QPM Work Group Agenda 6-23-14

VT Health Care Innovation Project
Quality and Performance Measures Work Group Meeting Agenda

June 23, 2014; 9:00 AM to 12 Noon

4th Floor Conference Room, Pavilion Office Building, Montpelier

Call-In Number: 1-877-273-4202 Passcode: 9883496

Item #	Time Frame	Topic	Relevant Attachments	Decision Needed?
1	9:00-9:10	Welcome and Introductions; Approval of Minutes	Attachment 1 – QPM Minutes 2014-05-29	YES
2	9:10-9:20	Updates • ACO attribution • Clinical measures data collection • Analytics contractor ***Public Comment***		
3	9:20-9:40	Continued Discussion on Criteria for Selection of Measures • Recommendations for Population Health Work Group's Proposed Criteria ***Public Comment***	Attachment 3 – Population Health Memo for QPM Work Group 2014-06-17	YES
4	9:40 to 10:00	Recommendation for Breast Cancer Screening Measure, in light of recent studies ***Public Comment***	Attachment 4A – Rambur e-mail mammography Attachment 4B – Likelihood that screening saved life Attachment 4C – Overscreening bmj Attachment 4D – Welch overscreening NEJM Attachment 4E – AMA Benefits and Risks of Mammography	YES (as part of Agenda Item #6)
5	10:00 to 10:25	Presentation on SBIRT Grant Measurement Activities ***Public Comment***		YES (as part of Agenda Item #6)

6	10:25-11:50	Review of Year 2 Measure Review Timeline Detailed Review of Year 2 Proposed Changes to Measures, Benchmarks and Targets, with Co-chair/Staff/Consultant Recommendations ***Public Comment***	Attachment 6 – Co-chair/Staff/Consultant recommendations for Year 2 SSP Measures (will be provided when available)	YES
7	11:50-12:00	Next Steps, Wrap-Up and Future Meeting Schedule Note: June 25 Webinar, 10:00 AM to 12:00 Noon, "CMS Quality Measurement Training and Reporting Overview" presented by Vicki Loner of OneCare Vermont		

Attachment 1 - QPM Minutes 5-29-14

VT Health Care Innovation Project
Quality & Performance Measures Work Group Meeting Minutes

Date of meeting: May 29, 2014 at 4th Floor Conference Room, Pavilion Office Building, Montpelier

Attendees: Cathy Fulton, Co-Chair; Georgia Maheras, AOA; Pat Jones, GMCB; Paul Harrington, VT Medical Society; Heidi Klein, , Robin Edelman, VDH; Lila Richardson, VT Legal Aid; Julia Shaw, HCA; Rachel Seelig, Senior Citizens Law Project; Heather Skeels, Bi-State; Cath Burns, Howard Center; Connie Colman, CVHHH; Alicia Cooper, Aaron French, Cynthia Thomas, Kimberly McNeil, DVHA; Joyce Gallimore, CHAC; Fran Keeler, Jen Woodard, DAIL; Kim McClellan, NCSS; Marlys Waller, VT Council of Dev. & Disabilities; Shawn Skaflestad, Julie Wasserman, AHS; Deborah Lisi-Baker, DLTSS Co-Chair; Vicki Loner, OneCare; Michael Bailit, Bailit Health Purchasing; Jenney Samuelson, Blueprint for Health; Deb Chambers, Joe Smith, MVP; Anna Noonan, FAHC; Susan Johnson, NCHC; Jessica Mendizabal, Nelson Lamothe, Project Management Team.

Agenda Item	Discussion	Next Steps
1. Welcome and Introductions; Approval of Minutes	Cathy Fulton called the meeting to order at 10:04 am. Laura Pelosi sent her regrets and was unable to attend the meeting. Aaron French moved to approve the minutes from April 28th, Vicki Loner seconded. The motion passed unanimously.	
2. Updates	• Estimates of Commercial and Medicaid attribution to ACOs: o Still in the process of developing attribution of lives. BCBS has been able to attribute 8,000 members for OneCare. BCBS currently has about 50,000 lives on the Exchange, so the number for OneCare should go up. Other ACOs have smaller numbers at the current time, and they're not ready to release them. o Joyce Gallimore noted CHAC is very interested in learning their attribution numbers so they can begin their planning. o Medicaid ran preliminary attribution estimates based on initial provider rosters:	

Agenda Item	Discussion	Next Steps
	approximately 20,000 attributed lives for CHAC and 27,000 for OneCare. Numbers are expected to change slightly. They will have updated numbers soon. o The measurement period will be for calendar year 2014 and there will be retroactivity, as agreed upon by the ACOs and Payers. • Determining if insurer clinical data samples can be used for ACO measures: o Representatives from the three ACOs and Payers met with GMCB and Cathy to share information about what payers are currently doing to collect clinical quality measures. For calendar year 2014, neither DHVA nor MVP will perform chart reviews for measures. BCBS will perform chart reviews. The group is planning on having another session to discuss future steps. o It will be challenging to use health plan data for clinical measures since two of the three payers are not going to do chart review. One idea is the possibility of jointly obtaining a vendor that can help collect that data to mitigate some of the financial burden. o ACOs reporting on the calendar year: would plans have to go back to Jan 1 and extract information from clinical records? Vicki Loner noted OneCare collected clinical measures at the end of January 2014 for the 2013 measures. CMS allows ACOs eight weeks to collect data, two additional weeks to make sure attribution is correct, and two weeks to validate. o There is time to continue the discussion on support for organizations to collect the data. o Paul Harrington asked if data for clinical measures is collected for the entire eligible population or for a sample. Pat Jones responded that for clinical measures it is based on a sample if the data is not being obtained electronically. The goal is to collect the data ultimately from the EHR. Paul noted the HIE work group is working with VITL to evaluate the feasibility of electronic reporting for Commercial, Medicare and Medicaid shared savings program measures; this is a two year project. o The sample will be derived from people attributed to the ACOs. o CHAC will be collecting the Medicare SSP measures beginning in January 2015 (for calendar year 2014).	

Agenda Item	Discussion	Next Steps
	• Analytics Contractor: o Contract materials are going through the State approval process and need CMMI approval. o Planning for a July 1 start date.	
3. Continued Discussion on Criteria for Selection of Measures	**<u>Review of Adopted Criteria</u>** • The group approved and adopted 12 criteria for selection of measures at the last meeting. • Additional Information on Population Health Work Group's Proposed Criteria (attachment 3b): o Heidi Klein reviewed clarifications on the criteria from the Population Health work group. o The clarification contains a new criterion: "use data on health trends and burden of illness to identify priorities." o The Population Health work group recommended that all of these criteria be considered in the selection of measures. Some of the criteria may be more important for Payment, Reporting, Monitoring, etc. o The Population Health work group intended that the criteria be considered for broader measures, not just those that apply to ACOs. o The last criterion is included to acknowledge the expanded timeframe needed to see change in some population health metrics. • The group discussed the idea that the recommended criteria might serve as guiding principles throughout the entire VHCIP project, instead of specific criteria for measure selection, noting they are good aspirational goals for other work groups as well. o There are measures that are included in a clinical setting for prevention and wellness that would show up in claims, and this fits with ACO measures. The same is true with risk and protective factors. o The possibility of weighting these criteria differently from the 12 previously approved criteria was discussed, but it was believed that a weighting system for	Pat, Heidi and Alicia will work on the recommendations from the Population Health work group and bring another proposal to this group. The group did not feel comfortable formally voting to accept the additional criteria.

Agenda Item	Discussion	Next Steps
	criteria may be too complicated for the selection process. Cathy proposed using the currently approved list of 12 criteria as operational criteria for measure selection; as the measures are discussed and reviewed, the work group could look to the criteria from Population Health to further assess the measure and to use as guiding principles for determining a measure's use (e.g. payment, reporting, M&E) in the program. Pat noted that two of the recommended criteria are essentially on the list already: "Use data on health trends and burden of illness to identify priorities," and "Focus on broader population and health outcomes." • <u>Vermont Legal Aid Proposal for Payment Measure Criterion #4:</u> o Pat reviewed attachment 3c, noting there was broad agreement on all criteria for payment measures at the last meeting except for #4 where concern was raised by Legal Aid on the language stating measures to impact quality and cost. o The group discussed the revised language and proposed another alternative: *The measure assesses outcomes; i.e., improving this measure will translate into improvements in quality outcomes and take cost into account if applicable.* Anna Noonan moved to approve the new language and Joyce Gallimore seconded. Lila Richardson and Rachel Seelig abstained. The motion passed. Heather Skeels moved to approve the entire set of criteria for payment measure selection and Fran Keeler seconded. The motion passed unanimously.	
4. Proposal for New Measures Process	Cathy reviewed the work group's tasks for Year 2 ACO measure review and modification: • Consider new measures; modify status of any adopted measures; review targets and benchmarks. • Finalize payment and reporting measure sets for year two by the end of September 2014. • Present to the Payment Models work group. • Release the measure specs by October 31, 2014. • Aim to complete the review of measures by the end of next month. Staff and Co-Chairs could bring a refined list to the group for further review in June. • A webinar is scheduled for June 25th from 10am to 12pm; Vicki Loner will present	In order to get through the amount of work, June and July meetings will start at 9 am instead of 10.

Agenda Item	Discussion	Next Steps
	OneCare's preliminary results for 2013 Medicare Shared Savings Program measures (which are similar Commercial and Medicaid measures). A formal invitation will be sent.	
5. Year 2 Proposed Changes to Reporting and Payment Measures – Work Group Input	Michael Bailit and Pat reviewed the measures and gathered high level feedback from the group. **Reporting measures:** Core-30 (Cervical Cancer Screening): This is a hybrid measure (i.e., relies on claims and clinical data) but may be able to use claims to collect the data. However, NCQA benchmarks are based on hybrid data. Michael confirmed HPV co-testing is now included. Core-34 (Prenatal and Postpartum Care): Attributions to ACOs are by PCP. This measure relates to care generally provided by OBGYNs, which may impact data collection. Core-35 (Influenza Immunization): Look into whether we could use claims-based specifications for this measure—may improve compliance. Core 37 and Core-44 alternate (Transition Record Transmittal and Transition Record with Specified Elements): paired by NQF; both measures used by AMA and require clinical records, no benchmarks exist and data collection involves a number of elements to be extracted. These were recommended by DLTSS and relate to care transitions. Core-44 (Percentage of Patients with Self-Management Plans): the Blueprint doesn't currently capture this in their data set, but it is used for NCQA recognition. Core-45 (SBIRT): Michael stated that Oregon created its own substance abuse Screening, Brief Intervention and Referral to Treatment (SBIRT) measure and used it in 2013. Based on experience they changed it in 2014. It can be challenging for a State to develop and use its own measures. Pat reported on screening measures used by Vermont's SBIRT project (screening for substance use and for co-occurring mental health and substance use disorders). **Payment measures:** Core-10 (Ambulatory Care Sensitive Conditions Admissions for COPD and Asthma): this could have a small denominator. Core-12 (Ambulatory Care Sensitive Conditions Admissions Composite): a recommendation to	Michael will prepare definitions for numerators and denominators for the group as soon as possible. Staff will share additional patient experience survey questions proposed by the DLTSS work group. Estimates of eligible populations per measure will be obtained if possible. Michael suggested refining the measures list first, before obtaining estimates. If estimates are available, they will be provided before a final vote by the work group. Staff, Co-Chairs and consultant will

Agenda Item	Discussion	Next Steps
	move this from reporting to payment from CMS; not a mandate. **<u>Recommended changes to Measures Table:</u>** • Reflect if a measure is used for Payment or Reporting under the MSSP. • Core-19 (Depression Screening and Follow Up): add that this measure is for people 12 and over. M&E-14 (Avoidable ED Visits): provide the algorithm to the group.	review in more detail and bring a refined list of measures to the next meeting.
6. Next Steps, Wrap up and Future Meeting Schedule	Pat thanked the other work groups, individuals, and organizations for bringing forth measures to QPM for consideration. Paul suggested reaching out to the third ACO (ACCGM/VCP) to join the conversation. The group is comfortable letting staff and co-chairs return with a recommendation for a refined measure set. **Next Steps:** The group should provide their thoughts on measures in writing to Pat and Alicia by Friday, June 6. **Next meeting:** Monday June 23, 2014, 9 am-12 pm, 4th Floor Conf. Room, Pavilion Building, Montpelier.	The group should provide their thoughts on measures in writing to Pat and Alicia by Friday, June 6.

Attachment 3 - Population Health Memo for QPM Work Group 6-17-14

Date: June 17, 2014

To: Quality and Performance Measures Working Group, VHCIP

From: Tracy Dolan and Karen Hein, Population Health Working Group, VHCIP

Re: Updated Recommendations for ACO Shared Savings Program Measure Selection Criteria

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The overall charge of the Population Health Work Group is to recommend ways in which the Vermont Health Care Innovation Project could better coordinate population health [1]improvement activities and more directly impact population health.

I. Proposed Criteria

The criteria proposed are in line with the population health framework which recognizes the multiple factors that contribute to health outcomes, focuses on primary prevention, and seeks opportunities to impact upstream factors that affect health outcomes. The Population Health Working Group submits this clarification on the **intended use** of the population health criteria originally proposed to the Quality and Performance Measures Work Group.

Payment and Reporting

Use data on health trends and burden of illness to identify priorities *(existing criterion)*
Focus on identified state priorities given burden of illness, known preventable diseases and evidence-based actions that have proven successful in changing health outcomes. The measure is evidence-based, important to making significant gains in population health and improving determinants of health and health outcomes of a population.

Focus on broader population and health outcomes *(existing criterion)*
Consider the health outcomes of a group of individuals, ***including the distribution of such outcomes within the group***, in order to develop priorities and target action. The measure enables evaluation of subpopulations and especially those most vulnerable – due to disability, age, income, etc. The measure can be applied to the entire population – those already presenting with illness and disease as well as those at risk in the future.

Focus on prevention and wellness by patient, physician and system
Focus on prevention, self-care and maintaining wellness. The measure would include actions taken to maintain wellness rather than solely on identifying and treating disease and illness.

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[1] Population Health is "the health outcomes of a group of individuals, including the distribution of such outcomes within the group" (Kindig and Stoddart, 2003). While not a part of the definition itself, it is understood that such population health outcomes are the product of multiple determinants of health, including medical care, public health, genetics, behaviors, social factors, and environmental factors. **Working Definition of Population Health, Institute Of Medicine, Roundtable on Population Health Improvement**
http://**www**.iom.edu/Activities/PublicHealth/PopulationHealthImprovementRT.aspx

Focus upstream to include risk and protective factors

Risk factors are conditions or variables associated with a lower likelihood of positive outcomes and a higher likelihood of negative or socially undesirable outcomes. **Protective factors** have the reverse effect: they enhance the likelihood of positive outcomes and lessen the likelihood of negative consequences from exposure to risk. http://www.who.int/hiv/pub/me/en/me_prev_ch4.pdf. The measure would capture personal health behaviors such as tobacco, diet and exercise, alcohol uses, sexual activity, as well as other health and mental health conditions that are known to contribute to health outcomes.

Monitoring and Evaluation

Link to social determinants and environmental factors

The social determinants of health are the circumstances in which people are born; grow up, live, work, and age, as well as the systems put in place to deal with illness. These circumstances are in turn shaped by a wider set of forces: economics, social policies, and politics http://www.cdc.gov/socialdeterminants/

The measures would include social factors and the physical environment such as: education, employment, income, family support, community, the built environment and environmental quality.

Expanded Timeframe

Many changes to population health will require a longer time frame than the duration of this project. Develop a balanced portfolio of measures with the potential for short term impact (within 3-5 years) and other measures with impact over a longer time frame (5-20 years).

II. Priority Measures

The Population Health Working Group previously submitted our recommendation regarding which pending measures should be moved into payment or reporting status based on the criteria above.

First priority to be moved into payment or reporting status:

Core-40	MSSP-21	Screening for High Blood Pressure and Follow-Up Plan Documented
Core-36	MSSP-17	Tobacco Use Assessment and Tobacco Cessation Intervention
Core-44		Percentage of Patients with Self-Management Plans
Core-34		Prenatal and Postpartum Care Timeliness

Second priority to be moved into payment or reporting status:

Core-9		Depression Screening by 18 Years of Age
Core-30		Cervical Cancer Screening
Core-35	MSSP-14	Influenza Immunization
Core-39	MSSP-28	Hypertension (HTN): Controlling High Blood Pressure
Core-45		Screening, Brief Intervention, and Referral to Treatment

We are glad the measures above are being considered by the QPM work group.

We now submit our support for moving the following selected measures from reporting to payment:

Core-15	MSSP	Pediatric Weight Assessment and Counseling
Core-16	MSSP-22-26	Diabetes composite
Core-17	MSSP-27	Diabetes Mellitus
Core-19	MSSP-18	Depression Screening and Follow Up
Core-20	MSSP-16	Adult Weight Screening and Follow Up

In addition, we expect to continue to explore in the longer term other options for developing a shared accountability for improving the health of the population which may include measures that demonstrate more 'upstream' factors for a broader set of stakeholders or geographic regions.

Thank you for the opportunity to contribute to this discussion. We would be glad to engage in more exploration of how measurement can play a role in changing incentives in the system to improve the health of the population.

Attachment 4A – Rambur e-mail mammography

February 20, 2014 E-mail from Betty Rambur, PhD, Member of Green Mountain Care Board

Pat:

As you are aware from our public meeting on the ACO quality criteria, I am greatly concerned by the inclusion of mammography as a metric. The literature had been conflicting at best, and last week's very large, longitudinal, randomized control trial certainly supports the idea that such a metric may not only drive overscreening, but also create metric induced harm. I am not sure if your committee reviewed the actual primary research or instead followed other practice guidelines, but I have attached some of the seminal research for consideration.

When I visited Dartmouth-Hitchcock a few weeks back, one of the senior leaders shared with the audience that they plan to have the mammogram metric be "one they miss," because of the compelling evidence that it leads to overtreatment. Moreover, my understanding is that the country of Switzerland—a nation with very high quality marks—has already removed mammogram from its standard of care.

This issue has also had a great deal of conversation in the popular press, for example, this article that suggests that many "survivors" are actually instead victims of overtreatment.

http://www.nytimes.com/2012/11/22/opinion/cancer-survivor-or-victim-of-overdiagnosis.html?_r=0

Obviously, a patient and provider can decide that mammogram is a correct choice. The issue of incentivizing something that has substantial conflicting evidence is quite another thing.

Thank you for your hard work on quality.

Best,
Betty

Betty Rambur, PhD, RN
Member, Green Mountain Care Board
89 Main Street
Montpelier, VT 05620-3101
802-505-3055

Betty.Rambur@state.vt.us

Attachment 4B – Likelihood that screening saved life

ONLINE FIRST | LESS IS MORE

Likelihood That a Woman With Screen-Detected Breast Cancer Has Had Her "Life Saved" by That Screening

H. Gilbert Welch, MD, MPH; Brittney A. Frankel

Background: Perhaps the most persuasive messages promoting screening mammography come from women who argue that the test "saved my life." Because other possibilities exist, we sought to determine how often lives were actually saved by mammography screening.

