative survival rate is approximately 89%,[1] some studies suggest that comorbid conditions may influence prognosis.[2,3]

As of 2010 approximately 8.3% of the US population has diabetes, and this comorbid condition may affect breast cancer survival. There are two main types of diabetes (type 1 and type 2) with type 2 accounting for 95% of all diagnoses.[4] The association between diabetes (primarily type 2) and breast cancer survival has been inconsistent in the literature,[5] but most studies have found that it is associated with decreased overall survival[6-13] and breast cancer-specific survival.[11, 14-16 11-14] A prospective cohort of one million U.S. adults reported a two-fold increased risk of all-cause mortality and a 16% increased risk of death from breast cancer 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 have examined the association of breast cancer survival with diabetes diagnosed prior to breast cancer.[5,6,8,9,11,17-19] In a large cohort study of stage I-III breast cancer patients treated at the MD Anderson Cancer Center, those with pre-existing diabetes had a higher risk of all-cause mortality (HR: 1.39, 95% CI: 1.10-1.77).[8] In another study based on the SEER-Medicare data, women diagnosed with diabetes prior to breast cancer had a higher all-cause mortality compared to women without diabetes.[19] To the best of our knowledge, the association between diabetes and survival, when diabetes is diagnosed at or after breast cancer diagnosis, has not been studied. Diabetes detected at or following breast cancer diagnosis may

differ from that diagnosed prior to breast cancer and it is possible that diabetes may be induced as a result breast cancer treatment.[20] Thus, an examination of the breast cancer survival-diabetes relationship by timing of diabetes may help to better understand the basis of the association.

Previous studies have been conducted in populations in which accessibility to healthcare may vary. Access to healthcare has been found to influence the detection/diagnosis of diabetes and its management, cancer detection/diagnosis and treatment, and overall survival.[21-24] If persons with and without diabetes differ in their accessibility to healthcare, any reported associations might be due to the effects of factors related to access to care. Research in an equal access system can reduce these potential effects and provide additional information to assess whether the relationship varies by demographics, obesity, and tumor characteristics when the access to care is equal. The Military Health System (MHS) of the U.S. Department of Defense (DoD) is an equal access system, providing all of its beneficiaries with healthcare at little or no charge. The objective of this study was to examine the relationship between timing of type 2 diabetes (DM-2) diagnosis and overall survival among breast cancer patients in the MHS.

Materials & Method

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 healthcare through the DoD's healthcare 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 cancer patients diagnosed and/or treated at military treatment

facilities (MTFs) by certified cancer registrars. 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 in-patient and out-patient 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 information on 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 this study (n=9,944). Women with type 1 diabetes (n=536), under 20 years of age (n=1), and those with missing survival information (n=9) were excluded from the analyses.

Study variables

Medical conditions were obtained using MDR. Women were classified as having DM-2 if they had ICD-9 diagnoses codes (250.x0, 250.x2, 357.2, 362.0, and 366.41) seen at least once as an in-patient, or three/more times as an out-patient.[25,26] DM-2 status was classified in two ways: (1) a dichotomized variable (no/yes) and (2) a categorical variable based on the timing of diabetes diagnosis relative to breast cancer diagnosis (no diagnosis, before breast cancer diagnosis, at or after breast cancer diagnosis). Other medical conditions included in the analyses were obesity, heart disease, kidney disease, chronic obstructive pulmonary disease, stroke, and

hypertension. They were considered to be present if codes were identified in one/more in-patient or three/more out-patient records.

Pathologic breast cancer features were obtained from CCR. They consist of AJCC tumor stage, histological grade, and hormone receptor status. AJCC tumor stage was categorized as stage I, stage II, stage III, stage IV, and unknown stage. Histologic grade was classified based on level of differentiation as well differentiated, moderately differentiated, poorly differentiated, and unknown. Hormone receptor status was categorized into four groupings as follows: ER+/PR+, ER-/PR-, ER+/PR- or ER-/PR+, unknown.

