Centro di Riferimento per l'Epidemiologia
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È tutto evidence-based nelle raccomandazioni internazionali?

Paola Armaroli

CPO-Piemonte AOU Città della Salute e della Scienza, Torino

WORKSHOP GISMa-ONS: Lo screening nelle donne giovani: va cambiato qualcosa?

Finalborgo 18 maggio 2016

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Breast-Cancer Screening — Viewpoint of the IARC Working Group

Béatrice Lauby-Secretan, Ph.D., Chiara Scoccianti, Ph.D., Dana Loomis, Ph.D., Lamia Benbrahim-Tallaa, Ph.D., Véronique Bouvard, Ph.D., Franca Bianchini, Ph.D., and Kurt Straif, M.P.H., M.D., Ph.D., for the International Agency for Research on Cancer Handbook Working Group

N ENGL J MED 372;24 NEJM.ORG JUNE 11, 2015

Special Communication

Breast Cancer Screening for Women at Average Risk
2015 Guideline Update From the American Cancer Society

Kevin C. Oeffinger, MD; Elizabeth T. H. Fontham, MPH, DrPH; Ruth Etzioni, PhD; Abbe Herzig, PhD; James S. Michaelson, PhD; Ya-Chen Tina Shih, PhD; Louise C. Walter, MD; Timothy R. Church, PhD; Christopher R. Flowers, MD, MS; Samuel J. LaMonte, MD; Andrew M. D. Wolf, MD; Carol DeSantis, MPH; Joannie Lortet-Tieulent, MSc; Kimberly Andrews; Deana Manassaram-Baptiste, PhD; Debbie Saslow, PhD; Robert A. Smith, PhD; Otis W. Brawley, MD; Richard Wender, MD

JAMA October 20, 2015 Volume 314, Number 15

European Code against Cancer, 4th Edition: Cancer screening☆

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Annals of Internal Medicine

CLINICAL GUIDELINE

Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement

Albert L. Siu, MD, MSPH, on behalf of the U.S. Preventive Services Task Force*

Annals of Internal Medicine • Vol. 164 No. 4 • 16 February 2016 279

Breast-Cancer Screening — Viewpoint of the IARC Working Group

N ENGL J MED 372;24 NEJM.ORG JUNE 11, 2015

Objective: to assess the cancer-preventive and adverse effects of different methods of screening for breast cancer, to update of the 2002 IARC handbook on breast-cancer screening

Table 1. Evaluation of Evidence Regarding the Beneficial and Adverse Effects of Different Methods of Screening for Breast Cancer in the General Population and in High-Risk Women.*

Method	Strength of Evidence†
Mammography	
Reduces breast-cancer mortality in women 50–69 yr of age	Sufficient
Reduces breast-cancer mortality in women 70–74 yr of age‡	Sufficient
Reduces breast-cancer mortality in women 40–44 yr of age§	Limited
Reduces breast-cancer mortality in women 45–49 yr of age§	Limited¶
Detects breast cancers that would never have been diagnosed or never have caused harm if women had not been screened (overdiagnosis)	Sufficient
Reduces breast-cancer mortality in women 50–74 yr of age to an extent that its benefits substantially outweigh the risk of radiation-induced cancer from mammography	Sufficient
Produces short-term negative psychological consequences when the result is false positive	Sufficient
Has a net benefit for women 50–69 yr of age who are invited to attend organized mammographic screening programs	Sufficient
Can be cost-effective among women 50–69 yr of age in countries with a high incidence of breast cancer	Sufficient
Can be cost-effective in low- and middle-income countries	Limited

‡ The evidence for a reduction in breast-cancer mortality from mammography screening in women in this age group was considered to be sufficient. However, published data for this age category did not allow for the evaluation of the net benefit.

§ The evidence for a reduction of breast-cancer mortality from mammography screening in women in this age group was considered to be limited. Consequently, the net benefit for women in this age group was not assessed.

¶ The majority of the voting members of the IARC Working Group considered the evidence as limited; however, the vote was almost evenly divided between limited and sufficient evidence.