Methods: We created a simple method to estimate the probability that a woman with screen-detected breast cancer has had her life saved because of screening. We used DevCan, the National Cancer Institute's software for analyzing Surveillance Epidemiology and End Results (SEER) data, to estimate the 10-year risk of diagnosis and the 20-year risk of death—a time horizon long enough to capture the downstream benefits of screening. Using a range of estimates on the ability of screening mammography to reduce breast cancer mortality (relative risk reduction [RRR], 5%-25%), we estimated the risk of dying from breast cancer in the presence and absence of mammography in women of various ages (ages 40, 50, 60, and 70 years).

Results: We found that for a 50-year-old woman, the estimated risk of having a screen-detected breast cancer in the next 10 years is 1910 per 100 000. Her observed 20-year risk of breast cancer death is 990 per 100 000. Assuming that mammography has already reduced this risk by 20%, the risk of death in the absence of screening would be 1240 per 100 000, which suggests that the mortality benefit accrued to 250 per 100 000. Thus, the probability that a woman with screen-detected breast cancer avoids a breast cancer death because of mammography is 13% (250/1910). This number falls to 3% if screening mammography reduces breast cancer mortality by 5%. Similar analyses of women of different ages all yield probability estimates below 25%.

Conclusions: Most women with screen-detected breast cancer have not had their life saved by screening. They are instead either diagnosed early (with no effect on their mortality) or overdiagnosed.

Arch Intern Med. 2011;171(22):2043-2046.
Published online October 24, 2011.
doi:10.1001/archinternmed.2011.476

CANCER SURVIVOR STORIES are important motivators for screening. They are common—a 4-month sample of 18 daily newspapers and magazines in 2005 found that, on average, each periodical published a new cancer survivor story at least once a month.[1]

See Invited Commentary at end of article

Narratives such as survivor stories also are more powerful than strictly didactic information. They are easier to understand,[2] more persuasive,[3] and more likely to impact viewers' and readers' behaviors, specifically by increasing screening behavior.[4] Celebrity survivor stories are particularly influential,[5] and in 1 case,[6] they were shown to double mammography rates. One explanation of this phenomenon—particularly in breast cancer—may be the general public's presumption that every survivor whose cancer was detected by screening has had her life saved because of screening.

Other outcomes, however, are possible. A woman may have had her breast cancer detected early yet not benefit from early detection because her cancer would have been equally treatable had it presented clinically. This possibility becomes more likely as treatment for early breast cancer improves.[7] Alternatively, a woman may have been overdiagnosed—diagnosed with a cancer not destined to cause symptoms or death.[8] Because it is important to acknowledge that these alternatives exist, in this article, we estimate the probability that a woman with screen-detected breast cancer—that is, one detected by screening mammography—has, in fact, had her life saved because of screening.

Author Affiliations: Dartmouth Institute for Health Policy and Clinical Practice, Dartmouth College, Hanover, New Hampshire.

Table. Simple Method Used to Calculate the Probability That a Breast Cancer Death Was Avoided Because of Screening

Measure	Source	Notation and Calculation	Base Case Data[a]
Probability of screen detection			
Observed risk of developing breast cancer in next 10 y	DevCan[9]	a	2990 per 100 000
Proportion of breast cancers found by mammography	Breen et al[10]	b	64%
Estimated risk of having screen-detected breast cancer in the next 10 y	Calculated	c = a × b	1910 per 100 000
Probability of death			
Observed risk of death in the next 20 y	DevCan[9]	d	990 per 100 000
Estimated risk of death in the absence of mammography	Calculated	e = d/(1.0 – 0.2)	1240 per 100 000
Probability of benefit			
Among all women			
Absolute risk reduction in mortality due to mammography	Calculated	f = e – d	250 per 100 000
Among all women with screen-detected breast cancer			
Probability that breast cancer death was avoided because of screening	Calculated	g = f/c	13%

[a]The base case example is for a 50-year-old woman and 20% relative risk reduction with mammography.

METHODS

OVERVIEW

To determine this probability, we wanted to devise a simple and transparent method. Our approach depends on 2 readily estimable probabilities for a woman in the general population of the United States: (1) the probability of having breast cancer detected by screening and (2) the probability of avoiding breast cancer death because of the screening. Both estimates are strongly related to age, and the second is also clearly related to the estimated relative risk reduction (RRR) in breast cancer mortality attributable to mammography. Consequently, we vary both inputs (ages, 40, 50, 60, and 70 years; RRRs, 5%, 10%, 15%, 20%, and 25%).

PROBABILITY OF SCREEN DETECTION

We used DevCan 6.5.0 to estimate the 10-year risk of developing breast cancer (both invasive cancer and ductal carcinoma in situ) in American women aged 40, 50, 60 and 70 years. DevCan was developed by the National Cancer Institute[9] to compute the risk of developing (or dying from) cancer, conditional on a specified age using cross-sectional data of incident cases from the standard areas of the Surveillance, Epidemiology, and End Results (SEER) Program.

The DevCan estimates, however, cannot distinguish between clinically detected and screen-detected cancer. Thus, we sought an alternative data source for the proportion of breast cancers detected by screening. We found a data source using the 2003 National Health Interview Survey[10] showing that in the 2001-2003 period, approximately 60% of all breast cancers were detected by screening mammograms. We contacted the authors, who shared the data stratified by our age groups (age ranges, 40-49 years, 63%; 50-59 years, 64%; 60-69 years, 61%; and 70-79 years, 52%).

The risk of having screen-detected cancer was estimated simply as the product of the risk of developing breast cancer and the proportion of breast cancers found by mammography.

PROBABILITY OF DEATH

We also used DevCan to estimate the 20-year risk of breast cancer death in American women aged 40, 50, 60, and 70 years. To capture the downstream benefit of screening, we made the optimistic assumption that a 10-year course of screening would influence mortality over a 20-year period. In other words, we assumed that the mortality benefit for screened women accrues for an additional 10 years after the 10-year screening period.

We then made another optimistic assumption: that the 20-year risk of breast cancer death currently observed has already been lowered by the population-wide use of mammography (ie, 100% penetration of mammography). To reflect this, we inflated the risk of death to estimate what it would have been in the absence of screening mammography. The magnitude of the inflation is directly related to the magnitude of the estimated relative risk reduction in breast cancer mortality attributable to mammography. If the observed risk of breast cancer death was 1000 per 100 000 and the estimated relative risk reduction was 20%, for example, we would estimate that the risk of breast cancer death without mammography would have been 1250 per 100 000 (=1000/[1.0-0.2]). We repeat these estimates for both inputs: each age group and 5 estimates about the RRR of mammography.

PROBABILITY OF BENEFIT

The absolute risk reduction in mortality due to mammography, or mortality benefit, was calculated as the difference between the estimated 20-year risk of death without mammography and the 20-year risk of death observed currently. The probability that a woman with screen-detected breast cancer has avoided breast cancer death because of screening was the ratio of the mortality benefit and the probability of having screen-detected breast cancer.

RESULTS

The **Table** details our method for a 50-year-old woman under the assumption that screening mammography reduces the risk of breast cancer death by 20%. Her observed risk of developing breast cancer in the next 10 years is 2990 per 100 000. In this age group, 64% of breast cancers are found by mammography, suggesting that her risk of having a screen-detected breast cancer during this period is 1910 per 100 000. Her observed 20-year probability of breast cancer death is 990 per 100 000. Assuming that screening has already reduced this risk by 20%, her risk of death in the absence of screening would be 1240 per 100 000, which suggests that the mortality benefit accrued to 250 per 100 000. Thus, the probability that a 50-year-old woman with screen-detected breast cancer avoids a breast cancer death because of mammography is 13% (250/1910).

The **Figure** shows that for a 50-year-old woman, this number rises to 17% if screening mammography reduces breast cancer mortality by 25% and falls to 3% if screening mammography reduces breast cancer mortality by 5%. The figure also shows a similar relationship for women of other ages: the probability that a woman with screen-detected breast cancer has her life saved because of screening increases as the RRR of mammography increases. This probability also rises with age. The effect is most dramatic for a 70-year-old woman because the proportion of screen-detected cancers in this age group is relatively low (52%). Regardless, all analyses yield probability estimates below 25%.

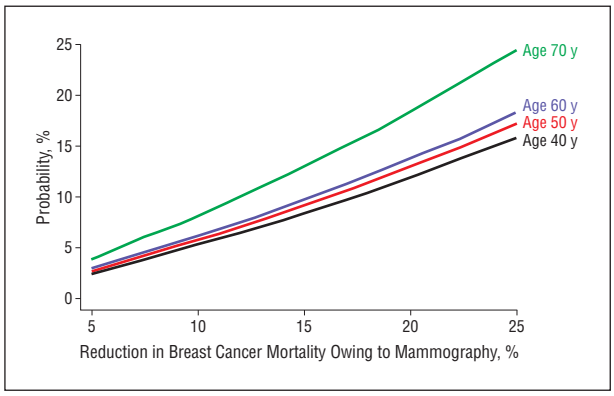

Figure. Probability that a woman with screen-detected breast cancer has her life saved because of the screening (using various ages and reductions in breast cancer mortality owing to mammography).

COMMENT

We devised a simple and transparent method to estimate the probability that a woman with screen-detected breast cancer benefited from screening. Using a variety of plausible estimates about the RRR attributable to mammography, we found that this probability is always less than 25%.

There are a number of limitations to our approach. First, it assumes that the underlying disease burden of breast cancer is stable over time. If the burden of disease is rising, then our approach would underestimate the probability of benefit; if it is falling, then our approach would overestimate benefit. Second, our data on the risk of having screen-detected breast cancer are dependent on the accuracy of the estimated proportion of breast cancers found by screening mammography. While our data come from a widely recognized national survey (the National Health Interview Survey of the Centers for Disease Control and Prevention),[10] they are based on patient self-report. It is reassuring, however, that we found similar estimates from a cohort study at a single cancer center, based on medical records.[11] Had we assumed instead that only 50% of breast cancers were screen detected, the base case shown in the Table would shift from 13% to 17% (and the range across ages and various risk reductions depicted in the Figure would shift from 2.5%-24.0% to 3.2%-25.0%).

Third, we were forced to make an assumption to capture the downstream benefit of screening: namely, that the mortality benefit for screened women accrues for an additional 10 years after the 10-year screening period. Long-term follow-up of the Swedish randomized trials of mammography found that mortality benefit for all women (aged 40 to 74 years) was maximal 3.5 years following the cessation of the trials[12] and 5.8 years for women in their 40s.[13] Thus, we are confident that this additional 10-year assumption was adequate to capture downstream benefits.

Finally, there are a number of reasons to believe that we have overestimated the probability that a woman with screen-detected breast cancer has benefited from screening. The additional 10-year assumption is likely excessive, leading us to overestimate the probability. Were we to have used only an additional 5 years (ie, a 15-year probability of breast cancer death), for example, the base case shown in the Table would shift from 13% to 9% (and the range depicted in the Figure would shift from 2.5%-24.0% to 1.5%-19.0%). Furthermore, the assumption of 100% penetration of mammography is also likely to be too generous. If so, our inflated estimate of mortality in the absence of mammography has been overinflated, also leading us to overestimate benefit.

Yet the most consequential variable in our analysis, by far, is the one we allowed to vary—the RRR attributable to mammography. We considered a range of values: namely, that screening mammography reduces breast cancer mortality anywhere from 5% to 25%. The values toward the high end (20%-25%) reflect the randomized trial data from more than a quarter century ago. Readers should be aware, however, that there are both theoretical and empirical reasons to believe that this mortality benefit has declined over time. As women with new breast lumps now present earlier for evaluation[14] (there is no debate about the value of diagnostic mammography), the benefit of screening would be expected to be less. As treatment of clinically detected breast cancer (that detected by means other than screening) has improved,[7] the benefit of screening would be expected to be less. Recent empirical data from European nations, in which the initiation of screening mammography has been a relatively discrete event, confirm that the current benefit of screening mammography is disappointingly small.[15,16] Consequently, we believe that readers should focus on the values toward the low end (5%-10%) and recognize that the probability that a woman with screen-detected breast cancer has, in fact, avoided a breast cancer death because of screening mammography is now likely to be well below 10%.

Against this backdrop of declining benefit is the increasing recognition of the problem of mammography overdiagnosis—the detection of cancers not destined to cause symptoms or death. It is a problem that is notoriously difficult to quantify: estimates of the ratio of the overdiagnosis harm to the mortality benefit range from 2:1 to 10:1.[17,18] Nevertheless, there is little doubt that the problem is only aggravated by the increasing resolution of mammographic imaging.

Today, more people are likely to know a cancer survivor than ever before. Between 1971 and 2007, the number of cancer survivors in the United States more than doubled, from 1.5% to 4.0% of the population.[19] Breast cancer survivors are particularly common: they now rep-

resent approximately 2.5 million, or one-fifth of the current survivor population.[20]

Earlier diagnosis (either via enhanced awareness or screening) and better treatment are clearly part of the explanation for this large survivor population. But so too is the enthusiasm for screening and the resulting overdiagnosis. And, ironically, this enthusiasm may, in turn, be the product of a large number of survivors. This self-reinforcing cycle (the more detection, the more enthusiasm—the so-called popularity paradox of screening)[21] is driven, in part, by the presumption that every screen-detected breast cancer survivor has had her "life saved" because of screening. Our analyses suggest this is an exaggeration. In fact, a woman with screen-detected cancer is considerably more likely not to have benefited from screening. We believe that this information is important to put cancer survivor stories in their proper context.

Accepted for Publication: August 7, 2011.
Published Online: October 24, 2011. doi:10.1001/archinternmed.2011.476
Correspondence: H. Gilbert Welch, MD, MPH, Dartmouth Institute of Health Policy and Clinical Practice, Dartmouth College, 35 Centerra Pkwy, Ste 202, Lebanon, NH 03766 (H.Gilbert.Welch@dartmouth.edu).
Author Contributions: *Study concept and design:* Welch. *Acquisition of data:* Frankel. *Analysis and interpretation of data:* Welch and Frankel. *Drafting of the manuscript:* Welch and Frankel. *Critical revision of the manuscript for important intellectual content:* Welch. *Statistical analysis:* Welch. *Administrative, technical, and material support:* Welch.
Financial Disclosure: None reported.
Additional Contributions: Nancy Breen, PhD, provided the age-stratified data from the 2003 National Health Interview Survey.

REFERENCES

1. Kromm EE, Smith KC, Singer RF. Survivors on cancer: the portrayal of survivors in print news. *J Cancer Surviv*. 2007;1(4):298-305.
2. McQueen A, Kreuter MW. Women's cognitive and affective reactions to breast cancer survivor stories: a structural equation analysis. *Patient Educ Couns*. 2010;81(Suppl):S15-S21.
3. Kreuter MW, Holmes K, Alcaraz K, et al. Comparing narrative and informational videos to increase mammography in low-income African American women. *Patient Educ Couns*. 2010;81(Suppl):S6-S14.
4. Cox D, Cox AD. Communicating the consequences of early detection: the role of evidence and framing. *J Marketing*. 2001;65(1):91-103.
5. Larson RJ, Woloshin S, Schwartz LM, Welch HG. Celebrity endorsements of cancer screening. *J Natl Cancer Inst*. 2005;97(9):693-695.
6. Chapman S, McLeod K, Wakefield M, Holding S. Impact of news of celebrity illness on breast cancer screening: Kylie Minogue's breast cancer diagnosis. *Med J Aust*. 2005;183(5):247-250.
7. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365(9472):1687-1717.
8. Welch HG, Black WC. Overdiagnosis in cancer. *J Natl Cancer Inst*. 2010;102(9):605-613.
9. National Cancer Institute. DevCan: Probability of Developing or Dying of Cancer. http://surveillance.cancer.gov/devcan. Accessed May 3, 2011.
10. Breen N, Yabroff KR, Meissner HI. What proportion of breast cancers are detected by mammography in the United States? *Cancer Detect Prev*. 2007;31(3):220-224.
11. Malmgren JA, Atwood MK, Kaplan HG. Increase in mammography detected breast cancer over time at a community based regional cancer center: a longitudinal cohort study 1990-2005. *BMC Cancer*. 2008;8:131-138.
12. Nyström L, Andersson I, Bjurstam N, Frisell J, Nordenskjöld B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet*. 2002;359(9310):909-919.
13. Larsson LG, Andersson I, Bjurstam N, et al. Updated overview of the Swedish Randomized Trials on Breast Cancer Screening with Mammography: age group 40-49 at randomization. *J Natl Cancer Inst Monogr*. 1997;22(22):57-61.
14. Rostgaard K, Vaeth M, Rootzén H, Lynge E. Why did the breast cancer lymph node status distribution improve in Denmark in the pre-mammography screening period of 1978-1994? *Acta Oncol*. 2010;49(3):313-321.
15. Kalager M, Zelen M, Langmark F, Adami H-O. Effect of screening mammography on breast-cancer mortality in Norway. *N Engl J Med*. 2010;363(13):1203-1210.
16. Autier P, Boniol M, Gavin A, Vatten LJ. Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database. *BMJ*. 2011;343:d4411.
17. Zackrisson S, Andersson I, Janzon L, Manjer J, Garne JP. Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study. *BMJ*. 2006;332(7543):689-692.
18. Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. *Cochrane Database Syst Rev*. 2011;(1):CD001877.
19. Centers for Disease Control and Prevention (CDC). Cancer survivors: United States, 2007. *MMWR Morb Mortal Wkly Rep*. 2011;60(9):269-272.
20. American Cancer Society. *Breast Cancer Facts and Figures, 2009-2010*. Atlanta, GA: American Cancer Society; 2009.
21. Raffle AE, Muir Gray JA. *Screening: Evidence and Practice*. New York, NY: Oxford University Press; 2007.

INVITED COMMENTARY

ONLINE FIRST

Screening

Simple Messages . . . Sometimes

In their article appearing in this issue of the *Archives*, Welch and Frankel[1] critically evaluate the common claim among cancer survivors that their "life was saved" by screening. After providing convincing evidence that this claim is markedly exaggerated, the authors express concerns that overly inflated perceptions of the benefits of mammography may lead to a self-perpetuating cycle of unwarranted demand for screening, overdiagnosis, overtreatment, and a continually growing population of breast cancer survivors who advocate mammography. The demographics of survivorship suggest that their concern is legitimate.

According to the National Cancer Institute,[2] there were an estimated 11.9 million cancer survivors (approxi-

Attachment 4C – Overscreening BMJ

BMJ

BMJ 2014;348:g366 doi: 10.1136/bmj.g366 (Published 11 February 2014)

RESEARCH

Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial


OPEN ACCESS

Anthony B Miller *professor emeritus*[1], Claus Wall *data manager*[1], Cornelia J Baines *professor emerita*[1], Ping Sun *statistician*[2], Teresa To *senior scientist*[3], Steven A Narod *professor*[1 2]

[1]Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario M5T 3M7, Canada; [2]Women's College Research Institute, Women's College Hospital, Toronto, Ontario M5G 1N8, Canada; [3]Child Health Evaluative Services, The Hospital for Sick Children, Toronto, Ontario, Canada

Abstract

Objective To compare breast cancer incidence and mortality up to 25 years in women aged 40-59 who did or did not undergo mammography screening.

