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Impact of subtypes and comorbidities on breast cancer relapse and survival in population-based studies

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ABSTRACT

Objective: To study the impact of subtypes and comorbidities on breast cancer (BC) relapse and survival in the heterogeneous patients of the real world.
Methods: We identified patients diagnosed with BC between January 2003 and December 2005 from six population-based Swiss cancer registries. Clinicopathologic data was completed with information on locoregional and distant relapse and date and cause of death for over 10-years. We approximated BC subtypes using grade and the immunohistochemical panel for oestrogen, progesterone and human epidermal growth factor 2 (HER2) receptor status. We studied factors affecting relapse and survival.
Results: Luminal A-like subtype represented 46% of all newly diagnosed BC (N = 1831), followed by luminal B-like (N = 1504, 38%), triple negative (N = 436, 11%) and HER2 enriched (N = 204, 5%). We observed regional disparities in subtype prevalence that contribute to explain regional differences in survival formerly described. Disease relapse and BC specific mortality differed by subtype and were lower for luminal A like tumours than for other subtypes for any stage at diagnosis. After a median follow-up of 10.9 years, 1311 (33%) had died, half of them 647 (16%) due to another disease, showing the importance of comorbidities. Omission of systemic therapies in selected patients was not associated with poorer BC specific survival, BC subtype and life expectancy playing a role.
Conclusions: Information on tumour subtype is necessary for an adequate interpretation of population-based BC studies. Measures of comorbidity or frailty help in the evaluation of quality of care in the highly heterogeneous patients of the real world.

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1. Introduction

Nowadays, breast cancer (BC) is recognized as a heterogeneous disease, both on a molecular basis and in terms of clinical behaviour. Microarray analysis has identified BC subtypes with distinct gene expression profiles [1]. Numerous subsequent studies have further shown that these molecular (intrinsic) subtypes predict recurrence and contribute additional prognostic value to standard clinicopathologic factors like tumour size and extent of nodal

involvement [2—4]. As gene expression signatures are not universally used, the prevalence and impact of intrinsic subtypes on survival in the general population of BC patients is less well characterised. In clinical practice subtypes are often approximated by immunohistochemistry (IHC) using the oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor 2 (HER2) receptor status and a marker of proliferation (Ki67 and/or grading) [5].

Epidemiologic data on BC outcomes by subtypes are scarce and highly needed for defining policies to reduce the burden of disease in the real world. Trials are often conducted in unrepresentative patient populations, patients that are younger and with less comorbidity than average clinical populations. Management strategies in real life practice require taking into account not only tumour biology and risk, but also host biology and patient preferences [6]. Variations on functional status, cognition and comorbidity may influence tolerance to cancer therapy as well as the overall risk-benefit ratio of cancer therapies [7]. Surveillance, Epidemiology and End Results (SEER) registries collect ER, PR and HER2 receptor status since 2010 allowing for tumour biology specific cancer incidence statistics. Hormone receptor (HR) positive and HER2 negative tumours had highest incidence rates among local stage cases and low poverty areas and were strongly positively correlated with mammography use [8]. More recently, Chavez-MacGregor et al. [9] showed the importance of incorporating subtypes to the anatomical stage system for patients of the California Cancer Registry when analysing BC specific survival (BCSS) and overall survival (OS). However, big epidemiological studies documenting survival differences of women with BC across European countries [10,11] and worldwide [12] have failed to adjust for BC subtypes. In Switzerland, regional disparities in 5-year stage-corrected survival rates [13] and in patterns of care [14,15] have been described, but the impact of BC subtypes on regional disparities in survival remained unclear so far.

The aim of the present study is to investigate the long-term (10-year) impact of tumour subtype, substandard therapies and comorbidities on disease relapse and BC specific mortality in the heterogeneous patients of the real world.