Medical care/recurrence variables included breast cancer treatment (surgery, chemotherapy, radiation therapy, and hormone therapy), diabetes treatment, surveillance mammography, and recurrence. Receipt of breast cancer surgery, chemotherapy, and radiation therapy was determined by combining data from CCR and MDR and considered "yes" if its occurrence was within three months following diagnosis in either database. Information on diabetes specific treatment and surveillance mammography were obtained from MDR. Hormone therapy data were obtained solely from CCR since the MDR hormone data were not available prior to 2002. Information on diabetes treatment and surveillance mammography was obtained from MDR. Use of diabetes medications (metformin, insulin, or insulin secretagogue), which may be related to cancer survival, [27,28] was defined as "yes" if there was at least one record of the medication being prescribed. Surveillance mammography was categorized as 'yes' if it was identified six months or more after a previous mammogram among women who received a bilateral mammogram and underwent breast conserving surgery or among women who received a unilateral mammogram and had undergone unilateral mastectomies. Mammograms received two months prior to a breast mass/other breast symptom were not considered as surveillance

procedures.[29] Recurrence was defined based on the CCR definition and supplemented with information obtained from MDR.[30]

Demographic characteristics were obtained from CCR, with missing values supplemented by MDR. Demographic variables included age at diagnosis, race, ethnicity, marital status at diagnosis, active duty status at diagnosis, affiliated 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 diabetic status. We then compared all-cause death among persons with and without diabetes using Kaplan-Meir analysis with follow-up beginning at the date of breast cancer diagnosis through the date of death, date of last contact, or study end (truncated to December 31, 2007). The difference between the two groups was tested using the log rank test. Finally, we used Cox proportional hazards models to assess the association between DM-2 and overall survival with adjustment for potential confounding factors. A potential confounder was defined if it was associated with both survival and diabetes and was not an intervening variable between diabetes and survival. The identified potential confounding variables included age at diagnosis, race, marital status at diagnosis, rank of active duty member/sponsor, insurance type at diagnosis, obesity, coronary heart disease, chronic obstructive pulmonary disease, stroke, hypertension, hormone receptor status, chemotherapy, metformin treatment, insulin treatment, tumor stage, and recurrence. Although tumor stage did not meet the confounder criteria, it was adjusted for in multivariate analyses due to its complex effects and theoretical significance for research. Since pharmacy data were available from 2002 onward, the

first date a beneficiary received either in-patient or out-patient services was used as a surrogate of missing information due to the lack of availability of data before 2002, and was adjusted in the models to distinguish between no use and no data. When the analysis was conducted based on timing of diabetes diagnosis, additional potential confounders were identified and adjusted for, these included tumor grade, surgery, radiation, hormone therapy, and surveillance mammography. We repeated Cox model analyses with the data stratified by race, menopausal status, obesity, hormone receptor status, and tumor stage. Information on menopausal status was not available in this dataset; therefore, age at diagnosis (<50 and ≥ 50 years) was used as a proxy based on the average age of natural menopause.[31] The proportional hazards assumption was tested for Cox model analyses, and no violations on model assumptions were found.

Statistical Analysis System (SAS) software (SAS Institute, Inc., Cary, North Carolina) was used to perform statistical analyses. All tests of significance were two-tailed and performed at an alpha of 0.05.

Results

Out of 9,398 study women, 1,991 had DM-2 (21%). Table 1 shows the distributions of demographic factors and other medical conditions by DM-2 status. Compared to women without diabetes, those with diabetes were more likely to be older, black or Asian/Pacific Islander, widowed, non-active duty service individuals, enlisted service members, and have non-prime TRICARE insurance at the time of diagnosis (p-value <0.01 for all the variables). Additionally, diabetics tended to have a higher frequency of obesity, coronary heart disease, kidney disease, chronic obstructive pulmonary disease, stroke, and hypertension (p-value <0.01 for all the variables).

Table 2 shows the distributions of treatment, surveillance and tumor characteristics by diabetes status. Diabetics were more likely to have estrogen and progesterone receptor positive (ER+/PR+) tumors compared to non-diabetics (p-value ≤ 0.03 for all). Conversely, diabetics were less likely to receive chemotherapy and have a breast cancer recurrence in comparison to those without diabetes (p-value ≤ 0.03 for both variables).

During the follow-up period, 11% of women with diabetes and 13% of those without diabetes died. The Kaplan-Meier analysis showed that diabetics experienced significantly better survival than non-diabetics (log-rank p-value < 0.01) (Figure 1). After adjusting for potential confounders, diabetes status was no longer associated with mortality risk (HR=1.00, 95% CI= 0.83, 1.20) (Table 3). However, women diagnosed with diabetes before breast cancer diagnosis had a risk of mortality two times higher than those without diabetes (HR=2.00, 95% CI 1.53-2.61). In contrast, women diagnosed with diabetes at or after breast cancer diagnosis had lower mortality than non-diabetics (HR= 0.81, 95% CI= 0.66-0.99). The results remained significant after additional adjustment for tumor grade, surgery, radiation, hormone therapy, and surveillance mammography (data not shown).

