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Effect of Depression on Diagnosis, Treatment, and Survival of Older Women with Breast Cancer

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Abstract

OBJECTIVES—To assess the effect of a prior diagnosis of depression on the diagnosis, treatment, and survival of older women with breast cancer.

DESIGN—Retrospective analysis of records from Surveillance, Epidemiology and End Results (SEER) and Medicare claims.

SETTING—Registries from seven major cities and five states.

PARTICIPANTS—A total of 24,696 women aged 67 to 90 diagnosed with breast cancer between 1993 and 1996 and included in the SEER Medicare linked database were studied.

MEASUREMENTS—Information on patient demographics, tumor characteristics, treatment received, and survival were obtained from SEER, and the Medicare inpatient and professional charges for the 2 years before diagnosis were searched for a diagnosis of depression.

RESULTS—A total of 1,841 of the 24,696 women (7.5%) had been given a diagnosis of depression sometime in the 2 years before the diagnosis of breast cancer. There was no difference in tumor size or stage at diagnosis between depressed and nondepressed women. Women diagnosed with depression were less likely to receive treatment generally considered definitive (59.7% vs 66.2%, $P < .0001$), and this difference remained after controlling for age, ethnicity, comorbidity, and SEER site. Also, women with a prior diagnosis of depression had a higher risk of death (hazard ratio =1.42; 95% confidence interval = 1.13–1.79) after controlling for other factors that might affect survival. The higher risk of death associated with a prior diagnosis of depression was also seen in analyses restricted to women who received definitive treatment.

CONCLUSION—Women with a recent diagnosis of depression are at greater risk for receiving nondefinitive treatment and experience worse survival after a diagnosis of breast cancer, but differences in treatment do not explain the worse survival.

Keywords

depression; breast cancer; access to care; survival; treatment

Depression is associated with impaired recovery from a number of medical illnesses, such as stroke, hip fracture, and myocardial infarction.[1–7] The exact mechanisms whereby depression influences recovery from illness have not been delineated but presumably involve multiple pathways.[8,9]

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Breast cancer is a major cause of morbidity and mortality in women. Breast cancer care has evolved from a relatively straightforward single therapy of modified radical mastectomy into a more complex process involving multiple medical providers and extending over a prolonged time. A large number of studies have demonstrated deficiencies in breast cancer care, including delays in diagnosis and inadequate treatments. Factors that are associated with less-than-optimal breast cancer care include advanced age, minority ethnicity, cognitive impairment, and poor social support.[10–17] It was hypothesized that patients with depression would also experience difficulty in breast cancer care, resulting in delays in diagnosis (i.e., increased size and stage at diagnosis), less-than-definitive treatment, and decreased survival.

The Surveillance Epidemiology and End Results (SEER) tumor registry, which has been linked to Medicare charge data at the National Cancer Institute, was used.[18] In women with breast cancer, Medicare Part A and B charge data for the 2 years before diagnosis were searched for any diagnosis of depression, and stage at diagnosis, choice of treatment, and survival of women with breast cancer with or without a prior diagnosis of depression were compared.

METHODS

Subjects

Data for the study were obtained from a database of linked tumor registry records from the SEER program and Medicare claims from the Health Care Financing Administration (HCFA; now called the Centers for Medicare and Medicaid Services).[18,19] The SEER Program supports population-based tumor registries from the metropolitan areas of Los Angeles, San Jose, San Francisco/Oakland, California; Detroit, Michigan; Atlanta, Georgia; and Seattle, Washington, and the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii.[20]

The study population consisted of all women in the SEER registries who were diagnosed with incident breast cancer in the years 1993–1996 and who linked with the Medicare data (n =52,010). Because diagnoses of depression in the 2 years before breast cancer diagnosis were assessed with the Medicare claims data, the subjects were limited to women who were aged 67 and older (range 67–90) on January 1 of the year of their breast cancer diagnosis (n =36,833), were enrolled in Medicare parts A and B, and were not members of a health maintenance organization for that same year (n =27,894). Subjects not meeting these criteria were excluded because their claims for medical services may not be complete. Also, subjects with a psychiatric diagnosis other than depression were excluded. This yielded 24,696 eligible women.

Measures

Tumor size was obtained from SEER data and treated as a continuous variable, measured in millimeters. Stage at diagnosis was measured using the American Joint Committee on Cancer (AJCC) staging classification.

