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Breast cancer among older women: The influence of age and cancer stage on survival☆

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ABSTRACT

Purpose of study: To describe the association between increasing age and survival among women aged over 65 years, diagnosed with breast cancer.

Materials and methods: A historical prospective cohort study, comparing 3270 breast cancer patients to 13,163 non cancer age matched controls. Baseline characteristics and cancer data gathered from the Israeli Central Bureau of Statistics (1995), the Israel Cancer Registry (2000–2010). Baseline measurements included age, socioeconomic status. Cancer stage at diagnosis was clustered as stage I, stage II–III and metastatic. Cox Proportional Hazards regression models were used to determine Hazards Ratios (HR) for mortality.

Results: Between ages 65–69 and ≥85, metastatic disease rose from 3.9% to 23.4% and stage I disease declined from 58.6% to 30.1%. At age 80–84, 50% life expectancy among controls, stage I, and stage II–III disease was 95,92 and 90 months respectively, compared to 2 months for metastatic disease. Compared to controls, between the age 65–69 to ≥85, adjusted HR's progressively decreased among subjects with stage I from HR 0.96 (95% CI 0.69–1.33) to 0.60 (95%CI 0.36–1.01), stage II–III from HR 3.26 (95%CI2.58–4.12) to HR 1.60 (95%CI 1.22–2.09), and metastatic disease from HR 57.40 (95%CI 39.56–83.29) to HR 20.76 (95%CI 14.73–29.24).

Conclusions: This study describes the increasingly poor prognosis and short life expectancy observed among women aged ≥80 diagnosed with metastatic breast. In contrast, our findings confirm the positive prognosis associated with rising age, among older women presenting with stage I breast cancer, among whom survival was similar, if not slightly better, than non-cancer age matched controls.

1. Introduction

Aging is a dominant risk factor for the development of cancer, and the number of older individuals with cancer is increasing, reflecting both the demographics of global aging, as well as continued advances in early detection and treatment of cancer (Rowland & Bellizzi, 2014; Schonberg, 2016; Schonberg, Silliman, McCarthy, & Marcantonio, 2012). Breast cancer is among the leading cancers in developed countries, with the incidence reaching its maximum among women 75–79 years of age (Silliman, 2009).

In order to rationally approach decision-making in breast cancer treatment among the elderly, it is important to anchor decisions with both quantitative estimates of life expectancy and risks of death. Data from the overall population indicates that the mean 5-year survival is greater than 80% for women diagnosed with breast cancer in Europe and over 90% in the United States (Rosso et al., 2010). Unfortunately, the more advanced the patients' age group, the less evidenced-based data there is available to make decisions concerning treatment efficacy (Schonberg et al., 2012). This is due to the consistent under representation and minimal participation of older patients in well-

*Abbreviation:*OECD, Organisation for Economic Co-operation

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designed studies (Lichtman et al., 2007; Scher & Hurria, 2012). For example, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) incorporates all data from individuals 70 years and older as one homogenous group, thus making modeling and generalizability challenging for individuals that are much older (Early Breast Cancer Trialists' Collaborative Group, 2011). The lack of certainty concerning survival among older women with breast cancer, particularly those over 80 years old, is compounded by conflicting data from heterogeneous age groups, various stages of illness, and lack of matched controls (Schonberg et al., 2010).

Like many other developed countries, breast cancer is the leading cancer among women in Israel, with an age adjusted incidence rate of 96.8/100,000 cases per year which is higher than the average rate among OECD countries (71.6/100,000) (State of Israel Ministry of Health Breast Cancer Data, 2010). Comprehensive health care coverage in Israel is a universal right of all citizens, is highly accessible, and is accepted as meeting the standards of Western medicine (Chernichovsky, 2009). The aim of the current study is to examine differences in survival among older women diagnosed with breast cancer, according to age and disease stage at time of diagnosis. To reach this end, we used nationwide data from the Israeli National Census, the Israel National Cancer Registry, and the Israeli Population Registry, to describe the survival of women aged 65 and older when diagnosed with breast cancer, according to cancer staging at diagnosis, and stratified into 5-year age groups, in comparison to a matched non-cancer control group.

2. Materials and methods

2.1. Study population

Israel is a small country; it is approximately 470 km long, and 135 km at its widest point, with a population of approximately 8 million people. This study is a nested case control study with cohort inception and baseline measurement from the Israeli Central Bureau of Statistics 1995 census (Rottenberg, Zick, Barchana, & Peretz, 2013). The study frame population includes two population groups: 1) a representative sample of the whole population who completed a comprehensive interview (20% of all the population in Israel) and 2) the entire population of northern Israel. These two groups were merged into a single database in order to avoid duplication. The final database consisted of 2,337,375 persons and encompassed an estimated more than one third of the entire population in Israel. Only women were included in the current study.