Design Follow-up of randomised screening trial by centre coordinators, the study's central office, and linkage to cancer registries and vital statistics databases.

Setting 15 screening centres in six Canadian provinces,1980-85 (Nova Scotia, Quebec, Ontario, Manitoba, Alberta, and British Columbia).

Participants 89 835 women, aged 40-59, randomly assigned to mammography (five annual mammography screens) or control (no mammography).

Interventions Women aged 40-49 in the mammography arm and all women aged 50-59 in both arms received annual physical breast examinations. Women aged 40-49 in the control arm received a single examination followed by usual care in the community.

Main outcome measure Deaths from breast cancer.

Results During the five year screening period, 666 invasive breast cancers were diagnosed in the mammography arm (n=44 925 participants) and 524 in the controls (n=44 910), and of these, 180 women in the mammography arm and 171 women in the control arm died of breast cancer during the 25 year follow-up period. The overall hazard ratio for death from breast cancer diagnosed during the screening period associated with mammography was 1.05 (95% confidence interval 0.85 to 1.30). The findings for women aged 40-49 and 50-59 were almost identical. During the entire study period, 3250 women in the mammography arm and 3133 in the control arm had a diagnosis of breast cancer, and 500 and 505, respectively, died of breast cancer. Thus the cumulative mortality from breast cancer was similar between women in the mammography arm and in the control arm (hazard ratio 0.99, 95% confidence interval 0.88 to 1.12). After 15 years of follow-up a residual excess of 106 cancers was observed in the mammography arm, attributable to over-diagnosis.

Conclusion Annual mammography in women aged 40-59 does not reduce mortality from breast cancer beyond that of physical examination or usual care when adjuvant therapy for breast cancer is freely available. Overall, 22% (106/484) of screen detected invasive breast cancers were over-diagnosed, representing one over-diagnosed breast cancer for every 424 women who received mammography screening in the trial.

Introduction

Regular mammography screening is done to reduce mortality from breast cancer. Mammogram detected non-palpable breast cancers are smaller on average than clinically palpable breast cancers. Small breast cancers confer a better prognosis than large ones. However, survival in the context of a screening programme is not predictive of reduced mortality because of lead time bias, length bias, or over-diagnosis.[1] Thus the benefit of mammography screening must be evaluated in randomised screening trials, with breast cancer mortality as the endpoint.

Over-diagnosis refers to the possibility that a screen detected cancer might not otherwise become clinically apparent during the lifetime of the woman.[2 3] Over-diagnosis can be estimated in a randomised screening trial when a sufficiently long period has elapsed from the cessation of screening—that is, when all cancers should have become clinically apparent in both trial arms.

In 1980 a randomised controlled trial of screening mammography and physical examination of breasts in 89 835 women, aged 40 to 59, was initiated in Canada, the Canadian National Breast Screening Study.[4-7] It was designed to tackle research questions that arose from a review of mammography screening in Canada[8] and the report by the working group to review the US Breast Cancer Detection and Demonstration projects.[9] At that time the only breast screening trial that had reported results was that conducted within the Health Insurance Plan of Greater New York.[10 11] Benefit from combined

Correspondence to: A B Miller ab.miller@utoronto.ca

mammography and breast physical examination screening was found in women aged 50-64, but not in women aged 40-49. Therefore the Canadian National Breast Screening Study was designed to evaluate the benefit of screening women aged 40-49 compared with usual care and the risk benefit of adding mammography to breast physical examination in women aged 50-59. It was not deemed ethical to include a no screening arm for women aged 50-59.

We have now followed the study participants for a mean of 22 years. Previously the trial was reported in two components, women aged 40-49[4 6] and women aged 50-59[5 7] on enrolment. As the results from the mammography and control arms were similar in both age groups, we have combined the age groups and compare breast cancer incidence and mortality rates up to 25 years between the two arms of the trial.

Methods

Participants were recruited to the study by a general publicity campaign, by reviewing population lists and sending personal invitation letters, by group mailings, and through family doctors.[4] Women were eligible if they were aged 40-59, had had no mammography in the previous 12 months, had no history of breast cancer, and were not pregnant. Recruitment was planned to enrol 50 000 women aged 40-49 and 40 000 aged 50-59 years. Before randomisation, the women who volunteered to participate signed an informed consent form approved by the University of Toronto's Human Experimentation Committee. The study was conducted in 15 screening centres in six Canadian provinces (Nova Scotia, Quebec, Ontario, Manitoba, Alberta, and British Columbia). All screening centres were located in teaching hospitals or in cancer centres. The central coordinating centre was at the University of Toronto.

Participants then had a physical (clinical) breast examination and were taught breast self examination by trained nurses, or in the province of Quebec, by doctors (fig 1⇓). The examiners had no role in the randomisation that followed; this was performed by the study coordinators in each centre. Randomisation was individual and stratified by centre and five year age group.[5] Irrespective of the findings on physical examination, women aged 40-49 were independently and blindly assigned randomly to receive mammography or no mammography. Those allocated to mammography were offered another four rounds of annual mammography and physical examination, those allocated to no mammography were told to remain under the care of their family doctor, thus receiving usual care in the community, although they were asked to complete four annual follow-up questionnaires. Women aged 50-59 were randomised to receive mammography or no mammography, and subsequently to receive four rounds of annual mammography and physical examination or annual physical breast examinations without mammography at their screening centre.

For those women enrolled in the final year of recruitment, a total of four annual screens were offered. The screening period was defined as the first five years from randomisation for each woman and the follow-up period as years 6 to 25. As previously reported,[4 5] in the mammography arm full compliance with screening after screen 1 (when compliance was 100%) varied from 86% (for screen 5) to 90% (for screen 2). In addition a small proportion (up to 3%) of the women attended and accepted breast examination but refused mammography. Of the women who failed to attend 3% to 7% submitted questionnaires. Over 93% of participants in the control arm aged 40-49 returned their annual questionnaire, whereas compliance with annual breast examination screening for those in the control arm aged 50-59 varied between 89% (for screen 2) and 85% (for screen 5); only questionnaires were obtained for 3% to 7% of the women.

Women with abnormal findings either on physical examination or on mammography were referred to a special review clinic directed by the surgeon affiliated with the study centre. If indicated, diagnostic mammography was performed. If further diagnostic investigation such as a biopsy was required, the woman was referred to a specialist chosen by her family doctor. Women for whom these investigations did not result in a diagnosis of breast cancer resumed their normal participation in the trial; women with a diagnosis of breast cancer were treated by specialists selected by the woman's family doctor and were followed by us through annual communication with the selected surgeon until 30 June 1996.

During the screening period, centre coordinators collected surgical and pathology reports for all diagnostic and therapeutic procedures, including those for women aged 40-49 who were not returning for further screening, and for interval cancers. A pathologist affiliated with the Canadian National Breast Screening Study obtained and reviewed representative slides of all biopsy samples. Cancer treatment was arranged through the participant's doctor and was not influenced by the study team. Canada has a universal healthcare system. No financial barrier exists to accessing appropriate diagnostic investigation or treatment.

Throughout the study two view film screen mammography was used. In accordance with standard practice in North America, craniocaudal and mediolateral views were used until 1985. Thereafter craniocaudal and mediolateral oblique views were used.[6] Facilities and equipment for modern film screen mammography were prerequisites.[6] Quality control procedures were established for radiation physics and mammography interpretation.[7] Breast examiners received a month of training by the centre surgeon before conducting examinations in the study.[5]

In the remainder of this report we refer to the mammography plus breast physical examination arm in both age groups as the mammography arm, and the no mammography arms (usual care for women aged 40-49 and annual breast physical examinations for women aged 50-59) as the control arm.

Follow-up

The screening centres closed in 1988. Thereafter the Canadian National Breast Screening Study coordinating centre continued to follow the women with a diagnosis of breast cancer in the screening period through their treating surgeon until 30 June 1996.[6 7] To determine the underlying cause of death for those women with breast cancer who died, expert oncologists blind as to allocation obtained and reviewed detailed documentation on the terminal illness.[6 7] Subsequent to 30 June 1996, passive follow-up of all participants was carried out through record linkage. The cut-off date for passive follow-up was 31 December 2005. Using linkage to the Canadian Cancer Registry and the Canadian national mortality database, maintained by Statistics Canada in Ottawa, we ascertained all dates of breast cancer diagnoses and all dates of death from breast cancer that occurred before the cut-off date. The study investigators received reports on all deaths, with the certified underlying cause of death as coded within Statistics Canada. The denominators for the breast cancer incidence and mortality rates reported were all women randomised to the two arms of the trial.

Statistical analysis

Tumour characteristics—We collected data on tumour size, lymph node status, and tumour palpability (yes or no) for women with a diagnosis of breast cancer in the screening period. For this analysis, we considered only invasive cancers as events. We also obtained similar data for 63% of the cancers diagnosed in years 6-11 of the follow-up period. Cancers in the mammography and control arms (including interval cancers) were compared for these three characteristics and the χ^2 test used to compare differences.

Survival rates—We evaluated the 10 year and 25 year survival rates for all women with a diagnosis of breast cancer in the screening period (years 1-5) and for all cases diagnosed during the entire study period (years 1 to 25). We also conducted analyses assuming the screening period to be six years and seven years. Survival was estimated from time of diagnosis to time of death from breast cancer, death from another cause, or date last known to be alive. Women not known to be dead were assumed to be alive on 31 December 2005. We carried out subanalyses, stratifying the participants by tumour size (cm), nodal status, palpability of tumour, and mammography and control arms.

Mortality rates—Participants were followed for death from breast cancer from the date of randomisation until 31 December 2005. Women who died from another cause were censored at the date of death. The primary analysis included only deaths from invasive breast cancers diagnosed during the screening period. We carried out subanalyses on deaths from prevalent cancers (cancers detected at the first screening round) and deaths from incident cancers (cancers detected at screening rounds 2 to 5) plus cancers detected between screening rounds and cancers detected within one year of the last screen (interval cancers). We used Cox proportional hazards model to calculate hazard ratios with 95% confidence intervals. A P value of 0.05 was used as the cut-off for statistical significance. All analyses were conducted using SAS.

Results

Breast cancer occurrence

The 89 835 women were followed for incident breast cancers for up to 25 years from the date of randomisation (mean 21.9 years). A total of 1190 breast cancers were diagnosed during the screening period (666 in the mammography arm and 524 in the control arm), and a further 5193 were ascertained in the follow-up period (2584 in the mammography arm and 2609 in the control arm) (table 1⇓). Of the 666 cancers detected in the mammography arm during the screening period, 484 were screen detected (73.3%), 176 were interval cancers (26.7%), and data were missing for six.

During the screening period the mean size of the cancers diagnosed in the mammography arm was 1.91 cm and in the control arm was 2.10 cm (P=0.01) (table 2⇓). In the mammography arm, 30.6% of cancers (n=204) were node positive and 68.2% (n=454) were palpable. In the control arm, 32.4% of the cancers (n=170) were node positive (P=0.53 for difference) and all were palpable. Overall, 454 palpable cancers were detected in the mammography arm and 524 in the control arm, whereas similar proportions of palpable cancers were identified as node positive. On average, palpable cancers were larger than cancers that were detected only by mammography (2.1 cm *v* 1.4 cm; P<0.001) and were more likely to be node positive (34.7% *v* 16.5%; P<0.001) (table 2).

Breast cancer survival

Overall, 1005 women died from breast cancer during the 25 year follow-up period (1.1%) including 351 of 1190 women (29.4%) with a diagnosis during the screening period. The 25 year survival was 77.1% for women with tumours of less than 2 cm, compared with 54.7% for tumours greater than 2 cm (hazard ratio 0.46, 95% confidence interval 0.37 to 0.58; P<0.001). The 25 year survival was 70.6% for women with breast cancer detected in the mammography arm and 62.8% for women with cancers diagnosed in the control arm (0.79, 0.64 to 0.97; P=0.02). The 25 year survival for women with a palpable cancer was similar between women in the mammography arm and control arm (66.3% and 62.8%). The 25 year survival of women with breast cancer diagnosed by mammography only (non-palpable) was 79.6%. In the mammography arm, the survival of women with a non-palpable cancer was much longer than that of women with a palpable cancer (0.58, 0.41 to 0.82; $P<10^{-4}$) as was the survival of women with a screen detected cancer compared with interval cancer (0.61, 0.45 to 0.82; P=0.001).

Breast cancer mortality

All cause mortality was 9477 (10.6%) in the follow-up period. The 25 year cumulative mortality from all causes of death was similar between women in the mammography and control arms (fig 2⇓) (1.02, 0.98 to 1.06; P=0.28). Overall, 1005 deaths occurred from breast cancer. The 25 year cumulative mortality from breast cancer was similar between women in the mammography arm and control arm (fig 2) (0.99, 0.88 to 1.12; P=0.87).

During the screening period, 361 deaths occurred from breast cancer (table 3⇓). Overall, the 25 year cumulative mortality from breast cancers diagnosed during the screening period was similar between women in the mammography and control arms (fig 3⇓) (1.05, 0.85 to 1.30; P=0.63). The hazard ratio remained similar if the screening period was extended to six years (1.06, 0.87 to 1.29; P=0.55) or seven years (1.07, 0.89 to 1.29; P=0.46). For women aged 40-49 at assignment the hazard ratio for 25 year breast cancer specific mortality associated with mammography was 1.09 (95% confidence interval 0.80 to 1.49; P=0.58) and for women aged 50-59 at assignment was 1.02 (0.77 to 1.36; P=0.88). The hazard ratio for 25 year breast cancer specific mortality associated with mammography from prevalent cancers only (diagnosed in first screening round) was 1.47 (1.01 to 2.13; P=0.04), and the hazard ratio for deaths from incident cancers (those diagnosed in years 2 to 5) was 0.90 (0.69 to 1.16; P=0.40).

Over-diagnosis

At the end of the screening period, an excess of 142 breast cancer cases occurred in the mammography arm compared with control arm (666 *v* 524) (fig 4⇓). Fifteen years after enrolment, the excess became constant at 106 cancers. This excess represents 22% of all screen detected invasive cancers—that is, one over-diagnosed breast cancer for every 424 women who received mammography screening in the trial.

Discussion

In this analysis of findings from the Canadian National Breast Screening Study, we have extended the previously reported follow-up at 11-16 years[6 7] to 25 years, and for the first time report an estimate of the amount of over-diagnosis resulting from mammography screening. We still found no reduction in

breast cancer mortality from mammography screening in a programme offering five annual screens, neither in women aged 40-49 at study entry nor in women aged 50-59. Although the difference in survival after a diagnosis of breast cancer was significant between those cancers diagnosed by mammography alone and those diagnosed by physical examination screening, this is due to lead time, length time bias, and over-diagnosis. At the end of the screening period, an excess of 142 breast cancers occurred in the mammography arm compared with the control arm, and at 15 years the excess remained at 106 cancers. This implies that 22% (106/484) of the screen detected invasive cancers in the mammography arm were over-diagnosed. This represents one over-diagnosed breast cancer for every 424 women who received mammography screening in the trial. Assuming that nearly all over-diagnosed cancers in the Canadian National Breast Screening Study were non-palpable, 50% (106/212) of mammogram detected, non-palpable cancers were over-diagnosed.

Strengths and limitations of this study

We believe that the lack of an impact of mammography screening on mortality from breast cancer in this study cannot be explained by design issues, lack of statistical power, or poor quality mammography. It has been suggested that women with a positive physical examination before randomisation were preferentially assigned to the mammography arm.[12 13] If this were so, the bias would only impact on the results from breast cancers diagnosed during the first round of screening (women retained their group assignment throughout the study). However, after excluding the prevalent breast cancers from the mortality analysis, the data do not support a benefit for mammography screening (hazard ratio 0.90, 95% confidence interval 0.69 to 1.16). It has also been suggested that women in the screening group might have been at higher a priori risk of developing breast cancer than women in the control group.[13] After the screening period ended, however, breast cancer was diagnosed in 5.8% of women in the mammography arm and in 5.9% of women in the control arm (P=0.80), showing that the risk of breast cancer was identical between the compared groups. It has also been suggested that the lack of benefit from mammography screening found in the study could have been due to mammography screening ongoing in the community. We tackled this issue for women aged 40-49 in an earlier report[7] and found that after adjusting for use of mammography in the community in the control group, largely for diagnosis, there was still no indication of benefit from the mammography screening in the intervention group. Mammography screening programmes fall under provincial jurisdiction and were not introduced in Canada until after screening ceased in the Canadian National Breast Screening Study, initially in British Columbia in 1988, then in Ontario and Alberta in 1990, Nova Scotia in 1991, Manitoba in 1995, and Quebec in 1998.[14] We do not have data on the participation of the participants in these programmes, but we have no reason to suspect it was differential between the two arms of the Canadian National Breast Screening Study. These programmes did not necessarily include breast examination and most excluded women in their 40s. In our analyses we included deaths of any woman with breast cancer detected by these programmes.

Long term follow-up was conducted passively on participants, by record linkage to national databases. This allowed us to capture incident cancers and deaths for women who moved within the country, and for Canadian women who died in the United States, as death certificates on such women are forwarded to Statistics Canada. An occupational cohort study estimated that record linkage to the Canadian national death index was at least 95% complete.[15]

We have shown that the sensitivity of the mammography employed in the screening centres was representative of the quality of the technology delivered at cancer centres and teaching hospitals and that the screening examination was properly conducted.[16-18] Of the 666 breast cancers diagnosed in the mammography arm during the screening period, 212 (32%) were detected by mammography only, and on average these were 0.7 cm smaller than those detected by physical examination (1.4 cm *v* 2.1 cm). Cancers detected in the mammography arm were significantly smaller than cancers detected in the control arm (1.9 cm *v* 2.1), and the 25 year survival of women with breast cancer diagnosed in the mammography arm was superior to that of the women with a diagnosis in the control arm (70.6% *v* 62.8%). Furthermore, during the screening period 70 fewer palpable cancers were detected in the mammography arm than in the control arm (454 *v* 524). Some of this difference may be due to random fluctuation, but this may also be the consequence of shifting 70 women from having a palpable to a non-palpable cancer at presentation through earlier detection, commensurate with the reduction in mean tumour size.

Our study is strengthened by the long follow-up period and the acquisition of information on incident cancers that occurred beyond the screening period. The interpretation of our results is aided by additional data we acquired on tumour size, nodal status, mammographic detection, and palpability of tumours. In particular, during the screening period we detected 524 cancers (all palpable, mean size 2.10 cm) in the control arm and 666 cancers (mean size 1.98 cm) in the mammography arm. Within the screening arm, 454 (68%) of the detected palpable cancers were (mean size 2.10 cm) identified at the time of the mammography through physical examination. Screening was annual, and therefore it is to be expected that in programmes with less frequent screening (for example, every two or three years) the proportion of invasive cancers detected in the mammography arm that would be palpable would be even higher. From this we infer that if there is benefit from a mammography only screening programme, it is derived through cancers detectable by a thorough breast physical examination.