Among women diagnosed with diabetes before breast cancer, a significant increase in the risk of mortality was consistently seen across most subgroups stratified by race, menopausal status, obesity status, hormone receptor status, or tumor stage (Table 4). For diabetes diagnosed at or after breast cancer, the risk of mortality tended to be lower than it was among women without diabetes who were white, 50+ years of age, ER+/PR- or ER-/PR+, or had stage I tumors. However, confidence intervals overlapped between these subgroups.

Discussion

This study showed no overall differences in survival between women with and without diabetes, after adjustment for demographic, health, and tumor and treatment variables. However, when the temporal relationship between diabetes and breast cancer diagnosis was considered, women diagnosed with diabetes before breast cancer experienced a two-fold increase in mortality compared to women without diabetes. In contrast, women diagnosed with diabetes at or after breast cancer tended to have increased survival compared to those without diabetes. These findings did not vary by demographics, obesity, or tumor characteristics.

Most previous studies used history of diabetes prior to breast cancer diagnosis. While the results were not consistent,[5] most found an increase in all-cause mortality among women diagnosed with diabetes prior to breast cancer.[6,8,9,17-19] This may be attributable to differences in the receipt of cancer treatments and the effects of diabetes on overall survival.

As a result of diabetes and its complications, women with diabetes may be less likely to receive breast cancer treatment such as adjuvant chemotherapy or radiation therapy.[19,32] Research has reported that physicians may use chemotherapy less frequently or aggressively to treat breast cancer patients with diabetes due to an increase in hospitalization for chemotherapy toxicity, as well as an increase in breast cancer specific mortality among diabetic patients who received chemotherapy treatment.[19] This was also demonstrated in the current study, in which women with diabetes tended to be less likely to receive chemotherapy than women without diabetes. However, breast cancer treatments, including chemotherapy, were adjusted for in the analysis and thus the potential effects that treatment may have on survival were reduced. Nevertheless, we do not exclude the possibility that diabetics diagnosed prior to breast cancer and non-diabetics differed in the intensity, type, timing, frequency, or duration of chemotherapy

as well as other cancer treatments, which might be associated with the risk of death among diabetic patients.

Since all-cause mortality was the study outcome, diabetes itself and related medical conditions affect the outcome. Hyperglycemia, a serious problem for many individuals with DM-2, may play a role in the decreased survival among women diagnosed with diabetes prior to breast cancer. Increased blood glucose levels have been found to increase cancer mortality,[33-35] with survival decreasing as glycemic control decreases. In addition, diabetic patients are more likely to suffer from obesity, coronary heart disease, kidney disease, chronic obstructive pulmonary disorder, stroke, and hypertension. Rates of these comorbid conditions were doubled among diabetics in our data; nonetheless, differences in survival were still apparent after adjustment for these variables.

To the best of our knowledge, our study is the first to assess the temporal relationship between the diagnoses of diabetes and breast cancer and overall survival. Patients diagnosed with diabetes at or after breast cancer diagnosis tended to have a better survival than those without diabetes. While the underlying reasons for this finding are not clear, there may be differences in the receipt of breast cancer treatment and follow-up care between diabetics diagnosed before and that at or after breast cancer diagnosis, which may contribute to the observed difference in survival.

When diabetes is diagnosed coincidently at breast cancer diagnosis or follow-up care, patients may be more likely to have a milder form of diabetes compared to those who were diagnosed before breast cancer and had a longer history of the disease. This possibility is suggested in our analysis showing that diabetics diagnosed at or after breast cancer diagnosis were less likely to receive metformin (52.7% for at or after breast cancer diagnosis vs. 72.5% for

before breast cancer diagnosis), insulin (10% for at or after breast cancer diagnosis vs. 21.3% for before breast cancer diagnosis), or insulin secretogogue treatment for diabetes (23.5% for at or after breast cancer diagnosis vs. 47% for before breast cancer diagnosis). For those with diabetes diagnosed after breast cancer diagnosis, the initial breast cancer treatment may occur before diabetes diagnosis and thus is not affected by diabetic status. Additionally, it is possible that women diagnosed with diabetes after breast cancer diagnosis receive more intensive therapies, such as chemotherapy, which may induce diabetes.[20] Thus, the better outcomes experienced by women who develop diabetes following breast cancer diagnosis may partially be attributed to the receipt of aggressive breast cancer treatment.

