The Breast 32 (2017) 130–134

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Family history of cancer other than breast or ovarian cancer in first-degree relatives is associated with poor breast cancer prognosis

Jun-Long Song [a, 1], Chuang Chen [a, 1], Jing-Ping Yuan [b], Juan-Juan Li [a], Sheng-Rong Sun [a, *]

[a] Department of Breast and Thyroid Surgery, Renmin Hospital of Wuhan University, Wuhan, Hubei, 430060, PR China
[b] Department of Pathology, Renmin Hospital of Wuhan University, Wuhan, Hubei, 430060, PR China

ARTICLE INFO

Article history:
Received 22 November 2016
Received in revised form
25 January 2017
Accepted 27 January 2017

Keywords:
Breast cancer
Family history of other cancer
Prognosis
Disease-free survival

ABSTRACT

Objective: Whether a first-degree family history of others cancers (FHOC) than breast or ovarian cancer (BOC) is associated with breast cancer prognosis remains unknown. Thus, the aim of the present study was to clarify this issue.

Methods: Women who were diagnosed with invasive breast cancer at the Renmin Hospital of Wuhan University from 2010 to 2013 were included in the study. The demographic and clinicopathological characteristics of these patients were extracted. FHOC was considered positive for any patient who had a relative who had been diagnosed with cancer other than BOC. Disease-free survival (DFS) was calculated based on the date of diagnosis. DFS was analyzed using the Cox proportional hazards model.

Results: A total of 434 breast cancer patients were included in this study. Among these patients, 61 (14.06%) had a positive FHOC in first-degree relatives. Patients with a positive FHOC tended to have HER2-positive breast cancer ($p = 0.03$). In the survival analysis, FHOC was associated with poor DFS in both univariate (HR = 2.21 (1.28–3.83), 95% CI: 1.28–3.83, $p < 0.01$) and multivariate (HR = 2.50, 95% CI: 1.24–5.04, $p = 0.01$) analyses, especially in patients with luminal A subtypes.

Conclusion: The results demonstrated an increased risk of recurrence in breast cancer patients with FHOC, especially in patients with luminal A subtype.

1. Introduction

Breast cancer has been the most frequently diagnosed cancer in women in China in 2015 [1]. It is a complex disease characterized by the complex interaction between genetic and environmental factors. Various risk factors that have been identified include being overweight, smoking, as well as reproductive and genetic factors [2]. A positive family history of breast cancer or ovarian cancer (BOC) is a well-established risk factor that could lead to a mean 2.1-fold increase in breast cancer risk [3]. Furthermore, in patients with a family history of breast cancer, breast cancer often occurs earlier and is more likely to be multifocal [4,5]. In theory, these factors could affect the survival of breast cancer patients. Many studies have been conducted to detect whether a family history of breast cancer has an impact on the prognosis of the disease. However, most studies have failed to demonstrate a poorer breast cancer prognosis in patients with family histories of BOC [6–8].

Similarly, a first-degree family history of other cancers (FHOC) than BOC has also been reported to be a risk factor for breast cancer. A family history of cancer of the esophagus, lung, digestive system, or prostate in first degree-relatives has been directly associated with an increased risk for breast cancer [9–11]. Furthermore, a FHOC has been associated with different hormonal status. For example, Bethea et al. demonstrated that FHOC was associated with an increased risk for breast cancer and that associations may differ by subtype in African American women. In addition, a family history of cervical cancer has been associated with an increased risk for estrogen receptor (ER)-negative cancer [10]. Zhou et al. found that breast cancer patients with a family history of digestive tract cancer were much younger [9]. All of these conditions may have an impact on the prognosis of breast cancer. To the best of our knowledge, few studies have detected an association between FHOC and breast cancer prognosis. This study was carried out to

* Corresponding author. Department of Breast and Thyroid Surgery, Renmin Hospital of Wuhan University, No 238 Jiefang Road, Wuchang District, Wuhan, Hubei, 430060, PR China.
E-mail address: sun137@sina.com (S.-R. Sun).
[1] These authors contributed equally to this work and should be considered co-first authors.

http://dx.doi.org/10.1016/j.breast.2017.01.016
0960-9776/

clarify this issue.

2. Material and methods

2.1. Population

A hospital-based cohort of women that were diagnosed with invasive breast cancer at the Renmin Hospital of Wuhan University from 2010 to 2013 were included in this retrospective study. Participants fulfilling the following criteria were selected from the cohort:

1 Patients diagnosed with invasive breast cancer;
2 Patients with complete documentation of first-degree family history;
3 Patients with stage I-III disease;
4 Patients with follow-up information.