Comparison with other studies

Our long term result differs from the finding of the 29 year follow-up of the Swedish Two-County Trial, which reported a 31% reduction in mortality associated with screening.[19] The analysis of the Swedish trial was based on invitation to screen (rather than actual screening), informed consent was not implemented, randomisation was at the county level (not individually), and screening was done every 24 to 33 months (not annually). The persisting divergence of breast cancer mortality with time suggests an initial imbalance of the compared groups, not a benefit of screening mammography. Of note, 68% of the cancers in the screening arm in the Swedish trial were detected through screening, compared with 74% in our study, and adjuvant therapy was not given,[20] whereas it was in the Canadian National Breast Screening Study.[1] Tumours in the control group of the Swedish Two-County study were on average 2.8 cm, larger than in our study.[21] The mean size of the tumours in our control group was relatively small (2.1 cm), and 66% were node negative. The difference in mortality associated with tumours less than 2 cm compared with larger tumours is substantial.

Our estimate of over-diagnosis is smaller than that of a review of data from the Surveillance, Epidemiology, and End Results

programme from 1976 to 2008, which estimated that over-diagnosis accounted for 31% of all breast cancers.[22] However, the reviewers considered a wider age range than in the Canadian National Breast Screening Study, and it is likely that over-diagnosis is greater at older than younger ages, as competing causes of death are more common. Other studies that resulted in lower estimates of over-diagnosis were based on indirect observations of the numbers of cancers detected in a population, before and after the introduction of screening programmes, and the extent of over-diagnosis was probably underestimated.[23 24]

Conclusions and policy implications

The results of the present study may not be generalisable to all countries. Early detection could be of greater benefit in communities where most cancers that present clinically are larger and a higher proportion are node positive.[25] However, in technically advanced countries, our results support the views of some commentators that the rationale for screening by mammography should be urgently reassessed by policy makers.[26] Nevertheless, education, early diagnosis, and excellent clinical care should continue to be provided to women to ensure that as many breast tumours as possible are diagnosed at or less than 2 cm.

In conclusion, our data show that annual mammography does not result in a reduction in breast cancer specific mortality for women aged 40-59 beyond that of physical examination alone or usual care in the community. The data suggest that the value of mammography screening should be reassessed.

Contributors: CW collated the data for analysis. PS performed the analysis. SAN, TT, and ABM planned the analysis. ABM and SAN drafted the manuscript. All authors checked the manuscript, tables, and figures for accuracy and completeness. ABM is guarantor.

Funding This study was supported by the Canadian Breast Cancer Research Alliance, Canadian Breast Cancer Research Initiative, Canadian Cancer Society, Health and Welfare Canada, National Cancer Institute of Canada, Alberta Heritage Fund for Cancer Research, Manitoba Health Services Commission, Medical Research Council of Canada, le Ministère de la Santé et des Services Soçiaux du Québec, Nova Scotia Department of Health, and Ontario Ministry of Health. ABM was supported in part by a national health scientist award from Health and Welfare Canada. The study sponsors (funders) had no role in the preparation, approval, or submission of this manuscript.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was originally approved by the University of Toronto's Human Experimentation Committee. The extended follow-up and its analysis was approved by the Women's College Hospital research ethics board (reference 2007-0025-B)

Data sharing: No additional data available.

Transparency: The lead author (the manuscript's guarantor), ABM, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies are disclosed.

1 Miller AB. Conundrums in screening for cancer. Mini review. *Int J Cancer* 2010;126:1039-46.
2 Moss S. Over-diagnosis in randomised controlled trials of breast cancer screening. *Breast Cancer Res* 2005;7:230-4.
3 Welch HG. Over-diagnosis and mammography screening. *BMJ* 2009;339:182-3.
4 Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years. *CMAJ* 1992;147:1459-76.
5 Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 2. Breast cancer detection and death rates among women aged 50 to 59 years. *CMAJ* 1992;147:1477-88.
6 Miller AB, To T, Baines CJ, Wall C. Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women age 50-59 years. *J Natl Cancer Inst* 2000;92:1490-9.
7 Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study-1: breast cancer mortality after 11 to 16 years of follow-up. A randomized screening trial of mammography in women age 40 to 49 years. *Ann Intern Med* 2002;137:305-12.
8 Leger JL, Naimark AP, Beique R, McFarlane DV, Miller S, Miller AB. Report of the "ad hoc" committee on mammography. *J Can Assoc Radiol* 1974;25:3-21.
9 Report of the Working Group to review the National Cancer Institute-American Cancer Society Breast Cancer Detection Demonstration Projects. *J Natl Cancer Inst* 1979;62:641-709.
10 Shapiro S, Strax P, Venet L. Periodic breast cancer screening in reducing mortality from breast cancer. *JAMA* 1971;215:1777-85.
11 Shapiro S. Evidence on screening for breast cancer from a randomized trial. *Cancer* 1977;39:2772-82.
12 Tarone RE. The excess of patients with advanced breast cancer in young women screened with mammography in the Canadian National Breast Screening Study. *Cancer* 1995;75:997-1003.
13 Mukherjee S. The emperor of all maladies. A biography of cancer. Simon and Shuster, 2010.
14 Canadian Breast Cancer Screening Database (CBCSD). Operational procedures and input data dictionary. Version 6. Public Health Agency of Canada, 2012.
15 Roberts RS, Julian JA, Sweezey D, Muir DC, Shannon HS, Mastromatteo E. A study of mortality in workers engaged in the mining, smelting, and refining of nickel. I: methodology and mortality by major cause groups. *Toxicol Ind Health* 1989;5:957-74.
16 Baines CJ, Miller AB, Kopans DB, Moskowitz M, Sanders DE, Sickles EA, et al. Canadian National Breast Screening Study: assessment of technical quality by external review. *Am J Roentgenol* 1990:155:743-7.
17 Miller AB, Baines CJ, Sickles EA. Canadian National Breast Screening Study. *Am J Roentgenol* 1990;155:1133-4.
18 Baines CJ, McFarlane DV, Wall C. Audit procedures in the National Breast Screening Study: mammography interpretation. *Can Assoc Radiol J* 1986;37:256-60.
19 Tabár L, Vitak B, Chen TH, Yen AM, Cohen A, Tot T, et al. Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades. *Radiology* 2011;260:658-63.
20 Tabar L, Chen H-H T, Duffy SW, Kruesmo UB. Primary and adjuvant therapy, prognostic factors and survival in 1053 breast cancers diagnosed in a trial of mammography screening. *Jpn J Clin Oncol* 1999;2129:608-16.
21 Narod SA. On being the right size: a reappraisal of mammography trials in Canada and Sweden. *Lancet* 1997;349:1846.
22 Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med* 2012;367:1998-2005.
23 Zackrisson S, Andersson I, Janzon L, Manjer J, Garne JP. Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study. *BMJ* 2006;332:689-92.
24 Zahl PH, Gøtzsche PC, Mæhlen J. Natural history of breast cancers detected in the Swedish mammography screening programme: a cohort study. *Lancet Oncol* 2011;12:1118-24.
25 Narod SA. Tumour size predicts long-term survival among women with lymph node-positive breast cancer. *Curr Oncol* 2012;19:249-53.
26 Gøtzsche PC, Jørgensen KJ, Zahl P-H, Mæhlen J. Why mammography screening has not lived up to expectations from the randomised trials. *Cancer Causes Control* 2012;23:15-21.

Accepted: 16 January 2014

Cite this as: *BMJ* 2014;348:g366

What is already known on this topic

Women with non-palpable breast cancer detected by mammography experience long term survival that is superior to that of women with palpable breast cancer

It is not known with accuracy to what extent the survival difference is a consequence of organised screening or of lead time bias and over-diagnosis

What this study adds

Annual mammography screening detected a significant number of small non-palpable breast cancers, but half of these were examples of over-diagnosis

22% of the screen detected invasive cancers in the mammography arm were over-diagnosed, representing one over-diagnosed breast cancer for every 424 women who received mammography screening in the trial

Annual mammography screening had no effect on breast cancer mortality beyond that of breast physical examinations

Tables

Table 1| **Number of breast cancers diagnosed in mammography arm and control arm, by study year**

	Mammography arm (n=44 925)		Control arm (n=44 910)	
Year of study	No of cancers detected	Mean size (cm)	No of cancers detected	Mean size (cm)
1	253	1.87	170	2.03
2	109	2.05	89	2.19
3	101	1.64	89	2.11
4	111	2.01	86	2.08
5	92	1.98	90	2.13
Subtotal years 1-5	666	1.91	524	2.10
6	83	2.15	83	2.42
7	82	1.99	93	2.24
8	107	2.01	133	2.04
9	115	1.86	119	1.90
10	127	1.69	128	1.71
Subtotal years 6-10	514	1.93	556	2.05
Subtotal years 11-25	2070	—	2053	—
Subtotal years 6-25	2584	—	2609	—
Total years 1-25	3250	—	3133	—

Table 2| **Comparison of breast cancers detected during screening phase (years 1 to 5) in mammography arm versus control arm. Values are numbers (percentages) unless stated otherwise**

		Cancers in mammography arm		
Variables	**Control arm (n=524)**	**Detected (n=666)**	**Palpable (n=454)**	**Non-palpable (n=212)**
Mean (range) age at diagnosis (years)	52.6 (40-64)	52.5 (40-64)	52.1 (40-64)	53.3 (46-64)
Died from breast cancer:				
No	353 (67.4)	486 (73.0)	316 (69.6)	170 (80.2)
Yes	171 (32.6)	180 (27.0)	138 (30.4)	42 (19.8)
Mean (range) age at death (years)	60.6 (43-83)	59.9 (43-80)	59.1 (43-80)	62.5 (46-77)
Tumour size (cm)	2.1 (0.2-7.0)	1.9 (0.2-9.0)	2.1 (0.2-9.0)	1.4 (0.2-9.0)
Missing data	58 (11.1)	87 (13.1)	56 (12.3)	31 (14.6)
Lymph node status:				
Negative	303 (57.8)	394 (59.2)	252 (55.5)	142 (67.0)
Positive	170 (32.4)	204 (30.6)	169 (37.2)	35 (16.5)
Missing data	51 (9.7)	68 (10.2)	33 (7.3)	35 (16.5)
Oestrogen receptor status:				
Negative	85 (16.2)	102 (15.3)	74 (21.4)	30 (14.2)
Equivocal	41 (7.8)	41 (6.2)	33 (9.5)	8 (3.8)
Positive	261 (49.8)	312 (46.9)	239 (69.1)	78 (36.8)
Missing data	137 (26.2)	211 (31.7)	138 (30.3)	96 (45.3)

Table 3| Deaths from breast cancer to 31 December 2005, by study arm and year of diagnosis. Values are numbers (percentages) unless stated otherwise

	Deaths by study arm	
Study year	**Mammography (n=44 925)**	**Control (n=44 910)**
Deaths from breast cancers detected in years 1-5 (screening period)*:		
Screen detected, year 1	52 (28.9)	26 (15.2)
Screen detected, years 2-5	63 (35.0)	29 (17.0)
Interval cancers, years 1-5	46 (25.6)	44 (25.7)
Incident cancers, year 5	19 (10.6)	72 (42.1)
Screen period, total	180 (100)	171 (100)
Breast cancer deaths per 10 000 women from cancers detected in years 1-5	40.1	38.1
Deaths from breast cancers detected in years 6-25 (follow-up period)*	298	321
Breast cancer deaths per 10 000 women from cancers detected in years 6-25	66.3	71.4
Total deaths(all breast cancers, all years)	500	505
Breast cancer deaths per 10 000 women (all breast cancers, all years)	108.4	110.2

*Year of diagnosis was not available for 35 additional women, 22 in mammography arm and 13 in control arm.

Figures

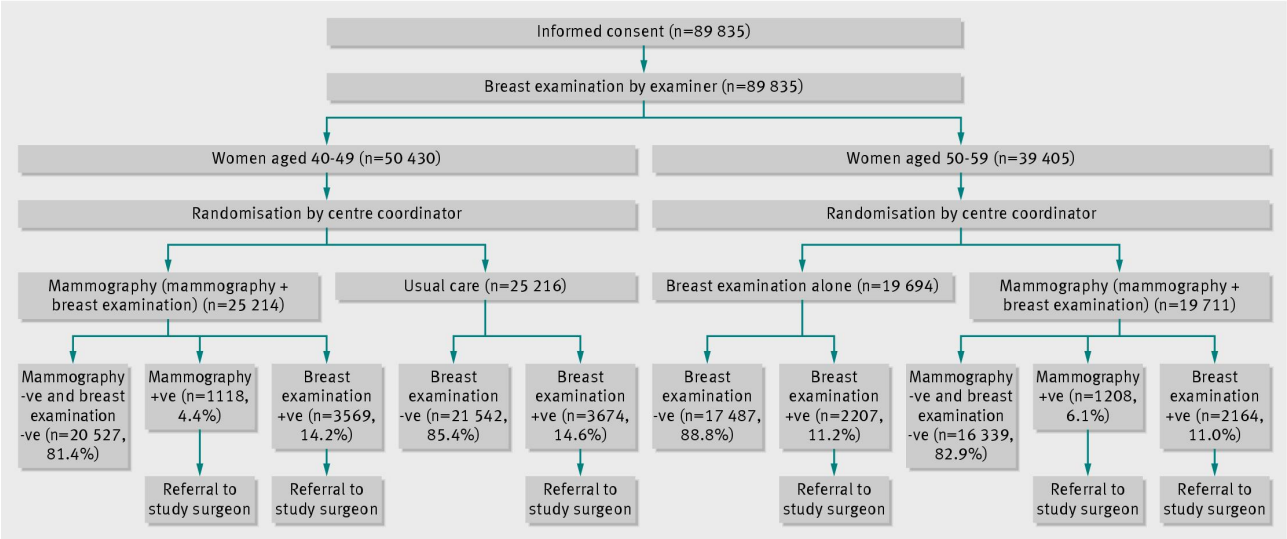

Fig 1 Process of randomisation and initial screening (screen 1). Breast examination was carried out by nurses unless stated otherwise (+ve indicates abnormality found by examiner, -ve no abnormality found). MA=mammography (+ve indicates abnormality found by radiologist, -ve no abnormality found). Study surgeon could order diagnostic mammography or consult with the study radiologist if necessary before sending recommendations to family doctors. Bracketed interventions indicate protocol at subsequent screens

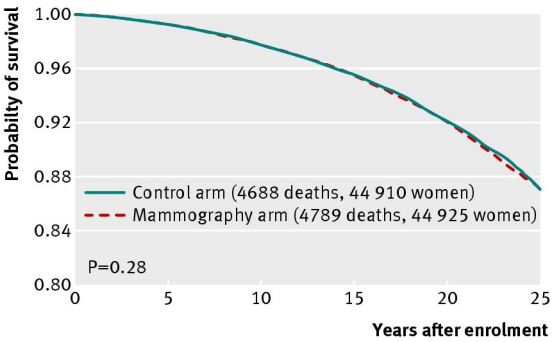

Fig 2 All cause mortality, by assignment to mammography or control arms (all participants)

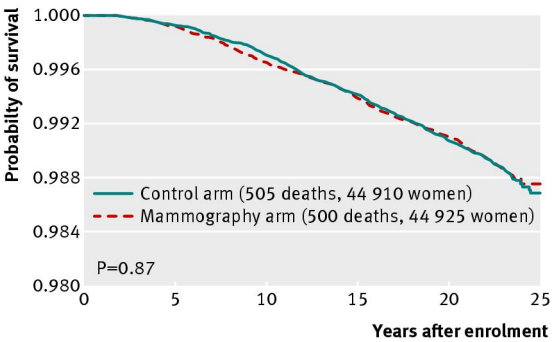

Fig 3 Breast cancer specific mortality, by assignment to mammography or control arms (all participants)

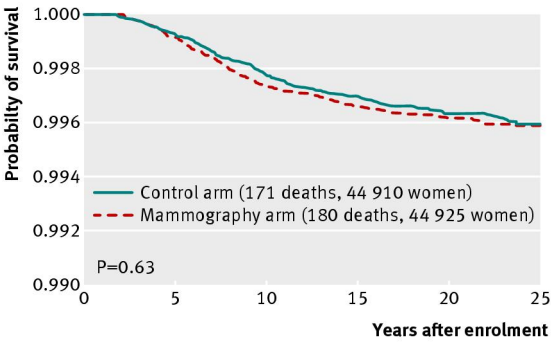

Fig 4 Breast cancer specific mortality from cancers diagnosed in screening period, by assignment to mammography or control arms

Attachment 4D – Welch overscreening NEJM

ORIGINAL ARTICLE

Effect of Three Decades of Screening Mammography on Breast-Cancer Incidence

Archie Bleyer, M.D., and H. Gilbert Welch, M.D., M.P.H.

ABSTRACT

BACKGROUND

To reduce mortality, screening must detect life-threatening disease at an earlier, more curable stage. Effective cancer-screening programs therefore both increase the incidence of cancer detected at an early stage and decrease the incidence of cancer presenting at a late stage.

METHODS

We used Surveillance, Epidemiology, and End Results data to examine trends from 1976 through 2008 in the incidence of early-stage breast cancer (ductal carcinoma in situ and localized disease) and late-stage breast cancer (regional and distant disease) among women 40 years of age or older.

RESULTS

The introduction of screening mammography in the United States has been associated with a doubling in the number of cases of early-stage breast cancer that are detected each year, from 112 to 234 cases per 100,000 women — an absolute increase of 122 cases per 100,000 women. Concomitantly, the rate at which women present with late-stage cancer has decreased by 8%, from 102 to 94 cases per 100,000 women — an absolute decrease of 8 cases per 100,000 women. With the assumption of a constant underlying disease burden, only 8 of the 122 additional early-stage cancers diagnosed were expected to progress to advanced disease. After excluding the transient excess incidence associated with hormone-replacement therapy and adjusting for trends in the incidence of breast cancer among women younger than 40 years of age, we estimated that breast cancer was overdiagnosed (i.e., tumors were detected on screening that would never have led to clinical symptoms) in 1.3 million U.S. women in the past 30 years. We estimated that in 2008, breast cancer was overdiagnosed in more than 70,000 women; this accounted for 31% of all breast cancers diagnosed.

CONCLUSIONS

Despite substantial increases in the number of cases of early-stage breast cancer detected, screening mammography has only marginally reduced the rate at which women present with advanced cancer. Although it is not certain which women have been affected, the imbalance suggests that there is substantial overdiagnosis, accounting for nearly a third of all newly diagnosed breast cancers, and that screening is having, at best, only a small effect on the rate of death from breast cancer.

From the Quality Department, St. Charles Health System, Central Oregon, and the Department of Radiation Medicine, Oregon Health and Science University, Portland (A.B.); the University of Texas Medical School at Houston, Houston (A.B.); and the Dartmouth Institute for Health Policy and Clinical Practice, Geisel School of Medicine at Dartmouth, Hanover, NH (H.G.W.). Address reprint requests to Dr. Bleyer at 2500 NE Neff Rd., Bend, OR 97701, or at ableyer@gmail.com.