A prior diagnosis of depression for each subject was based on a search for depression diagnoses in all outpatient and inpatient Medicare charges in the 24 months before diagnosis of breast cancer (*International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) 296.2, 296.3, 296.5, 296.6, 296.7, 298.0, 301.10, 301.12, 301.13, 309.0, 309.1, 311). Of the 1,841 subjects with a diagnosis of depression, 1,315 (71.4%) had multiple depression diagnoses during the 2-year period, whereas 526 (28.6%) had only one such diagnosis. Of the 526 with only one diagnosis, 434 had additional depression diagnoses outside the 2-year period before the diagnosis of breast cancer.

Information on sociodemographic characteristics was obtained from SEER data and used to categorize subjects by age at diagnosis, marital status (currently married or currently not

married), and race/ethnicity (non-Hispanic white, African American, Hispanic American, or other).

Comorbidity was measured using an adaptation of the Charlson Comorbidity Index[21] that was developed for Medicare claims data.[22] This adaptation is based on using comorbidity information from the ICD-9-CM diagnosis codes (and one procedure code) in hospital and physician claims (inpatient and outpatient), with a date of service in the year before the cancer diagnosis. Depression diagnoses and breast cancer were excluded from the comorbidity assessment.

Initial therapy for breast cancer was based on SEER data as therapy received within 4 months of diagnosis.[23] Appropriate initial therapy was defined as follows: for Stage 0, simple mastectomy or breast-conserving surgery plus adjuvant irradiation; for Stage 1 or 2, modified radical mastectomy or breast-conserving surgery with axillary dissection and adjuvant irradiation; and for Stages 3 or 4, chemotherapy. These definitions were based on published consensus recommendations[24] and have been used in other studies of breast cancer treatment.[17,25,26]

Receipt of radiation therapy was determined using SEER for radiation therapy within 4 months after diagnosis. Receipt of chemotherapy within 6 months of diagnosis was determined from Medicare data, as previously described.[27,28] Frequency of doctors' visits was counted by using HCFA provider claims data for 24 months before diagnosis and counting each day with one or more provider claims as one visit. Visits for depression were not excluded in calculating frequency of doctor's visits.

Breast cancer–specific death was defined as breast cancer as underlying cause of death in SEER (ICD-9-CM 174xx). Deaths from all other causes were censored. Information on months of survival from the date of diagnosis was provided in SEER. The last date of the follow-up for this cohort was December 31, 1998.

Analysis

SAS version 8.01 (SAS Institute, Inc., Cary, NC) was used for all analyses. The comparison of the characteristics of women with and without diagnosis of depression was based on Pearson chi-square for cross-classified data and Student *t* test for paired interval data.

The analysis of the size and stage at diagnosis began with univariate comparisons between the depression and nondepression groups. Subjects with unknown size or stage information were excluded from these analyses. A logistic regression model then supplemented the univariate analyses. In the logistic model, tumor size was categorized into five categories based on 10-mm intervals. A logistic model also was used to evaluate odds of receiving nondefinitive treatment as a function of a prior diagnosis of depression. The logistic regression yields a prediction equation for the odds of receiving nondefinitive treatment between depression groups, controlling for age, ethnicity, comorbidity, and SEER site, because these factors have been shown to be associated with receipt of treatment.[10–13]

The Cox proportional hazards model was used to analyze 3-year cancer-specific survival for depression groups, controlling for age, ethnicity, comorbidity, AJCC stage, and SEER site. The survival time was censored on December 1998, 36 months after diagnosis, or at date of last follow-up in SEER, whichever came first.

RESULTS

Table 1 presents the demographic characteristics of 24,696 women aged 67 to 90 diagnosed with breast cancer in one of 10 SEER areas from 1993 to 1996. Approximately 7.5% of these women had been given a diagnosis of depression by a physician in the 2 years before diagnosis. The women with a prior diagnosis of depression were, on average, older, more likely to be non-Hispanic white, less likely to be married, likely to have more comorbid illnesses, and more likely to have had a substantially greater number of doctor visits in the 2 years before the diagnosis of breast cancer.

Table 2 presents data on size and stage at diagnosis and choice of treatment of women diagnosed with breast cancer, stratified by whether they had been given a diagnosis of depression in the 2 years before the cancer diagnosis. There were no differences in tumor size at diagnosis in women with or without a prior diagnosis of depression. There was a significant difference in the distribution of stage at diagnosis between the depressed and nondepressed groups, but there was no clear increase or decrease in stage at diagnosis associated with a diagnosis of depression. However, in multivariate analysis controlling for total number of physician visits in the year before the breast cancer diagnosis, a diagnosis of depression was associated with increased size (odds ratio (OR) =1.31, 95% confidence interval (CI) =1.16–1.47, for each 10-mm increase in size) and stage (OR =1.25, 95% CI =1.11–1.41, for each increase in AJCC stage). In addition, women with a history of depression were significantly less likely to receive treatment consistent with consensus conference standards (59.7% vs 66.2%, $P<.0001$), and women with a history of depression who were diagnosed with Stage 2 or higher breast cancer were less likely to receive chemotherapy than women without a prior diagnosis of depression (24.2% vs 17.3%, $P<.0001$).

