Breast Cancer Screening: From Science to Recommendation[1]

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In July 2008, the U.S. Preventive Services Task Force (USPSTF) voted on an update of its 2002 breast cancer screening recommendations (1). Owing to a number of factors outside the control of the USPSTF, these recommendations were not published until November 2009, when they generated substantial interest from the public as well as medical professional organizations. The response from the American College of Radiology was among the most critical of the newly revised USPSTF recommendations.

To constructively inform the science surrounding the debate and controversy, the editor of *Radiology* graciously invited members of the USPSTF to provide an overview of the USPSTF, its responsibilities and activities, the process through which the new guidelines were issued, and a review of the evidence considered, as well as the actual recommendations.

The USPSTF

The USPSTF was established in 1984 by the Public Health Service. The current USPSTF, with a rotating membership and a process of continuous reviews and recommendation releases, was created and codified as an independent body by a congressional mandate in 1998. The mission of the USPSTF is to review the scientific evidence for clinical preventive services and to develop rigorous evidence-based recommendations for primary care clinicians, as well as the broader health care community. While Public Law §915 mandates that the Agency for Healthcare Research and Quality (AHRQ) convene the USPSTF to conduct scientific evidence reviews and make evidence-based recommendations for primary care, the sole role of the AHRQ in the process is to support the USPSTF in specific activities, including providing space for meetings, organizing conference calls, managing the contracts for systematic evidence reviews, and providing staffing by medical officers to support the USPSTF processes. No person at the AHRQ has a vote or otherwise influences the priorities or decisions of the USPSTF.

Since 2001, the USPSTF has been a standing task force of 16 members who serve terms of 4–6 years and are appointed by the AHRQ director from recommendations developed by the USPSTF chair and vice-chair following a public nomination process. As USPSTF recommendations cover a diverse array of topics that target primary care providers, its membership is composed of a broad range of experts in primary care and preventive health–related disciplines, including internal medicine, family medicine, geriatrics, behavioral medicine, pediatrics, obstetrics and gynecology, preventive medicine, and nursing. The USPSTF includes experts in evidence-based clinical research, screening, clinical epidemiology, behavioral science, health services research, outcomes and effectiveness in clinical preventive medicine, and decision modeling.

While USPSTF members also commonly have topic-specific expertise, individuals with disease-specific expertise outside the task force are routinely asked to review and comment on the work at three critical points in the process. The initial analytic framework and key questions that drive the systematic review, as well as the draft review itself, are sent for review and comment to USPSTF partner organizations (2), selected subspecialist experts in the disease topic at hand, and other stakeholders, which may include subspecialty professional societies. The draft recommendation statement itself is similarly disseminated for review. Comments are reviewed and summarized, following which the recommendations may be revised before being finalized, submitted for

publication, and posted on the USPSTF Web site.

Evidence-based practice center scientists, AHRQ support staff, and representatives from 24 partner organizations representing all primary care specialties, key federal agencies and selected other key stakeholders attend and participate in the process of systematic evidence review and recommendation development. There is careful attention to conflicts of interest for USPSTF members: Members with financial conflicts are recused, and members with strong intellectual conflicts have restricted roles. A core value of the USPSTF is that the evaluation of the evidence must be conducted free from the influence of advocacy, special interests, and politics.

The USPSTF operates as a body of the whole, three standing subcommittees (Methods, Topic Prioritization, and Dissemination and Implementation), and ad hoc work groups. The core activity of issuing evidence-based recommendations about primary care preventive services is conducted by using a formal process to address key questions through a prespecified problem-specific formal chain of evidence within an analytic framework following explicit criteria described in the USPSTF Methods Manual. Directed by an ad hoc topic work group of USPSTF members specifically constituted for each problem being addressed, an AHRQ evidence-based practice center conducts a systematic review of the scientific evidence to enable the topic work group to develop estimates of the magnitude and certainty of benefits and harms, which then are subjected to extensive critical review by the full USPSTF, which reaches consensus and formally votes upon final recommendations. While attendance at USPSTF meetings is by invitation only, minutes of proceedings are available to the public. The evidence report and recommendation are peer reviewed by a diverse range of experts and stakeholders before being finalized and formally issued.

