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Impact of schizophrenia and related disorders on mortality from breast cancer: A population-based cohort study in Denmark, 1995–2011

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ABSTRACT

Objectives: To investigate overall and breast cancer-specific mortality in early-stage breast cancer patients with and without schizophrenia or related disorders.
Methods: We used Danish national registers to identify all women with no prior history of cancer or organic mental disorders, who were diagnosed with early-stage breast cancer 1995–2011. Logistic regression models were used to calculate the odds ratios (ORs) for not being allocated to guideline treatment. Cox regression models were used to compute hazard ratios (HRs) for overall and breast cancer-specific deaths among women allocated or not allocated to guideline treatment.
Results: We identified 56,152 women with early-stage breast cancer diagnosed in 1995–2011, of whom 499 women also had been diagnosed with schizophrenia or related disorders. The likelihood of women with schizophrenia or related disorders for not being allocated to guideline treatment was increased (adjusted OR, 1.50; 95% confidence interval (CI), 1.15–1.94). The adjusted HR for all-cause mortality was 1.55; 95% CI, 1.32–1.82 and 1.12 (95% CI, 0.98–1.50) for breast cancer-specific mortality; women allocated to guideline treatment had an adjusted HR for breast cancer-specific death of 1.42 (95% CI, 1.11–1.82). The adjusted HR for death due to unnatural causes was 3.67 (95% CI, 1.80–7.35).
Conclusion: The survival of women with schizophrenia or related disorders after breast cancer is significantly worse than that of women without these disorders. These patients are less likely to be allocated to guideline treatment, and, among those who are, mortality from both breast cancer and other causes is increased.

1. Introduction

People with schizophrenia are at higher risk for death from all causes; cardiorespiratory diseases, suicide and cancer are the leading causes of death [1,2]. It has been reported that patients with schizophrenia die 10–25 years earlier than expected [3,4] and that this mortality gap has increased in the recent decades [5] indicating that the health of people with schizophrenia and related disorders require urgent attention.

Interest in cancer diagnosis and management in patients with severe mental illness, including schizophrenia, has been growing [6–8]. The accumulated results of studies of overall mortality among these patients indicate that they are 2–2.5 times more likely to die of their cancer than the general population [9–12].

Breast cancer is a major burden on health care services [13], and schizophrenia and related psychotic disorders are another major challenge, as they affect approximately 1% of the population. With schizophrenia diagnosed in 1/4000 people each year, mainly the

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young, and about 21 million people with this disorder worldwide, it represents a heavy burden for patients, their caregivers and society [14–16]. Women with schizophrenia may be at slightly higher risk for breast cancer than women without schizophrenia [17–19], although the estimates may be limited by confounding due to nulliparity, obesity and use of antipsychotics [20], and other studies indicate that the rate of breast cancer screening among women with mental illness is low [21–24]. Furthermore, a number of population-based studies have shown that patients with schizophrenia have worse survival after cancer [25–27], including breast cancer, perhaps due to later stage at diagnosis and lack of or insufficient treatment [25–30].

The association between schizophrenia and the outcomes of breast cancer should be further studied in large, well-conducted studies for meaningful analyses of cancer outcomes in order to deliver the best possible care to all patients. We conducted a Danish nationwide register-based study of the survival of women with schizophrenia and related disorders after breast cancer in comparison with that of breast cancer patients with no history of such disorders.

2. Materials and methods

2.1. Register linkage

All residents of Denmark are registered in the Central Population Registry [31] with a unique personal identification number, and the register holds information on sex, date of birth and migration. We used the personal identification numbers to link data from multiple registers accurately.

2.2. Information on breast cancer

The Danish Breast Cancer Group has conducted randomised trials of surgery, radiation, chemotherapy and endocrine therapy in Denmark since 1977; 70% of patients are now treated according to their protocols, and >95% of all women with breast cancer are registered in their database [32]. We identified all women who underwent surgery for early-stage breast cancer in 1995–2011 and obtained information on date of surgery, menopausal status, tumour size, number of tumour-positive axillary lymph nodes, oestrogen receptor status, type of surgery, type of adjuvant therapy (chemotherapy, endocrine therapy, chemotherapy and endocrine therapy, no adjuvant therapy or unknown) and allocation to guideline breast cancer treatment. We defined the date of surgery as the date of diagnosis.

