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Original Research

Survival in familial and non-familial breast cancer by age and stage at diagnosis

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Abstract We aimed to compare the survival in familial and sporadic breast cancer (BC) patients who were diagnosed at an identical age and TNM stage. The Nationwide Swedish Family-Cancer Database including all Swedes born after 1931 and their biological parents, totalling >14.7 million individuals, was used. Hazard ratios (HRs) were calculated for women with BC in a first-degree relative (FDR) versus BC patients without positive family history. There was no difference in survival of familial BC patients who were diagnosed at higher TNM status or older age (>40) compared to sporadic BC cases diagnosed at the same late TNM stage. Young BC patients (age <40) in early stages had the worst survival when their FDR was diagnosed with single (HR: 2.0–3.7) or multiple (HR: 2.4–7.1) BC at any age. We concluded that there is no difference in survival of familial and non-familial BC patients who are diagnosed at higher TNM status or older ages (>40). Young familial BC patients (age <40), diagnosed at early stage, have the poorer survival compared to sporadic cases. Our results urge the need for identifying the underling genetic component for such a difference in survival of familial BC.

1. Introduction

In women, breast cancer (BC) is the leading cause of death due to cancer. BC mortality is mainly due to metastases rather than the primary tumour per se [1]. The size of the tumour and the number of affected

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auxiliary lymph nodes at the time of diagnosis are the key factors related to risk of metastases in BC [1]. Significant family history has been proposed as one of the most important predictor of hereditary BC [2]. In the Swedish Family-Cancer Database, 16% of women with BC had a positive history of BC in at least one of their first-degree family members [3].

Studies on differences in survival of familial and non-familial BCs are far from conclusive. While some studies suggest familial BC might have a poorer survival due to some genetic component, others show survival does not appear to be influenced by family history [4–6]. It has been proposed that familial BC occurs at earlier ages and had poorer prognosis compared to sporadic cases [7]. However, results of our recent study showed that familial risks exist even in cancers of very old ages and >40% of familial BC cases occurred in those whose parent was diagnosed with the concordant cancer at an old age (>69 years) [3]. Some studies have suggested that the prognosis in BC is in part heritable as both poor and good survival in BC aggregates in families [8,9]. The effect of BRCA1 or BRCA2 mutations on survival of BC is unclear. Both negative and neutral effects have been reported [10,11].

In the present population-based study, we aimed to estimate the effects of existence of single and multiple BCs in a first-degree relative (FDR) and the stage at diagnosis on the survival of early- and late-onset BC patients using the world largest family cancer database, the Swedish Family-Cancer Database.

2. Material and methods

In this nationwide cohort study, we used the Swedish Family-Cancer Database which was created by linking information from the Multi-generation Register, national censuses, Swedish Cancer Registry, and death notifications using Swedes' unique national identification number (Fig. S1) [12]. Children born in Sweden from 1932 onwards are registered with their biological parents as families in the Multi-generation Register. In this study, offspring were 0–78 years; however, there was no limitation for parents' age (Fig. S2). Cancer registration in Sweden is based on compulsory reporting of diagnosed cases; and the completeness of this registry is considered to be near to 90% [13]. For all cancer cases, a four-digit diagnostic code according to the seventh revision of the International Classification of Diseases (ICD-7) and the subsequent ICD classifications are available. National census data contain the socioeconomic background. The current update of the database includes >14.7 million individuals, with >1.7 million cancer patients with a first primary tumour. Survival of BC patients was investigated separately according to register-based diagnosis of single (only one BC) and multiple (two or more) BCs in a mother or sister, stratified by age at diagnosis of first BC, TNM and staging.

The Cox proportional hazard models (PROC PHREG, SAS software version 9.3; SAS Institute Inc., Cary, NC, USA) were used to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs) for death in female BC patients with affected mother or sister with a single or multiple BC, compared to female BC cases without such a positive family history. Calendar years of entering and leaving the study were used as underlying time variables. Kaplan–Meier curve and log-rank sum test were presented for significant results. The analyses were stratified by the age at diagnosis of the first BC in the index BC patients. The follow-up was started for each patients at year of diagnosis of the first BC and terminated on the year of death, emigration, or the closing date of the study, 31st December 2010 (whichever came first). All HRs were adjusted for age at diagnosis of first BC; age at first child birth; total number of children; hospitalisation for obesity (yes/no); chronic obstructive pulmonary disease or alcoholism (yes/no); socioeconomic status (farmer, manual worker, low- to middle-income office worker, high-income office worker/professional, company owner [except farmer], or other/unspecified); and residential region (large cities, South Sweden, North Sweden, or unspecified). These analyses were also stratified by tumour size and local growth (T), regional lymph node involvement (N) and the presence of metastasis (M) status and overall TNM stage.

We have the data on TNM status of our patients since 1992. The TNM classification system is based on the American Joint Committee on Cancer. We used logistic regression to calculate odds ratios (ORs) (PROC LOGISTIC; SAS software version 9.3) for assessing the familial and non-familial BC according to the TNM classification, using T0–T1, N0, M0 and stage 0–I as the references for T2–T4, N1–N3, M1 and stage II–IV, respectively. All analyses were adjusted for age at diagnosis, age at first childbirth, parity, socioeconomic status and residential region. The 95% CIs and p-values were also calculated. This study has been approved by the Lund Regional Ethics Committee.

3. Results

There were 30,075 female BC patients with available information on their TNM status at diagnosis, among them 25,366 cases had no history of BC in their mother or sister, 4139 patients had a history of a single BC in their mother or sister, and 516 patients had history of multiple BC in their mother or sister. Table 1 represents the association between TNM status at diagnosis by history of single/multiple BC in FDRs. We found no evidence for familial BC cases being diagnosed at an earlier TNM status compared to sporadic cases (Table 1). In some