N Engl J Med 2012;367:1998-2005.
DOI: 10.1056/NEJMoa1206809

There are two prerequisites for screening to reduce the rate of death from cancer.[1,2] First, screening must advance the time of diagnosis of cancers that are destined to cause death. Second, early treatment of these cancers must confer some advantage over treatment at clinical presentation. Screening programs that meet the first prerequisite will have a predictable effect on the stage-specific incidence of cancer. As the time of diagnosis is advanced, more cancers will be detected at an early stage and the incidence of early-stage cancer will increase. If the time of diagnosis of cancers that will progress to a late stage is advanced, then fewer cancers will be present at a late stage and the incidence of late-stage cancer will decrease.[3]

In the United States, clinicians now have more than three decades of experience with the widespread use of screening mammography in women who are 40 years of age or older. We examined the temporal effects of mammography on the stage-specific incidence of breast cancer. Specifically, we quantified the expected increase in the incidence of early-stage cancer and determined the extent to which this has led to a corresponding decrease in the incidence of late-stage cancer.

Methods

Overview

We obtained trend data on the use of screening mammography and the stage-specific incidence of breast cancer among women 40 years of age or older. To calculate the number of additional women with a diagnosis of early-stage cancer (as well as the reduction in the number of women with a diagnosis of late-stage cancer), we determined a baseline incidence before screening, calculated the surplus (or deficit) incidence relative to the baseline in each subsequent calendar year, and transformed data on the change in incidence to data on nationwide counts.

We used the direct method to adjust the incidence rates according to age in the U.S. standard population in the year 2000. All analyses were performed with the use of either (SEER*Stat or Microsoft Excel software. In an effort to make our method transparent, the data on Surveillance, Epidemiology, and End Results (SEER) stage–specific incidence and all calculations are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. Both authors vouch for the completeness and accuracy of the reported data and analysis and the fidelity of the study to the protocol.

Data Sources

We obtained trend data from the National Health Interview Survey on the proportion of women 40 years of age or older who underwent screening mammography.[4,5] Trend data on incidence and survival rates were obtained from the nine longstanding SEER areas[6]; these data accounted for approximately 10% of the U.S. population.[7] Annual estimates of the population of women 40 years of age or older were obtained from the U.S. Census.[8]

Stage at Diagnosis

We used SEER historic stage A as the foundation for our categorization of early- and late-stage cancer. The four stages in this system are the following: in situ disease; localized disease, defined as invasive cancer that is confined to the organ of disease origin; regional disease, defined as disease that extends outside of and adjacent to or contiguous with the organ of disease origin (in breast cancer, most regional disease indicates nodal involvement, not direct extension[9]); and distant disease, defined as metastasis to organs that are not adjacent to the organ of disease origin. We restricted in situ cancers to ductal carcinoma in situ (DCIS), specifically excluding lobular carcinoma in situ, as done in other studies.[10] We defined early-stage cancer as DCIS or localized disease, and late-stage cancer as regional or distant disease.

Baseline Incidence

The incidence data from the first year in which breast-cancer incidence was recorded (1973) were almost certainly spuriously low (which would bias our estimates of excess detection upward). The data from the subsequent 2 years (1974 and 1975) were above average for the decade, reflecting the sharp uptick in early detection after First Lady Betty Ford's breast-cancer diagnosis.[11] Consequently, we chose the 3-year period 1976 through 1978 to obtain our estimate of the baseline incidence of breast cancer that was detected without mammography. During this period, the incidence of breast cancer was stable and few cases of DCIS were

detected; these findings are compatible with the very limited use of screening mammography.

CURRENT INCIDENCE AND REMOVAL OF THE EFFECT OF HORMONE-REPLACEMENT THERAPY

We based our estimate of the current incidence of breast cancer on the 3-year period from 2006 through 2008. To eliminate the effect of hormone-replacement therapy, we truncated the observed incidence each year from 1990 through 2005 if it was higher than the estimate of the current incidence (Table S2 and Fig. S1 in the Supplementary Appendix). In other words, we did not allow the annual incidence of DCIS to exceed 56.5 cases, localized disease to exceed 177.5 cases, regional disease to exceed 77.6 cases, and distant disease to exceed 16.6 cases (all expressed per 100,000 women) during the period from 1990 through 2005. Other researchers have dated the end of the effect of hormone-replacement therapy at 2006.[12] Thus, our approach was simply to remove all excess incidence in previous years.

ESTIMATES OF THE NUMBER OF WOMEN AFFECTED

Base-Case Estimate

For each year after 1978, we calculated the absolute change in the incidence of early- and late-stage cancer relative to the 1976–1978 baseline incidence (after removing the transient increase in incidence associated with hormone-replacement therapy during the period from 1990 through 2005, as described above). To calculate the excess in the number of women with a diagnosis of early-stage cancer detected on screening mammography, we multiplied the absolute increase in incidence observed in a given year by the number of women in the population who were 40 years of age or older in the same year. We used a similar approach to calculate the reduction in the number of women with a diagnosis of late-stage cancer. Finally, we summed the data across the three decades.

Subsequent Estimates

The base-case estimate implicitly assumes that, with the exception of the effect of hormone-replacement therapy, the underlying incidence of breast cancer is constant. To make an inference about any other changes in the underlying incidence, we examined incidence trends in the portion of the population that generally did not have exposure to screening: women younger than 40 years of age. In this age group, the SEER calculation for the annual percent change from 1979 through 2008 was 0.25% per year (95% confidence interval [CI], 0.04 to 0.47). To account for this growth, we repeated our analysis, allowing our baseline incidence among women 40 years of age or older to increase by 0.25% per year (applied to both early- and late-stage disease). We called this estimate the "best guess."

Finally, we wanted to provide estimates that were clearly biased in favor of screening mammography — ones that would minimize the surplus diagnoses of early-stage cancer and maximize the deficit of diagnoses of late-stage cancer. First, we assumed that the underlying incidence was increasing at a rate of 0.5% per year — twice as high as that observed among the population of women who were younger than 40 years of age. We called this estimate the "extreme" assumption. Second, in addition to the increase of 0.5% per year, we revised the baseline incidence of late-stage breast cancer by using the highest incidence observed in the data (113 cases per 100,000 women in 1985) — thereby maximizing the deficit of diagnoses of late-stage cancer. We called this estimate the "very extreme assumption."

RESULTS

CHANGES IN INCIDENCE ASSOCIATED WITH IMPLEMENTATION OF SCREENING

Figure 1A shows the substantial increase in the use of screening mammography during the 1980s and early 1990s among women 40 years of age or older in the United States. Figure 1A also shows that there was a substantial concomitant increase in the incidence of early-stage breast cancer among these women. In addition, a small decrease is evident in the incidence of late-stage breast cancer. As shown in Figure 1B, there was little change in breast-cancer incidence among women who generally did not have exposure to screening mammography — women younger than 40 years of age.

Table 1 shows the changes in the stage-specific annual incidence of breast cancer over the past three decades among women 40 years of age or older. The large increase in cases of early-stage cancer (from 112 to 234 cancers per 100,000 women — an absolute increase of 122 cancers per 100,000) reflects both detection of more cases of localized disease and the advent of the detection of DCIS (which was virtually not detected before mammography was available). The smaller

decrease in cases of late-stage cancer (from 102 to 94 cases per 100,000 women — an absolute decrease of 8 cases per 100,000 women) largely reflects detection of fewer cases of regional disease. If a constant underlying disease burden is assumed, only 8 of the 122 additional early diagnoses were destined to progress to advanced disease, implying a detection of 114 excess cases per 100,000 women. Table 1 also shows the estimated number of women affected by these changes (after removal of the transient excess cases associated with hormone-replacement therapy). These estimates are shown in terms of both the surplus in diagnoses of early-stage breast cancers and the reduction in diagnoses of late-stage breast cancers — again, under the assumption of a constant underlying disease burden.

OVERDIAGNOSED CANCER AND EFFECT OF SCREENING ON REGIONAL AND DISTANT DISEASE

Table 2 shows the effects of relaxing the assumption of a constant underlying disease burden on the estimate of the number of women with cancer that was overdiagnosed. The base-case estimate incorporates the data in Table 1. In the best-guess estimate, it was assumed that the trend in the underlying incidence was best approximated by the incidence observed among women younger than 40 years of age (Fig. 1B). This approach suggests that the excess detection attributable to mammography in the United States involved more than 1.3 million women in the past 30 years. In the extreme and very extreme estimates, it was assumed that the underlying incidence was increasing at double the rate observed among women younger than 40 years of age. Finally, in the very extreme estimate, it was assumed that the incidence of late-stage cancer was the highest incidence ever observed (thereby maximizing the deficit of diagnoses of late-stage cancer).

Regardless of the approach used, our estimate of overdiagnosed cancers attributable to mammography over the past 30 years involved more than 1 million women. In 2008, the number of women 40 years of age or older with overdiagnosed cancers was more than 70,000 per year according to the best-guess estimate, more than 60,000 per year according to the extreme estimate, and more than 50,000 per year according to the very extreme estimate. The corresponding estimates of the proportions of cancers that were overdiagnosed are 31%, 26%, and 22%.

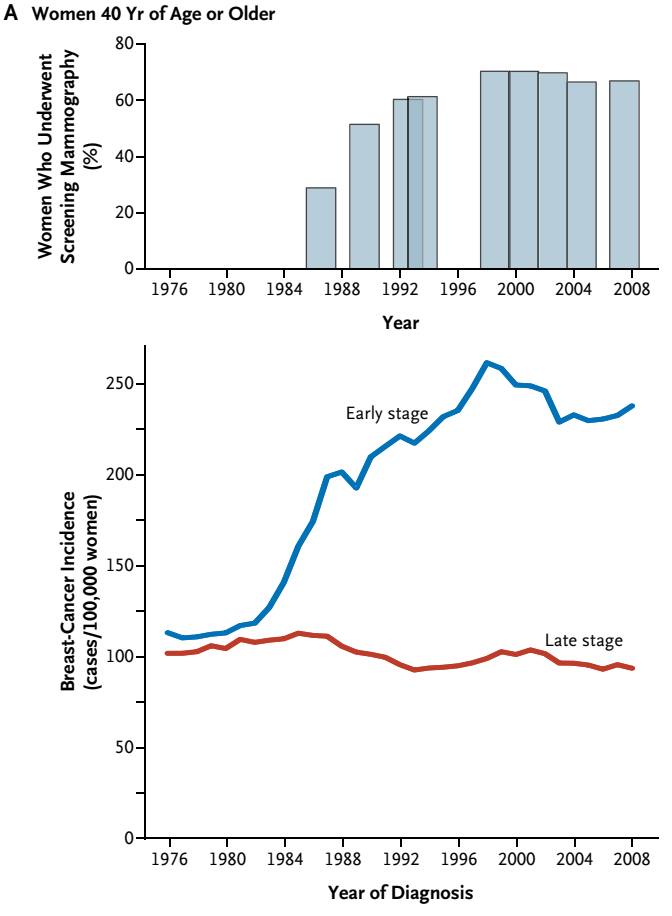

Figure 1. Use of Screening Mammography and Incidence of Stage-Specific Breast Cancer in the United States, 1976–2008.

Panel A shows the self-reported use of screening mammography and the incidence of stage-specific breast cancer among women 40 years of age or older. Panel B shows the incidence of stage-specific breast cancer among women who generally did not have exposure to screening mammography — those younger than 40 years of age.

Figure 2 shows the trends in regional and distant late-stage breast cancer. The variable pattern in late-stage cancer (which includes the excess diagnoses associated with hormone-replacement therapy in the late 1990s and early 2000s) was

Table 1. Absolute Change in the Incidence of Stage-Specific Breast Cancer among Women 40 Years of Age or Older after the Introduction of Screening Mammography.*

Variable	Annual Breast-Cancer Incidence			Women Affected over the Three Decades†
	Before Mammography (1976–1978)	Three Decades Later (2006–2008)	Absolute Change	
	number of cases per 100,000 women			*estimated number of women*
Increase in cases of early-stage breast cancer				
DCIS	7	56	50	573,000
Localized disease	105	178	72	1,012,000
Total	112	234	122	1,585,000
Decrease in cases of late-stage breast cancer				
Regional disease	85	78	–8‡	59,000
Distant disease	17	17	0§	8,000
Total	102	94	–8	67,000

* DCIS denotes ductal carcinoma in situ.
† These data exclude excess cases associated with hormone-replacement therapy.
‡ Because of rounding, the absolute change appears to be inconsistent with the subtracted values for annual breast-cancer incidence. See Table S1 in the Supplementary Appendix for precise values.
§ Without rounding, the absolute change is –0.3.

virtually entirely attributable to changes in the incidence of regional (largely node-positive) disease. The incidence of distant (metastatic) disease, however, has remained unchanged (95% CI for the annual percent change, –0.19 to 0.14).

DISCUSSION

Screening can result in both the benefit of a reduction in mortality and the harm of overdiagnosis. Our analysis suggests that whatever the mortality benefit, breast-cancer screening involved a substantial harm of excess detection of additional early-stage cancers that was not matched by a reduction in late-stage cancers. This imbalance indicates a considerable amount of overdiagnosis involving more than 1 million women in the past three decades — and, according to our best-guess estimate, more than 70,000 women in 2008 (accounting for 31% of all breast cancers diagnosed in women 40 years of age or older).

Over the same period, the rate of death from breast cancer decreased considerably. Among women 40 years of age or older, deaths from breast cancer decreased from 71 to 51 deaths per 100,000 women — a 28% decrease.[6] This reduction in mortality is probably due to some combination of the effects of screening mammography and better treatment. Seven separate modeling exercises by the Cancer Intervention and Surveillance Modeling Network investigators provided a wide range of estimates for the relative contribution of each effect: screening mammography might be responsible for as little as 28% or as much as 65% of the observed reduction in mortality (the remainder being the effect of better treatment).[13]

Our data show that the true contribution of mammography to decreasing mortality must be at the low end of this range. They suggest that mammography has largely not met the first prerequisite for screening to reduce cancer-specific mortality — a reduction in the number of women who present with late-stage cancer. Because the absolute reduction in deaths (20 deaths per 100,000 women) is larger than the absolute reduction in the number of cases of late-stage cancer (8 cases per 100,000 women), the contribution of early detection to decreasing numbers of deaths must be small. Furthermore, as noted by others,[14] the small reduction in cases of late-stage cancer that has occurred has been confined to regional (largely node-positive) disease — a stage that can now

Table 2. Four Estimates of the Excess Detection (Overdiagnosis) of Breast Cancer Associated with Three Decades of Screening Mammography, 1979–2008.

Estimate	Assumption Regarding Underlying Incidence of Breast Cancer	Surplus in Diagnoses of Early-Stage Disease	Reduction in Diagnoses of Late-Stage Disease	Excess Detection
			number of women	
Base case	It was constant	1,585,000	67,000	1,518,000
Best guess	It increased at a rate of 0.25%/yr*	1,507,000	138,000	1,369,000
Extreme assumption	It increased at a rate of 0.5%/yr†	1,426,000	213,000	1,213,000
Very extreme assumption	It increased at a rate of 0.5%/yr and baseline incidence of late-stage disease was the highest ever observed‡	1,426,000	410,000	1,016,000

* This increase in incidence was observed among women younger than 40 years of age.
† This increase in incidence was twice that observed among women younger than 40 years of age.
‡ The peak in the incidence of late-stage breast cancer was 113 cases per 100,000 women in 1985.

often be treated successfully, with an expected 5-year survival rate of 85% among women 40 years of age or older.[15,16] Unfortunately, however, the number of women in the United States who present with distant disease, only 25% of whom survive for 5 years,[15] appears not to have been affected by screening.

Whereas the decrease in the rate of death from breast cancer was 28% among women 40 years of age or older, the concurrent rate decrease was 42% among women younger than 40 years of age.[6] In other words, there was a larger relative reduction in mortality among women who were not exposed to screening mammography than among those who were exposed. We are left to conclude, as others have,[17,18] that the good news in breast cancer — decreasing mortality — must largely be the result of improved treatment, not screening. Ironically, improvements in treatment tend to deteriorate the benefit of screening. As treatment of clinically detected disease (detected by means other than screening) improves, the benefit of screening diminishes. For example, since pneumonia can be treated successfully, no one would suggest that we screen for pneumonia.

Our finding of substantial overdiagnosis of breast cancer with the use of screening mammography in the United States replicates the findings of investigators in other countries (Table S5 in the Supplementary Appendix). Nevertheless, our analysis has several limitations. Overdiagnosis can never be directly observed and thus can only be inferred from that which is observed — reported incidence. Figures 1 and 2 are based on unaltered, long-standing, carefully collected federal data that are generally considered to be incontrovertible. Tables 1 and 2, however, are based on assumptions that warrant a more critical evaluation.

First, our results might be sensitive to the period (1976 through 1978) that we chose to obtain data for the baseline incidence of breast cancer (before mammography). If the period were expanded to begin with the first years of SEER data (i.e., 1973 through 1978), the baseline incidence of early-stage cancer would be slightly lower (0.9%) and the incidence of late-stage cancer would be slightly higher (1.4%). These changes offset each other and have a negligible effect on our estimates.

Second, our ability to remove the effect of hormone-replacement therapy (Fig. S1 in the Supplementary Appendix) is admittedly imprecise. Although there is general agreement that this effect had largely ceased by 2006, its onset is not as discrete. We chose to cap the incidence of each disease stage as far back as 1990. However, the pattern of regional disease (Fig. 2) suggests that the bulk of the effect of hormone-replacement therapy probably began later, in the mid-1990s, such that our assumption probably overcorrects for the effect of hormone-replacement therapy.

Third, we were forced to make some assumptions about the pattern of the underlying incidence — the incidence that would have been observed in the absence of screening. The simplest approach was to assume that the underlying incidence was constant (the base case). In our best-guess estimate, however, we posited that the

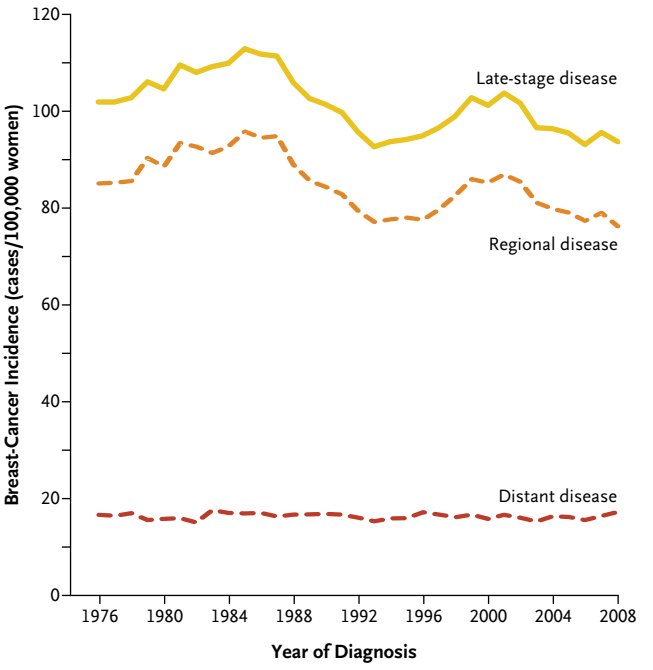

Figure 2. Trends in the Annual Incidence of Late-Stage Breast Cancer and Its Two Components (Regional and Distant Disease) among U.S. Women 40 Years of Age or Older, 1976–2008.

underlying incidence was that observed in the population of women without exposure to mammography; this underlying incidence was increasing at a rate of 0.25% per year. Our assumption of an increase of 0.5% per year (in the extreme and very extreme estimates) was admittedly arbitrary. It was twice the rate of increase observed among women younger than 40 years of age and was outside the 95% confidence interval. Perspective on the uncertainty about the underlying incidence, however, is provided in Figure 2. The finding of a stable rate of distant disease argues against dramatic changes in the underlying incidence of breast cancer.