The USPSTF evaluates the benefits of individual services on the basis of age, sex, and risk factors for disease and makes recommendations about which

preventive services should be incorporated routinely into primary medical care for which populations (3). All recommendations are issued a letter grade, which is based on two factors: the magnitude of net health benefit (ie, the balance between benefits and harms as indicated by the systematic evidence review) and the certainty of the net benefit (ie, the level of confidence by the USPSTF that the scientific evidence is correct and the likelihood that the recommendation may or may not change based on future research) (Table 1). The USPSTF only considers scientific evidence of health benefits and health harms, following strict rules of evidence and an explicit process outlined in a methods manual published on the USPSTF Web site (2). Cost and cost-effectiveness of specific prevention services are not considered by the USPSTF, either in its deliberations or in developing recommendations. The USPSTF does not advise insurers or make coverage decisions.

Grade A recommendations (ie, use is recommended) require high certainty of substantial net benefit and consistent results from well-designed well-conducted studies in representative primary care populations that are unlikely to be substantially affected by the results of future studies. Grade B recommendations (ie, use is recommended) require at least a moderate certainty of at least a moderate net benefit. While evidence for grade B recommendations is sufficient to determine the effects of the preventive service on health outcomes, confidence in the assessment is constrained by the number, size, or

quality of studies; consistency of findings across studies; limited generalizability to routine primary care; and/or lack of coherence in the evidence chain. Thus, the magnitude or direction of effect might change and may be large enough to alter conclusions as more information becomes available. The USPSTF recommends that primary care clinicians implement grade A and B services routinely for appropriate patients. Grade C recommendations are issued when there is at least moderate certainty of a small net benefit. A grade D recommendation requires at least a moderate certainty that the service provides no benefit or leads to harms in excess of benefits; it is recommended that primary care clinicians not provide this service. A grade I statement indicates that the evidence is insufficient to make a recommendation for or against providing the service and that more research is needed to fill in the gaps in evidence.

In 2007, in response to input from primary care clinicians, the USPSTF revised its wording for a grade C recommendation from "does not recommend for or against" to "recommends against routine" provision of the preventive service. In the 2007 publication providing guidance on interpreting recommendations, the USPSTF noted that "The concept of the close balance of benefits and harms...is meant to indicate that although there is evidence of a small net benefit, the USPSTF has judged that this net benefit is too small to justify routine implementation of the service in the target population" (5). This language was intended to communicate that, where the

Table 1

USPSTF Recommendation Grid

Certainty of Net Benefit	Magnitude of Net Benefit			
	Substantial	Moderate	Small	Zero or Negative
High	A	B	C	D
Moderate	B	B	C	D
Low	I	I	I	I

Source.—Reference 4.

Note.—A and B = recommend use. C = recommend against routine use. D = recommend against use. I = no recommendation, insufficient evidence.

net benefit of the preventive service is small, clinician judgment and individual patient circumstances and values are particularly important factors to be considered in clinical decision making, rather than routinely or automatically providing the service. The language regarding grade C recommendations ("the USPSTF recommends against *routine* provision" [italics added]), while intended for consideration for primary care clinicians, was frequently misinterpreted and played out in unintended ways with regard to the recent breast cancer screening recommendation.

2009 USPSTF Recommendation on Breast Cancer Screening

The USPSTF previously released evidence-based breast cancer screening recommendations in 1989, 1996, and 2002. These recommendations consistently supported screening for women aged 50 years and older every 1–2 years (with variation in the upper age limit). The 1989 recommendation stated that for women younger than 50 years "it may be prudent to begin mammography at an earlier age for women at high risk of breast cancer." The 1996 update concluded that there was insufficient evidence to make a recommendation regarding routine breast cancer screening in 40–49-year-old women. In 2002, the USPSTF issued a grade B recommendation for screening women 40 years of age and older every 1–2 years. In recognition of the fact that in the 40–49-year-old group the benefits were significantly less and the harms greater than for older women and that the balance of benefits and harms improved as a woman got closer to 50 years of age, the statement's supporting clinical considerations were heavily nuanced for women younger than 50 years and recommended that primary care clinicians discuss the best time to start screening with their patients.

The USPSTF strives to update its recommendations at least every 5 years and will do so more frequently if new pivotal information becomes available. Several important studies were published subsequent to the 2002 recommendation on breast cancer screening, prompting an update of the evidence review. In assessing the effectiveness and harms of breast cancer screening modalities, the USPSTF carefully reviewed, critiqued, and commissioned independent meta-analyses of randomized controlled trials (RCTs) of screening effectiveness from the USPSTF 2002 review that were judged to be of fair quality or better (by using standardized prespecified study assessment criteria as defined in the USPSTF procedural manual) and all new trials or updates of previous trials since the 2002 review.