Table 3 presents the results of multivariate analysis examining the effect of depression on likelihood of receiving definitive treatment, after controlling for other factors that might influence choice of treatment. A prior diagnosis of depression is associated with a 19% increase in odds of receiving less-than-definitive therapy. In these analyses, women with Stage 0 through 4 were included. Similar results were seen when just examining early-stage (Stage 1 and 2) cancer.

Table 4 presents an analysis of the effects of a prior diagnosis of depression on survival after the diagnosis of breast cancer. After controlling for other factors that might affect survival (age, ethnicity, comorbidity, marital status, number of physician visits, and SEER area), women with a diagnosis of depression had a 42% higher risk of death from breast cancer during 3-year follow-up. Receipt of definitive treatment did not appear to mediate this increased risk of death associated with depression. When the analysis was restricted to women who received definitive treatment, the increased risk associated with a prior diagnosis of depression was not substantially altered (Table 4). The analyses in Table 4 were also repeated using all-cause mortality rather than breast cancer–specific mortality as an outcome. The pattern of the results and the effect of depression on survival were similar to what is shown in Table 4. For example, in all subjects, a prior diagnosis of depression was associated with a hazard ratio of 1.39 (95% CI =1.23–1.55) for all cause mortality, whereas for subjects receiving definitive treatment, depression was associated with a hazard ratio of 1.37 (95% CI =1.17–1.62) for all-cause mortality.

DISCUSSION

The results of this study can be summarized as follows. A prior diagnosis of depression is not associated with delays in diagnosis of breast cancer, but women with a prior diagnosis of depression are less likely to receive treatment that is generally recognized as appropriate and

also have poorer survival than women without a diagnosis of depression. The decreased survival associated with depression remains after controlling for other factors that might influence survival, but it is not explained by the greater risk of receiving less-than-definitive treatment of the women with a prior diagnosis of depression. Finally, a prior diagnosis of depression is associated with significant reductions in breast cancer–specific and all-cause survival.

Many studies have shown that depression is associated with increased mortality, although the magnitude of the effect would appear to be less in the elderly.[29–32] Depression could influence mortality through several pathways.[32] For example, depression might interact with other illnesses to produce decreased survival for individuals with a serious medical illness plus concomitant depression.[7,33]

It had been expected that a prior diagnosis of depression would be found to be associated with delays in diagnosis of breast cancer, but this was not the case. Mean size of tumor or the percentage of women diagnosed at advanced stages did not vary between women with a prior diagnosis of depression and those without (Table 2). A potential explanation for this finding is that the increased use of medical services associated with depression offset any negative effect of depression on diagnosis.[34,35] This increased use of medical services would in turn increase the opportunities for cancer to be diagnosed. Indeed, in a multivariate analysis controlling for total number of visits to a physician in the prior 2 years, a diagnosis of depression was associated with increased size and stage at diagnosis, whereas there was no such association between depression and size or stage at diagnosis in analyses not controlling for the number of physician visits in the prior 2 years.

Although a diagnosis of depression has long been known to be associated with decreased survival, the mechanism for this association is unknown. Two broad categories of explanation exist. The first category postulates that depression renders the individual less capable of functioning successfully in modern society. More specifically, depression would lower survival in an interaction with other illnesses. The depressed individual would be less likely to receive appropriate health screenings, less likely to seek appropriate care when ill, and less likely to adhere to medical recommendations. Thus, depression would increase mortality by increasing deaths from other illnesses such as infectious diseases that could have been prevented by vaccinations, cancers that could have been discovered at a curable stage, or strokes and heart disease that could have been avoided with better adherence to blood pressure medicines.

The second category of explanations sees depression as an indication of global brain dysfunction. In other words, depression influences not only affective state, but also the neuro-endocrine axis, neuro-immunological function, and other central nervous system activities. This central nervous system dysregulation then puts the organism at greater risk for morbidity and mortality.

