EDITORIAL

Benefits of Breast Cancer Screening and Treatment on Mortality

Stephanie B. Wheeler, PhD, MPH; Gabrielle Rocque, MD; Ethan Basch, MD

Breast cancer mortality has declined precipitously in the past 5 decades, from 48 per 100 000 females in 1975 to 27 per 100 000 in 2019.[1] This large improvement in outcomes is a testament to the development and dissemination of evidence-based strategies to improve early detection and timely treatment of breast cancer—achieved through decades of public and private investment in research and research translation. However, it is challenging to quantify the relative contributions of prior investments or advances in breast cancer screening and treatment. Without such knowledge, decisions about setting future research priorities will be incompletely informed. An approach that can provide this key information is simulation modeling.

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The Cancer Intervention and Surveillance Network (CISNET), funded by the National Cancer Institute, is a multiinstitutional collaborative simulation modeling consortium that is uniquely positioned to answer questions about how population-level interventions such as screening and treatment advancements can change health outcomes at scale. CISNET models leverage varied epidemiologic data resources, including cancer registry data, and sophisticated analytic and programming expertise to create real-world estimates of cancer risk, disease progression and survival, as well as the impacts of screening, treatment, and follow-up care on cancer outcomes.

In the study by Caswell-Jin and colleagues published in *JAMA*,[2] the authors used 4 CISNET breast cancer models with shared input parameters (eg, estimates of screening coverage, cancer incidence, early-stage treatment benefits, competing mortality risks), but different modeling approaches and structural assumptions, to estimate the relative contributions of improvements in screening and treatment over time to breast cancer mortality reductions, with a particular focus on metastatic disease. Modeling metastatic disease and postmetastatic treatment and survival is tricky, given the dynamic nature of tumor progression and the fact that cancer registries do not routinely track recurrence or progression. Thus, for patients diagnosed with early-stage breast cancer who eventually progress to metastatic disease, isolating the exact time of metastatic transition is impossible to observe and requires making assumptions about progression based on observed data only—namely, clinical detection of metastatic recurrence and/or receipt of metastatic treatments. As a result, the 4 models approached the problem of capturing metastatic disease slightly differently, but they all incorporated estrogen receptor (ER) status and *ERBB2*+ oncogene status to accommodate subtype-specific differences in progression and mortality risks. In addition, the external validity of model survival estimates was assessed in independent data.

The 4 CISNET breast cancer models featured in this article found that 55% to 61% of the reduction in breast cancer mortality from 1975 to 2019 was associated with combined screening and treatment improvements. Nearly half of this portion of breast cancer mortality reduction was associated with treatment for early-stage breast cancer, while approximately one-quarter was associated with screening, and slightly more than one-quarter was associated with treatment of metastatic breast cancer. In particular, improvements in survival after metastasis were largely concentrated in the past 10 years, with a mean survival improvement of 1.4 years across all 4 models, coinciding with a large increase in the approval of drugs to treat metastatic breast cancer during the same period.

The largest reductions in breast cancer mortality were among those with ER+/*ERBB2*+ disease, largely due to treatment advances for these subtypes, whereas for those with ER−/*ERBB2*− disease, mortality reductions over time were less pronounced and screening instead was associated with the largest relative mortality reduction (40%) in this group. This finding, as the authors note, is surely related to the development and efficacy of newer treatments targeting ER+ and *ERBB2*+ cancers.

When considering drug development during this time, it is notable that the number of drugs approved for metastatic disease treatment is more than 6-fold higher at 26 drugs, compared with 4 drugs approved for early-stage disease. This reflects a common paradigm in drug development of initial testing in the metastatic setting followed by transition to the early-stage setting through successive clinical trials, as is seen with the addition of adjuvant immunotherapy for triple-negative early-stage breast cancer.[3] It is also worth calling attention to the emergence of promising antibody drug conjugates in metastatic breast cancer,[4] which have yet to be approved for early-stage disease but show significant promise for triple-negative breast cancer. Finally, value-based care delivery interventions (eg, navigation services, patient-reported outcomes, palliative care, supportive care medications) can contribute both to the ability to tolerate treatments and to survival benefits in contemporary care and can benefit patients with both early- and late-stage breast cancer.[5]

Despite overall progress in reducing breast cancer mortality, reductions have not been equally distributed across all patient populations. Rural, Black, and uninsured patient populations remain at greatest risk of dying from breast cancer, with minimal relative improvements in outcome disparities for these groups compared with urban, White, and insured patients.[6] Understanding and quantifying how, and to what extent, improvements in screening and treatment have influenced subpopulation-level outcomes remains

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a critical need to inform public health programming, optimize clinical care delivery, and enhance intervention efforts tailored to marginalized populations to address disparities in outcomes.

Limitations of this work[2] that should be addressed in future analyses include the lack of evaluation of subpopulation-specific estimates of mortality reductions in marginalized populations that continue to experience breast cancer care quality and outcomes disparities. Differential distribution of screening and treatment access, as well as disease subtypes, across racial, ethnic, geographic, and socioeconomic subgroups likely mean that certain populations are advantaged whereas others are adversely affected by screening and treatment advances concentrated in one group. Such nuances may mean that disparities may worsen over time in unexpected ways. For example, Black women are at higher risk for triple-negative disease, the group for which mortality reductions over time were the smallest, relatively speaking. Similarly, improvements in screening may be limited to those with insurance and robust primary care infrastructure, which can be challenging in rural or socially disadvantaged communities. As advances in care are disseminated, care should be taken to ensure that marginalized groups are not left behind and that the unintended consequences of research and clinical care advancements do not neglect certain groups. Future modeling work should evaluate how changes in screening and treatment affect care and outcome disparities across subpopulations to inform research and implementation planning, as well as interventions and policies to help address gaps and improve equity.

The findings of the study by Caswell-Jin et al[2] have widespread implications for the oncology field and for understanding metastatic disease outcomes. Advancements in the treatment of metastatic breast cancer have proliferated, and there are increasing numbers of people living with advanced disease, underlining the need for research focused on supportive care approaches to optimize long-term quality of life. At the same time, there remain both individuals with rapid disease progression who do not respond to current therapies and those with higher mortality rates without adequate treatment options, such as those with triple-negative breast cancer. Resources should be committed toward achieving advances across the continuum of disease and with particular attention to populations that face unequal care outcomes to ensure that benefits of innovation reach all patients.

Model-based estimates elucidate opportunities for additional screening and treatment efforts to combat breast cancer mortality and highlight the continued need to invest in both early detection and linkage to timely, guideline-concordant treatments for all patients. Models such as those developed by CISNET investigators serve as an essential tool to help clarify and quantify for decision-makers the population health return on decades-long investments in research, clinical care, and public health programming.

ARTICLE INFORMATION

Author Affiliations: Department of Health Policy and Management, Gillings School of Global Public Health, University of North Carolina at Chapel Hill (Wheeler, Basch); Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill (Wheeler, Basch); O'Neal Comprehensive Cancer Center, Birmingham, Alabama (Rocque); Department of Medicine, Divisions of Hematology & Oncology and Gerontology, Geriatrics, & Palliative Care, University of Alabama at Birmingham (Rocque); Division of Oncology, Department of Medicine, School of Medicine, University of North Carolina at Chapel Hill (Basch); Associate Editor, *JAMA* (Basch).

Corresponding Author: Stephanie Wheeler, PhD, Department of Health Policy and Management, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, McGavran-Greenberg Hall, Chapel Hill, NC 27516 (Stephanie_Wheeler@unc.edu).

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