Fourth, our best-guess estimate of the frequency of overdiagnosis — 31% of all breast cancers — did not distinguish between DCIS and invasive breast cancer. Our method did not allow us to disentangle the two. We did, however, estimate the frequency of overdiagnosis of invasive breast cancer under the assumption that all cases of DCIS were overdiagnosed. This analysis suggested that invasive disease accounted for about half the overdiagnoses shown in Table 2 and that about 20% of all invasive breast cancers were overdiagnosed; these findings replicate those of other studies.[19]

Finally, some investigators might point out that our best-guess estimate of the frequency of overdiagnosis — 31% — was based on the wrong denominator. Our denominator was the number of all diagnosed breast cancers. Many investigators would argue that because overdiagnosis is the result of screening, the correct denominator is screening-detected breast cancers. Unfortunately, because the SEER program does not collect data on the method of detection, we were unable to distinguish screening-detected from clinically detected cancers. Self-reported data from the National Health Interview Survey, however, suggest that approximately 60% of all breast cancers were detected by means of screening in the period from 2001 through 2003.[20]

Breast-cancer overdiagnosis is a complex and sometimes contentious issue. Ideally, reliable estimates about the magnitude of overdiagnosis would come from long-term follow-up after a randomized trial.[21] Among the nine randomized trials of mammography, the lone example of this is the 15-year follow-up after the end of the Malmö Trial,[22] which showed that about a quarter of mammographically detected cancers were overdiagnosed.[23] Unfortunately, trials also provide a relatively narrow view involving one subgroup of patients, one research protocol, and one point in time. We are concerned that the trials — now generally three decades old — no longer provide relevant data on either the benefit with respect to reduced mortality (because treatment has improved) or the harm of overdiagnosis (because of enhancements in mammographic imaging and lower radiologic and pathological diagnostic thresholds).

Our investigation takes a different view, which might be considered the view from space. It does not involve a selected group of patients, a specific protocol, or a single point in time. Instead, it considers national data over a period of three decades and details what has actually happened since the introduction of screening mammography. There has been plenty of time for the surplus of diagnoses of early-stage cancer to translate into a reduction in diagnoses of late-stage cancer — thus eliminating concern about lead time.[24] This broad view is the major strength of our study.

Our study raises serious questions about the value of screening mammography. It clarifies that the benefit of mortality reduction is probably

smaller, and the harm of overdiagnosis probably larger, than has been previously recognized. And although no one can say with certainty which women have cancers that are overdiagnosed, there is certainty about what happens to them: they undergo surgery, radiation therapy, hormonal therapy for 5 years or more, chemotherapy, or (usually) a combination of these treatments for abnormalities that otherwise would not have caused illness. Proponents of screening should provide women with data from a randomized screening trial that reflects improvements in current therapy and includes strategies to mitigate overdiagnosis in the intervention group. Women should recognize that our study does not answer the question "Should I be screened for breast cancer?" However, they can rest assured that the question has more than one right answer.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Lynn Ries, M.S., of the Surveillance Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, for her help in analyzing Surveillance, Epidemiology, and End Results data.

REFERENCES

1. Introduction. In: Morrison AS. Screening in chronic disease. 2nd ed. New York: Oxford University Press, 1992:3-42.
2. Welch HG, Black WC. Evaluating randomized trials of screening. J Gen Intern Med 1997;12:118-24.
3. Chu KC, Kramer BS, Smart CR. Analysis of the role of cancer prevention and control measures in reducing cancer mortality. J Natl Cancer Inst 1991;83:1636-43.
4. Table 86 (page 1 of 3). Use of mammography among women 40 years of age and over, by selected characteristics: United States, selected years 1987–2008. Atlanta: Centers for Disease Control and Prevention (http://www.cdc.gov/nchs/data/hus/2010/086.pdf).
5. Use of mammography among women 40 years of age and over. Atlanta: Centers for Disease Control and Prevention (http://www.cdc.gov/nchs/health_policy/mammography.htm).
6. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence — SEER 9 Regs Research Data, Nov 2010 Sub (1973–2008) <Katrina/Rita Population Adjustment> — Linked to County Attributes — Total U.S., 1969–2009 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2011 (updated 10/28/2011), based on November 2010 submission (http://seer.cancer.gov/seerstat).
7. SEER data, 1973–2009 (including July–December 2005 Hurricane Katrina impacted Louisiana cases) (http://www.seer.cancer.gov/data/seerstat/nov2011).
8. United States Census Bureau. Population estimates (http://www.census.gov/popest/data).
9. Ries LAG, Eisner MP. Cancer of the female breast. In: SEER survival monograph — cancer survival among adults: U.S. SEER Program, 1988–2001. Bethesda, MD: National Cancer Institute, 2007: 105 (Table 13.6) (http://seer.cancer.gov/publications/survival/).
10. Ernster VL, Barclay J, Kerlikowske K, Grady D, Henderson C. Incidence of and treatment for ductal carcinoma in situ of the breast. JAMA 1996;275:913-8.
11. Welch HG, Schwartz LM, Woloshin S. Overdiagnosed: making people sick in the pursuit of health. Boston: Beacon Press, 2011:84-5.
12. De P, Neutel I, Olivotto I, Morrison H. Breast cancer incidence and hormone replacement therapy in Canada. J Natl Cancer Inst 2010;102:1489-95.
13. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 2005;353:1784-92.
14. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. JAMA 2009;302:1685-92.
15. Surveillance, Epidemiology, and End Results (SEER) Program. SEER*Stat Database: Incidence — SEER 17 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2010 Sub (1973–2008 varying) — Linked to County Attributes — Total U.S., 1969–2009 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2011 (updated 10/28/2011), based on the November 2010 submission (http://seer.cancer.gov/seerstat).
16. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-717.
17. Kalager M, Zelen M, Langmark F, Adami H-O. Effect of screening mammography on breast-cancer mortality in Norway. N Engl J Med 2010;363:1203-10.
18. Autier P, Boniol M, Gavin A, Vatten LJ. Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database. BMJ 2011;343:d4411.
19. Zahl PH, Maehlen J, Welch HG. The natural history of invasive breast cancers detected by screening mammography. Arch Intern Med 2008;168:2311-6.
20. Breen N, Yabroff KR, Meissner HI. What proportion of breast cancers are detected by mammography in the United States? Cancer Detect Prev 2007;31:220-4.
21. Welch HG, Black WC. Overdiagnosis in cancer. J Natl Cancer Inst 2010;102:605-13.
22. Zackrisson S, Andersson I, Janzon L, Manjer J, Garne JP. Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study. BMJ 2006;332:689-92.
23. Welch HG, Schwartz LM, Woloshin S. Ramifications of screening for breast cancer: 1 in 4 cancers detected by mammography are pseudocancers. BMJ 2006;332:727.
24. Kopans DB, Smith RA, Duffy SW. Mammographic screening and "overdiagnosis." Radiology 2011;260:616-20.

Attachment 4E – AMA Benefits and Risks of Mammography

Review

A Systematic Assessment of Benefits and Risks to Guide Breast Cancer Screening Decisions

Lydia E. Pace, MD, MPH; Nancy L. Keating, MD, MPH

IMPORTANCE Breast cancer is the second leading cause of cancer deaths among US women. Mammography screening may be associated with reduced breast cancer mortality but can also cause harm. Guidelines recommend individualizing screening decisions, particularly for younger women.

OBJECTIVES We reviewed the evidence on the mortality benefit and chief harms of mammography screening and what is known about how to individualize mammography screening decisions, including communicating risks and benefits to patients.

EVIDENCE ACQUISITION We searched MEDLINE from 1960-2014 to describe (1) benefits of mammography, (2) harms of mammography, and (3) individualizing screening decisions and promoting informed decision making. We also manually searched reference lists of key articles retrieved, selected reviews, meta-analyses, and practice recommendations. We rated the level of evidence using the American Heart Association guidelines.

RESULTS Mammography screening is associated with a 19% overall reduction of breast cancer mortality (approximately 15% for women in their 40s and 32% for women in their 60s). For a 40- or 50-year-old woman undergoing 10 years of annual mammograms, the cumulative risk of a false-positive result is about 61%. About 19% of the cancers diagnosed during that 10-year period would not have become clinically apparent without screening (overdiagnosis), although there is uncertainty about this estimate. The net benefit of screening depends greatly on baseline breast cancer risk, which should be incorporated into screening decisions. Decision aids have the potential to help patients integrate information about risks and benefits with their own values and priorities, although they are not yet widely available for use in clinical practice.

CONCLUSIONS AND RELEVANCE To maximize the benefit of mammography screening, decisions should be individualized based on patients' risk profiles and preferences. Risk models and decision aids are useful tools, but more research is needed to optimize these and to further quantify overdiagnosis. Research should also explore other breast cancer screening strategies.

JAMA. 2014;311(13):1327-1335. doi:10.1001/jama.2014.1398

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Author Affiliations: Division of Women's Health, Brigham and Women's Hospital, Boston, Massachusetts (Pace); Division of General Internal Medicine, Brigham and Women's Hospital, Boston, Massachusetts (Keating); Department of Health Care Policy, Harvard Medical School, Boston, Massachusetts (Keating).

Corresponding Author: Nancy L. Keating, MD, MPH, Department of Health Care Policy, 180 Longwood Ave, Boston MA 02115 (keating@hcp.med.harvard.edu).

Section Editor: Mary McGrae McDermott, MD, Senior Editor.

Breast cancer is the most common noncutaneous cancer and the second leading cause of cancer death among women in the United States. About 40 000 women die of breast cancer in the United States each year.[1] For decades, there has been strong interest in screening strategies that will detect early cancers before they progress, thereby reducing mortality. Some trials have demonstrated that mammography is associated with decreased breast cancer mortality, but these data and increasing evidence about the harms of mammography screening have generated controversy. In 2009, in light of evidence that the benefit-risk ratio is higher among women older than 50 years and with less frequent screening, the US Preventive Services Task Force (USPSTF) reversed its previous recommendation of mammography every 1 to 2 years beginning at age 40 years and recommended routine screening every 2 years starting at age 50.[2] This was consistent with recommendations in many European countries[3,4] but contrasted with several other US organizations,[5,6] revitalizing the recurring debate in both the medical community and mainstream media about mammography policy and practice. Recent evidence suggests that use of mammography in the United States has not changed following the USPSTF 2009 recommendations.[7]

The USPSTF stated that "the decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take into account patient context, including the patient's values regarding specific benefits and harms."[2] The central issue for clinicians, which is infrequently addressed in the medi-

Table 1. Pooled Results from Randomized Clinical Trials on Mortality Reductions With Mammography Screening by Age Group

Age, y	No. of Studies	Total Events in Group/Total No.		RR (95% CI) With Mammography Screening[9]	ARR With Mammography Screening	NNI to Screening[9]
		Invited Group	Control Group			
39-49	8[8,10-14]	448/152 300	625/195 919	0.85 (0.75 0.96)	0.0005	1904
50-59	6[11,13-15]	361/78 465	410/69 849	0.86 (0.75-0.99)	0.0007	1339
60-69	2[13]	110/19 093	155/18 377	0.68 (0.54- 0.87)	0.0027	377
70-74	1[13]	42/5073	36/4859	1.12 (0.73-1.72)	NA	NA

Abbreviations: ARR, adjusted risk ratio; NA, not available; NNI, number needed to invite; RR, risk ratio.

cal literature, is how to individualize mammography recommendations and foster informed decisions by patients. To accomplish this, clinicians must assess a patient's individual risk for breast cancer, effectively communicate the risks and benefits of screening, identify how a patient's characteristics might modify those risks and benefits, and elicit patients' personal preferences and values. This review will address the following key clinical questions: (1) What is the benefit of mammography screening, and how does that vary by age and patient risk? (2) What are the harms of mammography screening? (3) What is known about how to incorporate individual characteristics into breast cancer screening recommendations? (4) How can patients be supported in making informed decisions about mammography screening?

Methods

We searched MEDLINE for relevant randomized clinical trials (RCTs), meta-analyses, systematic reviews, and observational studies from 1960 to January 19, 2014 (search terms are reported in the eBox in Supplement). We also manually searched the references of key articles, reviews, meta-analyses, and practice recommendations. For describing the breast cancer mortality benefit of mammography we included meta-analyses of RCTs of mammography screening examining breast cancer mortality. From 525 articles identified, 20 meta-analyses met these criteria. We focused on the 5 meta-analyses published after 2006, when the most recent RCT, the Age Trial,[8] was published (eFigure 1 in Supplement).

To describe mammography's harms we focused on false-positive results, unnecessary biopsies, and overdiagnosis, conducting 2 separate searches. The first included systematic reviews and meta-analyses through December 2008, the period for the review informing the 2009 USPSTF decision.[9] The second included primary studies and reviews published since December 2008. We identified 374 articles, including 14 systematic reviews or meta-analyses published before 2008 and 72 studies or reviews published after 2008 (eFigures 2 and 3 in Supplement).

For studies on (1) individualizing information about risks and benefits and (2) communicating the benefits and risks to patients considering mammography screening, we searched for interventions (including decision aids) providing probabilistic information to women on the benefits and risks of screening, their own individual breast cancer risk, or both. We did not include interventions designed to increase screening rates without considering screening risks or a woman's baseline breast cancer risk. From 907 citations, we identified 23 studies (eFigure 4 in Supplement). From MEDLINE searches and reviews of citations, we additionally identified 25 articles on breast cancer risk models and using risk profiles to guide mammography decisions.

In **Table 1**, we provide summary risk ratios and number needed to invite (NNI) to screening from Nelson et al's meta-analysis conducted for the USPSTF.[9] We also report absolute risk ratios calculated by inverting the NNI.[9] In **Table 2**, we report estimated benefits and harms of breast cancer screening for 10 000 women undergoing annual mammography during a 10-year period. To estimate the number of women diagnosed with invasive breast cancer or ductal carcinoma in situ (DCIS) (column 1), we used Surveillance, Epidemiology, and End Results (SEER) estimates from a recent review by Welch and Passow.[16,17] The numbers of breast cancer deaths over 15 years (column 2) use Welch and Passow's estimates of the 15-year risks of dying of breast cancer in a screened population. The lower number reflects a minimal breast cancer mortality reduction of 5% based on RCTs reporting no benefit,[10,15] and the upper number reflects a reduction of 36% based on the trial reporting the highest benefit.[11] Column 3 provides Welch and Passow's upper and lower estimates of the number of deaths averted through screening, based on the same range of RCT results. To estimate the number of invasive breast cancers or DCIS diagnosed that would never become clinically important (overdiagnosis, column 4), we report absolute numbers calculated by Welch and Passow based on the Malmö trial and an epidemiologic study.[17,20,21] To estimate the number of women with at least 1 false-positive mammogram or unnecessary biopsy (columns 5 and 6), we report the cumulative incidence (with 95% CIs) from 2 studies using Breast Cancer Surveillance Consortium data[22,23] multiplied by 10 000.

Results

Benefits of Screening Mammography

Between the 1960s and the 1990s, 8 large RCTs assessed breast cancer mortality associated with screening. Meta-analyses of these trials generally demonstrate a 15% to 20% decrease in the relative risk of breast cancer–specific mortality. The variation in estimates is largely attributable to differences in trial quality and inclusion criteria. The Edinburgh trial has been most consistently excluded because of concerns about its cluster randomization strategy.[24] However in other trials, concerns have been raised about randomization, contamination, and assignment of breast cancer mortality.[25]

In addition, some argue that the RCTs are unlikely to be applicable to women undergoing screening today, because they preceded treatment advances that have powerfully influenced breast

Table 2. Estimated Benefits and Harms of Mammography Screening for 10 000 Women Who Undergo Annual Screening Mammography Over a 10-Year Period

Age, y	No. Diagnosed With Invasive Breast Cancer or DCIS During the 10 y of Screening[a]	No. of Breast Cancer Deaths in next 15 y[b]	No. of Deaths Averted With Mammography Screening Over Next 15 y[c]	No. of Breast Cancers or DCIS Diagnosed During the 10 y That Would Never Become Clinically Important (Overdiagnosis)[d]	No. (95% CI) With ≥1 False-Positive Result During the 10 y[e]	No. (95% CI) With ≥1 Unnecessary Biopsy During the 10 y[e]
40	190	27-32	1-16	?-104[f]	6130 (5940-6310)	700 (610-780)
50	302	56-64	3-32	30-137	6130 (5800-6470)	940 (740-1150)
60	438	87-97	5-49	64-194	4970 (4780-5150)	980 (840-1130)

Abbreviation: DCIS, ductal carcinoma in situ.

[a] Number of cancers expected to be diagnosed in the next 10 years from Surveillance, Epidemiology, and End Results (SEER) statistics[16] and also reported by Welch and Passow.[17] These numbers are from SEER incidence rates and reflect a combination of screened and unscreened women, so they would be higher in a completely screened population such as these 10 000 women by a number that depends on the magnitude of overdiagnosis.

[b] Number of women expected to die of breast cancer in the next 15 years among a screened cohort are from Welch and Passow,[17] who used SEER statistics[18] adjusted for mammography rates reported in the 2008 National Health Interview Survey.[19] The lower bound numbers represent death rates under the assumption of a breast cancer mortality risk reduction of 0.64 from mammography screening based on the benefit noted in the Swedish 2-County Trial[11]; the upper bound represents death rates under the assumption of a breast cancer mortality risk reduction of 0.95 based on the minimal benefit noted in the Canadian Trials.[10,15]

[c] Number of deaths averted are from Welch and Passow[17]; the lower bound represents breast cancer mortality reduction if the breast cancer mortality RR were 0.95 (based on minimal benefit from the Canadian trials[10,15]), and the upper bound represents the breast cancer mortality reduction if the RR were 0.64 (based on the Swedish 2-County Trial[11]).

[d] Overdiagnosed cases are calculated by Welch and Passow[17]; the lower bound represents overdiagnosis based on results from the Malmö trial,[20] whereas the upper bound represents the estimate from Bleyer and Welch.[21]

[e] False-positive and biopsy estimates and 95% CIs are 10-year cumulative risks reported in Hubbard et al[22] and Braithwaite et al.[23] For 60-year-old women we used estimates of false-positive results or biopsies in women aged 66 to 74 years with a Charlson score of 0.

