Survival After Early-Stage Breast Cancer of Women Previously Treated for Depression: A Nationwide Danish Cohort Study

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ABSTRACT

Purpose

The aim of this nationwide, register-based cohort study was to determine whether women treated for depression before primary early-stage breast cancer are at increased risk for receiving treatment that is not in accordance with national guidelines and for poorer survival.

Material and Methods

We identified 45,325 women with early breast cancer diagnosed in Denmark from 1998 to 2011. Of these, 744 women (2%) had had a previous hospital contact (as an inpatient or outpatient) for depression and another 6,068 (13%) had been treated with antidepressants. Associations between previous treatment of depression and risk of receiving nonguideline treatment of breast cancer were assessed in multivariable logistic regression analyses. We compared the overall survival, breast cancer–specific survival, and risk of death by suicide of women who were and were not treated for depression before breast cancer in multivariable Cox regression analyses.

Results

Tumor stage did not indicate a delay in diagnosis of breast cancer in women previously treated for depression; however, those given antidepressants before breast cancer had a significantly increased risk of receiving nonguideline treatment (odds ratio, 1.14; 95% CI, 1.03 to 1.27) and significantly worse overall survival (hazard ratio, 1.21; 95% CI, 1.14 to 1.28) and breast cancer–specific survival (hazard ratio, 1.11; 95% CI, 1.03 to 1.20). Increased but nonsignificant estimated risks were also found for women with previous hospital contacts for depression. In subgroup analyses, the association of depression with poor survival was particularly strong among women who did not receive the indicated adjuvant systemic therapy.

Conclusion

Women previously treated for depression constitute a large subgroup of patients with breast cancer who are at risk for receiving nonguideline breast cancer treatment, which probably contributes to poorer overall and breast cancer–specific survival.

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INTRODUCTION

The hypothesized association between depression and poor survival after breast cancer has been studied previously¹⁻⁷; however, some of the studies were limited by low statistical power^{1,2,4,7} or did not include clinical variables,⁵ and the design of others did not allow ascertainment of the direction of the hypothesized associations between depression and poor breast cancer prognosis.^{4,6} The latter is a crucial question, because impending death has been found to increase depressive symptoms and use of antidepressants in patients with cancer.^{8,9} We showed previously that the number of tumor-

positive axillary lymph nodes predicts the risk for treatment of depression after a breast cancer diagnosis.¹⁰

One way of addressing the clinically relevant question of whether women with depression are a vulnerable patient group that does not receive optimal breast cancer treatment and thus have poor survival is to identify women with depression before diagnosis of breast cancer. To our knowledge, only three such studies have been reported¹¹⁻¹³; however, one included only women with breast cancer diagnosed at the age of 67 years or older, limiting the generalizability of results,¹² and the other two did not address breast cancer–specific survival or whether depression was associated with

receiving nonguideline treatment.^{11,13} The aim of this study was to determine whether prior depression is associated with breast cancer treatment according to national guidelines, with overall survival, with breast cancer–specific survival, and with death by suicide among women with early-stage breast cancer.

MATERIAL AND METHODS

We conducted a nationwide cohort study, using registers that cover all residents of Denmark and the unique personal identification number assigned to all Danish residents, which ensures accurate linkage among registers.¹⁴

Data Sources

Since 1977, the Danish Breast Cancer Group (DBCG) has issued successive national guidelines for diagnosing and treating breast cancer.¹⁵ The Group also manages a clinical database that contains detailed individual information on more than 95% of histopathologically verified breast cancers diagnosed in Denmark and their treatment.¹⁵ From this register, we obtained the date of breast cancer diagnosis, defined as the date of primary surgery or biopsy if primary surgery was not performed. We classified patients with locally advanced and distant metastases as having late-stage disease; all other breast cancers were classified as early stage. Furthermore, we obtained information on menopausal status, tumor size, number of tumor-positive axillary lymph nodes, estrogen receptor status, type of surgery, and allocation to adjuvant systemic therapy according to the DBCG guidelines. For women allocated to guideline treatment, we obtained information on type of adjuvant systemic therapy indicated according to the guidelines and type of adjuvant systemic therapy initiated. In the DBCG database, women with the best prognosis are classified as having low-risk breast cancer, and guideline treatment of these women does not involve adjuvant systemic therapy. Finally, we determined breast cancer stage on the basis of tumor size and number of tumor-positive axillary lymph nodes.¹⁶ From the Danish Cancer Registry, we obtained the date of diagnosis of all cancers diagnosed from 1943 to 2011.¹⁷