Breast-Cancer Screening — Viewpoint of the IARC Working Group

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Ultrasonography as an adjunct to mammography in women with dense breasts and negative results on mammography	
Reduces breast-cancer mortality	Inadequate
Increases the breast-cancer detection rate	Limited
Reduces the rate of interval cancer‖	Inadequate
Increases the proportion of false positive screening outcomes	Sufficient
Mammography with tomosynthesis vs. mammography alone	
Reduces breast-cancer mortality	Inadequate
Increases the detection rate of in situ and invasive cancers	Sufficient
Preferentially increases the detection of invasive cancers	Limited
Reduces the rate of interval cancer‖	Inadequate
Reduces the proportion of false positive screening outcomes	Limited
Clinical breast examination	
Reduces breast-cancer mortality	Inadequate
Shifts the stage distribution of tumors detected toward a lower stage	Sufficient
Breast self-examination	
Reduces breast-cancer mortality when taught	Inadequate
Reduces the rate of interval cancer when taught‖	Inadequate
Reduces breast-cancer mortality when practiced competently and regularly	Inadequate

Breast-Cancer Screening — Viewpoint of the IARC Working Group

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Screening of high-risk women	
MRI as an adjunct to mammography	
Reduces breast-cancer mortality in women with a *BRCA1* or *BRCA2* mutation	Inadequate
Increases the detection rate of breast cancer in women with lobular carcinoma in situ or atypical proliferations	Inadequate
Clinical breast examination as an adjunct to MRI and mammography	
Increases the detection rate of breast cancer in women with a high familial risk	Inadequate
Ultrasonography as an adjunct to mammography	
Increases the detection rate of breast cancer in women with a personal history of breast cancer	Inadequate
Increases the proportion of false positive screening outcomes in women with a personal history of breast cancer as compared with those without such a history	Inadequate
MRI as an adjunct to mammography plus ultrasonography	
Increases the proportion of false positive screening outcomes in women with a personal history of breast cancer as compared with those without such a history	Inadequate
MRI as an adjunct to mammography vs. mammography alone	
Increases the proportion of false positive screening outcomes in women with lobular carcinoma in situ or atypical proliferations	Limited

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Handbooks of Cancer Prevention

Volume 15: Breast Cancer Screening

WORKING PROCEDURES

LYON, FRANCE
2014

http://handbooks.iarc.fr/docs/Handbook15_Working-Procedures.pdf

The objectives of the Working Group are:

(1) To evaluate the strength of the evidence for the preventive efficacy of a screening procedure;

(2) To assess the effectiveness of defined screening interventions in defined populations;

(3) To assess the balance of benefit and harm in target populations;

IARC scientific staff performed searches of the openly available scientific literature according to topics listed in an agreed-upon table of contents;
searches were supplemented by members of the working group on the basis of their areas of expertise.

Group chairs and subgroup members were selected by the IARC according to field of expertise and the absence of real or apparent conflicts of interest.

During the meeting, care was taken to ensure that each study summary was written or reviewed by someone who was not associated with the study being considered.
All studies were assessed and fully debated, and a consensus on the preliminary evaluations was achieved in subgroups before the evaluations were reviewed by the entire working group.

During the final evaluation process, the working group discussed preliminary evaluations to reach consensus evaluations.

Sufficient evidence for the efficacy and effectiveness of a cancer-preventive activity will apply when screening interventions by a defined procedure are consistently associated with a reduction in mortality from the cancer and/or a reduction in the incidence of invasive cancer, and chance and bias can be ruled out with reasonable confidence.

Limited evidence for the efficacy and effectiveness of a cancer-preventive activity will apply when screening interventions by a defined procedure are associated with a reduction in mortality from the cancer and/or a reduction in the incidence of invasive cancer, or a reduction in the incidence of clinically advanced cancer, but bias or confounding cannot be ruled out with reasonable confidence as alternative explanations for these associations.

Inadequate evidence for the efficacy and effectiveness of a cancer-preventive activity will apply when data are lacking, or when the available information is insufficient or too heterogeneous to allow an evaluation.