For those with diabetes initially diagnosed at breast cancer diagnosis, diabetes may be mild, which may not affect the utilization of breast cancer treatment. On the other hand, these women may receive more follow-up care and surveillance of breast cancer as a result of newly diagnosed diabetes in addition to breast cancer itself. Our analysis demonstrated more radiation treatment, chemotherapy, hormone therapy and surveillance mammography among diabetics diagnosed at or after breast cancer diagnosis than those diagnosed before breast cancer, supporting this conjecture (data not shown). While the effects of mild diabetes itself on survival may not be identified without a very long follow up, the positive effects of more follow-up care and surveillance of breast cancer on survival may appear during the follow-up period of the study.

Our additional analysis showed that women diagnosed with diabetes at or after breast cancer diagnosis are more likely to undergo surgery, radiation, and chemotherapy, as well as receive hormone therapy (data not shown). Although cancer treatment variables defined as receipt or no receipt were adjusted for in our analysis, the timing, frequency, and duration of

breast cancer treatment might differ between this group and patients without or with diabetes diagnosed before breast cancer diagnosis. However, when stratified by demographic, health, and tumor characteristics, no variation in survival was observed as confidence intervals overlapped between subgroups.

Limitations in this study included possible misclassification of diabetes status because individuals who were diagnosed with diabetes before 1998 might have been classified as non-diabetics due to the lack of data prior to 1998. However, such misclassification was likely limited as patients were able to receive continuous medical care after medical records data became available in 1998 and thus could be identified in the data. In addition, such misclassification was likely to occur only for diabetes diagnosed before breast cancer because the initial year for breast cancer diagnosis was 1998 and diabetes diagnosed in or after breast cancer diagnosis should be included in the data. This misclassification might dilute rather than overestimate the association between diabetes prior to breast cancer and survival. We cannot exclude residual confounding by the frequency, intensity, timing, and duration of breast cancer treatment, as mentioned above. We also do not exclude the possibility of immortal time bias (death could not occur before the occurrence of diabetes defined after breast cancer diagnosis and therefore survival is longer). If this had occurred, the group of diabetes identified after breast cancer diagnosis might have been more prone to factors associated with a longer survival, which led a higher possibility of diabetes diagnosis. However, the group had a higher frequencies of factors related to a shorter survival such as obesity, coronary heart disease, hypertension, and stroke than those without diabetes and tumor stage was not significantly different between the two (data not shown). In addition, these factors were adjusted in the analysis. Furthermore, there might be incomplete information and inaccurate coding in our data as any medical records

data. Nonetheless, the extent of these limitations might not be substantial enough to change the results.

In addition to being the first study that took into account the temporal relationship between diabetes and breast diagnoses on overall survival, our study included and adjusted for a number of variables that might influence results, such as diabetes treatment and comorbid medical conditions, which other studies have not be able to do.[5,6,9,10,15] Furthermore, by performing this study in an equal-access healthcare system, the effects of factors related to access to healthcare on the study results might have been reduced.

In summary, our findings indicate that breast cancer patients with preexisting diabetes are at a two-fold risk of mortality compared to those without diabetes. Conversely, women diagnosed with diabetes at/after breast cancer diagnosis had better survival than those who did not develop diabetes. Further research is warranted to demonstrate our findings.

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References

1. American Cancer Society. Breast Cancer Facts & Figures 2013-2014. Atlanta: American Cancer Society, Inc. 2013.

2. Louwman WJ, Janssen-Heijnen ML, Houterman S, et al. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. Eur J Cancer. Mar 2005;41(5):779-785.

3. Yancik R, Wesley MN, Ries LA, et al. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA. Feb 21 2001;285(7):885-892.

4. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.

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. Jun 2005;91(3):243-248.

6. Cleveland RJ, North KE, Stevens J, et al. The association of diabetes with breast cancer incidence and mortality in the Long Island Breast Cancer Study Project. Cancer Causes Control. Jul 2012;23(7):1193-1203.

7. Griffiths RI, Danese MD, Gleeson ML, et al. 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, et al. Obesity, diabetes, and survival outcomes in a large

cohort of early-stage breast cancer patients. Ann Oncol. Jun 21 2013.

9. Lipscombe LL, Goodwin PJ, Zinman B, McLaughlin JR, Hux JE. The impact of diabetes on survival following breast cancer. Breast Cancer Res Treat. May 2008;109(2):389-395.

10. Campbell PT, Newton CC, Patel AV, et al. Diabetes and cause-specific mortality in a prospective cohort of one million U.S. adults. Diabetes Care. Sep 2012;35(9):1835-1844.

