Original Article

MDM Medical Decision Making

Medical Decision Making
2018, Vol. 38(1S) 3S–8S

DOI: 10.1177/0272989X17737507
journals.sagepub.com/home/mdm
SAGE

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

Oguzhan Alagoz, Donald A. Berry, Harry J. de Koning, Eric J. Feuer, Sandra J. Lee, Sylvia K. Plevritis, Clyde B. Schechter, Natasha K. Stout, Amy Trentham-Dietz, and Jeanne S. Mandelblatt, on behalf of CISNET Breast Cancer Working Group members

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

breast cancer control, breast cancer epidemiology, cancer simulation, simulation models

Date received: August 8, 2016; accepted: September 22, 2017

The past 2 decades have seen a remarkable explosion in knowledge and interventions with the potential to reduce the burden of breast cancer in the United States 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

Corresponding Author

Oguzhan Alagoz, Department of Industrial and Systems Engineering, University of Wisconsin–Madison, 3242 Mechanical Engineering Building, 1513 University Avenue, Madison, WI 53706, USA; telephone: (608) 890-0399; fax: (608) 262-8454. (alagoz@engr.wisc.edu)

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 overdiagnosis 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 as 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, disseminate new screening and treatment modalities alone or in combination, and portray the 4 primary molecular subtypes of breast cancer (based on estrogen receptor [ER] and human epidermal growth factor 2 receptor [HER2]) along with new treatments. In addition, 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 6 breast cancer modeling groups: Dana-Farber (D), Erasmus (E), Georgetown-Einstein (GE), M. D. Anderson (M), Stanford (S), and Wisconsin-Harvard (W). Earlier versions of the models were described extensively in a 2006 publication of the *Journal of the National Cancer Institute* (*JNCI*) monograph.[6] There are 2 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 International Society for Pharmacoeconomics and Outcomes Research—Society for Medical Decision Making (ISPOR-SMDM) Modeling Good Research Practices Task Force suggests that 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,

Department of Industrial and Systems Engineering, University of Wisconsin-Madison, Madison, WI, USA (OA); Department of Biostatistics, University of Texas M. D. Anderson Cancer Center, Houston, TX, USA (DAB); Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD, USA (EJF); Department of Public Health, Erasmus Medical Center, Rotterdam, the Netherlands (HJd); Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute and Harvard Medical School and Department of Biostatistics, Harvard T. H. Chan School of Public Health, Boston, MA, USA (SJL); Department of Radiology, School of Medicine, Stanford University, Stanford, CA, USA (SP); Departments of Family and Social Medicine and Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA (CBS); Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA (NKS); Department of Population Health Sciences and Carbone Cancer Center, University of Wisconsin–Madison, Madison, WI, USA (AT); and Department of Oncology, Georgetown University Medical Center and Cancer Prevention and Control Program, Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC, USA (JSM). *This work was done by 6 independent modeling teams from Dana-Farber Cancer Institute (principal investigator [PI]: Lee), Erasmus Medical Center (PI: de Koning), Georgetown University Medical Center, Lombardi Comprehensive Cancer Center/Albert Einstein College of Medicine (PI: Mandelblatt/Schechter), Harvard Medical School, University of Wisconsin/Harvard Pilgrim Health Care (PI: Trentham-Dietz/Stout/Alagoz), M. D. Anderson Comprehensive Cancer Center (PI: Berry), and Stanford University (PI: Plevritis). Jeanne Mandelblatt was the senior author and Eric Feuer was responsible for overall CISNET project direction. This work was supported by the National Institutes of Health under National Cancer Institute grants U01CA152958, U01CA199218, U01CA088278, U01CA088211, U01CA088202, U01CA088283, U01CA088248, U01CA088270, U01CA088177, U01CA88293A, and U01CA116532.

Table 1 Major Changes in Cancer Intervention and Surveillance Modeling Network Breast Cancer Models Since 2006[6,11,29–34]

Component	Description
Breast cancer molecular subtype	Portrayal of 4 distinct molecular subtypes based on estrogen receptor and human epidermal growth factor 2 receptor 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

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 6 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 meets 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 a selected number of modeling teams who lead individual projects.

Although the 6 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), 3) using common data about screening behavior and treatment use based on known accuracy and effectiveness (e.g., mammography sensitivity, mammography dissemination over time), 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 phenomena, 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 2 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 6 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 long-standing 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 the 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 1 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 Centers for Disease Control and Prevention's (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 United States 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 3 main sections. Section I[11,27,28] describes the common inputs used in the models, where the article by Gangnon and others[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 den Broek and others[12] compares the models with respect to the structure and assumptions and provides insights into how these differences lead to variations in model outputs and conclusions. The study by van Ravesteyn and others[13] compares how models represent ductal carcinoma in situ (DCIS), the most common type of noninvasive breast cancer that could become invasive breast cancer. The article by van den Broek and others[35] describes how the models replicated the Age Trial in the United Kingdom 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.