Special Communication

Breast Cancer Screening for Women at Average Risk
2015 Guideline Update From the American Cancer Society

Kevin C. Oeffinger, MD; Elizabeth T. H. Fontham, MPH, DrPH; Ruth Etzioni, PhD; Abbe Herzig, PhD; James S. Michaelson, PhD; Ya-Chen Tina Shih, PhD; Louise C. Walter, MD; Timothy R. Church, PhD; Christopher R. Flowers, MD, MS; Samuel J. LaMonte, MD; Andrew M. D. Wolf, MD; Carol DeSantis, MPH; Joannie Lortet-Tieulent, MSc; Kimberly Andrews; Deana Manassaram-Baptiste, PhD; Debbie Saslow, PhD; Robert A. Smith, PhD; Otis W. Brawley, MD; Richard Wender, MD

JAMA October 20, 2015 Volume 314, Number 15

Box 2. American Cancer Society Guideline for Breast Cancer Screening, 2015

These recommendations represent guidance from the American Cancer Society (ACS) for women at average risk of breast cancer: women without a personal history of breast cancer, a suspected or confirmed genetic mutation known to increase risk of breast cancer (eg, *BRCA*), or a history of previous radiotherapy to the chest at a young age.

The ACS recommends that all women should become familiar with the potential benefits, limitations, and harms associated with breast cancer screening.

Recommendations[a]

1. Women with an average risk of breast cancer should undergo regular screening mammography starting at age 45 years. (*Strong Recommendation*)
   1a. Women aged 45 to 54 years should be screened annually. *(Qualified Recommendation)*
   1b. Women 55 years and older should transition to biennial screening or have the opportunity to continue screening annually. *(Qualified Recommendation)*
   1c. Women should have the opportunity to begin annual screening between the ages of 40 and 44 years. *(Qualified Recommendation)*
2. Women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer. *(Qualified Recommendation)*
3. The ACS does not recommend clinical breast examination for breast cancer screening among average-risk women at any age. *(Qualified Recommendation)*

[a] A strong recommendation conveys the consensus that the benefits of adherence to that intervention outweigh the undesirable effects that may result from screening. Qualified recommendations indicate there is clear evidence of benefit of screening but less certainty about the balance of benefits and harms, or about patients' values and preferences, which could lead to different decisions about screening.[12,13]

In 2011, the ACS incorporated standards recommended by the Institute of Medicine into its guidelines development protocol to ensure a more trustworthy, transparent, and consistent process for developing and communicating guidelines.

The Process

The ACS organized an **interdisciplinary guideline development group** (GDG) consisting of clinicians (n = 4), biostatisticians (n = 2), epidemiologists (n = 2),an economist (n = 1),and patient representatives (n = 2).

The GDG developed 5 key questions using the general approach of specifying populations, interventions, comparisons, outcomes, timing of outcomes, and settings (PICOTS) for each question.

After evaluating available methods to grade the evidence and the strength of recommendations, the GDG selected the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system.

The GDG deliberations on the evidence and framing of the recommendations were guided by the GRADE domains:

- the balance between desirable and undesirable outcomes,
- the diversity in women's values and preferences,
- confidence in the magnitude of the effects on outcomes

The ACS GDG selected the Duke University Evidence Synthesis Group to conduct an independent systematic evidence review of the breast cancer screening literature, after a response to a request for proposals.

The GDG members voted on agreement or disagreement with each recommendation and on the strength of recommendation.

The panel attempted to achieve100% agreement whenever possible, but a three-quarters majority was considered acceptable

26 relevant outside organizations and 22 expert advisors were invited to participate in an external review of the guideline.

All participants in the guideline development process were required to disclose all financial and nonfinancial (personal, intellectual, practice-related) relationships and activities that might be perceived as posing a conflict of interest in development of the breast cancer screening guidelines

The Systematic Evidence Review

New meta-analyses of the RCTs would not be useful. Recent meta-analyses results could be used to estimate efficacy associated with screening but not to estimate effectiveness.

The GDG considered that it was preferable to estimate benefits and harms of screening using contemporary data from which exposure to screening can be ascertained; observational studies, especially population-based studies of service screening derived from large national databases (published since 2000 that included 1000 or more average-risk women), were included.