11. Gold HT, Makarem N, Nicholson JM, et al. Treatment and outcomes in diabetic breast cancer patients. Breast Cancer Res Treat. Feb 2014;143(3):551-570.

12. Luo J, Virnig B, Hendryx M et al. Diabetes, diabetes treatment and breast cancer prognosis. Breast Cancer Res Treat. Sep 2014; 148:153–162.

13. Yeh HC, Platz EA, Wang NY, et al. A prospective study of the associations between treated diabetes and cancer outcomes. Diabetes Care. Jan 2012; 35:113-118.

14. Minicozzi P, Berrino F, Sebastiani 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. Dec 2013;49(18):3881-3888.

15. 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. Jun 15 2004;159(12):1160-1167.

16. De Bruijn KM, Arends LR, Hansen BE, et al. Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer. Br J Surg. Oct 2013;100(11):1421-1429.

17. Peairs KS, Barone BB, Snyder CF, et al. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. J Clin Oncol. Jan 1 2011;29(1):40-46.

18. Yerrabothala S, Shaaban H, Capo G, et al. The Impact of Diabetes Mellitus on Breast Cancer

Outcomes: A Single Center Retrospective Study. Pathol Oncol Res. Jul 6 2013.

19. Srokowski TP, Fang S, Hortobagyi GN, et al. Impact of diabetes mellitus on complications and outcomes of adjuvant chemotherapy in older patients with breast cancer. J Clin Oncol. May 1 2009;27(13):2170-2176.

20. Lipscombe LL, Chan WW, Yun L, et al. Incidence of diabetes among postmenopausal breast cancer survivors. Diabetologia. Mar 2013;56(3):476-483.

21. Zhang X, Geiss LS, Cheng YJ, et al. The missed patient with diabetes: how access to health care affects the detection of diabetes. Diabetes Care. Sep 2008;31(9):1748-1753.

22. Nelson KM, Chapko MK, Reiber G, et al. The association between health insurance coverage and diabetes care; data from the 2000 Behavioral Risk Factor Surveillance System. Health Serv Res. Apr 2005;40(2):361-372.

23 Vest BM, Kahn LS, Danzo A, et al. Diabetes self-management in a low-income population: impacts of social support and relationships with the health care system. Chronic Illn. Jun 2013;9(2):145-155.

24. Ward E, Halpern M, Schrag N, et al. Association of insurance with cancer care utilization and outcomes. CA Cancer J Clin. Jan-Feb 2008;58(1):9-31.

25. Chen WW, Shao YY, Shau WY, et al. The impact of diabetes mellitus on prognosis of early breast cancer in Asia. Oncologist. 2012;17(4):485-491.

26. Gill KS, Muntner P, Lafayette RA, et al. Red blood cell transfusion use in patients with chronic kidney disease. Nephrol Dial Transplant. Jun 2013;28(6):1504-1515.

27. Col NF, Ochs L, Springmann V, Aragaki AK, et al. Metformin and breast cancer risk: a meta-analysis and critical literature review. Breast Cancer Res Treat. Oct 2012;135(3):639-646.

28. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in

type 2 diabetes. Diabetologia. Sep 2009;52(9):1766-1777.

29. Enewold L, McGlynn KA, Zahm SH, et al. Surveillance mammography among female Department of Defense beneficiaries: A study by race and ethnicity. Cancer. Aug 1 2013.

30. Cheng L, Swartz MD, Zhao H, 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. May 2012;21(5):800-809.

31. Thomas F, Renaud F, Benefice E, et al. International variability of ages at menarche and menopause: patterns and main determinants. Hum Biol. Apr 2001;73(2):271-290.

32. 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. May 1 2007;120(9):1986-1992.

33. Seshasai SR, Kaptoge S, Thompson A, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med. Mar 3 2011;364(9):829-841.

34. Saydah SH, Loria CM, Eberhardt MS, et al. Abnormal glucose tolerance and the risk of cancer death in the United States. Am J Epidemiol. Jun 15 2003;157(12):1092-1100.

35. Erickson K, Patterson RE, Flatt SW, et al. Clinically defined type 2 diabetes mellitus and prognosis in early-stage breast cancer. J Clin Oncol. Jan 1 2011;29(1):54-60.

Table 1: Demographic and health characteristics of women diagnosed with breast cancer from 1998 to 2007 in the Military Health System, by diabetes status (N=9,398).