The Danish Psychiatric Central Research Register contains data on all admissions to Danish psychiatric inpatient facilities since 1969 and information on outpatient contacts since 1995.¹⁸ We identified the dates of admission for all inpatient and outpatient hospital contacts from 1969 to 2011 with valid diagnoses of unipolar depression^{19,20} (International Classification of Disease, 8th revision [ICD-8]: 296.09, 296.29 or ICD, 10th revision [ICD-10]: F32-F33) and other major psychiatric disorders, defined as organic mental disorder, mental or behavioral disorder due to use of a psychoactive substance, schizophrenia, schizotypal or delusional disorder, or manic or bipolar episodes (ICD-8: 290-295.99, 296.19, 296.39, 303.00-304.99, and ICD-10: F00-F31).

The dates of redemption of all prescriptions for antidepressants (group N06A of the Anatomic Therapeutic Chemical classification system) from 1995 to 2011 were obtained from the Danish National Prescription Registry.²¹ In Denmark, antidepressants are available by prescription only, and all drugs redeemed with a prescription at Danish pharmacies have been registered since 1995.

Individual information on highest level of attained education is registered in the Population Education Register,²² which is updated annually on October 1; we also obtained information on the educational level in the year preceding a diagnosis of breast cancer. Educational level was categorized as basic school/high school, vocational training, higher education, and unknown.

From the Civil Registration System, we obtained the dates of migration from 1973 to 2011 and cohabitation status as of January 1 in the year of breast cancer diagnosis. Patients were categorized as living alone or with a spouse.¹⁴

Information on comorbid conditions was obtained from the Danish Patient Registry for 1978 to 2011.²³ We calculated a Charlson Comorbidity Index score²⁴ for each woman at the time of diagnosis of breast cancer, as 0, 1, or ≥ 2 , not including breast cancer.

In the Danish Register of Causes of Death, we obtained the dates and causes of all deaths in our study population through 2011.²⁵ Breast cancer (ICD-10: C50) and suicide (ICD-10: X60-X84 + Y870) were identified as specific causes of death.²⁶

Study Population

Our study population comprised women residing in Denmark with primary, unilateral breast cancer diagnosed between April 1, 1998, and December 31, 2011. We excluded women with previous cancer (except nonmelanoma skin cancer) or previous major psychiatric disorders (except unipolar depression). To ensure identification of use of antidepressants, we excluded women who had not lived continuously in Denmark for 3 years and 3 months before diagnosis of breast cancer. Furthermore, women for whom dates of migration, birth, breast cancer, and death conflicted among registers were excluded. Finally, we excluded women with late-stage breast cancer, because they were treated according to different guidelines from those for early-stage breast cancer (Fig 1).

To identify the most severe treated cases of depression, we retrieved all hospital contacts for unipolar depression from 3 months before diagnosis of breast cancer dating back to 1969. In addition, as a more inclusive measure of treated depression, we identified treatment with antidepressants from 3 months before diagnosis of breast cancer and 3 years previously. Accordingly, we classified women at diagnosis of breast cancer as (1) having had no hospital contact for depression and no pharmacologic treatment of depression before breast cancer, (2) having been treated with antidepressants but with no hospital contact for depression before breast cancer, or (3) having had a hospital contact for depression before breast cancer.

Statistical Analyses

Differences in sociodemographic variables, tumor characteristics, and breast cancer treatment were evaluated in χ^2 tests and by analysis of variance. We analyzed differences in risk for unfavorable selection for adjuvant systemic therapy according to previous treatment of depression using multivariable logistic regression models that included sociodemographic and clinical variables.

We plotted cumulative breast cancer–specific mortality with death from other causes as a competing risk and used Gray's test for differences between groups with adjustment for age in 5-year strata. We used multivariable Cox proportional hazards regression models to evaluate differences in overall survival, breast cancer–specific survival, and risk of death by suicide according to previous treatment of depression. Sociodemographic and clinical covariables were added stepwise in four increasingly comprehensive models.