[f] The lower bound estimate for overdiagnosis reported by Welch and Passow[17] came from the Malmö study,[20] which did not enroll women younger than 50 years.

cancer mortality and used older mammography techniques.[17] However, the RCTs nevertheless provide the best data available.

Two recent meta-analyses examined breast cancer mortality across all age groups.[25,26] The summary risk ratio (RR) for breast cancer mortality reduction with mammography screening at median 11.4 years follow-up was 0.81 (95% CI, 0.74-0.88) in the meta-analysis for the Canadian Task Force that included all RCTs except the Edinburgh trial.[26] The Cochrane reviewers reported a summary RR of 0.90 (95% CI, 0.79-1.02) when including only the 3 trials they considered of adequate quality.[25] When the Cochrane reviewers included all the trials except Edinburgh, with 13 years of follow-up, their results were consistent with the Canadian review (RR, 0.81 [0.74-0.87]).[25] In January 2014, 25-year follow-up results from 2 Canadian trials were published,[27] showing no mortality benefit from mammography screening (hazard ratio, 1.05 [95% CI, 0.88-1.12]). These results are consistent with earlier reports from these trials (at 13 years' follow-up, the mortality rate ratio for women aged 50-59 years was 1.02 [95% CI, 0.78-1.33][15] and at 11-16 years' follow-up among women aged 40-49 years, it was 0.97 [95% CI, 0.74-1.27][10]) and would be unlikely to substantially change meta-analysis results.

Three meta-analyses assessed mortality reduction within multiple age groups,[9,25,26] and 2 focused on women aged 40 to 49 years only.[28,29] For women aged 40 to 49 years, these 5 meta-analyses provided summary RRs ranging from 0.81 to 0.85. Variation in the estimated RRs again resulted from differing decisions about trial quality and inclusion. In 3 analyses excluding the Edinburgh trial alone, summary RRs for women aged 40 to 49 years were 0.84 (95% CI, 0.75-0.96)[9,26] and 0.84 (95% CI, 0.73-0.96).[25] Table 1 shows estimates from the meta-analysis conducted for the USPSTF.[9]

Despite similar relative benefits across age groups, because baseline breast cancer risk varies, the absolute benefit and NNI to screening to prevent 1 breast cancer death vary by age (Table 1). Based on the meta-analysis by Nelson et al,[9] about 1904 women aged 39 to 49 would need to be invited to prevent 1 breast cancer death, vs 377 women aged 60 to 69. To address the "psychological magnification" of relative risks and most patients' limited numeracy, experts recommend using natural frequencies (eg, the number of cancers diagnosed among a certain number screened) to aid comprehension of such findings.[30,31] Table 2 provides published estimates from Welch and Passow of mammography's benefits using natural frequencies. Welch and Passow provide a range for number of breast cancer deaths in a screened population using results from RCTs with markedly contrasting results—the Canadian trials, which showed no significant breast cancer mortality benefit (Welch and Passow use a more conservative estimate of 5%)[10,15] and the Swedish 2-County trial, which showed about a 36% risk reduction among those attending screening.[11] Welch and Passow calculated these numbers based on SEER 15-year breast cancer mortality rates[18] (assuming that the benefit of mammography would extend beyond the screening period) and adjusted for self-reported mammography rates in the United States,[19] providing a range to reflect the uncertainty about the benefit. Based on these estimates, among 10 000 women aged 50 years undergoing annual screening for 10 years, approximately 302 would be diagnosed with invasive breast cancer or DCIS, between 56 and 64 women would die of breast cancer despite screening, and between 3 and 32 breast cancer deaths would be averted through screening depending on the true effect of mammography. Some might argue that the ranges overemphasize extreme RCT results (concerns have been raised about suboptimal randomization in the Swedish trial[25]) and may be difficult to communicate to patients, and that meta-analyses can at least provide a "best estimate." If Welch and Passow's methodology is used but Nelson et al's[9] meta-analysis results are applied to the adjusted SEER breast cancer death rates, among 10 000 women aged 40 years undergoing annual mammography for 10 years, 31 deaths would occur despite screening and 5 deaths would be averted; among 50-year-olds, 62 deaths would occur despite screening and

10 would be averted; and among 60-year-olds, 88 deaths would occur despite screening and 42 would be averted.

Harms of Screening Mammography

False-Positive Results

False-positive results raise suspicion for breast cancer and lead to further testing, such as additional imaging or biopsy, but do not result in a cancer diagnosis.[32] Recent evidence from the Breast Cancer Surveillance Consortium suggests that the 10-year cumulative risk of at least 1 false-positive result is 61.3% for women starting screening at ages 40 or 50 years and 49.7% for women aged 66 to 74 years undergoing annual screening.[22,23] Table 2 shows that among 10 000 women aged 50 years undergoing annual mammography for 10 years, approximately 6130 (95% CI, 5800-6470) will have at least 1 false-positive result.

The risk of false-positive results increases when screening starts at younger ages or occurs annually, leading to more mammograms[32,33]; this was a key consideration influencing the USPSTF recommendation to pursue biennial screening starting at age 50.[2] The significance of a false-positive result for an individual woman, however, is debated, and likely varies substantially by patient. A review of 23 observational studies concluded that false-positive mammography results increase anxiety and distress related to mammography and breast cancer but do not increase clinically diagnosed anxiety and depression.[34] There are conflicting data regarding the persistence of anxiety or depressive symptoms over time,[35-38] and whether women are more or less likely to return for subsequent mammograms after a false-positive finding.[34,39-42] About 7.0% to 9.8% of women experience unnecessary biopsies after 10 years of annual screening[22,23]—approximately 940 (95% CI, 740-1150) of the 10 000 women aged 50 years undergoing annual mammography reported in Table 2.

Overdiagnosis

Overdiagnosis is the detection of a tumor through screening that would not have become clinically evident in the absence of screening. Overdiagnosis can occur either because of a tumor's indolent pathological features or because of competing mortality risks attributable to older age or comorbidities.[43] Previously overdiagnosis was considered primarily explained by DCIS, but it is now thought that some invasive cancer diagnoses also represent overdiagnosis; both types of cases are generally included in analyses, since both are treated. Treatment of an overdiagnosed cancer subjects a patient to the harms of treatment without benefits, since the tumor would not have caused problems if undetected.[43]

There has been a sharp recent increase in studies examining overdiagnosis, and many authors now describe overdiagnosis as the most concerning potential harm of mammography screening.[44] However, substantial uncertainty exists around its magnitude. To measure overdiagnosis, ideally one would compare the number of cancers diagnosed in screened vs unscreened women with the same underlying risk factors and representing the same historical period and region, from the onset of screening until death.[43] Adequate follow-up time is needed to account for the lead time gained by screening and to avoid counting cancers detected early through screening as "excess," or overdiagnosed, cancers.[43] Long-term follow up of RCTs comparing screened with unscreened women minimizes these concerns, providing the best estimates of overdiagnosis.[45] Three RCTs, the Malmö trial and the 2 Canadian trials, never invited their control groups to screening,[10,15,20] allowing assessment of excess cancer incidence in the screened group 6 to 15 years after screening ended. A meta-analysis of overdiagnosis estimates from these 3 trials estimated that among women invited to screen, 19% of all cancers diagnosed during the screening period (and 11% during the entire observation period) were overdiagnosed.[44,46] This proportion represents the excess incidence of cancers detected in the screened group over long-term follow-up, as a fraction of all cancers diagnosed in the screened group during the screening period (or the entire observation period).

The RCT findings have limitations, including possible underestimation of overdiagnosis because some screening occurred in the control groups (in the Canadian National Breast Screening Study 1, 26.3% of the control group had at least 1 mammogram outside the study).[10,47] Overestimation is also possible since women were not followed up until all had died, although in the recent update of the Canadian trials, excess cases still represented 22% of screening-detected cancers.[27,45] The applicability of the RCTs to women undergoing mammography screening today in the United States is also uncertain.[17] Because the Malmö trial screened women only every 18 to 24 months and used older, less sensitive mammography techniques, Welch and Passow used the Malmö estimate as a "lower bound" estimate of overdiagnosis risk.[17]

Published estimates of overdiagnosis from observational studies vary from less than 5% to more than 50%[43,48-50] because of differing populations, assumptions, and measurement methods.[43] To identify incidence rates in the absence of screening, observational studies often use historical incidence rates or incidence in an unscreened geographical region. A recent study based on SEER incidence and survival trends using historical incidence rates as a comparison reported that 31% of all breast cancers diagnosed in the United States represented overdiagnosis.[21] Welch and Passow used these data as their "upper bound" estimate of overdiagnosis risk.[17] In Table 2, we include Welch and Passow's lower and upper bound estimates to convey the uncertainty and methodological limitations around measuring overdiagnosis[17]; the estimate from the meta-analysis of 3 RCTs (19%)[44] lies between these extremes. It is thus likely that among 10 000 women aged 50 years undergoing annual mammography for 10 years, of 302 cases of cancer or DCIS, between 30 and 137 would reflect overdiagnosis, with a best guess being 57 based on the meta-analysis estimate of 19%.

Individualizing Mammography Screening Decisions

For a woman in the United States, the average lifetime risk of breast cancer is about 12.3%; the 10-year risks of invasive breast cancer at ages 40, 50, and 60 years are 1.5%, 2.3%, and 3.5% respectively.[1] Numerous risk factors have been identified for breast cancer, although up to 60% of breast cancers occur in the absence of known risk factors.[51] Each individual risk factor confers only a modest relative risk increase, and most are common in the general population; therefore, combinations of risk factors are most frequently used in efforts to estimate breast cancer risk.[52] Several risk models attempt to use these risk factors to predict both breast cancer incidence in populations and individuals' absolute risk. The Gail model, developed in a population of women undergoing annual screening and including age at menarche, age at first birth, number of first-degree relatives with breast cancer, number of previous breast biopsies, and presence of atypical hyperplasia as risk factors, was one

Table 3. Existing Guidelines for Mammography Screening

Organization and Year of Guidelines	Recommendations Regarding Mammography Screening
Norwegian Breast Cancer Screening Program, 1996[4]	Screening mammography every 2 y for women between ages 50 y and 69 y
US Preventive Services Task Force, 2009[2]	Biennial screening mammography for women between ages 50 y and 74 y The decision to start regular, biennial screening mammography before age 50 y should be an individual one and take into account patient context, including the patient's values regarding specific benefits and harms
National Health Service Breast Screening Program (United Kingdom), 2010[3,a]	Screening mammography every 3 y for women aged 47-73 y
Canadian Task Force on Preventive Health Care, 2011[81]	Routine screening mammography for women aged 50-74 y
National Cancer Institute (United States), 2012[6]	Screening mammograms every 1 to 2 y in women ≥40 y
American Cancer Society (United States), 2013[5]	Yearly mammograms starting at age 40 y

[a] Prior guidelines had recommended mammography every 3 years for women 50 years and older; in 2010, the age range was extended to include women aged 47 to 73 years.

of the first.[53,54] Several limitations of the Gail model have been described, including its omission of breast density and its limited applicability in certain racial/ethnic groups and high-risk populations.[51,55,56] Revisions of the model include more diverse populations[57] and breast density,[56,58,59] which is associated with a 1.5- to 2-fold increased risk of breast cancer among women aged 40 to 50 years[60] but raises the challenging question of whether a baseline mammogram should be obtained in all women. Although these models help refine understanding of a woman's absolute risk for breast cancer and can help communicate risk to women, they are more accurate in predicting incidence in population subgroups and far less useful in identifying which individual women will or will not get cancer.[52,55] Despite its limitations, the Gail model has been validated in 3 large populations and, as the basis for the National Cancer Institute's online Breast Cancer Risk Assessment Tool (http://www.cancer.gov/bcrisktool), is commonly used in clinical practice.

Several decision analysis models have attempted to estimate how individual risk profiles influence the benefits and harms of screening.[61-63] Older age and other factors that increase breast cancer risk also increase the absolute breast cancer mortality benefit with mammography. The risk of false-positive results also generally increases with certain individual characteristics such as breast density.[22,64] Older age and more comorbidity increase the risk of overdiagnosis because of decreasing life expectancy,[33] as do characteristics of the cancer itself (aggressive tumors are less likely overdiagnosed than indolent tumors because of shorter lead time). A comparative study of 4 microsimulation models found that for women aged 40 to 49 years with a Gail-model breast cancer risk twice average, biennial mammography screening yielded the same ratio of benefits and harms as biennial screening for women 50 years or older at average risk.[63] Similarly, a cost-utility model found that biennial screening among women aged 40 to 49 years with high breast density and either a first-degree relative with breast cancer or a history of a breast biopsy had similar ratios of benefits to harms as biennial screening of women in their 50s without those risk factors.[61] Of note, however, none of these models considered overdiagnosis in their main analysis.[61,63]

If a healthy 40-year-old woman had twice the average risk of breast cancer because of dense breasts, she would be expected to have twice the absolute benefit of annual screening (eg, 10 lives saved per 10 000 instead of 5) (Table 2). She would, however, also have a higher risk of false-positive findings.[22]

Supporting Informed Decision-Making

Decisions about mammography should involve discussion of risks, benefits, uncertainties, alternatives, and patient preferences.[65,66] Although numerous interventions have aimed to increase mammography uptake, including interventions tailored to individuals' psychological readiness to adopt screening or to individuals' own risk profiles,[67-75] fewer studies examine measures of an informed decision as an outcome. A Cochrane review of RCTs examined the effects of personalized risk communication on informed decision making about screening for a range of diseases.[76] Eighteen studies focused on mammography screening; those assessing outcomes related to informed decisions generally showed an increase in knowledge, quality of life, and accuracy of risk perception with personalized risk communication. Notably, meta-analysis of 4 studies of interventions providing women with numerical information about their risk showed that among women 40 years or older, there was no association between provision of numerical information and uptake of mammography (odds ratio, 0.84 [95% CI, 0.68-1.03]).[76]

Informed decisions require reconciling information about the risks and benefits of screening with a patient's values. Decision aids using pamphlets, videos, or Internet tools can provide information, elicit preferences, and help patients make decisions. A Cochrane review[77] defined decision aids as "interventions designed to help people make specific and deliberative choices… by providing (at the minimum) information on the options and outcomes relevant to a person's health status," and helping patients "to clarify… the value they place on the benefits, harms, and scientific uncertainties." Overall, decision aids increased knowledge, decreased decisional conflict and anxiety, and had variable effect on uptake of the test or treatment in question. The review's only mammography study recruited 70-year-old Australian women nearing the upper age cutoff for screening.[78] Exposure to the decision aid led to less indecision about continuing mammography, although there was no difference in screening participation the next month. A more recent study among US women 75 years or older administered a paper decision aid just before a primary care encounter. Women who received the decision aid reported knowing more about benefits and risks and screening, decreased intentions to be screened, and were less likely to undergo mammography in the following 2 years.[79] One RCT since the Cochrane review examined an online decision aid among women aged 38 to 45 years.[80] The decision aid summarized the risks and benefits of mammography and provided a val-

Box. **Suggested Discussion Points for Informed Decision Making About Mammography Screening**

Mammography Is Not a Perfect Screening Test, and Understanding of Its Benefits and Harms Is Incomplete

Some cancers will be missed, and some women will die of breast cancer regardless of whether they are screened.

Many cancers will be found, but most women diagnosed with breast cancer will be cured regardless of whether the cancer was found by a mammogram.

Some cancers that are found would have never caused problems. This is called "overdiagnosis."

Often, women are called back for further testing because of an abnormality that is not cancer; this is called a "false-positive" result.

Studies of the benefits and harms of mammography have limitations and inconsistent results. The numbers reported below are estimates based on what most experts consider the best available evidence, but uncertainty about these estimates remains.

Benefits of Mammography

Mammography decreases the number of women who will die from breast cancer. This benefit is greater for women who are at higher risk for breast cancer based on older age or other risk factors such as family history.

The number of women whose lives are saved because of mammography varies by age. For every 10 000 women who get regular mammograms for the next 10 years, the number whose lives will be saved because of the mammogram by age group is approximately

5 of 10 000 women aged 40 to 49 years

10 of 10 000 women aged 50 to 59 years

42 of 10 000 women aged 60 to 69 years

If your breast cancer risk is higher than average, you may benefit more from a mammogram than someone with average risk.

Harms of Mammography

About half or more of women who have a mammogram yearly for 10 years will have a false-positive mammogram, and up to 20% of these women will need a biopsy. If you do decide to have a mammogram, you can anticipate that you will have at least 1 false-positive finding for which you are called back for additional images and perhaps a biopsy. Most of these findings are false alarms.

For some women undergoing regular screening, the mammogram may find an invasive cancer or noninvasive condition (ie, ductal carcinoma in situ) that would never have caused problems ("overdiagnosis"). We cannot tell which these are, so they will be treated just like all other cancers. Experts are uncertain of how frequently this happens, but estimates suggest that if a woman undergoing a screening mammogram is diagnosed with cancer or ductal carcinoma in situ, there is about a 19% chance that the cancer is being overdiagnosed, and she will receive unnecessary treatment.

Making a Decision About Mammography

Experts recommend that women aged 50 to 74 years undergo a screening mammogram every 2 years.

Whether you are likely to benefit from starting mammograms earlier or having them more frequently depends on your risks for breast cancer and your values and preferences.

Each woman may feel differently about the possibility of having a false-positive result or being diagnosed with and treated for cancer that might not have caused problems. It is important for you to consider what these experiences might mean for you. It is also important to consider how you might feel if you decide not to undergo screening mammography and you are later diagnosed with breast cancer, even if the likelihood that mammography would have made a difference is small.

ues clarification worksheet. Compared with controls, women who used the decision aid were more knowledgeable and were less likely to report that they would initiate screening now.[80]

Discussion

Evidence suggests that mammography screening is associated with reduced breast cancer mortality, but the benefit is modest. Although better data are needed to estimate the magnitude of overdiagnosis, the risks of mammography screening are significant, decreasing the net benefit of screening. The net benefit is less for younger women, who have a lower absolute risk of breast cancer and greater risk of false-positive findings, and with annual screening, which increases false-positive findings and would also be expected to increase overdiagnosis.[33]

Table 3 includes current guidelines from the United States, Canada, and Europe. Despite offering clinicians and patients a general framework for evidence-based decisions, because of their limited incorporation of individual risk profiles other than age, variation across guidelines, and inherent population-based approaches, they have limited utility for guiding patient counseling and decisions. Because risk factors other than age influence the net benefit of screening,[33,63,64] guidelines ideally should incorporate such risk factors; for example, clinicians and patients who would normally consider starting screening at age 50 years for an average-risk woman should consider starting at age 40 for a woman with risk factors placing her at twice average risk.[63] However, a better understanding of overdiagnosis is needed to inform how individual characteristics influence the harms of mammography, and breast cancer risk models with better discriminatory accuracy are needed to more accurately individualize information about the benefits and harms of screening. In the meantime, the online Breast Cancer Risk Assessment Tool from the National Cancer Institute can assist physicians and patients in estimating risk.