Because all but one of the breast cancer screening RCTs were conducted outside the United States, the USPSTF also commissioned the Oregon Evidence-based Practice Center to perform an in-depth analysis of the data from the Breast Cancer Surveillance Consortium (BCSC) from 2000 to 2005 (6) to provide a more in-depth evaluation of the potential harms associated with mammographic screening. The BCSC, a collaborative network of five mammography registries with two affiliated sites with linkages to pathology and tumor registries that is supported by a central statistical coordinating center, is a National Institutes of Health–sponsored research resource designed to assess the delivery and quality of breast cancer screening and related patient outcomes. While many of the RCTs providing evidence of mammography benefit were conducted in Europe, the BCSC database, which includes information from both screen-film and digital mammography, contains outcome data on over 2 million women, 7.5 million screening mammographic examinations, and more than 86000 breast cancer cases (as of May 2008), all in the United States (7).

The BCSC data are provided by age (in decades) beginning at age 40 years (with data on women aged 70 years or older collapsed into a single category). BCSC data reflect actual U.S. practice. Analysis of BCSC data included all women screened between 2000 and 2005 at any of the seven BCSC sites who had at least one prior screening mammogram within 2 years (ie, routine screening) and was used to derive U.S. estimates on screening mammography rates, proportions, sensitivity, specificity, recall rates, and potential harms. The BCSC analyses revealed that cancer rates increase and false-positive mammogram rates decrease with age, that the number of women undergoing additional imaging and biopsy to diagnose one case of cancer decreases with age, that biopsy rates were only slightly lower in younger women than in older women, and that rates of false-positive findings and recall rates in the United States are at least twice those in Canada and Europe, while cancer detection rates were similar.

The USPSTF also engaged the six independent National Cancer Institute–sponsored Cancer Intervention and Surveillance Modeling Network (CISNET) breast cancer grantees (whose models have been validated and subjected to peer review) to provide additional information to help guide the USPSTF in its update (8) by modeling the impact of screening mammography on breast cancer natural history and conducting extensive sensitivity analyses to assess the robustness of alternative assumptions and ranges of RCT result point estimates. These analyses provided longitudinal estimates of the impact on breast cancer mortality of alternative ages for initiating and stopping screening mammography and of alternative screening intervals. The models also examined RCT limitations that some have claimed may underestimate screening mammography benefits (eg, to assess the impact of screening mammography among those women who actually obtained screening as opposed to RCT "intention to treat" analyses that calculated results based on "invitation to be screened," to adjust for RCT attrition and contamination, to incorporate sensitivity and specificity estimates representative of current screening mammography technologies and techniques currently used in the United States, and to extend the analytical time horizon to capture late benefits of screening mammography). The modeling also examined the impact of excluding individual controversial screening mammography RCTs, including the Health Insurance Plan of Greater New York study (9) and the Canadian National Breast Screening

Study-1 (10). Among the many sources of data used in the modeling process, the BCSC data provided inputs for the operating characteristics of mammography, such as sensitivity and false-positive rates. The modeling estimates used were a best case, or optimistic, scenario for women, as they assumed 100% adherence to screening regimens and state of the science management of detected cancers with no variations from recommended care, did not capture morbidity associated with surgery for screening-detected disease or decrements in quality of life associated with false-positive results or overdiagnosis, and did not discount benefits for time effects (8).

Outcome tables were constructed to estimate the magnitude of screening benefits and harms by age for each of these three information sources. The ensuing review, study, and critique were intensive, spanning 18 months, and the findings were analyzed and critiqued in two separate USPSTF meetings before the new recommendations were developed.

The recommendations are summarized and discussed below, in reverse order of how they appear in the *Annals of Internal Medicine* (1):

1. "The USPSTF concludes that the current evidence is insufficient to assess additional benefits and harms of either digital mammography or magnetic resonance imaging instead of film mammography as screening modalities for breast cancer. (I statement)"—This is not a recommendation against the use of these modalities but is an acknowledgment that the evidence is not robust enough at this point to support an evidence-based recommendation. Although digital mammography has somewhat higher overall sensitivity in women younger than 50 years, there is not supporting evidence that this translates into enhanced mortality reduction, and it at least has the potential of increasing overdiagnosis and false-positive findings. A grade I conclusion identifies a need for additional research.

