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Risk of cancer death by comorbidity severity and use of adjuvant chemotherapy among women with locoregional breast cancer

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ABSTRACT

Objectives: To examine the associations of comorbidity and chemotherapy with breast cancer- and non-breast cancer-related death.
Materials and methods: Included were women with invasive locoregional breast cancer diagnosed in 2004 from seven population-based cancer registries. Data were abstracted from medical records and verified with treating physicians when there were inconsistencies and missing information on cancer treatment. Comorbidity severity was quantified using the Adult Comorbidity Evaluation 27. Treatment guideline concordance was determined by comparing treatment received with the National Comprehensive Cancer Network guidelines. Kaplan–Meier method and multivariable Cox proportional hazards regressions were employed for statistical analyses.
Results: Of 5852 patients, 76% were under 70 years old and 69% received guideline concordant adjuvant chemotherapy. Comorbidity was more prevalent in women age 70 and older (79% vs. 51%; $p < 0.001$). After adjusting for tumor characteristics and treatment, severe comorbidity burden was associated with significantly higher cancer-related mortality in older patients (Hazard Ratio [HR] = 2.38, 95% CI 1.08–5.24), but not in younger patients (HR = 1.78, 95% CI 0.87–3.64). Among patients receiving guideline adjuvant chemotherapy, cancer-related mortality was significantly higher in older patients (HR = 2.35, 95% CI 1.52–3.62), and those with severe comorbidity (HR = 3.79, 95% CI 1.72–8.33).
Conclusions: Findings suggest that, compared to women with no comorbidity, patients with breast cancer age 70 and older with severe comorbidity are at increased risk of dying from breast cancer, even after adjustment for adjuvant chemotherapy and other tumor and treatment differences. This information adds to risk–benefit discussions and emphasizes the need for further study of the role for adjuvant chemotherapy in these patient groups.

1. Introduction

Providing appropriate treatment to older patients with breast cancer with comorbidities is a challenge due to lack of high quality evidence from clinical trials. Most patients with breast cancer, however, are age 50 years or older at diagnosis and have at least one comorbidity [1]. With aging of the general population, even more women with comorbidities will be diagnosed and treated for breast cancer.

Studies show a direct relationship between comorbidity and both breast cancer-related and competing-cause mortality, but an inverse association between comorbidity and adjuvant chemotherapy use, such that it is difficult to determine how much of the higher cancer mortality rate in women with comorbidity is due to lack of appropriate adjuvant treatment [2–4]. Admittedly, higher cancer mortality may be due to either differential treatment quality, which is directly correlated with outcome; or it may be due to the direct effects of comorbidities or their treatment on disease biology. Hypertension, cardiovascular

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disease, and diabetes, for instance, have differential effects on breast cancer survival, disease course, and treatment [2,5,6]. In general, however, more severe comorbidity is associated with under-treatment, a phenomenon that, with adjuvant chemotherapy for breast cancer, may partly be due to withholding chemotherapy because of concern about undue toxicity [7,8]. The impact of comorbidity on the risk of cancer and non-cancer-related death among patients with breast cancer receiving adjuvant chemotherapy, however, has not been well studied.

In this study, we aimed to examine the relationship of comorbidity severity to five-year breast cancer-specific and non-breast cancer mortality in women receiving adjuvant treatment for breast cancer. Data were analyzed from a large population-based pattern of care (PoC) study in which registry data were enhanced with data abstracted from charts, allowing for the inclusion of key modifying factors, including guideline-concordant treatment, age, and others, in the analysis.

2. Methods

2.1. Data Sources

Breast cancer cases diagnosed in 2004 were randomly selected across strata of race/ethnicity in seven population-based state cancer registries (California, Georgia, Kentucky, Louisiana, North Carolina, Minnesota, and Wisconsin) for the Centers for Disease Control and Prevention's National Program of Cancer Registries (CDC-NPCR) Breast and Prostate Cancer Data Quality and Patterns of Care Study (POC-BP) study [9,10]. Information on initial course of treatment and comorbidities was re-abstracted from medical records at hospitals, pathology laboratories, free-standing radiation facilities, and ambulatory surgery centers to supplement data that these registries routinely collected. Treating physicians were contacted to obtain or verify required information, especially regarding adjuvant chemotherapy, when it was missing or incomplete in hospital medical records. Date of last contact, vital status, and cause of death were obtained from states' death certificate files and linkages with the National Death Index. All patients were followed through Dec 31, 2009, except those who died prior to this date.

The Institutional Review Board's approval was obtained from each participating institution.