	Diabetes				
	No (n= 7,407)		Yes (n=1,991)		
Characteristic	n	%	n	%	*p*-value[a]
Age at diagnosis, years					<0.01
20-39	1,032	13.9	77	3.9	
40-49	1,987	26.8	291	14.6	
50-59	1,858	25.1	583	29.3	
60-69	1,540	20.8	635	31.9	
70-79	737	10.0	322	16.2	
80+	253	3.4	83	4.2	
Race					<0.01
White	5,498	74.2	1,348	67.7	
Black	1,055	14.2	325	16.3	
Asian/Pacific Islander	649	8.8	261	13.1	
American Indian/Alaska Native	14	0.2	8	0.4	
Unknown	191	2.6	49	2.5	
Ethnicity					0.40
Non-Hispanic	6,458	87.2	1,721	86.4	
Hispanic	344	4.6	107	5.4	
Unknown	605	8.2	163	8.2	
Marital status at diagnosis					<0.01
Married	5,886	79.5	1,559	78.3	
Never married	193	2.6	26	1.3	
Separated	58	0.8	16	0.8	
Divorced	258	3.5	54	2.7	
Widowed	799	10.8	284	14.3	
Unknown	213	2.9	52	2.6	
Active duty status at diagnosis					<0.01
No	6,937	93.7	1,946	97.7	
Yes	470	6.3	45	2.3	
Service branch at diagnosis[b]					0.14
Army	2,504	33.8	717	36.0	
Air Force	2,001	27.0	483	24.3	
Marines	1,314	17.7	356	17.9	
Navy	1,235	16.7	337	16.9	
Other	353	4.8	98	4.9	
Rank[b]					<0.01
Enlisted	3,573	48.2	1,118	56.2	
Officer	1,868	25.2	336	16.9	
Other	61	0.8	9	0.5	
Unknown	1,905	25.7	528	26.5	
Benefit type at diagnosis					<0.01
TRICARE prime	4,659	62.9	986	49.5	
TRICARE non-prime	1,714	23.1	713	35.8	
Unknown	1,034	14.0	292	14.7	

Obese					<0.01
No	5,815	78.5	1,136	57.1	
Yes	1,592	21.5	855	42.9	
Coronary heart diease					<0.01
No	6,646	89.7	1,496	75.1	
Yes	761	10.3	495	24.9	
Kidney disease					<0.01
No	6,375	86.1	1,528	76.7	
Yes	1,032	13.9	463	23.3	
Chronic obstructive pulmonary disease					<0.01
No	6,633	89.6	1,631	81.9	
Yes	774	10.4	360	18.1	
Stroke					<0.01
No	7,195	97.1	1,857	93.3	
Yes	212	2.9	134	6.7	
Hypertension					<0.01
No	3,431	46.3	194	9.7	
Yes	3,976	53.7	1,797	90.3	

[a]2-sided *p*-value.

[b]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 2007 in the Military Health System, by diabetes status (N=9,398).

	Diabetes				
	No (n= 7,407)		Yes (n=1,991)		
Characteristic	n	%	n	%	*p*-value[a]
Tumor stage					0.11
Stage I	3,505	47.3	962	48.3	
Stage II	2,706	36.5	746	37.5	
Stage III	768	10.4	196	9.8	
Stage IV	239	3.2	44	2.2	
Unknown	189	2.6	43	2.2	
Tumor grade					0.14
Well differentiated	1,502	20.3	428	21.5	
Moderately differentiated	2,630	35.5	730	36.7	
Poorly differentiated	2,386	32.2	588	29.5	
Unknown	889	12.0	245	12.3	
Hormone receptor status					0.03
ER+/PR+	3,928	53.0	1,119	56.2	
ER-/PR-	1,481	20.0	345	17.3	
ER+/PR- or ER-/PR+	827	11.2	210	10.5	
Unknown	1,171	15.8	317	15.9	
Surgery					0.35
No	159	2.1	36	1.8	
Yes	7,248	97.9	1,955	98.2	
Radiation					0.06
No	2,644	35.7	756	38.0	
Yes	4,763	64.3	1,235	62.0	
Chemotherapy					<0.01
No	2,486	33.6	786	39.5	
Yes	4,921	66.4	1,205	60.5	
Hormone therapy[b]					0.07
No	1,838	38.7	498	37.5	
Yes	2,647	55.7	733	55.2	
Unknown	270	5.7	98	7.4	
Surveillance mammography					1.00
No	3,218	67.7	865	65.1	
Yes	4,189	88.1	1,126	84.7	
Metformin[c]					<0.01
No	4,115	98.3	366	33.5	
Yes	72	1.7	726	66.5	
Insulin[c]					<0.01
No	4,099	97.9	916	83.9	
Yes	88	2.1	176	16.1	
Insulin secretogogue[c]					<0.01
No	4,183	99.9	735	67.3	
Yes	4	0.1	357	32.7	

Recurrence					0.03
No	5,906	79.7	1,631	81.9	
Yes	1,501	20.3	360	18.1	

[a]2-sided *p*-value.
[b]Restricted to women who are hormone receptor positive.
[c]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 2007.

