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Competing mortality risks among women aged 50–79 years when diagnosed with invasive breast cancer, Queensland, 1997–2012

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ABSTRACT

Background: Understanding the burden of competing (non-breast cancer) mortality is important for the growing number of breast cancer survivors. We quantity these patterns, and the impact of two leading non-cancer causes of death, within ten years of breast cancer diagnosis.
Methods: Population based cancer registry study of 23,809 women aged 50–79 diagnosed with first primary breast cancer in Queensland, Australia, 1997 to 2012 with additional data linkage to identify individual non-cancer mortality causes. Flexible parametric competing-risks models were used to estimate the crude and adjusted probabilities of death.
Results: While overall mortality increased with age at diagnosis, this effect was strongest for non-cancer (such as cardiovascular and cerebrovascular disease) mortality. Women diagnosed with advanced breast cancer had a higher crude probability of breast cancer death (23.1% versus 4.5% for localised) but similar probability of competing mortality (11.6% versus 11.3%). Within each category of spread of disease, the probability of breast-cancer deaths remained relatively constant with age, while the probability of competing deaths increased. The 10-year probability of dying from breast cancer was 3.7%, 4.2% and 5.6% among women with localised disease aged 50 to 59, 60–69 and 70–79 respectively, but 3.1%, 7.8% and 22.9% for competing mortality. Increasing age, advanced disease and being unpartnered were independently associated with increased risk of breast cancer and competing deaths.
Conclusions: Promotion of improved health behaviors after a cancer diagnosis and development of individualized strategies for clinical management should be prioritized as part of optimal care for breast cancer survivors.

1. Introduction

Breast cancer remains a major health burden among females worldwide [1]. Advances in early detection and treatment [2] have contributed to the growing number of breast cancer survivors in developed countries [3]. However, a corollary of improved survival is the greater opportunity to develop other conditions including second primary cancers [4] or cardiovascular disease [5,6].

Given the increasing number of breast cancer survivors, there is a need to understand, at the population level, which subgroups of women are at higher risk of dying from causes other than their breast cancer. Competing risk methods allow the estimation of an absolute measure of the probabilities of dying from specific causes, thereby potentially providing women with better-informed prognostic information based on individual characteristics [7,8].

"Competing deaths" in the context of this study refers to mutually exclusive causes of death other than the primary breast cancer. Several population-based studies [9–13] have reported that the crude probability of competing deaths increased with

Abbreviations: Australian Bureau of Statistics, ABS; Bayesian Information Criterion, BIC; Socioeconomic status, SES; Queensland Cancer Registry, QCR.

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advancing age at breast cancer diagnosis. Up to 10 years after diagnosis, breast cancer remained the most probable cause of death among younger women, while older women were as likely or more likely to die from other causes [9–13], notably cardiovascular disease, within this period [12,13]. However, most of these studies [9–11] treated all non-breast cancer deaths as a single competing event, with only two [12,13] considering individual causes of competing mortality.

As part of a competing risks study across multiple cancer sites, we have previously reported the risks and crude probability of breast cancer, other cancers and non-cancer deaths for women diagnosed with breast cancer in Queensland, Australia, 1996 to 2012 [14]. Here, we quantity these patterns in greater detail especially regarding the impact of prognostic factors on the risks of overall and specific non-cancer mortality causes.

2. Material and methods

Ethical approval was obtained from the Griffith University Human Research Ethics Committee (PBH/34/13/HREC) and Queensland Health.

2.1. Study cohort

We identified all women aged 50–79 years diagnosed with a first primary invasive breast cancer (ICD-O3 C50) during 1997–2012 from the population-based Queensland Cancer Registry (QCR), to which notification of all new non-keratinocytic cancers is a statutory requirement [15]. Cases identified at death or autopsy (n = 34, 0.1%), with multiple primary breast cancers (n = 53, 0.2%) or who survived for less than one day (n = 24, 0.1%) were excluded.

Although the QCR does not collect stage information, data collected since 1997 on maximum tumour diameter and lymph node status [15] allowed a measure of breast cancer spread of disease at diagnosis to be determined [16]. Cases were defined as 'localised' if $\leq$ 20 mm diameter with no evident nodal spread or metastases while all other cases were categorized as 'advanced.