Finally, we used multivariable Cox proportional hazards regression models for six analyses of breast cancer–specific survival separately for (1) women not allocated to treatment according to the guidelines of the DBCG,¹⁵ (2) women with low-risk breast cancer, (3) women with high-risk breast cancer not given adjuvant systemic therapy according to the guidelines, (4) women given chemotherapy, (5) women given chemotherapy and endocrine therapy, and (6) women given endocrine therapy only.

In all Cox models, women were followed from the date of breast cancer diagnosis until death; emigration; hospital contact for a major psychiatric disorder (organic mental disorders, mental disorders due to psychoactive substance use, schizophrenia and related disorders, bipolar disorder; ICD-10: F00–F31); a new primary cancer; or December 31, 2011, whichever came first. After assessment of linearity, age and calendar year were included as continuous variables in all models, when possible. To evaluate the assumption of proportionality, we visually assessed plots of log minus log of the survival density functions versus log of follow-up time; all Cox models were stratified on variables that violated the assumption of

Fig 1. Study diagram of women with primary early-stage breast cancer identified from the clinical database of the Danish Breast Cancer Group according to use of antidepressants and hospital contacts for depression before diagnosis of breast cancer.

proportionality. Characteristics at diagnosis of breast cancer were analyzed and logistic regressions and Cox regressions were performed with the FREQ, UNIVARIATE, LOGISTIC, and PHREG procedures in SAS (version 9.3; SAS Institute, Cary, NC). Cumulative incidence was analyzed with the cmprsk package in R (version 3.1.2; R Foundation, Vienna, Austria).^{27,28}

RESULTS

After exclusions, our study population consisted of 45,325 women with primary early-stage breast cancer, of whom 6,068 (13%) had previously used antidepressants and 744 (2%) had had a hospital contact for depression (Fig 1). Compared with women who had not used antidepressants before breast cancer, those with a previous hospital contact for depression or who had used antidepressants were statistically significantly likely to be older, have less education, live alone, have comorbid somatic disease, and have breast cancer diagnosed in later calendar years (Table 1). More women who had used antidepressants received only a biopsy and not surgery and were therefore more likely to have unknown tumor size, number of tumor-positive axillary lymph nodes, and estrogen receptor status. Statistically significantly fewer women who had used antidepressants were allocated to guideline systemic adjuvant therapy. After diagnosis of breast cancer, 80% of women previously treated for depression used antidepressants, whereas 23% of women not previously treated for depression initiated use of antidepressants after the diagnosis of breast cancer.

Allocation to and Initiation of Guideline Adjuvant Systemic Therapy

The multivariable logistic regression analyses with socio-demographic and clinical covariables showed a significantly increased

odds ratio (OR) that women who had used antidepressants were not allocated to guideline breast cancer treatment (OR, 1.14; 95% CI, 1.03 to 1.27; Fig 2). For women with a previous hospital contact for depression, we observed elevated ORs for not being allocated to guideline breast cancer treatment (OR, 1.32; 95% CI, 0.99 to 1.77) and being classified as having low-risk breast cancer (OR, 1.24; 95% CI, 0.98 to 1.58); these estimates did not reach statistical significance. For the 30,829 women with high-risk breast cancer, we found no differences in initiation of guideline adjuvant systemic therapy.

Cumulative Breast Cancer–Specific Mortality

Women who had used antidepressants before breast cancer had a significantly higher cumulative breast cancer–specific mortality rate than did those who had not (Fig 3; Gray's test: $P = .002$). Thus, 13% of women who had used antidepressants and 11% of those who had not had died of breast cancer 5 years after diagnosis. There was no difference in cumulative breast cancer–specific mortality between women with a previous hospital contact for depression and women who had not used antidepressants (Fig 3; Gray's test: $P = .32$).

Overall Survival, Breast Cancer–Specific Survival, and Death by Suicide

In all models, women who had used antidepressants had worse overall survival (fully adjusted model: hazard ratio [HR], 1.21; 95% CI, 1.14 to 1.28) and worse breast cancer–specific survival (fully adjusted model: HR, 1.11; 95% CI, 1.03 to 1.20; Table 2). Addition of educational level, cohabitation, and comorbidity score slightly attenuated the risks of overall and breast cancer–specific

Table 1. Characteristics of 45,325 Women With Primary Early-Stage Breast Cancer Diagnosed in Denmark, 1998 to 2011, According to Treatment of Depression Before Diagnosis of Breast Cancer