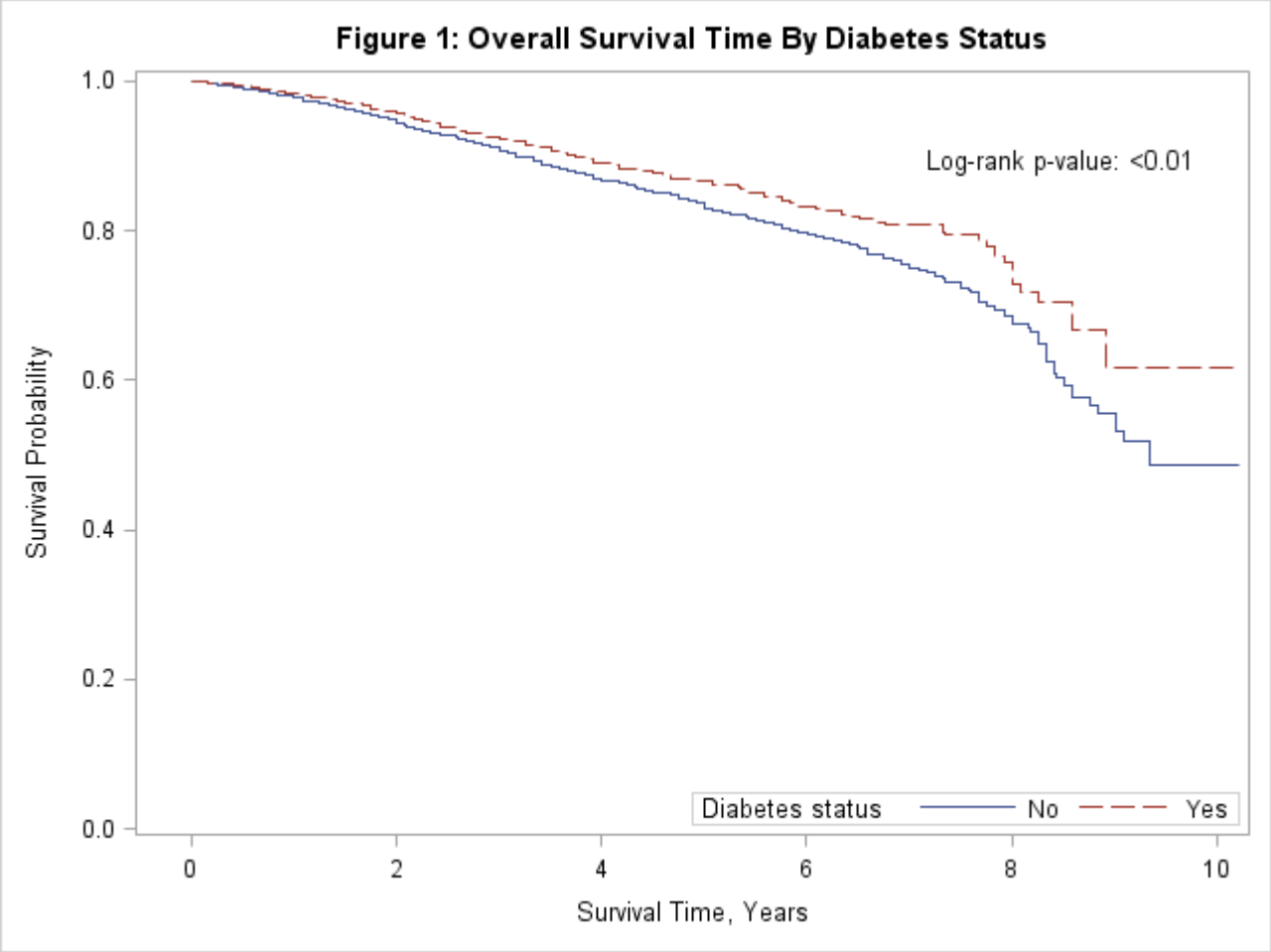
Figure 1: Overall Survival Time By Diabetes Status
Log-rank p-value: <0.01
Survival Probability
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
Survival Time, Years
Diabetes status
No
Yes

Table 3. Multivariate analysis for diabetes in relation to survival among 9,398 Department of Defense beneficiaries with breast cancer, 1998-2007.