2.3. Information on schizophrenia and related disorders

Since 1969, Danish psychiatric hospitals have reported dates and diagnoses at discharge of all inpatients to the Danish Psychiatric Central Research Register [33]. In 1995, data on outpatient contacts and emergency contacts were added. As there are no private psychiatric hospitals in Denmark, tracking of severe mental illness leading to a hospital contact is almost complete. The International Classification of Diseases (version 8) (ICD-8) system was used from April 1966 until 1 January 1994, when it was replaced by the ICD-10 system. For all women, we obtained the dates of all hospital contacts for schizophrenia or related conditions before a diagnosis of breast cancer, using ICD-8 codes 295 (schizophrenia), 297 (paranoid states), 298 (other psychoses; excluding 298.0, reactive depressive psychosis; 298.1, reactive excitation) and 299 (unspecified psychosis) or ICD-10 codes F20–29 (schizophrenia, schizotypal, delusional and other non-mood psychotic disorders). Further, we identified organic mental disorders with ICD-8 codes 290–94.9 and ICD-10 codes F00–09.

2.4. Information on covariates and outcome

The Danish Cancer Register was used to obtain information on all cancers diagnosed in Denmark in 1943–2011, excluding non-melanoma skin cancer [34]. From the National Patient Registry, which has recorded information on all hospitalisations since 1978 and outpatient contacts since 1994 [35], we obtained information on comorbid conditions in order to compute a modified Charlson comorbidity index score [36] (not including the breast cancer diagnosis) at diagnosis. Somatic comorbidity was scored as 0 (none), 1 or ≥ 2. From the Registers of Education administered at Statistics Denmark [37], we obtained the highest level of education attained by each woman at the time of breast cancer diagnosis and classified it as basic (mandatory school with or without high school), vocational or higher education. We obtained dates and causes of death in 1995–2011 from the Danish Register of Causes of Death [38] and classified the causes as breast cancer-specific, other natural causes and unnatural causes (suicide or violent death).

2.5. Study population and follow-up

We identified 56,152 women with primary, early-stage breast cancer diagnosed in Denmark in 1995–2011 with no prior history of cancer or of hospital contact for an organic mental disorder. We defined exposed women as all those in whom schizophrenia or a related disorder had been diagnosed before their diagnosis of breast cancer. All women were followed from the date of breast cancer diagnosis until date of death, new primary cancer (except non-melanoma skin cancer), a diagnosis of schizophrenia or related disorders, or an organic mental disorder, disappearance, emigration or the end of the study on 31 January 2011, whichever occurred first.

2.6. Statistical analysis

We used logistic regression models to investigate the likelihood of not being allocated to guideline breast cancer treatment, adjusting for age at diagnosis, calendar period, level of education and Charlson comorbidity index score. We used Cox proportional hazard models to obtain hazard ratios (HRs) for the overall survival of women with schizophrenia or a related condition by comparing them with women with no such diagnosis, using time since breast cancer diagnosis as the underlying time scale. We also calculated HRs for breast cancer-specific and for other natural and other unnatural deaths.

We developed four models, in which we entered covariates stepwise: 1) adjustment for confounders (age at diagnosis and calendar year); 2) adjustment as 1 and for individual factors (level of education and Charlson comorbidity index score); 3) adjustment as 2 and for cancer-related factors (tumour size, positive lymph nodes, menopausal status and oestrogen receptor status); and 4) adjustment as 3 and for treatment (types of surgery and adjuvant therapy).

Age at breast cancer diagnosis, year of diagnosis, tumour size and number of tumour-positive axillary lymph nodes were tested for linearity by introducing the same variables raised to the second and the third and testing for model reduction; only tumour size could be included as a linear variable. The assumption of proportionality for each Cox model was assessed visually from plots of log minus log of the survival density function versus log of survival time. All variables were considered adherent to the assumption. All statistical analyses were performed with the procedures LOGREG and PHREG in SAS 9.3.