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Introduction to the Cancer Intervention and Surveillance Modeling Network (CISNET) Breast Cancer Models

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Abstract

The Cancer Intervention and Surveillance Modeling Network (CISNET) Breast Cancer Working Group is a consortium of National Cancer Institute – sponsored investigators who use statistical and simulation modeling to evaluate the impact of cancer control interventions on long-term population-level breast cancer outcomes such as incidence and mortality and to determine the impact of different breast cancer control strategies. The CISNET breast cancer models have been continuously funded since 2000. The models have gone through several updates since their inception to reflect advances in the understanding of the molecular basis of breast cancer, changes in the prevalence of common risk factors, and improvements in therapy and early detection technology. This article provides an overview and history of the CISNET breast cancer models, provides an overview of the major changes in the model inputs over time, and presents examples for how CISNET breast cancer models have been used for policy evaluation.

Keywords

Cancer simulation; breast cancer epidemiology; simulation models; breast cancer control

Background

The last two decades have seen a remarkable explosion in knowledge and interventions with the potential to reduce the burden of breast cancer in the U.S. and worldwide.[1,2] While clinical trials remain the standard of evidence to evaluate the efficacy of these new screening technologies and cancer treatments, the rapid pace of discovery makes it difficult to determine which approaches have the greatest ability to reduce morbidity and mortality, alone or in combination. It is generally not feasible within a single randomized clinical trial (RCT) to evaluate efficacy in different subgroups of women that vary by age, risk of and genetic susceptibility to breast cancer, tumor molecular features, risk of recurrence, effectiveness of treatment, responses to therapy, and/or competing causes of death. Moreover, RCTs can generally only provide data about short-term outcomes of interventions, but health policy decisions typically need to consider the long-term consequences of health interventions. Finally, RCTs only provide results that apply to enrolled participants and may not translate to impact on population morbidity and mortality outcomes.

In this situation, simulation modeling has been recommended by the Institute of Medicine and others as a “virtual laboratory” to conduct synthetic experiments comparing different scenarios for the delivery of interventions to estimate population impact under a variety of conditions.[3–5] Use of several models to address the same research questions may become an efficient method to replicate these “experiments”, especially when primary data collection via large-scale new trials is not feasible. Results can then be examined across models for the

consistency of qualitative and quantitative conclusions, similar to conducting a systematic review. All models make assumptions about unobservable events (e.g., tumor growth or over-diagnosis of cancer). Therefore, use of multiple high-quality models provides a range of plausible effects and illustrates the effects of variation in known treatment or screening effects as well the impact of model uncertainty. Decision makers and other consumers can have more confidence in the results of collaborative modeling if all models demonstrate meaningful, qualitatively similar outcomes despite differences in structure and approach. Finally, although RCTs provide essential data to build the models, compared to RCTs conducted in different times, places, and conditions and post-hoc meta-analysis of divergent research, comparative modeling has the advantage of being able to replicate the same conditions (e.g., screening intervals, test sensitivity and specificity), facilitating evidence synthesis and head-to-head comparisons.

To support collaborative modeling, beginning in 2000, the National Cancer Institute funded several independent groups to develop and apply models to evaluate the impact of cancer control interventions on long-term population trends in breast cancer incidence and mortality and project future trends. These groups constitute the Breast Cancer Working group of the Cancer Intervention and Surveillance Modeling Network (CISNET). In addition to breast, CISNET also includes groups modeling cervical, colorectal, esophageal, lung, and prostate cancers.

Since their initial development,[6] the breast cancer models have been updated to consider changes in the prevalence of common risk factors, dissemination of new screening and treatment modalities alone or in combination, and to portray the four primary molecular subtypes of breast cancer (based on estrogen receptor (ER) and human epidermal growth factor-2 receptor (HER2)) along with new treatments. Additionally, some or all of the models have also added the ability to capture breast cancer risk level (e.g., based on breast density, obesity, polygenic risk), differences in detection rates by breast density, and how comorbidity-specific life expectancy affects screening and treatment outcomes.