Characteristic	No Use of Antidepressants n = 38,513		Treated with Antidepressants n = 6,068		Hospital Contact for Depression n = 744	
	No.	%	No.	%	No.	%
Sociodemographic variables						
Age at diagnosis, years						
< 40	1,764	5	157	3	29	4
40-49	5,882	15	655	11	100	13
50-59	10,394	27	1,477	24	159	21
60-69	11,276	29	1,746	29	265	36
70-79	5,828	15	1,139	19	137	18
≥ 80	3,369	9	894	15	54	7
Mean age, years (5%, 95% percentiles)	61.2 (40.5, 83.6)		64.6 (43.5, 86.8)		62.3 (40.9, 81.4)	
Level of education						
High school	9,240	24	1,137	19	164	22
Vocational	18,256	47	2,648	44	340	46
Basic	8,645	22	1,676	28	227	31
Unknown	2,372	6	607	10	13	2
Cohabiting						
Yes	25,637	67	3,256	54	391	53
No	12,876	33	2,812	46	353	47
Charlson Comorbidity Index score						
0	31,298	81	4,019	66	513	69
1	5,252	14	1,293	21	151	20
≥ 2	1,963	5	756	12	80	11
Clinical variables						
Mean calendar year at diagnosis (5%, 95% percentiles)	2005.0 (1999, 2011)		2005.3 (1999, 2011)		2006.0 (1999, 2011)	
Type of surgery						
Mastectomy	18,706	49	2,985	49	340	46
Lumpectomy	18,775	49	2,810	46	384	52
Biopsy only	1,032	3	273	5	20	3
Tumor size (mm)						
< 20	19,736	51	3,120	51	382	51
20-49	15,207	39	2,308	38	306	41
≥ 50	1,783	5	271	4	27	4
Unknown	1,787	5	369	6	29	4
Tumor-positive axillary lymph nodes						
0	19,185	50	2,976	49	369	50
1-3	11,202	29	1,622	27	234	31
4-9	3,562	9	5,424	9	70	9
≥ 10	2,224	6	337	6	36	5
Unknown	2,340	6	591	10	35	5
Breast cancer stage						
I	12,778	33	2,019	33	253	34
II	16,786	44	2,445	40	338	45
III	6,196	16	958	16	113	15
Unknown	2,753	7	646	11	40	5
Estrogen receptor status						
Positive	30,027	78	4,716	78	597	80
Negative	7,006	18	1,036	17	130	17
Unknown	1,480	4	316	5	17	2
Adjuvant systemic therapy						
Not allocated to guideline treatment	4,894	13	1,107	18	83	11
Low risk, not indicated	7,175	19	1,087	18	150	20
High risk, guideline not initiated	4,199	11	727	12	90	12
High risk, guideline initiated:						
Chemotherapy	4,376	11	523	9	72	10
Chemotherapy and endocrine therapy	6,445	17	855	14	106	14
Endocrine therapy	11,424	30	1,769	29	243	33

NOTE. Differences between groups were tested with χ^2 tests and analysis of variance. Treatment with antidepressants versus no use of antidepressants: all *P* values were < .001. Hospital contact for depression versus no use of antidepressants: sociodemographic variables—aside from mean age (*P* = .027)—all *P* values were < .001; clinical variables—aside from calendar year at diagnosis (categorically in 1-year intervals as well as continuously measured, *P* < .001)—no statistically significant differences were observed.

Fig 2. Risk of potentially unfavorable selection for initiation of guideline adjuvant systemic therapy associated with treatment with antidepressants and hospital contacts for depression before diagnosis of breast cancer among 45,325 women with primary early-stage breast cancer diagnosed in Denmark, 1998 to 2011. Odds ratios (ORs) were calculated in multivariable logistics regression models, including the following covariates: age and menopausal status (< 40 years, 40 to 49 years, 50 to 59 years and premenopausal, 50 to 59 years and postmenopausal, 60 to 69 years, 70 to 79 years, ≥ 80 years); educational level (high school, vocational, basic, unknown); cohabiting (yes/no); Charlson Comorbidity Index score (0, 1, ≥ 2); calendar year at diagnosis (continuous); tumor size (< 20 mm, 20–49 mm, ≥ 50 mm, unknown); number of tumor-positive axillary lymph nodes (0, 1 to 3, 4 to 9, ≥ 10, unknown); and estrogen receptor status (positive, negative, unknown).

survival, but the estimates were robust to the addition of clinical and treatment variables. We found significantly increased HRs for death by suicide for both women who had used antidepressants (fully adjusted model: HR, 5.38; 95% CI, 2.16 to 13.37) and women with a previous hospital contact for depression (fully adjusted model: HR, 19.81; 95% CI, 5.32 to 73.86).