Table 2. Critical and Important Outcomes of Screening Mammography and Clinical Breast Examination (CBE) in the Systematic Evidence Review

	Definition
Critical Outcomes	
Breast cancer mortality	Breast cancer deaths prevented by screening
Quality of life	Quality-adjusted life-years gained by screening
Life expectancy	Life-years gained by screening
False-positive findings	Recall for additional testing (imaging and/or biopsy) after abnormal CBE or mammography, in which further evaluation determines that the initial abnormal finding was not cancer
Overdiagnosis	Screen-detected cancers that would not have led to symptomatic breast cancer if undetected by screening
Overtreatment	Cancer therapies (surgery, radiation, chemotherapy) performed for screen-detected cancers that would not have led to symptomatic breast cancer if undetected by screening
Important but Not Critical Outcomes	
Breast cancer stage	Tumor characteristics at diagnosis (including stage, tumor size, and nodal status)
Short- and long-term emotional effects	Anxiety, depression, quality of life associated with positive results (ie, true and false positives)

2015 Guideline Update From the American Cancer Society *JAMA*. 2015;314(15):1599-1614

For each outcome considered for every key question, the strength of the overall body of evidence across all included study designs was rated, with consideration of risk of bias, consistency, directness, and precision, as well as strength of association (magnitude of effect).

Results from meta-analyses were used when evaluating consistency, precision, and strength of association.

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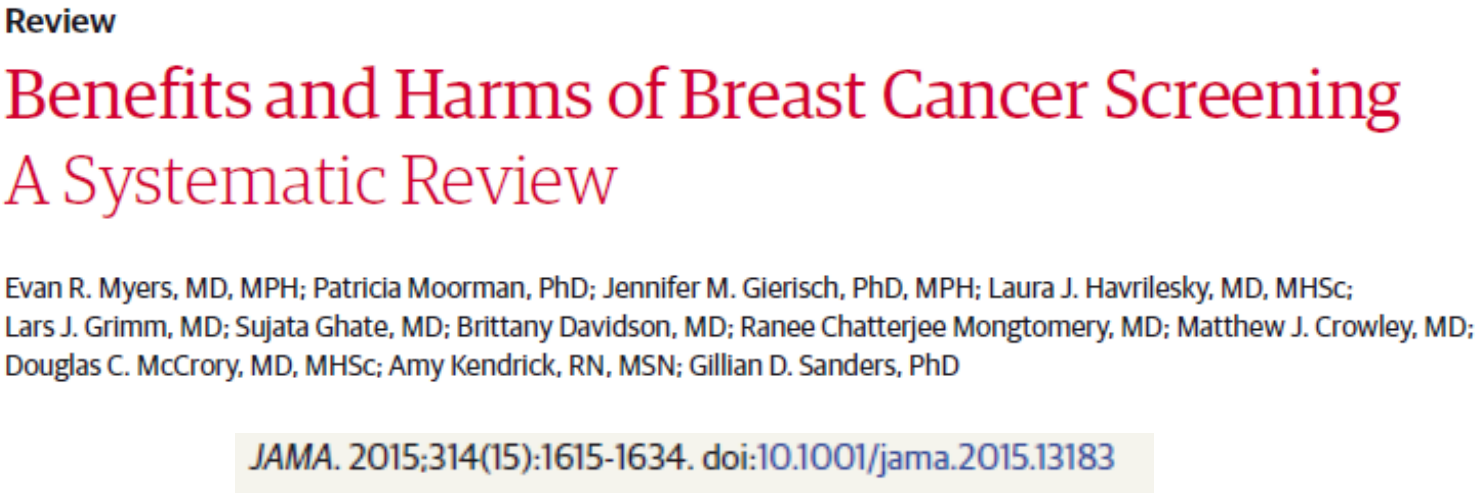
The evidence summary and a detailed description of the evidence review methodology