2. Methods

2.1. Study population and variables

The present study is a follow-up of patients recruited for the "Patterns of Care in Breast Cancer in Switzerland Study". The methodology for this study has been described elsewhere [14]. In short, female patients diagnosed with invasive BC between January 2003 and December 2005 and living in the catchment area of six population based cancer registries in Switzerland (Geneva, Valais, Ticino, Zürich, St. Gallen-Appenzell and Grisons-Glarus) were included in the study. These registries are regular and long-time contributors to the International Agency for Research on Cancer (IARC). Cases diagnosed solely on autopsy or death certificate were excluded from the study as well as patients with non-epithelial neoplasia ($N = 16$) and patients with previous BC ($N = 192$). We ascertained clinicopathologic and patient demographic data including patient age and place of residence at the time of diagnosis, clinical presentation of disease, tumour size, number of examined and positive lymph nodes and tumour grade. Type of surgery, administration of radiotherapy and systemic therapies and the regimens used were assessed. Patients were followed for vital status, date and type of disease relapse, treatments at first relapse, cause and date of death. Cause of death was ascertained by medical chart review and from the cause of death statistic of the Federal Statistical Office. Patients that moved outside the catchment area of the registry and for whom no information on vital status and disease relapse was available were considered lost to follow up at the date of last contact. Comorbidities were extracted from medical reports and evaluated using the Charlson comorbidity index.

Primary endpoints of this study were BC specific outcomes: BC death, distant recurrence and isolated locoregional recurrence (LRR). Isolated local recurrence was defined as disease relapse within the breast after breast-sparing surgery or within the ipsilateral chest wall after mastectomy or in the ipsilateral axillary, supraclavicular or internal mammary lymph nodes in the absence of distant relapse. A breast carcinoma developing in the contralateral breast was viewed as a new primary tumour and not as relapse. Distant recurrence was defined as metastasis to other sites. The secondary endpoint of this study was overall survival (OS), defined as the time elapsed from date of first diagnosis to death of any cause; while BC specific survival was defined as the time elapsed from date of first diagnosis to death with progression of BC. Follow − up duration was calculated in the subgroup of living patients as the time elapsed between the date of diagnosis and the date of end of follow-up.

Subtype approximation was performed based on IHC biomarkers including expression of ER, PR, HER2 status and grade as a proxy for proliferation according to the St Gallen Consensus Conference 2017 [5] and the Cancer Genome Atlas Network [16]. We used histological grade, as marker for proliferation because information on Ki67 was not always available. HER2 unknown status was considered as negative. We classified tumours as luminal A like (lumA-like) if they presented high (>50%) ER/PR expression, HER2 negative status and low-intermediate histological grade (grade 1 and 2). We included in the luminal B like (lumB-like) category those tumours with ER and/or PR expression not qualifying for lumA-like category. We classified as HER2 enriched those tumours with no expression of ER and PR receptors and HER2 over-expressed or amplified. We included in the TN group those tumours with no expression of ER, PR and non-amplified HER2 status. We excluded 126 women (3%) that could not be classified within one of these subtypes because of unknown ER, PR and HER2 status.

2.1.1. Statistical analyses

We compared categorical variables using the chi-square test. To analyse factors influencing disease relapse, BC death and overall survival we used time-to-event methods that accounted for censoring and follow-up time. Kaplan-Meier methods were used to analyse rates of disease relapse or survival, whereas we used Cox proportional hazards regression analysis to estimate hazard ratios (HRs) and 95% confidence intervals (CI) of the outcome of interest in multivariate analysis. The proportional hazard assumption was checked. All models included subtype, age and stage at diagnosis, received therapies, comorbidities, and canton of residence. Patients not experiencing the outcome of interest, i.e. disease relapse or BC death, were censored at the date of the last contact. In order to study the effect of censoring of patients dying from other causes on the hazard of dying from BC we performed for BCSS a competing risk regression according to the method of Fine and Gray [17] using the stcrreg function from Stata. Results from Cox and competing risk regression were similar.

We used margin estimations (performed by the "margins" command) to estimate and visualize adjusted predictions of BC specific mortality for the different subtypes at different stages at diagnosis after fitting a model including stage, age at diagnosis and subtype.

All tests of significance were two sided; $P < 0.05$ was considered to be significant. All statistical analyses were carried out using STATA 14.1 software (STATA Corp., College Station, TX).