In the subgroup analysis of women with high-risk breast cancer who did not receive adjuvant systemic therapy according to the guidelines, we found statistically significantly worse survival of women who had used antidepressants (HR, 1.51; 95% CI, 1.26 to 1.82) and nonsignificantly worse survival of women with a previous hospital contact for depression (HR, 1.57; 95% CI,

0.99 to 2.49; Table 3). Among women who received guideline adjuvant systemic therapy, we found no statistically significant difference in breast cancer–specific survival.

DISCUSSION

In this nationwide study, we found an increased risk of not receiving relevant breast cancer treatment and poorer overall and breast cancer–specific survival among women with depression. We were reassured, however, that the survival of women with previous depression was similar to that of women without depression if they

Fig 3. Estimated cumulative mortality from breast cancer among 45,325 women with primary early-stage breast cancer diagnosed in Denmark, 1998 to 2011, for women not previously treated with antidepressants (AD; $n = 38,513$), women previously treated with AD ($n = 6,068$), and women with previous hospital contact for depression ($n = 744$). Gray's test for difference adjusted for age in 5-year strata; previous use of AD versus no previous use of AD: $P = .002$; and previous hospital contact for depression versus no previous use of AD (No prev. use of AD), women previously treated with AD (Prev. treat. w. AD), and women with a hospital contact for depression before diagnosis of breast cancer (Prev. hosp. dep.).

received adjuvant treatment according to the guidelines. Our access to national registers with high coverage and valid, detailed information on sociodemographic variables, tumor characteristics, adjuvant systemic therapy, and cause of death provided the basis for these novel, clinically important results.

Our finding that women previously treated for depression are at increased risk for not receiving guideline breast cancer treatment indicates the potential for improvement of breast cancer treatment of a large, vulnerable group of patients. Goodwin et al¹² reported similar findings in a population of patients with breast cancer ≥ 67 years of age, whereas our results relate to women of all ages.

We had expected that women with previous depression or use of antidepressants would present with more advanced disease characteristics, reflecting diagnostic delay. However, this study does not indicate that the poorer prognosis of patients with breast cancer with previous depression can be explained by more advanced disease at diagnosis, in line with a previous report.¹²

Two other population-based studies of survival after breast cancer reported reduced overall survival among women with preexisting depression, with estimates similar to ours.^{11,13} These studies relied exclusively on hospital contacts for depression. They found that 1% to 3% of their total populations of patients with breast cancer had depression before breast cancer, equivalent to the

Table 2. Multivariable Cox Analyses of the Association Between Previous Treatment of Depression and Overall Survival, Breast Cancer–Specific Survival, and Death by Suicide for 45,325 Women With Early-Stage Breast Cancer Diagnosed in Denmark, 1998–2011

Suicide for 45,525 Women with Early-Stage Breast Cancer Diagnosed in Denmark, 1998–2011									
Survival	Deaths	Model I		Model II		Model III		Model IV	
		HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Overall survival									
No use of antidepressants	6,733	1	—	1	—	1	—	1	—
Treated with antidepressants	1,450	1.33	1.25 to 1.41	1.20	1.14 to 1.27	1.22	1.15 to 1.30	1.21	1.14 to 1.28
Hospital contact for depression	116	1.19	0.99 to 1.44	1.11	0.93 to 1.34	1.16	0.97 to 1.40	1.15	0.96 to 1.38
Breast cancer–specific survival									
No use of antidepressants	4,361	1	–	1	–	1	–	1	–
Treated with antidepressants	742	1.13	1.05 to 1.22	1.08	1.00 to 1.17	1.12	1.03 to 1.21	1.11	1.03 to 1.20
Hospital contact for depression	64	1.01	0.79 to 1.29	0.96	0.75 to 1.23	1.00	0.78 to 1.28	1.00	0.78 to 1.28
Suicide									
No use of antidepressants	11	1	–	1	–	1	–	1	–
Treated with antidepressants	9	5.65	2.32 to 13.77	5.64	2.29 to 13.92	5.38	2.17 to 13.33	5.38	2.16 to 13.37
Hospital contact for depression	3	18.18	5.04 to 65.61	18.73	5.11 to 68.64	20.03	5.43 to 73.95	19.81	5.32 to 73.86