Review

Benefits and Harms of Breast Cancer Screening
A Systematic Review

Evan R. Myers, MD, MPH; Patricia Moorman, PhD; Jennifer M. Gierisch, PhD, MPH; Laura J. Havrilesky, MD, MHSc; Lars J. Grimm, MD; Sujata Ghate, MD; Brittany Davidson, MD; Ranee Chatterjee Mongtomery, MD; Matthew J. Crowley, MD; Douglas C. McCrory, MD, MHSc; Amy Kendrick, RN, MSN; Gillian D. Sanders, PhD

JAMA. 2015;314(15):1615-1634. doi:10.1001/jama.2015.13183

Table 1. Summary of Available Evidence on Critical Outcomes by Key Question

Outcome	Study Design and No. of Studies Within Each Design Category	Individual Study Level Quality: No. of Studies With Each Quality Rating[a]	Overall Evidence Quality[b]		Comment
			Direction of Association	Magnitude of Association	
Key Question 1: Mammography vs No Mammography					
Breast cancer mortality (see Table 2 for details)	RCTs 4 meta-analyses 10 individual studies	High: 8 Moderate: 2	High	Moderate	Limited direct evidence applicable to current US practice
	Observational 3 meta-analyses 22 cohort studies 13 case-control	Moderate: 18 Low: 17	High	Moderate	More biased study designs found greater mortality reduction
	Modeling 1 study	High	Moderate	Moderate	Indirect evidence
Overdiagnosis (see Table 3 for details)	RCTs 2 meta-analyses 8 individual studies	Low: 8	Low	Very low	Substantial variability based on definitions, methods—no consensus method to judge quality
	Observational 17 cohort studies	Low: 17	Low	Very low	Substantial variability based on definitions, methods—no consensus method to judge quality
False-positive biopsy (see Table 4 for details)	Observational 1 pooled analysis of 20 European programs 2 cohort studies from US	Moderate: 3	High	Moderate (10-y cumulative probability after beginning screening)	Direct evidence
	Modeling 1 study	High	Low	Low (lifetime cumulative probability after beginning screening)	Indirect evidence
Life expectancy (see Table 5 for details)	Unadjusted Modeling 1 study	High	Low	Low	Indirect evidence
	Quality adjusted modeling 1 study	High	Low	Low	

Abbbreviation: RCT, randomized clinical trial.

[a] Indicates number of individual studies rated as high, moderate, low, or very low quality using Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria based on risk of bias (eAppendix 1 in the Supplement); all individual studies included in the meta-analyses are also counted as individual studies.

[b] Indicates assessment of overall evidence quality across all studies, using same GRADE rating of high, moderate, low, or very low, based on risk of bias, consistency, directness of measure of outcome or setting, and precision. "Direction of association" refers to estimates of qualitative association between screening and overall reduction or increase in probability of each outcome; "magnitude of association" refers to quantitative estimates of reduction or increase in probability.

Table 1. Summary of Available Evidence on Critical Outcomes by Key Question

Outcome	Study Design and No. of Studies Within Each Design Category	Individual Study Level Quality: No. of Studies With Each Quality Rating[a]	Overall Evidence Quality[b]		Comment
			Direction of Association	Magnitude of Association	
Key Question 2: Screening Interval for Mammography					
Breast cancer mortality (see Table 2 for details)	RCTs 1 meta-analysis 7 individual studies	High: 7	Moderate	Low	No direct comparisons within RCTs
	Observational 2 cohort	Low: 2	Low	Low	
	Modeling 1 study	High	Moderate	Low	Indirect evidence
Overdiagnosis (see Table 3 for details)	Observational 1 cohort	Moderate	Low	Low	Direction of effect varied by patient characteristics
	Modeling 1 study	High	Low	Very low	Quantitative effects not presented
False-positive biopsy (see Table 4 for details)	Observational 5 cohort	Moderate: 5	Moderate	Moderate (10-y cumulative probability after beginning screening)	Direct estimates
	Modeling 1 study	High	Low	Very low (lifetime cumulative probability after beginning screening)	Indirect evidence
Life expectancy (see Table 5 for details)	Unadjusted modeling 1 study	High	Low	Low	Indirect evidence
	Quality adjusted modeling 1 study	High	Low	Low	

Abbbreviation: RCT, randomized clinical trial.