The current study does not directly test the role of either of these categories of explanations in explaining how depression is associated with decreased survival, but if depression decreases survival by interfering with the diagnosis and treatment of other illnesses, it would have been expected that depression would influence cancer-specific mortality more than all-cause mortality. Also, one would have expected diminution of the effect of depression on survival after controlling for stage at diagnosis and whether the patient received definitive treatment. These were not found.

The results of this study must be interpreted in the light of certain limitations in the methodology. First, because Medicare data were used and 2 years of data before the diagnosis of cancer was required, the investigation was limited to women aged 67 and older who had

Medicare Part A and B coverage. The findings may not be relevant to younger women or to women enrolled in Medicare health maintenance organizations. Second, depression was identified using physician diagnosis on their professional charges. This may be an insensitive measure to identify women with depression because physicians frequently overlook this condition.[36,37] However, the 7.5% prevalence rate of a diagnosis of depression found in this study is not that different from the rates that have been reported in population-based studies using active screening for depression.[36] It is probable that the women identified as depressed by their physicians might differ from the universe of older depressed women; for example, more severely depressed women might have a greater chance of receiving such a diagnosis. It is also possible that coding errors would make a depression diagnosis unreliable, but the accuracy of diagnostic information in Medicare charge data has clearly improved over time.[38,39] One finding that would argue against the likelihood that coding errors are responsible for a substantial number of the depression diagnoses is that, although only 7.5% of women had a depression diagnosis, 95% of those women had more than one physician diagnosis of depression in their records (see Methods).

Third, although comorbidity was controlled for in the analyses, depression may still be a marker for other unmeasured health indicators, such as poor functional status, that may be mediating the observed effect of depression on treatment and survival. Recently, a group of researchers[32] postulated double feedback loops whereby depression promotes poor function and poor function in turn promotes depression, which makes models delineating the exact mechanism of how depression influences diagnosis and treatment problematic.

In summary, depression would appear to be a risk factor for decreased survival after a diagnosis of breast cancer. This is consistent with studies of depression and other acute illnesses such as hip fracture and myocardial infarction.[1–8]

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Table 1

Characteristics of 24,696 Women Aged 67 to 90 Diagnosed with Breast Cancer in 1993–96, by Whether They Had a Prior Diagnosis of Depression

Characteristic	Nondepressed (n =22,855)	Depressed (n =1,841)	*P*-value
Age at diagnosis, mean±SD*	75.8±6.0	76.5±6.0	<.0001
Ethnicity, %			<.0001
Non-Hispanic white	86.9	90.8	
African American	6.1	4.0	
Hispanic American	2.9	3.0	
Other	4.1	2.2	
Married, %	44.3	33.5	<.0001
Surveillance, Epidemiology and End Results site, %			<.0001
Atlanta	5.9	7.0	
Connecticut	14.7	16.7	
Detroit	16.5	12.2	
Hawaii	2.0	1.3	
Iowa	13.5	14.3	
Los Angeles	14.9	17.0	
New Mexico	3.7	3.7	
San Francisco	8.5	7.4	
San Jose	5.0	4.2	
Seattle	11.4	10.7	
Utah	4.1	5.6	
Comorbidities, mean±SD	1.4±1.8	2.0±2.9	<.0001
Subjects with >1 comorbidity, %	16.2	34.8	<.0001
Number of doctor visits in prior 2 years, mean ±SD	24.7±21.5	53.3±38.3	<.0001

SD =standard deviation.

Table 2

Size and Stage at Diagnosis and Choice of Treatment of 24,696 Women Aged 67 to 90 Diagnosed with Breast Cancer Between 1993 and 1996 by Whether They Had a Prior Diagnosis of Depression

Size and Stage at Diagnosis and Choice of Treatment	Nondepressed (n =22,855)	Depressed (n =1,841)	*P*-value
Size, mm, mean±standard deviation	19.9±18.1	19.4±14.8	.1879
Stage at diagnosis, %			
0 (n =2,776)	11.3	10.1	
1 (n =10,879)	44.0	44.8	
2 (n =6,852)	27.6	29.8	
3 (n =1,289)	5.3	4.4	
4 (n =1,094)	4.5	3.2	
Unknown (n =1,806)	7.3	7.7	.0093
AJCC Stage 2 or greater, %[*]	40.3	40.5	.8721
Definitive treatment, %[†]	66.2	59.7	<.0001
Received chemotherapy, %			
Stage 2 (n =6,852)	20.1	14.9	.0033
Stage 3 (n =1,289)	37.1	32.1	.3675
Stage 4 (n =1,094)	34.1	18.6	.0142
Stages 2–4 (n =9,235)	24.2	17.3	<.0001
Hormone receptor status, %[‡]			
Estrogen-receptor positive	56.5	55.1	.2565
Progesterone-receptor positive	46.1	44.4	.1874

[*] Subjects with unknown stage not included in the analysis of percent of women diagnosed at American Joint Committee in Cancer (AJCC) Stage 2 or greater.

