Cancer registries - guardians of breast cancer biomarker information: A systematic review

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Abstract

Background: Breast cancer is the most common cancer and the leading cause of cancer-related death in females, with a large societal and economic impact. Decisions regarding its treatment are largely affected by the categorization into different subtypes with hormone receptor status and HER2 status being the most important predictive factors. Other biological markers play an important role for prognostic and predictive reasons. The data collection and harmonization of cancer cases are performed by cancer registries whose collection of parameters largely differs, partially including results from biomarker testing.

Methods: This systematic literature review consisting of a total of 729 reports determined whether information about biomarker testing in breast cancer cases is collected and published by cancer registries worldwide.

Results: The number of publications using breast cancer biomarker data from registries steeply rose with the beginning of the 21st century and some hospital-based and population-based cancer registries reacted with immediate collection of biomarker data following the recommendation of clinical guidelines. For female breast cancer, biomarkers have achieved an essential clinical value and this review points to a steady increase in the collection of biomarker data by cancer registries during the last decade.

Conclusions: In the future, recommendations for biomarker data collection and coding by cancer registries may be required to ensure harmonization and comparability of the data.

Keywords

Biomarkers, cancer registries, breast cancer < disease sites, prognostic/predictive markers < markers, molecular markers

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Introduction

Biomarkers generally measure biological states that are objectively determinable by experiments. Biomarkers can be used as indicators for normal biological processes, treatment response, or pathogenic processes. The definition of biomarkers in the context of cancer includes substances produced by the cancer cells themselves or by the body in response to the tumor. These substances range from macromolecules such as RNA, DNA, genetic mutations, or proteins to whole cells. To date, no biomarker is sufficiently specific for cancer screening purposes. However, they are used in diagnosis, prognosis, staging, subtype differentiation, or treatment response of different types of cancer. While the research and discovery of new
Results and discussion

Onset of the collection of BC biomarker data by cancer registries

Cancer registries are a valuable source of information to evaluate cancer burden in the population, plus cancer care quality and treatment effects in the real world. Their scope, with respect to the number and types of variables collected, may differ between countries, regions, and individual registries. We used this study to identify the data on biomarkers included in clinical guidelines for BC and collected by cancer registries. The review comprised 729 publications (Figure A(1)), with sample numbers ranging from 10 patients to 34 million patients (SN3; Figure A(2)). The first reports were published as early as 1984 (Figure 1(a)). A substantial increase in the number of publications using BC biomarker data collected by registries occurred at the beginning of the 21st century. The same trend was observed for hospital-based and population-based registries, which meant that the data were available immediately to population-based registries with minimal time delay (Figure A(3); Figure 1(b)). Our search string resulted in a higher number of publications with data from population-based cancer registries (578) compared to hospital-based registries (155). This may be explained by the better availability of the data from population-based cancer registries to the research environment, but it also may be affected by the search string itself as hospitals, which did not carry “registr*” in their name in the title, abstract, or keywords of an article, were not included in the analysis. An overview of the temporal distribution of publications from population-based cancer registries for individual countries is displayed in Figure A(4)). In summary, the onset of frequent biomarker data use collected by cancer registries for publication is around 2000, with a development paralleling the recommendations issued in clinical guidelines.

Geographical distribution of biomarker data use from cancer registries

Geographically, more than half of the publications (449) used data from North America—more specifically the US (418) (Figure 2). The number of publications from Europe was around half of that of the US (214). A total of 73 studies used data from Asia, 26 from Australia and New Zealand, 9 from Africa, and 6 from Central and South America. The distribution of publications within Europe ranged from numbers down to zero for some Eastern European countries (a total of 3 publications) and up to 20–30 publications in countries from Northern (total of 79), Western (91), and Southern (41) Europe (Figure A(5)). Interestingly, the temporal distribution of the published biomarker data collected by cancer registries did not differ between North America and Europe (Figure A(6)). An overview of the registries found to publish biomarker data is shown in Supplementary Table A(1).