There are currently six breast cancer modeling groups: Dana-Farber (D), Erasmus (E), Georgetown-Einstein (GE), MD Anderson (M), Stanford (S), and Wisconsin-Harvard (W). Earlier versions of the models were described extensively in a 2006 publication of JNCI monograph.[6] There are two main purposes for this special issue. First, we describe the most up-to-date versions of the models and their evolution over time, with a focus on issues related to collaborative modeling. Table 1 includes a complete list of all updates in the models since the publication of the 2006 issue of the JNCI monograph.[6]

Second, the recent ISPOR-SMDM Modeling Good Research Practices Task Force suggests that in order to achieve confidence in health care models, models should be transparent and validated. [7] Since CISNET breast cancer models have been increasingly used in breast cancer guidelines,[8–10] it becomes more important to increase the accessibility to, and transparency and evaluation of models by potential end users and decision makers. To this end, this special issue provides readers with information to understand how the models are built and how well they reproduce breast cancer trends.[7]

Collaborative Modeling

The CISNET breast cancer models include a unique modeling approach, whereby several groups develop their own models while working collaboratively. There are several distinctive aspects of this collaborative approach. The six independent groups meet regularly (face-to-face twice a year and monthly conference calls) and discuss issues related to the model development and results. More specifically, the modeling groups review the other models, discuss the implementation of common input parameters and the approach,, and critically assess the validity of the results of other groups. In addition, a standing CISNET breast cancer working group steering committee consisting of the principal investigators of the modeling groups meet on a monthly basis to discuss strategies and issues related to the project. All CISNET breast cancer working group members and affiliates submit paper proposals prior to initiating the research work and the steering committee provides feedback and approves these plans. Furthermore, all papers that are directly related to CISNET breast cancer projects are reviewed by other members prior to submission to ensure high quality. Models are also expected to share their ongoing work that are not directly funded by CISNET to minimize the overlap between modeling groups. Finally, because the CISNET breast cancer modelers work on multiple projects, there are smaller working groups that consist of selected number of modeling teams who lead individual projects.

Although the six models vary in terms of their modeling approach, structure, and assumptions, they share common features, including: 1) following multiple birth cohorts over time, 2) incorporating known data on breast cancer biology (e.g., breast cancer incidence, stage distribution, etc.), 3) using common data about screening behavior and treatment use based on known accuracy and effectiveness (e.g., mammography sensitivity, mammography dissemination over time, etc.), and 4) projecting future benefits and harms.

Each model begins with a distinct depiction of breast cancer natural history in the absence of screening and treatment. The models then apply common inputs[11] describing observable phenomenon, such as population dynamics, other-cause mortality, screening use and performance, and treatment effects. All models replicate the major changes in observed trends in breast cancer incidence and mortality from 1975 through 2010. [8,10] Major model differences and similarities are summarized in two articles in this special issue [12,13]. Comparisons of model outputs (e.g., breast cancer mortality) help to reveal how differences in model structure affect results.

Despite the differences among the model structures, in previous research involving all six models the results are similar for estimates of the ranking of screening strategies and/or the relative contributions of screening and adjuvant treatment to mortality trends while also providing a range of likely values [9,10,14–17]. In general, our previous research showed that there is more consistency across models when comparing relative (e.g. rankings of strategies) rather than absolute (e.g. incidence or mortality rates) measures, since absolute measures require accurate modeling of factors extraneous to the problem of interest, while these factors generally cancel out of calculation of relative measures [9,10,14–17].

In contrast to a single independent model, this longstanding collaborative modeling approach has several features that make it uniquely suited to comparative effectiveness research: 1) use of multiple models with varying structures provides a range of plausible effects and illustrates the influence of differences in model assumptions, increasing transparency, as recommended by ISPOR-SMDM Modeling Good Research Practices Task Force for good modeling [7], 2) collaboration provides efficiency in gathering and evaluating data resources, and 3) the models are well-established and widely disseminated, which increases transparency and the reliability of the models.