2. "The USPSTF recommends against clinicians teaching women how to perform breast self-examination. (Grade D recommendation)"—This recommendation is targeted at the teaching of breast self-examination by primary care providers, not at its performance by women. Two RCTs of good quality on teaching breast self-examination have now been published (one subsequent to 2002), with both reporting no benefit to this practice and at least small harms from an increase in negative breast biopsies (11,12).

3. "The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of clinical breast examination beyond screening mammography in women 40 years or older. (I statement)"—This statement is unchanged from 2002 and is not a recommendation against this service. Rather, it reflects an absence of evidence of incremental benefits of clinical breast examination in addition to screening mammography.

4. "The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of screening mammography in women 75 years or older. (I statement)"—This change from the 2002 recommendation reflects the fact that the USPSTF expanded the grade B recommendation supporting routine breast cancer screening mammography to include women aged 70–74 years. No adequate trial data exist to guide recommendations for women who are 70 years or older. With the support provided by the CISNET models, the USPSTF felt comfortable extrapolating the benefits from studies in younger women, particularly 60–69-year-old women. However, the USPSTF recognized that the screening benefits take several years to accrue, that women in the older age group die more often of other unrelated conditions, and that fewer of these women survive long enough to realize the potential benefit of screening. Overdiagnosis and unnecessary treatment of a breast cancer that would not shorten or otherwise affect a woman's life are greater risks in this age group, as supported by the CISNET modeling studies. In light of these factors, the USPSTF could not determine the balance of benefits and harms in women 75 years of age or older with sufficient certainty. As with all insufficient evidence statements, this is not a recommendation against performing the service, but rather signals that clinicians and patients must make decisions without adequate evidence of the net benefit of the service.

5. "The USPSTF recommends biennial screening mammography for women between the ages of 50 and 74 years. (Grade B recommendation)"—Previously, the USPSTF recommended breast cancer screening mammography every 1–2 years on the basis of evidence from large screening trials that suggested no additional mortality reduction associated with biennial versus annual screening. However, there are no head-to-head trials of alternative screening intervals. The CISNET models provided evidence that biennial screening retained more than 80% of the mortality reduction benefit of annual screening while reducing false-positive and related negative biopsies by almost half (and to a somewhat lesser degree, overdiagnosis). On the basis of this balance of benefits and harms, the USPSTF recommended biennial screening.

6. "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. (Grade C recommendation)"—Breast cancer risk and, thus, the absolute benefit of effective screening procedures vary with age. The important question of the age at which to begin mammographic screening has long been a difficult and contentious issue, with many questioning the benefit of initiating mammographic screening among women prior to the age of 50 years.

The USPSTF determined that, compared with initiating screening at 50 years of age, screening mammography provides a small benefit (approximately one death and 12 life-years gained per 1000 women screened annually for a decade) when performed in women ages 40–49 and is frequently accompanied by the harms of false-positive tests and their resultant follow-up, as well as the harms of overdiagnosis and

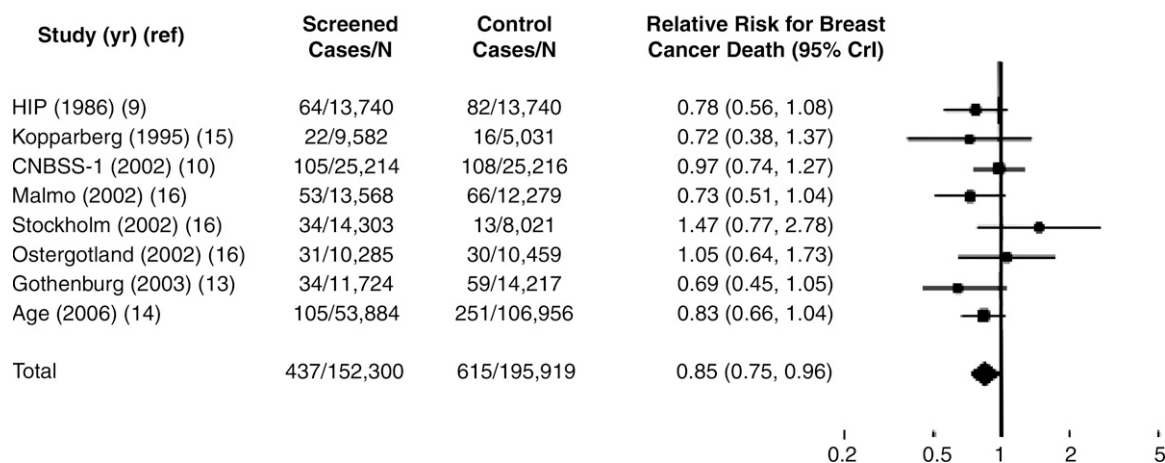| Study (yr) (ref)	Screened Cases/N	Control Cases/N	Relative Risk for Breast Cancer Death (95% CrI)
HIP (1986) (9)	64/13,740	82/13,740	0.78 (0.56, 1.08)
Kopparberg (1995) (15)	22/9,582	16/5,031	0.72 (0.38, 1.37)
CNBSS-1 (2002) (10)	105/25,214	108/25,216	0.97 (0.74, 1.27)
Malmo (2002) (16)	53/13,568	66/12,279	0.73 (0.51, 1.04)
Stockholm (2002) (16)	34/14,303	13/8,021	1.47 (0.77, 2.78)
Ostergotland (2002) (16)	31/10,285	30/10,459	1.05 (0.64, 1.73)
Gothenburg (2003) (13)	34/11,724	59/14,217	0.69 (0.45, 1.05)
Age (2006) (14)	105/53,884	251/106,956	0.83 (0.66, 1.04)
Total	437/152,300	615/195,919	0.85 (0.75, 0.96)