Acknowledgments

The authors thank all members of CISNET Breast Cancer Working Group for their contribution to this project. These include (Model D) Hui Huang, Sandra J. Lee (PI), and Harald Weedon-Fekjaer; (Model E) Harry de Koning (PI), Eveline Heijnsdijk, Jeroen van den Broek, and Nicolien Van Ravesteyn; (Model GE) Young Chandler (aka Yaojen Chang), Jinani Jayasekera, Jeanne Mandelblatt (PI), Aimee Near, Clyde Schechter (PI); (Model M) Donald Berry (PI), Xuelin Huang, Yisheng Li, and Juhee Song; (Model S) Diego Munoz, Sylvia K. Plevritis (PI), and Helen (Cong) Xu; (Model W) Oguzhan Alagoz (PI), Mucahit Cevik, Mehmet Ali Ergun, Ronald

Gangnon, John M. Hampton, Natasha K. Stout (PI), and Amy Trentham-Dietz (PI); (NCI) Eric Feuer, Daisy Frearson, and Brandy Heckman-Stoddard; (NCI/Cornerstone) Lauren Clarke; (BCSC) Ellen O'Meara; and (Consultants) Cecile Janssens, Peter Kraft, Reena Puglia, Allison Kurian, Martin Yaffe, Karla Kerlikowske, Michael C. Wolfson, Brian L. Sprague, Donald Weaver, Elizabeth S. Burnside, Anna N. A. Tosteson, and Diana Miglioretti.

REFERENCES

1. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. Lancet. 2012;380(9855):1778–86.
2. Stewart B and Wild CP. World cancer report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press; 2015.
3. Mandelblatt JS, Fryback D, Weinstein M, Russell L, Gold M and Hadorn D. Assessing the effectiveness of health interventions for cost-effectiveness analysis. *J Gen Intern Med*. 1997;12:551–8.
4. Sox HC and Greenfield S. Comparative effectiveness research: a report from the Institute of Medicine. *Ann Intern Med*. 2009;151(3):203–5.
5. Sox HC. Quality of life and guidelines for PSA screening. *N Engl J Med*. 2012;367(7):669–71.
6. Feuer EJ. Modeling the impact of adjuvant therapy and screening mammography on US breast cancer mortality between 1975 and 2000: introduction to the problem. J Natl Cancer Inst. 2006;(36):2–6.
7. Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM and Wong JB. Model transparency and validation a report of the ISPOR-SMDM Modeling Good Research Practices Task Force–7. *Med Decis Making*. 2012;32(5):733–743.
8. Mandelblatt JS, Cronin K, de Koning H, Miglioretti DL, Schechter C and Stout NK. Modeling report: collaborative modeling of U.S. breast cancer screening strategies: breast cancer: screening. 2015. Available from: http://www.uspreventiveservicestaskforce.org/Page/Document/modeling-report-collaborative-modeling-of-us-breast-cancer-1/breast-cancer-screening1
9. Mandelblatt JS, Cronin KA, Bailey S, et al. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. *Ann Intern Med*. 2009;151(10):738–47.
10. Mandelblatt JS, Stout NK, Schechter CB, et al. Collaborative modeling of the benefits and harms associated with different US breast cancer screening strategies. *Ann Intern Med*. 2016;164(4):215–25.
11. Mandelblatt JS, Near AM, Miglioretti DL, et al. Common model inputs in collaborative breast cancer modeling. *Med Decis Making*. 2018;38(1S):9–23.
12. van den Broek JJ, van Ravesteyn NT, Cevik M, et al. Comparing CISNET breast cancer models using the maximum clinical incidence reduction methodology. *Med Decis Making*. 2018;38(1S):112–125.
13. van Ravesteyn NT, van den Broek JJ, Li X, et al. Modeling ductal carcinoma in situ (DCIS): An overview of CISNET model approaches. *Med Decis Making*. 2018;38(1S):126–139.
14. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005;353(17):1784–92.
15. Munoz D, Near AM, van Ravesteyn NT, et al. Effects of screening and systemic adjuvant therapy on ER-specific US breast cancer mortality. *J Natl Cancer Inst Monogr*. 2014;106(11):dju289.
16. Sprague BL, Stout NK, Schechter C, et al. Benefits, harms, and cost-effectiveness of supplemental ultrasonography screening for women with dense breasts. *Ann Intern Med*. 2015;162(3):157–66.
17. Plevritis S, Munoz D, Kurian A, et al. Contributions of screening and systemic therapy to molecular subtype-specific US breast cancer mortality from 2000 to 2010. Submitted for publication.
18. Cronin KA, Feuer EJ, Clarke LD and Plevritis SK. Impact of adjuvant therapy and mammography on US mortality from 1975 to 2000: comparison of mortality results from the CISNET breast cancer base case analysis. J Natl Cancer Inst Monogr. 2005;(36):112–21.
19. van Ravesteyn NT, van Lier L, Schechter CB, et al. Transition from film to digital mammography: impact for breast cancer screening through the National Breast and Cervical Cancer Early Detection Program. *Am J Prev Med*. 2015;48(5):535–42.
20. Mandelblatt J, van Ravesteyn N, Schechter C, et al. Which strategies reduce breast cancer mortality most? *Cancer*. 2013;119(14):2541–8.
21. Near AM, Mandelblatt JS, Schechter CB and Stoto MA. Using simulation modeling to inform strategies to reduce breast cancer mortality in black women in the District of Columbia. *Epidemiol Res Int*. 2012;2012:241340.
22. Mittmann N, Stout NK, Lee P, Tosteson AN, Trentham-Dietz A, Alagoz O, Yaffe MJ. Total cost-effectiveness of mammography screening strategies. Health Reports. 2015;(12):16–25.
23. Sankatsing VD, Heijnsdijk EA, van Luijt PA, van Ravesteyn NT, Fracheboud J and de Koning HJ. Cost-effectiveness of digital mammography screening before the age of 50 in the Netherlands. *Int J Cancer*. 2015;137(8):1990–9.
24. Lansdorp-Vogelaar I, Gulati R, Mariotto AB, et al. Personalizing age of cancer screening cessation based on comorbid conditions: model estimates of harms and benefits. *Ann Intern Med*. 2014;161(2):104–12.
25. Van Ravesteyn NT, Stout NK, Schechter CB, et al. Benefits and harms of mammography screening after age 74 years: model estimates of overdiagnosis. *J Natl Cancer Inst*. 2015;107(7):djv103.
26. Stout NK, Lee SJ, Schechter CB, et al. Benefits, harms, and costs for breast cancer screening after US