The travel time from a woman's residential area at diagnosis to nearest radiation facilities was used as a measure of accessibility to optimal cancer treatment [17]. Area-level socioeconomic status (SES) was measured by the Index of Relative Socioeconomic Advantage and Disadvantage [18].

2.2. Causes of death

The QCR routinely matches all cancer notifications against the Queensland Registrar of Births, Deaths and Marriages and the National Death Index and independently assigns the specific cause of death codes for all cancer deaths [15].

Information on specific non-cancer mortality causes up to 31 December 2013 were obtained by matching the QCR dataset against national death data compiled by the Australian Bureau of Statistics (ABS) [19]. Broad disease categories were defined using ICD-9 (before 1999) and ICD-10 classifications (1999 onwards) [20].

Due to the additional information used by the QCR in assigning specific causes of cancer deaths, QCR codes were used for all cancer deaths [15,21].

2.3. Survival

Survival was measured in days from the date of diagnosis to death, 10 years after diagnosis, or the study end point (31 December 2013), whichever came first. Cases alive at the end of the follow up period were censored.

Cause of death was grouped into the four leading categories: breast cancer, other cancers, cardiovascular disease and cerebrovascular disease with all remaining non-cancer causes being combined as "Other causes" (to give sufficient numbers in cells for modelling) (Supplemental Table 1).

2.4. Statistical analysis

All statistical analyses were performed with Stata/SE version 14.2 (StataCorp, TX, USA).

Competing risk analyses were conducted within a flexible parametric framework, which use restricted cubic splines to estimate the baseline log hazard function with additional splines to relax the assumption of linearity of log time [22]. All models were fitted using the *stpm2* package [22].

Flexible parametric models can estimate both the impact of covariates on cause-specific hazard rates and an absolute measure of the crude probabilities of death in competing risk scenario, which is advantageous in terms of better understanding the risk factors and realistic implications for patients [12]. This differs from the standard Cox models for estimating cause-specific hazards [23,24] or Fine and Grey competing risk method for modelling covariate effects on the crude probabilities of death [25].

Flexible parametric models were used to determine the five cause-specific mortality rates simultaneously [12,26] with the baseline hazard function being allowed to vary for each cause [14]. Final models were adjusted for age, partner status, spread of disease, grade, surgery, residential accessibility and disadvantage. Interaction terms between each cause of death and each covariate allowed the covariate effect to differ across the five causes. Likelihood ratio-tests supported the inclusion of age and spread of disease as time-varying components. The optimal number of knots for the baseline hazard (five) and time-varying (four) effects were determined based on the Bayesian Information Criterion (BIC).

Results are presented as model-based estimates of both the impact of covariates on hazard rates and an absolute measure of the cause specific crude probabilities of death using cumulative incidence functions. Adjusted cause-specific hazard ratios (HRs) with associated 95% confidence intervals (CI), were derived from the models. Crude probabilities of death were calculated as a function of time since diagnosis through a transformation of the cause-specific hazards from the same models using the post-estimation command *stpm2cif* [26]. Confidence intervals for these probabilities could not be generated due to computational problems during their numerical integration [26].

Sensitivity analyses for the effect of unknown spread of disease (6% of cohort) were performed by repeating analyses assuming all unknown cases were either localised, advanced or randomly distributed equally over the two categories.

Standardised mortality rate ratios (SMR), calculated as the ratio of observed to expected number of deaths, were also estimated by each cause of death to gain insight into the relative mortality risks for our cohort versus the general female population in Queensland. Unit record file population mortality data for Queensland from the ABS [27] and the Australian Coordinating Registry [28] were categorized into same broad disease categories (Supplemental Table 1) as for the cancer cohort. Full details of the calculation method have been published previously [29].

3. Results

The final cohort comprised 23,809 women, of whom 4167 (11%) died within 10 years of diagnosis. Of those deaths, 2660 (64%) were from breast cancer, 475 (11%) other cancers, 325 (8%) cardiovascular disease, 153 (4%) cerebrovascular disease and 554 (13%) from other non-cancer causes (Table 1). Breast cancer accounted for 82% of