2.2. Subjects with Breast cancer

Data on cancer incidence was ascertained using the Israel National Cancer Registry updated to 2010. Completeness of the registry was found to be about 95% for solid tumors (Barchana, Liphshitz, & Rozen, 2004). All patients who were diagnosed with breast cancer, aged 65 years old and more at time of diagnosis between January 2000 and December 2010, were included in the current study. Breast cancers were clustered as stage I,stage II–III (tumor larger than 5 centimeters or breast cancer cells found in the lymph nodes) or metastatic disease. A total of 4966 women were identified with breast cancer between the 1st January 2000–31st December 2010, of whom 1696 had missing data concerning staging or incomplete data. The resulting 3270 women with breast cancer were included in the study.

2.3. Controls

Non-cancer controls were randomly sampled in ratio 1:4 from the general population group according to 5 year age groups (65–69, 70–74, 75–79, 80–84, > 85 years). Controls with a diagnosis of any cancer, or who had died before diagnosis of the matched breast cancer patient, were excluded. Matching using five-year age groups resulted in 13,163 non-cancer controls.

2.4. Study variables

Variables assessed in relation to mortality risk after diagnosis of breast cancer included: age; staging at diagnosis (stage I, stage II–III, metastatic); socio-economic status based upon residential location according to a verified national classification, (continuous variable graded 1–10 from lowest to highest status) (Levine et al., 2013); and ethnicity (self-defined Jewish vs. Non-Jewish). For persons in the non-cancer control group, follow-up was defined based on the time of diagnosis of the match to the cancer patient.

2.5. Survival outcome

Start of follow-up was from the date of diagnosis (between January1st 2000–December 31st 2010) until date of death or December 31st 2011, whichever was first. Mortality data were collected from January 1st 2000–31st December 2011, thus resulting in a maximum possible follow-up of 144 months (12 years), and a minimum potential follow-up of 12 months.

2.6. Statistical analyses

We compared survival by age groups using Kaplan-Meier curves, and determined survival time (months) at 25%, 50%, and 75% percentiles. To examine the impact of cancer stage upon mortality, we constructed Cox Proportional Hazards regression models, stratified per age groups (ages group: 65–69, 70–74, 75–79, 80–84 and 85 years and more), adjusting for cancer stage, socio-economic status and ethnicity. We verified the proportional hazards assumption by inspecting log-minus-log plots. Mortality Hazards (HR) ratios were calculated in reference to the control group (HR = 1.0). For all analyses $p < 0.05$ was considered statistically significant. The SPSS program (15th version; Chicago, Illinois) was used for the statistical analysis. This study was approved by the Committee on Human Research at the Hadassah Hebrew University Medical Center.

3. Results

A total of 3270 breast cancer patients and 13,163 matched controls, aged > 65 years old, were included in the current study. During the follow-up period, the overall mortality among the breast cancer patients was 27.95% (n = 914/3270) compared to 20.3% (n = 2677/13163) among the controls. The overall frequency at diagnosis of stage I, stage II–III or metastatic breast cancer was 56.7%, 37.0%, and 6.3% respectively. Between ages 65–69 and ≥85, metastatic disease rose from 3.9% to 23.4% ($p < 0.001$), stage I disease declined from 58.6% to 30.1% ($p < 0.001$), and stage II–III disease at diagnosis increased from 37.4% to 46.4%($p = 0.04$, Table 1). Certain differences between control, stage I, stage II–III, and metastatic disease at each age group were observed for socioeconomic status, ethnicity, and duration of follow-up: poor socioeconomic status was generally least frequent among subjects with stage I, Jewish ethnicity was generally more common among women with cancer, and duration of follow-up consistently declined with advancing cancer stage.

As seen in Fig. 1, survival curves among women with stage I breast cancer at diagnosis were identical to controls at ages 65–69. With advancing age survival was actually observed to be greatest among women with stage I breast cancer, such that by age > 85 years the 25%, 50%, and 75% percentile life expectancy for controls was 29, 54, and 86 months versus 40, 68, and 101 months for stage I breast cancer (Table 2). While survival was consistently worse among individuals with stage II–III breast cancer at diagnosis, the magnitude of the difference was observed to gradually decline with rising age. In contrast,