Chart of meta-analysis of screening RCTs of women aged 39–49 years. In far right plot, values below one favor screening and values above one favor control. *Screened Cases/N* = number of cases of breast cancer per number of screened patients. *Control Cases/N* = number of cases of breast cancer per number of control patients. *CrI* = credible interval, *HIP* = Health Insurance Plan of Greater New York study, *CNBSS-1* = Canadian National Breast Screening Study-1, *ref* = reference. Adapted, with permission, from reference 6.

overtreatment. Thus, the net benefit of routine screening in this age group was considered to be small and was assigned grade C. In the context of a small net benefit, the USPSTF recommended that screening mammography in this age group should not be automatic but, rather, should be the result of an informed individual decision based on a woman's specific clinical situation, preferences, and values regarding the potential benefits and harms. When the recent breast cancer screening recommendation was first issued, the original wording stated: "The USPSTF recommends against routine screening mammography in women age 40-49 years," followed immediately by the sentence given in recommendation 6 above. However, many people interpreted the language as opposing screening mammography in this group. To clarify the intent of the USPSTF, the original language was modified after a unanimous vote of the members to remove the initial sentence including the phrase "against routine screening" and leave only the wording in recommendation 6 above. The members also unanimously voiced support of the assignment of the grade C, as originally voted in July 2008.

Because all but one of the RCTs of the clinical effectiveness of mammographic screening included women aged 40–70 years, assessment of this question inherently required extensive retrospective analysis. The USPSTF used several sources of evidence and conducted extensive sensitivity analysis in making this recommendation. The previous meta-analysis of the RCTs of mammography was updated with additional data from a previously reported Swedish study (13) and the British RCT (14) that was specifically designed to evaluate mammography in more than 160 000 women aged 40–49 years. Summing across these studies, 448 women of 152 300 in the screening groups and 625 women of 195 919 in the control groups died of breast cancer, translating to a 15% relative risk reduction in mortality, an absolute risk reduction in mortality of only 0.025%, and a number needed to invite to screening of 1904. Participation from women in the screening groups was high, such that a subanalysis that ignored the random assignment and evaluated only participating women (an analysis biased toward higher effectiveness) yielded only a slightly higher estimate of benefit and did not change overall assessment of net benefit by the USPSTF. Similarly, sensitivity analysis that excluded the Health Insurance Plan of Greater New York study trial (>30 years old) (9) and the Canadian National Breast Screening Study-1 trial (10) did not significantly influence the results of the meta-analysis. The Figure summarizes the RCT meta-analysis; sensitivity analysis is included in the evidence update (6).

The USPSTF also considered harms associated with mammography, with data extracted directly from the BCSC. Per screening round of 1000 women (which, for annual screening between the ages of 40 and 49 years, would translate to 10 rounds), there were 1.0 false-negative results and 97.8 false-positive results, including 84.3 cases where additional images were performed and 9.3 cases where biopsies were performed.

Finally, the USPSTF considered the results of the CISNET breast cancer screening model results, which were consistent and robust across all six models over a broad range of plausible assumptions. The CISNET models indicated that beginning annual screening mammography at 40 years of age, compared with 50 years, provided a small incremental benefit (an additional relative 3% mortality reduction) and an additional 2250 false positives for every 1000 women screened in this age interval (Table 2). The USPSTF also considered the eight available studies of overdiagnosis, with rates ranging from 1% to 30%, most in the 10% range (6).