implementation of digital mammography. *J Natl Cancer Inst*. 2014;106(6):dju092.
27. Gangnon RE, Stout NK, Alagoz O, Hampton JM, Sprague BL and Trentham-Dietz A. Contribution of breast cancer to overall mortality for U.S. women. Med Decis Making. 2018;38(1S):24–31.
28. Munoz D and Plevritis SK. Estimating breast cancer progression features and survival by molecular subtype in the absence of screening and treatment. *Med Decis Making*. 2018;38(1S):32–43.
29. Lee SJ, Li X and Huang H. The Dana-Farber CISNET model for breast cancer screening strategies: An update. *Med Decis Making*. 2018;38(1S):44–53.
30. van den Broek JJ, van Ravesteyn NT, Heijnsdijk EA and de Koning H. Simulating the impact of risk-based screening and treatment on breast cancer outcomes with MISCAN-Fadia. *Med Decis Making*. 2018;38(1S):54–65.
31. Schechter CB, Near AM, Jayasekera J, Chang Y and Mandelblatt JS. Structure, function, and applications of the Georgetown-Einstein (GE) breast cancer simulation model. *Med Decis Making*. 2018;38(1S):66–77.
32. Huang Xuelin, Li Y, Song J and Berry D. A Bayesian simulation model for breast cancer screening, incidence, treatment, and mortality. *Med Decis Making*. 2018;38(1S): 78–88.
33. Alagoz O, Ergun MA, Cevik M, et al. The University of Wisconsin breast cancer epidemiology simulation model: an update. *Med Decis Making*. 2018;38(1S):99–111.
34. Munoz D, Xu C and Plevritis SK. A molecular subtype-specific stochastic simulation model of US breast cancer incidence and mortality trends from 1975 to 2010. *Med Decis Making*. 2018;38(1S):89–98.
35. van den Broek JJ, van Ravesteyn NT, Mandelblatt JS, et al. Comparing CISNET breast cancer incidence and mortality predictions to observed clinical trial results of mammography screening from ages 40 to 49. *Med Decis Making*. 2018;38(1S):112–125.