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Original article

Breast cancer diagnosis and mortality by tumor stage and migration background in a nationwide cohort study in Sweden

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ABSTRACT

Introduction: Survival in breast cancer patients has steadily increased over the years, but with considerable disparities between individuals with different migration background and social position. We explored differences in diagnosis and all-cause mortality in breast cancer patients by stage of disease at the time of diagnosis and by country of birth, while considering the effect of comorbidity, regional and socio-demographic factors.

Methods: We used Swedish national registers to follow a cohort of 35,268 patients (4232 foreign-born) with breast cancer between 2004 and 2009 in Sweden. We estimated relative risk ratio (RRR) for diagnosis, hazard ratio (HR) for all-cause mortality and relative excess rate (RER) for breast cancer mortality using multinomial logistic regression models, multivariable Cox proportional hazard, and Poisson regression, respectively.

Results: We observed 4178 deaths due to any causes. Among them 418 women were born abroad. Foreign-born patients were on average 3 years younger at the time of breast cancer diagnosis and had higher risk of stage II tumors compared with Sweden-born women (RRR = 1.09, 95% CI 1.00–1.19). Risk of dying was 20% higher in foreign-born compared with Sweden-born breast cancer patients, if the tumor was diagnosed at stages III-IV after adjustment for age at diagnosis, education, county of residence and Charlson's comorbidity index (HR = 1.20, 95% CI 0.95–1.51 and RER = 1.21, 95% CI 0.95–1.55).

Conclusions: The worse prognosis in foreign-born patients with advanced tumors compared with Sweden-born patients is not explained by educational level or comorbidity. The reasons behind the observed disparities should be further studied.

Introduction

Survival is a key indicator for the overall effectiveness of health care in the management of cancer patients [1]. Since multimodality treatment for breast cancer became available, survival has improved, but there are still substantial disparities within [2,3] and between countries [1]. In Europe, the 5-year relative survival is highest in the Nordic countries and in most Southern and Central European countries [4]. In low- and middle income countries reliable data for breast cancer are lacking but outcomes are likely to be poor [5]. In Sweden, despite the high survival rate when compared with countries with comparable health care such as Finland, Iceland, Norway, and Denmark [4], breast cancer survival disparities across migration background has repeatedly been observed [6,7]. Reasons behind these inequities; ranging from biology, treatment, comorbidity, clinical stages at diagnosis and socioeconomic factors have been discussed, albeit primarily across different ethnic groups in the US.

Using national Swedish registers, in a cohort of all breast cancer patients diagnosed between 2004 and 2009, we estimated the risk of breast cancer, all-cause mortality and excess mortality for patients after breast cancer diagnosis by clinical stage at presentation and country of birth. We further evaluated if a more advanced stage

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of disease at the time of the diagnosis in foreign-born could explain disparities in survival, while considering the effect of comorbidity, regional and socio-demographic factors.

Material and methods

Data

We conducted a national cohort study using the Migration and Health Cohort (M&H Co) data for 2004–2009. The M&H Co was built by linking several Swedish national registers with information on vital status and health through the Swedish personal identification number. The data used in this study were retrieved from M&H Co and included information from the following five registers: (1) The Total Population Register from the Swedish administrative agency Statistics Sweden encompasses demographic characteristics, country of birth and data on emigration and immigration. (2) The Cancer Registry contains data on diagnosis of breast cancer since 1958. The completeness of this register regarding verified cases is considered to be close to 100% [8]. (3) The Cause of Death Register contains yearly updated data on the date and the main cause of death from 1961 onwards. The non-reporting rate has been estimated as to be less than 2% [9]. (4) The Swedish National In-patient Register where we retrieved data on comorbid diseases in hospitalized patients. The In-Patient Register was established in 1964 and reached nationwide coverage in 1987. The positive predictive value for most diseases included in this register ranges from 85% to 95% [10]. (5) Finally, the longitudinal integration database for health insurance and labor market studies (LISA) from Statistics Sweden provides information on the highest attained level of education since 1990 [11].

This study was approved by the Regional Board of The Ethics Committee of Stockholm (Dnr. 2009/2033-32).