Table 2

Incremental Changes in Breast Cancer Mortality and Life-Years Gained if Screening Is Initiated at 40 Years versus 50 Years

CISNET Model	Difference in Percentage of Reduction in Breast Cancer Mortality		Difference in Breast Cancer Deaths Averted per 1000 Women		Difference in Life-Years Gained per 1000 Women	
	Annual	Biennial	Annual	Biennial	Annual	Biennial
Dana-Farber Cancer Institute	3	2	1	1	25	20
Erasmus Medical Center	8	5	2	1	58	40
Georgetown University	3	3	1	1	34	29
M. D. Anderson Cancer Center	2	3	1	1	11	18
Stanford University	2	1	1	1	32	21
University of Wisconsin/Harvard	10	6	2	1	57	37
Median across models	3	3	1	1	33	25

Note.—Incremental differences between screening from 40 to 69 years of age versus 50 to 69 years of age. Adapted, with permission, from reference 8.

Much attention has been directed toward the estimated number needed to treat of 1904 for women between the ages of 40–49 years. As described in a previous publication (4) and outlined in its methods manual (2), the USPSTF does not have a single number needed to treat, screen, or harm nor a fixed formula or threshold for drawing a conclusion about the magnitude of net benefit or assigning recommendation grades. The 1904 women between 40 and 49 years needed to invite was assessed in the context of the harms from the BCSC data, and the net benefit was judged as small (leading to the C recommendation). The 1339 women between 50 and 59 years needed to invite and the 377 women between 60 and 69 years needed to invite were assessed in the context of the lower rate of harms in these age groups found in the BCSC analysis, resulting in a net benefit judged as moderate in these age groups (leading to a B grade). The age range for this recommendation was extended to 74 years because the small amount of data available for women aged 70–74 years supported a conclusion of similar benefit. However, as for all diseases, the distribution of incidence, prevalence, and severity and the benefits and harms of screening (and intervention) are continuous; thus, decision thresholds are not absolute or discrete. Rather, categorization of guidelines represents a simplification device required to practically implement what inherently is a continuous function balancing benefits and harms. For mammographic screening, the net benefits of mammographic screening increase with age, with the greatest absolute benefits among women aged 50–74 years.

Summary

We greatly appreciate the invitation from the editor of *Radiology* to provide a brief description of the USPSTF and the methods and procedures used to develop our recent recommendations on breast cancer screening; a focused overview of the recommendations, including clarification of aspects of the recommendations that have been misinterpreted by some; and the opportunity to address a number of incorrect statements made by critics of the recommendations.

Neither of two RCTs found benefits of physicians teaching breast self-examination to women. There is insufficient evidence to demonstrate an incremental benefit of breast self-examination by women who undergo annual or biennial screening mammography. However, abnormal findings detected at breast self-examination warrant clinical evaluation and follow-up.

Our comprehensive systematic review of RCTs confirms the net benefits and underscores the strong recommendation for routine screening mammography in women between the ages of 50 and 70 years. Furthermore, rigorous decision model analyses of breast cancer screening and natural history provide moderate evidence of the benefits of extending routine mammographic screening to women aged 70–74 years. However, evidence from the BCSC and the decision models indicate that most of the benefits of annual screening mammography can be attained through biennial screening, while dramatically reducing harms associated with mammographic screening. Similarly, the results of the AGE trial that was designed to assess the net benefit of screening mammography in women aged 40–49 years and the systematic review, the meta-analysis of previous RCTs (including those with extended follow-up), and the breast cancer screening models all demonstrate a small net benefit of screening mammography among women aged 40–49 years. Thus, screening among women in this age range is best addressed by individualized decision making between a woman and her primary care physician, incorporating the woman's preferences and values. There is insufficient evidence to make any informed recommendation regarding screening mammography in women 75 years or older or regarding superior net population benefit of digital mammography or screening with breast magnetic resonance imaging.

Breast cancer remains a major source of morbidity and mortality in the United States, affecting approximately one (12.5%) in eight women who live to the age of 90 years. Screening mammography leads to earlier detection and reduced mortality in women aged 40–74

years, with the magnitude of the benefit small for women aged 40–49 years and greatest for women aged 50–74 years. Further progress in reducing breast cancer morbidity and mortality will require a better understanding of methods for primary prevention, more effective therapy, and improved diagnostic tests that reduce false-positive results and identify women with lesions likely to benefit from therapeutic intervention.

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