Exemplary Applications

In addition to a very strong record of publications (over 174 manuscripts as of August 2017, a complete list of publications is available at http://cisnet.cancer.gov/publications/cancer-site.html), the CISNET breast cancer working group has also been very successful in translating model-based results into policy and has had direct impact on public health [9,14,18]. More specifically, the breast cancer models were used by the US Preventive Services Task Force (USPSTF) to conduct comparative analyses of different ages of starting and stopping and intervals of breast cancer screening. The modeling results were one source of information that was used to inform the USPSTF's breast cancer screening guidelines both in 2009 and 2015 [8,9]. Other recent policy-related work includes joint work with the CDC's National Breast and Cervical Cancer Early Detection Program [19], the American Cancer Society [20], local organizations such as the DC Cancer Consortium [21] and international groups including the Canadian Breast Cancer Foundation [22] and the Dutch Screening Program [23]. The models were also used to investigate emerging issues in breast cancer control including the impact of recent breast density legislation (i.e., many states in the US passed laws that require clinicians to inform women undergoing mammography about the risks associated with breast density) on long-term breast cancer outcomes [16], impact of comorbidities on the stopping age for screening [24] and overdiagnosis [25], and the benefits and costs of the transition from plain-film to digital screening[26].

Special Issue Outline

This special issue consists of three main sections. Section I [11,27,28] describes the common inputs used in the models, where the article by Gangnon et al. [27] summarizes how mortality rates due to breast cancer and all other causes are estimated and the research of Munoz and Plevritis[28] describes the statistical methods used to estimate the molecular subtype-specific breast cancer survival expected in the absence of any screening or treatment. Section II [29–34] includes a detailed description of each model, and Section III [12,13,35] focuses on cross-model comparisons. Specifically, the study by van der Broek et al. [12] compares the models with respect to the structure and assumptions and provides insights into and how these differences lead to variations in model outputs and conclusions. The study by van Ravesteyn et al.[13] compares how models represent ductal carcinoma in situ (DCIS), the most common type of non-invasive breast cancer that could become invasive breast cancer. The article by van der Broek et al.[35] describes how the models replicated the Age trial in the U.K. and compares the observed Age trial results to the results predicted by the models, providing an independent validation experiment for the models.

In summary, this special issue contributes to advancing the body of knowledge about modeling science, provides readers and policy makers with an in-depth review of the CISNET breast cancer models, and enhances the transparency of the models as they are increasingly used in addressing important breast cancer control questions and policy making.

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Table 1

Major changes in CISNET breast cancer models since 2006 [6,11,29–34]

Component	Description
Breast cancer molecular subtype	portrayal of four distinct molecular subtypes based on estrogen receptor (ER) and human epidermal growth factor-2 receptor (HER2) status, each with its own underlying natural history (survival, sojourn times, screen detectability, and impact of therapeutic advances on survival)
Incidence	incidence of breast cancer to reflect the current trends in underlying risk and by molecular subtype
Non-breast cancer mortality	non-breast cancer mortality inputs to reflect changes in medical care and competing causes of death
Screening dissemination	the use and dissemination of digital mammography
Accuracy of mammography	sensitivity and specificity of film and digital mammography with recent data reflecting the improvements in the accuracy of mammography over time
Treatment dissemination	dissemination of the most current therapies including anthracyclines, taxanes, and herceptin
Treatment effectiveness	treatment effectiveness using data from more recent trials
Risk factors	risk factors such as breast density, postmenopausal hormone use and body mass index are added to some models
Ductal carcinoma in situ (DCIS)	DCIS representations in the models have been improved
Comorbidities	Some models have been updated to account for comorbidities

CISNET, Cancer Intervention and Surveillance Modeling Network.

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