Study cohort

The study cohort consisted of 35,542 female patients with the diagnosis of invasive breast cancer with no previous diagnosis of any cancer except for non-melanoma skin cancer (ICD-7 code: 191) among women living in Sweden at any time between January 1st, 2004 and December 31st, 2009. We excluded foreign-born breast cancer patients that had resided in Sweden for less than 5 years (274 cases) before diagnosis to exclude patients diagnosed prior to immigration and to minimize possible detection bias resulting from the limited access to health care in the first years of residence in Sweden. The final cohort included 4232 foreign-born (12%) and 31,036 Sweden-born patients (88%).

Follow-up

The cohort was followed from the date of breast cancer diagnosis (ICD-7 code: breast cancer 170), until the date of death due to any cause, the date of first emigration, or the end of follow-up on December 31, 2009, whichever occurred first.

Breast cancer staging

Staging of cancer was based on three components including the size of the tumor (T), the number of lymph nodes involved (N), and metastasis (M). According to TNM classifications, invasive breast cancer is divided into 4 main stages or tumor stages (1-IV). Stage at diagnosis is classified as missing if information on any of the variables tumor size (T), number of lymph nodes involved (N) or metastasis (M) are missing or unidentifiable. TNM classification has been recorded in the Swedish Cancer Registry since 2004.

Statistical methods

We used multinomial logistic regression to estimate the risk of being in one of the tumor stages (I, II, III, and IV) at the time of diagnosis. Tumor stage I was considered the baseline category. We calculated relative risk ratio (RRR) with 95% confidence interval (CI) in foreign-born versus Sweden-born women. We also calculated hazard ratio (HR) and 95% confidence interval (CI) for all-cause mortality in breast cancer patients by stage of disease at the time of diagnosis and country of birth using Cox proportional hazard regression models.

We further completed all-causes of death analysis by relative survival ratio (RSR) to estimate breast cancer-specific survival. Relative survival does not rely on accurate cause of death, and it measures the excess mortality experienced by cancer patient whether or not the excess mortality is directly attributable to the cancer [12]. It is the ratio of all-cause survival observed in patients with a specific disease to the survival that would have been expected if they had been subjected to the mortality rates of the general population. In this study we used the ratio of all-cause survival observed in patients with breast cancer in our cohort to the expected survival for the cohort members free of breast cancer matched by age, calendar year and education [13]. We additionally calculated cumulative one- and two-year RSR with 95% confidence interval (CI) by stage (stages I, II, III, IV, and missing) and country of birth. For that, patients diagnosed later than 2008 were excluded as they could not be followed for at least 2 years. The cumulative one- and two-year RSR can be interpreted as the proportion of breast cancer patients alive after one and two years of follow-up where the breast cancer is the only possible cause of death. We modeled relative excess mortality (relative excess rate (RER) of death) and 95% confidence interval (CI) by stage of disease at the time of diagnosis and country of birth, to allow multivariable adjustment for potential confounding factors, with Poisson regression based on collapsed data using exact survival times [14].

Comorbidity burden was assessed using an updated version of the Charlson's comorbidity index (CCI) [15]. Using the index we classified patients according to the burden of their comorbidity through information on diagnosis of diseases other than breast cancer. To assess patient comorbidity, we calculated the CCI score at least seven years before the date of breast cancer diagnosis (Supplementary Table A.1). We grouped the CCI scores into four categories (0, 1, 2 and $\geq$3).

In all analyses we adjusted for age at breast cancer diagnosis, categorized in 14 groups (<25, 25–29, 30–34, …, 75–79, 80–84, and 85+ years), the highest attained educational level in four categories (0–9 years, 10–12 years, more than 12 years, and unknown), medical county of residence based on six geographically divided health care regions in Sweden (Stockholm, Gothenburg, Linköping, Lund-Malmö, Umeå, and Uppsala), and CCI.

The mortality analyses were additionally adjusted for tumor stage. The analyses were performed using SAS version 9.4. The relative survival analyses were performed with publicly available SAS macros [16].

Results

Among 35,268 female patients (4232 foreign-born) with the first primary diagnosis of breast cancer during the study period, we observed 4178 deaths due to any causes (418 foreign-born). Foreign-born patients were on average approximately 3 years younger than Sweden-born patients at the time of breast cancer diagnosis (mean age SD; foreign-born: 60.4 ± 13.4 years; Sweden-born: 63.6 ± 13.9 years) and 6 years younger at death due to any causes (the mean age of the total female population living in