	Number of patients				
Diabetes status	Alive	Dead	HR[a]	95% CI[b]	
No	6,434	973	1.00	reference	
Yes	1,763	228	1.00	0.83	1.20
Before breast cancer diagnosis	696	96	2.00	1.53	2.61
At/after breast cancer diagnosis	1067	132	0.81	0.66	0.99

[a]Hazard ratio (HR) and [b]95% confidence intervals (CI) adjusted for age at diagnosis, race, marital status at diagnosis, rank of active duty member or sponsor of family members, beneficiary type at diagnosis, date of first visit, obesity, coronary heart disease, chronic obstructive pulmonary disease, stroke, hypertension, hormone receptor status, chemotherapy, metformin, insulin, tumor stage, and recurrence. Missing pharmacy data for diabetes medications were adjusted as the missing category in the models.

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.

Strata	Diabetes	Number of patients Alive	Dead	HR[a]	95% CI[b]	
Race[c]						
White	No	4,757	741	1.00	reference	
	Yes: Before BC[d] dx	448	67	2.08	1.51	2.85
	At/after BC dx	743	90	0.72	0.56	0.92
Black	No	891	164	1.00	reference	
	Yes: Before BC dx	123	19	1.86	0.99	3.50
	At/after BC dx	155	28	0.99	0.62	1.58
Asian/Pacific Islander	No	593	56	1.00	reference	
	Yes: Before BC dx	105	9	2.76	0.78	9.76
	At/after BC dx	135	12	1.43	0.68	3.03
Menopausal status						
<50 years	No	2,713	306	1.00	reference	
	Yes: Before BC dx	83	9	2.82	1.34	5.93
	At/after BC dx	244	32	1.35	0.84	2.16
≥50 years	No	3,721	667	1.00	reference	
	Yes: Before BC dx	613	87	2.09	1.57	2.78
	At/after BC dx	823	100	0.73	0.58	0.92
Obese						
No	No	4,968	847	1.00	reference	
	Yes: Before BC dx	362	60	1.62	1.17	2.24
	At/after BC dx	612	102	0.84	0.67	1.06
Yes	No	1,466	126	1.00	reference	
	Yes: Before BC dx	334	36	3.46	2.07	5.78
	At/after BC dx	455	30	0.74	0.47	1.17
Hormone receptor status						
ER+/PR+	No	3,552	376	1.00	reference	
	Yes: Before BC dx	417	36	2.39	1.54	3.71
	At/after BC dx	614	52	0.74	0.54	1.02
ER-/PR-	No	1,223	258	1.00	reference	
	Yes: Before BC dx	112	30	2.88	1.77	4.68
	At/after BC dx	165	38	1.41	0.93	2.14
ER+/PR- or ER-/PR+	No	700	127	1.00	reference	
	Yes: Before BC dx	76	9	1.75	0.71	4.35
	At/after BC dx	111	14	0.32	0.15	0.68
Unknown	No	959	212	1.00	reference	
	Yes: Before BC dx	91	21	0.96	0.52	1.78
	At/after BC dx	177	28	0.76	0.49	1.19
Tumor stage						
Stage I	No	3,255	250	1.00	reference	
	Yes: Before BC dx	368	23	1.34	0.77	2.32
	At/after BC dx	535	36	0.57	0.39	0.84
Stage II	No	2,361	345	1.00	reference	

	Yes: Before BC dx	254	30	2.13	1.33	3.42
	At/after BC dx	406	56	1.07	0.78	1.48
Stage III	No	583	185	1.00	reference	
	Yes: Before BC dx	53	25	2.18	1.25	3.80
	At/after BC dx	94	24	0.72	0.43	1.21
Stage IV	No	82	157	1.00	reference	
	Yes: Before BC dx	7	14	2.08	0.82	5.32
	At/after BC dx	9	14	0.55	0.27	1.10
Unknown stage	No	153	36	1.00	reference	
	Yes: Before BC dx	14	4	16.83	2.54	111.39
	At/after BC dx	23	2	1.15	0.18	7.39

[a]Hazard ratio (HR) and [b]95% confidence intervals (CI) 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, metformin, insulin, tumor stage, and recurrence. Missing pharmacy data for diabetes medications were adjusted as the missing category in the models. Stratified variables were not included in stratified analyses.

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