2.2. Eligibility Criteria and Case Selection

Women age 20 years or older who were residents in the catchment areas and had surgery for microscopically confirmed first primary invasive, nonmetastatic breast cancer (International Classification of Diseases for Oncology, third edition, site codes C50.0–C50.9) in 2004 with no subsequent primary within four months were included. Excluded were cases with previous diagnoses of reportable cancers, Paget's disease, mesothelioma, Kaposi's sarcoma, or lymphoma. Cases from Veteran's Administration hospitals and those identified solely from death certificates or autopsies were also excluded.

The initial sample included 9142 cases. Exclusion criteria eliminated 3290 cases: more than one primary (n = 39); in-situ cancer (n = 1515); unknown American Joint Committee on Cancer (AJCC) stage (n = 256), distant stage (n = 400); unknown tumor size or lymph nodes status (n = 53); unknown hormone receptor status (n = 363); unknown comorbidity status (n = 111); no surgery or unknown surgery type (n = 80); unknown primary treatment status (n = 88); unknown guideline chemotherapy status (n = 142); unknown guideline hormone therapy (n = 124); cases where treatment received was in excess of guidelines (n = 91); loss to follow-up (n = 5); unknown cause of death (n = 23). The final 5852 cases were included in this data analysis.

2.3. Comorbidity

Comorbidity burden was measured using the Adult Comorbidity Evaluation-27 (ACE-27) index, which is specific for patients with cancer and has a dose–response relationship to survival [11,12]. This index includes 26 comorbid conditions with three levels of decompensation/severity (i.e., mild, moderate, and severe decompensation). The 26 comorbid conditions were grouped into twelve body organ systems: cardiovascular disease (myocardial infarction, coronary artery disease, congestive heart failure, arrhythmias, hypertension, venous disease, and peripheral arterial disease), respiratory disease, gastrointestinal diseases (hepatic, stomach/intestine, pancreas), renal disease, diabetes mellitus, nervous system (stroke or cerebrovascular accident, dementia, paralysis, neuromuscular disorders), psychiatric, rheumatological, acquired immunodeficiency syndrome (AIDS), cancer (solid tumor, leukemia, lymphoma) excluding the index cancer (i.e., breast cancer), substance abuse (alcohol abuse, illicit drugs), and morbid obesity.

Abstractors were trained with a validated internet-based program to obtain information on comorbidity severity by reviewing medical records. Levels of severity were determined according to diagnosis, medical history, and clinical and laboratory tests [13]. Comorbidities present at or prior to the cancer diagnosis were included; complications caused by cancer or cancer treatment were excluded. Each patient was assigned an overall comorbidity score (0-none, 1-low, 2-moderate, or 3-severe) based on the comorbidity with the highest rank single ailment, except in the situation where two or more moderate decompensations occurred in different organ systems, in which case, the overall comorbidity score was designated severe. A zero comorbidity score was defined as having no comorbidity or no comorbidity mentioned in medical records.

2.4. Cancer Treatment

All patients included in this analysis had a surgical intervention: lumpectomy or mastectomy. Local therapy included three groups: mastectomy, lumpectomy with radiation, and lumpectomy without radiation. Guideline adjuvant chemotherapy was defined based on the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, version 1, 2003, (https://www.nccn.org/) which applied to the breast cancers diagnosed in 2004. If a patient received chemotherapy, regardless of agent/regimens or dosages, they were included as 'received chemotherapy'. Adjuvant chemotherapy was categorized into three groups: did not receive chemotherapy because it was not recommended by the guidelines (not indicated by guideline), received chemotherapy recommended by guidelines (received guideline), and did not receive chemotherapy recommended by the guidelines (under treated). Endocrine therapy was grouped into three categories, parallel to those defined for receipt of adjuvant chemotherapy.

2.5. Explanatory Variables

We treated patients 70 years and older the same as younger patients when determining whether adjuvant chemotherapy was recommended by the NCCN guidelines (https://www.nccn.org/) in the univariate analysis, though guidelines acknowledge that data is sparse for those over 70 years old and treatment recommendations should be individualized based on comorbidity burden. Due to the small number of cases, especially in the group of severe comorbidity, sociodemographic variables were not included in the analysis except for age and race/ethnicity (i.e., non-Hispanic white, non-Hispanic black, Asian/Pacific Islander, American Indian/Alaska Native, and Hispanic). Clinical variables included tumor characteristics (i.e., regional lymph node status, tumor size, tumor grade, and hormone receptor status) and treatment type (i.e., surgery, radiation therapy, chemotherapy, and endocrine therapy).

Hormone receptor status was defined as positive [estrogen receptor (ER) + and/or progesterone receptor (PR)+], negative (ER and PR negative), or unknown (no information on ER and PR status). Human epidermal growth factor receptor 2 (HER2) status was defined as positive [3+ by immunohistochemistry (IHC) or amplified by fluorescent