Patients were excluded if there was no documentation of their family history and/or if they were diagnosed with stage IV disease. Patients diagnosed with carcinoma *in situ* were also excluded from this study. Given the poor reliability in terms of the recollection of cancer in second-degree relatives [12], only first-degree relatives were used in our analysis to obtain the most reliable family history. This study was performed with the approval of the Ethics Committee of the Renmin Hospital of Wuhan University, and all the participating patients provided written informed consent for their clinical data to be reviewed and applied in this study.

2.2. Histological evaluation

Immunohistochemistry (IHC) was used to evaluate the ER, progesterone receptor (PgR) status. ER and PgR were reported as positive when ≥1% tumor cells showed nuclear positivity. The Ki-67-labelling index was considered high when staining was present in >14% of tumor cells. Human epidermal growth factor receptor type 2 (HER2) status was evaluated by IHC first. In IHC analysis, score of 0 and 1 + were considered negative, and scores of 3 + as positive. Patients with score of 2 + were subjected to analysis by fluorescence *in situ* hybridization. According to theses IHC markers, breast cancer was divided into for subtypes: luminal A (ER+, PgR+, HER2-, and Ki-67 low), luminal B (ER+, HER- and either Ki-67 high or PgR-), luminal B-like (ER+, HER2+, any Ki-67, and any PgR), HER2+ (ER-, PgR-, and HER2+), and triple negative (TN) (ER-, PgR-, and HER2-).

2.3. Treatment

All of the patients received surgical treatment for the primary tumor with or without axillary lymph node dissection depending on the sentinel lymph node status. Adjuvant or neoadjuvant chemotherapy were recommended for indicated patients. Most of the chemotherapy regimens included anthracycline-based chemotherapy. Three or four cycles of epirubicin/cyclophosphamide with or without fluorouracil, followed by three or four cycles of docetaxel ((F)EC-T), was the most commonly used regimen. Four or six cycles of TC or FEC were also recommended for patients. For those patients with stage I luminal A breast cancer, endocrine therapy rather than chemotherapy was recommended. Generally, tamoxifen was administered to breast cancer patients. But for postmenopausal patients, aromatase inhibitors were also prescribed. Radiotherapy was recommended for those patients with lymph node involvement or breast conserving surgery.

2.4. Data collection

The following demographic and clinical characteristics were extracted: age, body mass index (BMI), menopausal status (yes or no), grade, Ki-67, TNM stage, ER, PgR and HER2 status, and systemic treatments (including chemotherapy, endocrine therapy, or radiotherapy). FHOC was patient-reported.

All the patients were followed up according to the hospital's standard procedure. If the patients did not return to the clinic for more than one year, they were followed up through telephone calls. All follow-up information, including the cause of death, date of death, date of last follow up, date of disease recurrence, and site of recurrence, were recorded. Due to the limited follow-up time, disease-free survival (DFS) was determined to be a more appropriate main endpoint. All patients were followed until the earliest date of death, the date last known to be alive, or the end of follow up (i.e., June 2016).

2.5. Statistical analysis

The distribution of clinical and pathologic features of the family histories was evaluated and compared using chi-square tests for categorical variables and the student's t-test for continuous variables. The follow-up time was defined as the start of treatment (start time of surgery or neoadjuvant chemotherapy) until recurrence or until the last follow-up. Survival was analyzed with the Kaplan–Meier method and the log-rank test. In addition, The Cox proportional-hazards model was used to assess the association between family history and the DFS. All models were adjusted for age, menopausal status, BMI, grade, Ki-67 score, hormone receptor status, HER2 status, TNM stage, systemic treatments and endocrine therapy duration, computing hazard ratios (HRs), and corresponding 95% confidence intervals (CIs) to assess the relative excess risk of recurrence among patients with a positive FHOC versus those with a negative FHOC. All the statistical calculations were performed using Stata version 12.0 (StataCorp, College Station, Texas). The significance level was set at $p < 0.05$.

3. Results

3.1. Characteristics of patients

A total of 48 women with missing follow-up or family history data and 16 patients who were diagnosed with carcinoma *in situ* were excluded. A total of 434 patients were included. The follow-up times ranged from 3 to 79 months (with a median of 39 months). With regard to the FHOC, the median follow-up time was 37 months for patients with FHOC and 39 months for patients with no FHOC. Of the included 434 breast cancer patients, 61 (14.06%) had a positive FHOC. Table 1 presents the types of family history cancer. And Table 2 presents the clinical and pathological characteristics of

Table 1
The types of family history cancer.

Family history of cancer	Number of patients	Proportion
Liver cancer	11	2.53%
Esophageal cancer	8	1.84%
Lung cancer	15	3.46%
Gastric cancer	10	2.30%
Lymphoma	4	0.92%
Colorectal cancer	3	0.69%
Cervical cancer	3	0.69%
Breast cancer	18	4.15%
Ovarian cancer	3	0.69%
Other cancer	12	2.76%