The significance of the harms of mammography also depends on individuals' values and preferences, and eliciting these requires provision of accurate and balanced information and values clarification. In light of the harms and modest benefit of screening, as well as the substantial uncertainty surrounding their relative weight for individual patients, clinicians' efforts must focus on promoting informed screening decisions. The **Box** offers some suggestions for such discussions.

Given time constraints in primary care, decision aids may complement the points in the Box, laying the groundwork for discussions between clinicians and patients. Decision aids can facilitate informed decision-making and improve quality of care when there is no clear superior treatment or screening option.[82] Limited evidence suggests that decision aids can improve and standardize informed decision-making in breast cancer screening,[78,80] but more research is needed to optimize their use and guide integra-

tion into practice. One challenge is how best to communicate the evidence.[30] Although natural frequencies are preferred, they are derived from absolute risks and require estimating individuals' baseline risk.[76] Research is needed on communicating scientific uncertainty, including regarding overdiagnosis. A recent qualitative study found that the influence of learning about overdiagnosis on screening intentions depended greatly on the magnitude of overdiagnosis presented.[83] Expert consensus on overdiagnosis, combined with improved understanding of how to describe this complex issue, may strengthen mammography decision aids. Research will also be needed to explore the long-term effects of decision aids for screening decisions, especially since women with more information may actually be less likely to engage in screening.[76,77] Provisions in the Affordable Care Act establishing shared medical decision making as a marker of quality of care could help speed development, dissemination, and evaluation of decision aids.[84]

This review has provided a broad overview of key considerations in mammography screening decisions and the related areas of uncertainty. It has several limitations. We have relied on evidence of screening benefits from RCTs conducted decades ago in Europe and Canada, which may not generalize to US women today.[17,85] Furthermore, reports about overdiagnosis are methodologically heterogeneous and controversial. The review does not address several other important facets of breast cancer screening, including the use of magnetic resonance imaging and newer mammography technologies. It also does not address the complex issue of DCIS.

Conclusions

Although some of the challenges of mammography can be resolved with further research to guide individualized decisions and thoughtful development and dissemination of decision aids, better breast cancer screening tests are needed. More sophisticated tools, for example, could distinguish aggressive vs indolent tumors, reducing the burden of overtreatment.[86] Mammography screening appears to be associated with reduced breast cancer mortality, but for some patients, the harms may outweigh the benefits. Until better screening methods are available, improved understanding of these harms, enhanced strategies to identify the highest-risk patients, and tools to help patients and clinicians incorporate these in their decisions should be research priorities.

ARTICLE INFORMATION

Author Contributions: Drs Pace and Keating had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Pace, Keating.
Acquisition, analysis, or interpretation of data: Pace, Keating.
Drafting of the manuscript: Pace, Keating.
Critical revision of the manuscript for important intellectual content: Pace, Keating.
Administrative, technical, or material support: Pace.
Study supervision: Keating.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Keating reported receiving research funding from the National Cancer Institute, the American Cancer Society, and the Komen for the Cure Foundation. Dr Pace reported no disclosures.

Funding/Support: Dr Pace's work on this review was funded by the Global Women's Health Fellowship at Brigham and Women's Hospital.

Role of the Sponsor: The funder played no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

REFERENCES

1. Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review (CSR), 1975-2010. Surveillance, Epidemiology, and End Results Program website. http://seer.cancer.gov/csr/1975_2010/. 2013. Accessed January 17, 2014.

2. US Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2009;151(10):716-726.

3. National Health Service (NHS) Breast Cancer Screening Programme. What Does the NHS Breast Screening Programme Do? NHS Breast Cancer Screening Programme website. http://www.cancerscreening.nhs.uk/breastscreen/screening-programme.html. Accessed January 21, 2014.

4. Norwegian Breast Cancer Screening Programme. Cancer Registry of Norway website. http://www.kreftregisteret.no/en/Cancer-prevention/Breast-Cancer-Screening-Programme/. 2012. Accessed January 21, 2014.

5. American Cancer Society. Press Release: American Cancer Society Responds to Changes to USPSTF Mammography Guidelines. American Cancer Society website. http://pressroom.cancer.org/index.php?s=43&item=201. 2009. Accessed October 7, 2012.

6. National Cancer Institute. Mammograms. National Cancer Institute website. http://www.cancer.gov/cancertopics/factsheet/detection/mammograms. 2012. Accessed October 11, 2013.

7. Pace LE, He Y, Keating NL. Trends in mammography screening rates after publication of the 2009 US Preventive Services Task Force recommendations. *Cancer*. 2013;119(14):2518-2523.

8. Moss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L; Trial Management Group. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. *Lancet*. 2006;368(9552):2053-2060.

9. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L; U.S. Preventive Services Task Force. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2009;151(10):727-737.

10. Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study-1: breast cancer mortality after 11 to 16 years of follow-up: a randomized screening trial of mammography in women age 40 to 49 years. *Ann Intern Med*. 2002;137(5, part 1):305-312.

11. Tabár L, Vitak B, Chen TH, et al. Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades. *Radiology*. 2011;260(3):658-663.

12. Habbema JD, van Oortmarssen GJ, van Putten DJ, Lubbe JT, van der Maas PJ. Age-specific reduction in breast cancer mortality by screening: an analysis of the results of the Health Insurance Plan of Greater New York study. *J Natl Cancer Inst*. 1986;77(2):317-320.

13. Nyström L, Andersson I, Bjurstam N, Frisell J, Nordenskjöld B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet*. 2002;359(9310):909-919.

14. Bjurstam N, Björneld L, Warwick J, et al. The Gothenburg Breast Screening Trial. *Cancer*. 2003;97(10):2387-2396.

15. Miller AB, To T, Baines CJ, Wall C. Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women aged 50-59 years. *J Natl Cancer Inst*. 2000;92(18):1490-1499.

16. National Cancer Institute (NCI). DevCan—Probability of Developing or Dying of Cancer. NCI Surveillance Research website. http://surveillance.cancer.gov/devcan. Accessed March 11, 2014.

17. Welch HG, Passow HJ. Quantifying the benefits and harms of screening mammography. *JAMA Intern Med*. 2014;174(3):448-454.

18. National Cancer Institute (NCI). SEER*Stat software version 8.0.4. NCI website. http://seer.cancer.gov/seerstat. Accessed March 11, 2014.

19. National Center for Health Statistics. *Health, United States, 2012: With Special Feature on Emergency Care*. Hyattsville, MD: National Center for Health Statistics; 2013.

20. Zackrisson S, Andersson I, Janzon L, Manjer J, Garne JP. Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study. *BMJ*. 2006;332(7543):689-692.

21. Bleyer A, Welch HG. Effect of three decades of screening mammography on breast-cancer incidence. *N Engl J Med*. 2012;367(21):1998-2005.

22. Hubbard RA, Kerlikowske K, Flowers CI, Yankaskas BC, Zhu W, Miglioretti DL. Cumulative probability of false-positive recall or biopsy recommendation after 10 years of screening mammography: a cohort study. *Ann Intern Med*. 2011;155(8):481-492.

23. Braithwaite D, Zhu W, Hubbard RA, et al; Breast Cancer Surveillance Consortium. Screening outcomes in older US women undergoing multiple mammograms in community practice: does interval, age, or comorbidity score affect tumor characteristics or false positive rates? *J Natl Cancer Inst*. 2013;105(5):334-341.

24. Alexander FE, Anderson TJ, Brown HK, et al. 14 years of follow-up from the Edinburgh randomised trial of breast-cancer screening. *Lancet*. 1999;353(9168):1903-1908.

25. Gøtzsche PC, Jørgensen KJ. Screening for breast cancer with mammography. *Cochrane Database Syst Rev*. 2013;6:CD001877.

26. Fitzpatrick-Lewis D, Hodgson N, Ciliska D, Peirson L, Gauld M, Liu YY. Breast Cancer Screening. Canadian Task Force on Preventive Health Care website. http://canadiantaskforce.ca/wp-content/uploads/2012/09/Systematic-review.pdf?447f29. 2011. Accessed October 12, 2013.

27. Miller AB, Wall C, Baines CJ, Sun P, To T, Narod SA. Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. *BMJ*. 2014;348:g366.

28. Bastardis-Zakas K, Iatrakis G, Navrozoglou I, et al. Maximizing the benefits of screening mammography for women 40-49 years old. *Clin Exp Obstet Gynecol*. 2010;37(4):278-282.

29. Magnus MC, Ping M, Shen MM, Bourgeois J, Magnus JH. Effectiveness of mammography screening in reducing breast cancer mortality in women aged 39-49 years: a meta-analysis. *J Womens Health (Larchmt)*. 2011;20(6):845-852.

30. Hanoch Y. Improving doctor-patient understanding of probability in communicating cancer-screening test findings. *J Health Commun*. 2004;9(4):327-335.

31. Barrett B, McKenna P. Communicating benefits and risks of screening for prostate, colon, and breast cancer. *Fam Med*. 2011;43(4):248-253.

32. Elmore JG, Barton MB, Moceri VM, Polk S, Arena PJ, Fletcher SW. Ten-year risk of false positive screening mammograms and clinical breast examinations. *N Engl J Med*. 1998;338(16):1089-1096.

33. Mandelblatt JS, Cronin KA, Bailey S, et al; Breast Cancer Working Group of the Cancer Intervention and Surveillance Modeling Network. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. *Ann Intern Med*. 2009;151(10):738-747.

34. Brewer NT, Salz T, Lillie SE. Systematic review: the long-term effects of false-positive mammograms. *Ann Intern Med*. 2007;146(7):502-510.

35. Hafslund B, Espehaug B, Nortvedt MW. Effects of false-positive results in a breast screening program on anxiety, depression and health-related quality of life. *Cancer Nurs*. 2012;35(5):26-34.

36. Espasa R, Murta-Nascimento C, Bayés R, et al. The psychological impact of a false-positive screening mammogram in Barcelona. *J Cancer Educ*. 2012;27(4):780-785.

37. van der Steeg AF, Keyzer-Dekker CM, De Vries J, Roukema JA. Effect of abnormal screening mammogram on quality of life. *Br J Surg*. 2011;98(4):537-542.

38. Brodersen J, Siersma VD. Long-term psychosocial consequences of false-positive screening mammography. *Ann Fam Med*. 2013;11(2):106-115.

39. Seigneurin A, Exbrayat C, Labarère J, Delafosse P, Poncet F, Colonna M. Association of diagnostic work-up with subsequent attendance in a breast cancer screening program for false-positive cases. *Breast Cancer Res Treat*. 2011;127(1):221-228.

40. Alamo-Junquera D, Murta-Nascimento C, Macià F, et al; Cumulative False-Positive Risk Group. Effect of false-positive results on reattendance at breast cancer screening programmes in Spain. *Eur J Public Health*. 2012;22(3):404-408.

41. Burman ML, Taplin SH, Herta DF, Elmore JG. Effect of false-positive mammograms on interval breast cancer screening in a health maintenance organization. *Ann Intern Med*. 1999;131(1):1-6.

42. Setz-Pels W, Duijm LE, Coebergh JW, Rutten M, Nederend J, Voogd AC. Re-attendance after false-positive screening mammography: a population-based study in the Netherlands. *Br J Cancer*. 2013;109(8):2044-2050.

43. Etzioni R, Gulati R, Mallinger L, Mandelblatt J. Influence of study features and methods on overdiagnosis estimates in breast and prostate cancer screening. *Ann Intern Med*. 2013;158(11):831-838.

44. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet*. 2012;380(9855):1778-1786.

45. Marmot MG. Sorting through the arguments on breast screening. *JAMA*. 2013;309(24):2553-2554.

46. Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M. The benefits and harms of breast cancer screening: an independent review. *Br J Cancer*. 2013;108(11):2205-2240.

47. Gøtzsche PC. Ramifications of screening for breast cancer: overdiagnosis in the Malmö trial was considerably underestimated. *BMJ*. 2006;332(7543):727.

48. Paci E; EUROSCREEN Working Group. Summary of the evidence of breast cancer service screening outcomes in Europe and first estimate of the benefit and harm balance sheet. *J Med Screen*. 2012;19(suppl 1):5-13.

49. Jørgensen KJ, Gøtzsche PC. Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends. *BMJ*. 2009;339:b2587.

50. Puliti D, Duffy SW, Miccinesi G, et al; EUROSCREEN Working Group. Overdiagnosis in mammographic screening for breast cancer in Europe: a literature review. *J Med Screen*. 2012;19(suppl 1):42-56.

51. Amir E, Freedman OC, Seruga B, Evans DG. Assessing women at high risk of breast cancer: a review of risk assessment models. *J Natl Cancer Inst*. 2010;102(10):680-691.

52. Cummings SR, Tice JA, Bauer S, et al. Prevention of breast cancer in postmenopausal women: approaches to estimating and reducing risk. *J Natl Cancer Inst*. 2009;101(6):384-398.

53. Gail M, Rimer B. Risk-based recommendations for mammographic screening for women in their forties. *J Clin Oncol*. 1998;16(9):3105-3114.

54. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst*. 1989;81(24):1879-1886.

55. Gail MH, Costantino JP. Validating and improving models for projecting the absolute risk of breast cancer. *J Natl Cancer Inst*. 2001;93(5):334-335.

56. Barlow WE, White E, Ballard-Barbash R, et al. Prospective breast cancer risk prediction model for women undergoing screening mammography. *J Natl Cancer Inst*. 2006;98(17):1204-1214.

57. Gail MH, Costantino JP, Pee D, et al. Projecting individualized absolute invasive breast cancer risk in African American women. *J Natl Cancer Inst*. 2007;99(23):1782-1792.

58. Chen J, Pee D, Ayyagari R, et al. Projecting absolute invasive breast cancer risk in white women with a model that includes mammographic density. *J Natl Cancer Inst*. 2006;98(17):1215-1226.

59. Tice JA, Cummings SR, Smith-Bindman R, Ichikawa L, Barlow WE, Kerlikowske K. Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. *Ann Intern Med*. 2008;148(5):337-347.

60. Nelson HD, Zakher B, Cantor A, et al. Risk factors for breast cancer for women aged 40 to 49 years: a systematic review and meta-analysis. *Ann Intern Med*. 2012;156(9):635-648.

61. Schousboe JT, Kerlikowske K, Loh A, Cummings SR. Personalizing mammography by breast density and other risk factors for breast cancer: analysis of health benefits and cost-effectiveness. *Ann Intern Med*. 2011;155(1):10-20.

62. Ayer T, Alagoz O, Stout NKOR. Forum—a POMDP approach to personalize mammography screening decisions. *Oper Res*. 2012;60(5):1019-1034.

63. van Ravesteyn NT, Miglioretti DL, Stout NK, et al. Tipping the balance of benefits and harms to favor screening mammography starting at age 40 years: a comparative modeling study of risk. *Ann Intern Med*. 2012;156(9):609-617.

64. Kerlikowske K, Zhu W, Hubbard RA, et al; Breast Cancer Surveillance Consortium. Outcomes of screening mammography by frequency, breast density, and postmenopausal hormone therapy. *JAMA Intern Med*. 2013;173(9):807-816.

65. Nekhlyudov L, Braddock CH III. An approach to enhance communication about screening mammography in primary care. *J Womens Health (Larchmt)*. 2009;18(9):1403-1412.

66. Braddock CH III, Edwards KA, Hasenberg NM, Laidley TL, Levinson W. Informed decision making in outpatient practice: time to get back to basics. *JAMA*. 1999;282(24):2313-2320.

67. Champion V, Maraj M, Hui S, et al. Comparison of tailored interventions to increase mammography screening in nonadherent older women. *Prev Med*. 2003;36(2):150-158.

68. Champion V, Skinner CS, Hui S, et al. The effect of telephone versus print tailoring for mammography adherence. *Patient Educ Couns*. 2007;65(3):416-423.

69. Stoddard AM, Fox SA, Costanza ME, et al; NCI Breast Screening Consortium. Effectiveness of telephone counseling for mammography: results from five randomized trials. *Prev Med*. 2002;34(1):90-99.

70. Yabroff KR, O'Malley A, Mangan P, Mandelblatt J. Inreach and outreach interventions to improve mammography use. *J Am Med Womens Assoc*. 2001;56(4):166-173.

71. Jibaja-Weiss ML, Volk RJ, Kingery P, Smith QW, Holcomb JD. Tailored messages for breast and cervical cancer screening of low-income and minority women using medical records data. *Patient Educ Couns*. 2003;50(2):123-132.

72. Lipkus IM, Biradavolu M, Fenn K, Keller P, Rimer BK. Informing women about their breast cancer risks: truth and consequences. *Health Commun*. 2001;13(2):205-226.

73. Rimer BK, Halabi S, Sugg Skinner C, et al. Effects of a mammography decision-making intervention at 12 and 24 months. *Am J Prev Med*. 2002;22(4):247-257.

74. Albada A, Ausems MG, Bensing JM, van Dulmen S. Tailored information about cancer risk and screening: a systematic review. *Patient Educ Couns*. 2009;77(2):155-171.

75. Schwartz MD, Rimer BK, Daly M, Sands C, Lerman C. A randomized trial of breast cancer risk counseling: the impact on self-reported mammography use. *Am J Public Health*. 1999;89(6):924-926.

76. Edwards AG, Naik G, Ahmed H, et al. Personalised risk communication for informed decision making about taking screening tests. *Cochrane Database Syst Rev*. 2013;2:CD001865.

77. Stacey D, Bennett CL, Barry MJ, et al. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev*. 2011;(10):CD001431.

78. Mathieu E, Barratt A, Davey HM, McGeechan K, Howard K, Houssami N. Informed choice in mammography screening: a randomized trial of a decision aid for 70-year-old women. *Arch Intern Med*. 2007;167(19):2039-2046.

79. Schonberg MA, Hamel MB, Davis RB, et al. Development and evaluation of a decision aid on mammography screening for women 75 years and older. *JAMA Intern Med*. 2014;174(3):417-424.

80. Mathieu E, Barratt AL, McGeechan K, Davey HM, Howard K, Houssami N. Helping women make choices about mammography screening: an online randomized trial of a decision aid for 40-year-old women. *Patient Educ Couns*. 2010;81(1):63-72.

81. Canadian Task Force on Preventive Health. Screening for Breast Cancer: Summary of Recommendations for Clinicians and Policy-makers. Canadian Task Force on Preventive Health website. http://canadiantaskforce.ca/guidelines/2011-breast-cancer/. Accessed January 21, 2014.

82. Arterburn D, Wellman R, Westbrook E, et al. Introducing decision aids at Group Health was linked to sharply lower hip and knee surgery rates and costs. *Health Aff (Millwood)*. 2012;31(9):2094-2104.

83. Hersch J, Jansen J, Barratt A, et al. Women's views on overdiagnosis in breast cancer screening: a qualitative study. *BMJ*. 2013;346:f158.

84. The Patient Protection and Affordable Care Act 2010.

85. Welch HG. *Breast cancer screenings: what we still don't know. New York Times.* December 29, 2013:Opinion.

86. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. *JAMA*. 2009;302(15):1685-1692.