NOTE. Model I: adjusted for age at diagnosis (included as a continuous variable when possible; otherwise, included as a categorical variable in 10-year intervals: < 30 , 30 to 39, ..., 80 to 89, ≥ 90) and calendar year at diagnosis (included as a continuous variable when possible; otherwise, included as a categorical variable in 1-year intervals). Model II: also adjusted for educational level (high school, vocational, basic, unknown); cohabiting (yes/no); and Charlson Comorbidity Index score (0, 1, ≥ 2). Model III: also adjusted for menopausal status (premenopausal, postmenopausal); type of surgery (mastectomy, lumpectomy, biopsy only); tumor size (< 20 mm, 20 to 49 mm, ≥ 50 mm, unknown); number of tumor-positive axillary lymph nodes (0, 1 to 3, 4 to 9, ≥ 10 , unknown); and estrogen receptor status (positive, negative, unknown). Menopausal status was adjusted for by combining age and menopausal status into one covariate (< 40 , 40 to 49, 50 to 59 years and premenopausal, 50 to 59 years and postmenopausal, 60 to 69 years, 70 to 79 years, ≥ 80 years). Model IV: also adjusted for type of adjuvant treatment initiated (chemotherapy, chemotherapy and endocrine therapy, endocrine therapy, no adjuvant treatment, unknown). Person-years: no use of antidepressants, 204,589; treated with antidepressants, 27,927; hospital contact for depression, 3,147. Abbreviation: HR, hazard ratio.

Table 3. Multivariable Cox Analyses of Associations Between Previous Treatment of Depression and Breast Cancer–Specific Survival of 45,325 Women With Early-Stage Breast Cancer Diagnosed in Denmark, 1998 to 2011, According to Allocation to and Initiation of Guideline Breast Cancer Treatment

Treatment Allocation and Initiation	Person-Years	Deaths	HR	95% CI
Not allocated to guideline treatment (n = 6,084)				
No use of antidepressants	27,146	1,339	1	—
Treated with antidepressants	4,957	280	1.00	0.87 to 1.14
Hospital contact for depression	409	16	0.82	0.50 to 1.34
Low-risk breast cancer, no adjuvant therapy indicated (n = 8,412)				
No use of antidepressants	44,743	338	1	—
Treated with antidepressants	6,200	54	1.13	0.84 to 1.52
Hospital contact for depression	724	6	1.25	0.55 to 1.82
High-risk breast cancer, no initiation of indicated adjuvant therapy (n = 5,016)				
No use of antidepressants	15,597	705	1	—
Treated with antidepressants	1,988	143	1.51	1.26 to 1.82
Hospital contact for depression	249	19	1.57	0.99 to 2.49
High-risk breast cancer, initiation of indicated adjuvant therapy (n = 25,813)				
Chemotherapy (n = 4,971)				
No use of antidepressants	25,309	658	1	—
Treated with antidepressants	2,654	83	1.24	0.98 to 1.57
Hospital contact for depression	308	6	0.74	0.33 to 1.67
Chemotherapy and endocrine therapy (n = 7,406)				
No use of antidepressants	29,882	293	1	—
Treated with antidepressants	3,433	28	0.76	0.51 to 1.13
Hospital contact for depression	361	3	0.77	0.24 to 2.45
Endocrine therapy (n = 13,436)				
No use of antidepressants	61,913	1,028	1	—
Treated with antidepressants	8,695	154	1.08	0.91 to 1.28
Hospital contact for depression	1,095	14	0.83	0.49 to 1.41

NOTE. Models adjusted for age and menopausal status (< 40, 40 to 49, 50 to 59 years and premenopausal, 50 to 59 years and postmenopausal, 60 to 69 years, 70 to 79 years, ≥ 80 years); calendar year (categorical variable in 1-year intervals); educational level (high school, vocational, basic, unknown); cohabiting (yes/no); Charlson Comorbidity Index score (0, 1, ≥ 2); type of surgery (mastectomy, lumpectomy, biopsy only); tumor size (< 20 mm, 20 to 49 mm, ≥ 50 mm, unknown); number of tumor-positive axillary lymph nodes (0, 1 to 3, 4 to 9, ≥ 10, unknown); and estrogen receptor status (positive, negative, unknown). Abbreviations: HR, hazard ratio.