Several reasons—apart from the collection of biomarker data by registries, such as the language of publication—can lead to the discrepancy in the number of publications from different regions of the world. Additionally, the use of biomarkers in the clinics may differ although American and European clinical guidelines have similar approaches on biomarker use.
It is interesting to note that more than half of the US–American publications retrieved their data from a common data source, the Surveillance, Epidemiology, and End Results Program (SEER), which has been collecting data regarding the ER and PgR status since 1990. The establishment of a common database of European cancer data is thus expected to greatly facilitate studies at the European level, and will result in a multitude of publications as the success of the SEER database indicates. Furthermore, the steep increase in the number of publications around the year 2000 was mainly influenced by publications using ER and PgR data (Figure 3(b)). Although the role of ER in BC has long been known, early biochemical testing of these receptors was only possible with large tissue sections, and routine ER and PgR testing could only be introduced upon the establishment of immunohistochemical (IHC) analysis. A first guideline discussing the promise of ER IHC testing was published by Hutter in 1990.

Biomarker testing for adjuvant treatment decisions was reported less frequently (Figure 3(a)). Ki-67 status was found in 3% of the publications only. A lack of standardization and comparability of Ki-67 testing results has been described, which makes a harmonized collection of Ki-67 data difficult, and may be one of the reasons that explains the low number of publications. CEA, CA15.3, or CA27.29 were found even less frequently (0.1%–0.2% of publications). A single value of these biomarkers is usually not expressive, and these biomarkers can be tested regularly to follow the treatment response or metastatic BC. These multiple tests make data collection more challenging for the registries. Surprisingly, we did not observe the use of uPA and PAI-1 data in any of the publications, although these biomarkers are recommended in clinical guidelines for adjuvant treatment decisions since 2005 and testing comes at low tissue requirements and costs. Multigene expression assays—such as the 21- or 70-gene recurrence score used for similar prognostic reasons and chemotherapy applications—on the other hand, were found by our literature search from 2015 onwards (1% of publications). Their use and cost effectiveness have been described in a large variety of publications. However, owing to the large number of different tests, their results may not be easily collected in a standard format by the cancer registries. Genetic testing of BRCA1, BRCA2, or p53 has been published by cancer registries since 2001 with a rise in the numbers of publications (3%, 2%, and 0.5%, respectively) from 2009 onwards.

When compared to national or international recommendations of these biomarkers in clinical guidelines, the immediate onset of the clinical use and data collection by the registries was visible as the difference between the first time point of clinical recommendations for each of the biomarkers is shown as an arrow of the respective color.
of recommendation and the publication (Figure 3(b)). A closer investigation of the time between the recommendation and publications by hospital-based or population-based cancer registries showed that the biomarker data of the three most frequently tested markers ER, PgR, and HER2 were collected and used by hospital-based and population-based registries almost simultaneously after recommendation (Figure 1 (b)). In addition, a few reports of biomarker data collection were even found before statements of recommendations were published. This is especially prominent in hospital-based registries, where publications using ER and PgR data can be found as early as 1984, and first publications using HER2 data appeared in 2002.

**Utilization of molecular biomarker status**

Biomarker data are analyzed for a variety of purposes including patient characteristics, cancer risk, staging, diagnosis, or subtype differentiation (SN5). As expected from the frequency of use of the biomarkers ER, PgR, and HER2, the largest number of the reviewed publications utilized the biomarker information for subtype differentiation leading to prognostic and predictive decisions (Figure A(7)).

**Conclusions**

This literature review clearly shows that biomarker data of BC patients are collected and used for publication by cancer registries. As this review is taking into account only registries using their biomarker data for publication, the total number of cancer registries collecting such information might be underestimated. At the same time, biomarker data could be collected for specific studies only and therefore a publication may not always be associated with the routine collection of biomarker data. The temporal trend of biomarker collection and publication of results using registry data seems to closely follow the inclusion of recommendations for biomarker use in the clinical guidelines. Furthermore, although the proportion of BC cases with available information regarding the biomarkers ER, PgR, and HER2 is high owing to their predictive values, an accurate and complete collection by registries is required for research and public health studies. Howlader et al., for example, determined that for 12% of the BC cases, information regarding these biomarkers was not available in the SEER 17 registry database. Additionally, it is necessary to consider the timeframe of biomarker collection; for example, HER2 data has only been collected by the SEER database since 2010. Furthermore, there is still a need for inter-clinical and inter-registry harmonization of the data; for example, the thresholds for positivity, which can be achieved by common registration and reporting guidelines. Considering the ongoing establishment of a European cancer database, such harmonization would facilitate the extension of the variable list to include biomarker status, thus extending the ongoing research in North America by a Europe-wide analysis of cancer cases with the possibility of using large sample sizes. Common guidelines on the
The collection of biomarker data by registries, a centralized collection, and harmonization will therefore lead to the better availability of the data to the research community enabling large scale real world data analyses.

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Supplemental material

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