[a] Indicates number of individual studies rated as high, moderate, low, or very low quality using Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria based on risk of bias (eAppendix 1 in the Supplement); all individual studies included in the meta-analyses are also counted as individual studies.

[b] Indicates assessment of overall evidence quality across all studies, using same GRADE rating of high, moderate, low, or very low, based on risk of bias, consistency, directness of measure of outcome or setting, and precision. "Direction of association" refers to estimates of qualitative association between screening and overall reduction or increase in probability of each outcome; "magnitude of association" refers to quantitative estimates of reduction or increase in probability.

Table 1. Summary of Available Evidence on Critical Outcomes by Key Question

Outcome	Study Design and No. of Studies Within Each Design Category	Individual Study Level Quality: No. of Studies With Each Quality Rating[a]	Overall Evidence Quality[b]		Comment
			Direction of Association	Magnitude of Association	
Key Question 3: Clinical Breast Examination With or Without Mammography					
Breast cancer mortality (see Table 6 for details)	1 1 case-control	RCT—low quality for outcome Case-control—low quality for outcome	Very low	Very low	No direct evidence on breast cancer mortality
Overdiagnosis	0				
False-positive biopsy (see Table 6 for details)	2 RCTs 3 cohort	RCT—low quality for outcome (primarily due to setting) Cohort-moderate	Moderate	Low	Cohort studies provide direct estimates of overall false positives
Life expectancy	0				

Abbbreviation: RCT, randomized clinical trial.

[a] Indicates number of individual studies rated as high, moderate, low, or very low quality using Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria based on risk of bias (eAppendix 1 in the Supplement); all individual studies included in the meta-analyses are also counted as individual studies.

[b] Indicates assessment of overall evidence quality across all studies, using same GRADE rating of high, moderate, low, or very low, based on risk of bias, consistency, directness of measure of outcome or setting, and precision. "Direction of association" refers to estimates of qualitative association between screening and overall reduction or increase in probability of each outcome; "magnitude of association" refers to quantitative estimates of reduction or increase in probability.

Findings

Across all ages of women at average risk, pooled estimates of association between mammography screening and mortality reduction after 13 years of follow-up were similar for 3 meta-analyses of clinical trials (UK Independent Panel: relative risk [RR], 0.80 [95%CI, 0.73- 0.89]; Canadian Task Force: RR, 0.82 [95%CI, 0.74-0.94]; Cochrane: RR, 0.81 [95%CI, 0.74- 0.87]); were greater in a meta-analysis of cohort studies (RR, 0.75 [95%CI, 0.69 to 0.81]); and were comparable in a modeling study (CISNET; median RR equivalent among 7 models, 0.85 [range, 0.77-0.93]).

Uncertainty remains about the magnitude of associated mortality reduction in the entire US population, among women 40 to 49 years, and with annual screening compared with biennial screening.

There is uncertainty about the magnitude of overdiagnosis associated with different screening strategies, attributable in part to lack of consensus on methods of estimation and the importance of ductal carcinoma in situ in overdiagnosis.

Findings

For women with a first mammography screening at age 40 years, estimated 10-year cumulative risk of a false-positive biopsy result was higher (7.0%[95%CI, 6.1%-7.8%]) for annual compared with biennial (4.8%[95%CI, 4.4%-5.2%]) screening.

Evidence for the relationship between screening and life expectancy and quality-adjusted life expectancy was low in quality.

There was no direct evidence for any additional mortality benefit associated with the addition of CBE to mammography, but observational evidence from the United States and Canada suggested an increase in false-positive findings compared with mammography alone, with both studies finding an estimated 55 additional false-positive findings per extra breast cancer detected with the addition of CBE.