2% with previous hospitalization for depression in our population. We found similarly poor survival in the much larger group of women with previous use of antidepressants (corresponding to 13%), indicating that poorer survival is not restricted to a small subgroup of women with the most severe depression but affects a large subgroup of patients on oncologic wards.

The significantly increased estimated risk for breast cancer–specific death in this study was lower than that reported by Goodwin et al.¹² This may be related to the full coverage of breast cancer treatment by the free medical care offered to all residents of Denmark, whereas the Medicare setting studied by Goodwin et al.¹² involves high costs for adjuvant cancer treatment, potentially discouraging some patients from receiving optimal cancer treatment.²⁹

The Cox regression analyses were robust to the addition of type of adjuvant systemic therapy as a potential mediator of estimated differences in overall and breast cancer–specific survival. However, subgroup analyses demonstrated that previous depression was associated with poor breast cancer–specific survival, especially among women not given the indicated adjuvant systemic therapy, whereas no difference was found for women who initiated guideline adjuvant systemic therapy. Somatic comorbid conditions have also been associated with poor breast cancer prognosis.³⁰

However, the prognosis of patients with breast cancer with somatic or psychiatric comorbidity who receive the breast cancer treatment they need according to the guidelines was similar to that of patients without comorbidity. The necessary measures should therefore be taken to increase enrollment and completion³¹ of guideline adjuvant therapy in women with depression.

The association found in this study between previously treated depression and worse survival after breast cancer must be interpreted in relation to the generally increased mortality among people with depression.³² Accordingly, women previously treated for depression had a higher burden of severe somatic comorbidity; however, our estimates of worse overall survival and breast cancer–specific survival remained statistically significant after adjustment in the analyses for this factor as a proxy for general somatic health. We therefore suggest that the worse survival after breast cancer of women with previously treated depression is related not only to an increased risk of death before diagnosis of breast cancer but also to the breast cancer per se.

Although we observed an increased HR for suicide among women with previously treated depression, we consider that this reflects a difference in risk that was present before the diagnosis of breast cancer. Thus, the rate of suicide in our population was approximately 10 per 100,000 person-years (Table 2), which is comparable to the rate in the total Danish female population

> 30 years of age in the same period.³³ Furthermore, the increased HR for death by suicide found among women who had a hospital contact for depression is similar to that in a recent study including the total Swedish population.³⁴

Our study has some limitations. As in the three previous studies,¹¹⁻¹³ our data on depression were derived from registers, which did not allow identification of women with undiagnosed or untreated depression or women with depression who received psychotherapy only. Furthermore, although depression is the indication for most prescribed antidepressants, other conditions, such as anxiety and pain, might account for more than 25% of prescribed antidepressants.³⁵⁻³⁷ In addition, although we adjusted for a range of comorbid diseases related to unhealthy lifestyles, our analyses, like those in previous studies,¹¹⁻¹³ were not directly adjusted for lifestyle factors, such as smoking and alcohol use, which might mediate the observed associations. Furthermore, in Denmark, autopsy is conducted in only 10% of deaths.²⁵ Consequently, cause of death is often a qualified guess on the basis of the preceding course of illness, inevitably leading to some misclassification in registration. Because most deaths attributed to breast cancer occur after a diagnosis of late-stage disease or recurrence, we assume that misclassification of breast cancer as the cause of death is limited. Finally, relatively few patients (n = 744) had a previous hospital contact for depression, decreasing the statistical power of these analyses.

In conclusion, in a nationwide cohort study of women with primary early-stage breast cancer, we found that women treated for

depression before the breast cancer diagnosis were at greater risk for not initiating guideline adjuvant systemic therapy, which probably partly explains the modest but significant increased risks of death and of breast cancer-specific death in this group. Our findings underline the importance of identifying women with previous depression to increase initiation of adjuvant systemic breast cancer therapy and of following up such women carefully to identify depressive relapse, nonadherence to breast cancer therapy, and suicidal ideation.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

AUTHOR CONTRIBUTIONS

Conception and design: Nis P. Suppli, Christoffer Johansen, Marianne Ewertz, Susanne O. Dalton

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Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Survival After Early-Stage Breast Cancer of Women Previously Treated for Depression: A Nationwide Danish Cohort Study

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