[†] Definitive treatment is defined as follows: for Stage 0, simple mastectomy or breast-conserving surgery plus adjuvant irradiation; for Stage 1 or 2, modified radical mastectomy or breast-conserving surgery with axillary dissection and adjuvant irradiation; and for Stage 3 or 4, chemotherapy.

[‡] Subjects with unknown hormone receptor status (approximately one-third of all cases) are included in these analyses.

Table 3

Multivariate Analysis of Odds of Receiving Nondefinitive Treatment as a Function of a Prior Diagnosis of Depression for Women Aged 67 to 90 Diagnosed with Breast Cancer

Characteristic	Odds Ratio (95% Confidence Interval)[†] (N =22,341)
Depression (yes vs no)	1.19 (1.06–1.33)
Age (continuous)	1.09 (1.08–1.09)
Ethnicity (all others vs non-Hispanic white)	1.15 (1.05–1.26)
Comorbidity (continuous)[*]	1.05 (1.03–1.07)
Unmarried (vs married)	1.10 (1.03–1.17)
Number of doctor visits (continuous)	1.00 (0.99–1.00)
Surveillance, Epidemiology and End Results site	
Atlanta	0.86 (0.75–0.99)
Connecticut	1.44 (1.30–1.59)
Detroit	0.89 (0.81–0.99)
Hawaii	0.74 (0.59–0.93)
Iowa	0.50 (0.45–0.56)
New Mexico	0.71 (0.60–0.84)
San Francisco	0.92 (0.82–1.04)
San Jose	0.85 (0.73–0.99)
Seattle	0.95 (0.85–1.06)
Utah	0.64 (0.54–0.75)
Los Angeles	1.00

[*] Comorbidity was assessed using the method of Klabunde et al.[22] Depression and breast cancer diagnoses were excluded from the calculation of comorbidity.

Table 4

Three-Year Hazard of Death from Breast Cancer after Diagnosis of Breast Cancer, as a Function of a Prior Diagnosis of Depression, for All Subjects and Stratified by Definitive Treatment

Variable	All subjects (N =19,645)	Subjects Receiving Definitive Treatment (n =13,269)
	Hazard Ratio (95% Confidence Interval)	
Depression (yes vs no)	1.42 (1.13–1.79)	1.46 (1.05–2.03)
Age (continuous)	1.02 (1.01–1.03)	1.03 (1.01–1.04)
Ethnicity (all others vs non-Hispanic white)	1.14 (0.96–1.34)	1.34 (1.06–1.70)
Comorbidity (continuous)	1.05 (1.03–1.06)	1.05 (1.03–1.07)
Unmarried (vs married)	1.23 (1.09–1.40)	1.11 (0.94–1.31)
Number of doctor visits (continuous)	0.99 (0.99–1.00)	0.99 (0.99–1.00)
Stages (2, 3, or 4 vs 1)	4.46 (4.20–4.74)	4.80 (4.42–5.21)
SEER site		
Atlanta	1.06 (0.82–1.39)	1.20 (0.85–1.71)
Connecticut	1.13 (0.92–1.39)	1.06 (0.78–1.43)
Detroit	1.13 (0.92–1.38)	0.98 (0.74–1.32)
Hawaii	0.66 (0.39–1.11)	0.49 (0.21–1.13)
Iowa	1.06 (0.85–1.33)	1.09 (0.80–1.48)
New Mexico	1.37 (1.02–1.84)	1.37 (0.88–2.13)
San Francisco	0.98 (0.75–1.26)	0.97 (0.68–1.38)
San Jose	0.85 (0.62–1.17)	0.78 (0.50–1.22)
Seattle	0.88 (0.70–1.12)	0.91 (0.64–1.28)
Utah	1.33 (0.96–1.84)	1.45 (0.94–2.22)
Los Angeles	1.00	1.00

Note: Cox hazard analysis of cancer-specific survival controlling for age, ethnicity, comorbidity, American Joint Committee on Cancer Stage, and Surveillance Epidemiology and End Results (SEER) site for 20,234 women with Stage 1, 2, 3, or 4 breast cancer at diagnosis.