Systematic review: AMSTAR checklist. This is a checklist which assesses the quality of conduct of a systematic review (Shea, 2007)

'a priori' design provided in a protocol**:**
duplicate study selection
duplicate data extraction
comprehensive literature search
status of publication not used as an inclusion criterion
list of studies (included and excluded) provided
characteristics of the included studies provided
scientific quality of the included studies assessed and documented
scientific quality of the included studies used in formulating conclusions
methods used to combine the findings of studies appropriate
likelihood of publication bias assessed
the conflict of interest included

Yes to every question:

high quality sistematic review

Supplementary Analyses and Evidence-I

To address the question of age to begin and to stop screening, the GDG examined: age specific incidence, mortality, age-specific incidence-based mortality, and years of potential life lost.

Table 4. Distribution of Female Population Size, 5-Year Absolute Breast Cancer Risk, and Age-Specific Breast Cancer Incidence Rates by Age

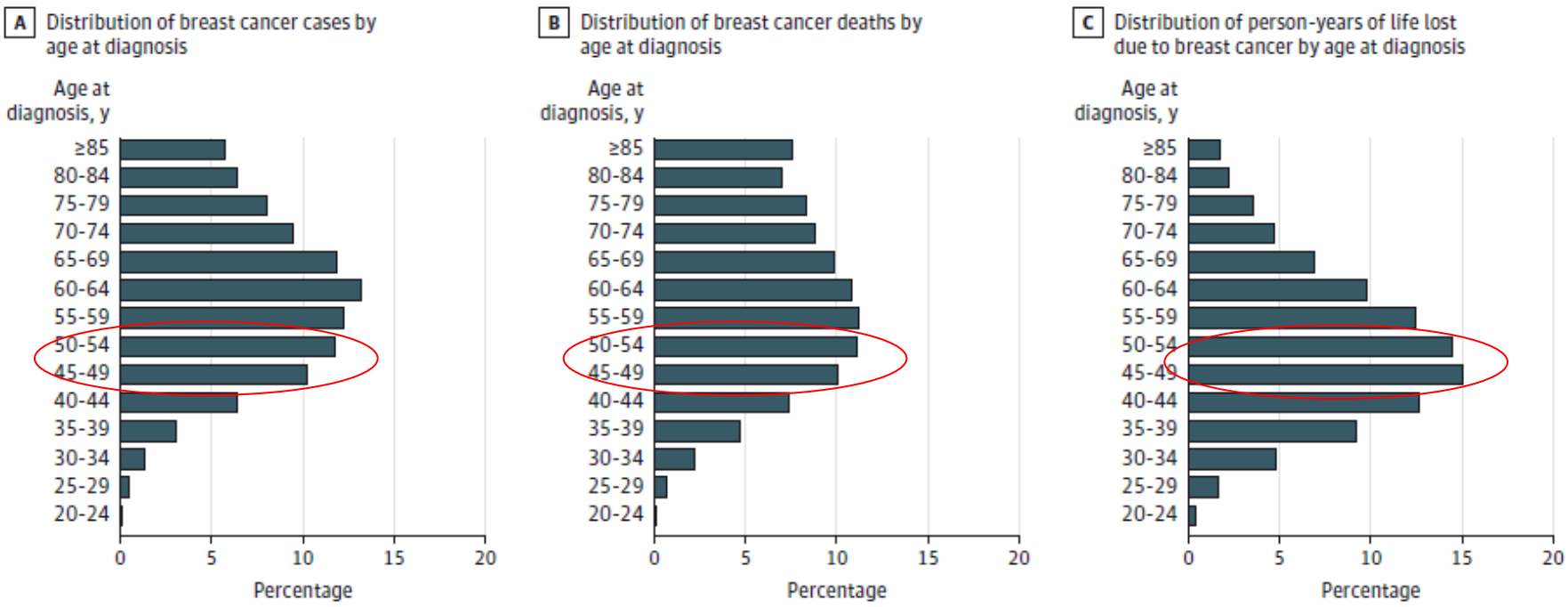
Age, y	2011 Population Size (in 1000s)[a]	5-Year Absolute Breast Cancer Risk, 2009-2011, %[b]	Breast Cancer Incidence Rate per 100 000 Population, 2007-2011[b]
30-34	10 232	0.1	26.8
35-39	9837	0.3	59.5
40-44	10 576	0.6	122.5
45-49	11 211	0.9	188.6
50-54	11 499	1.1	224.0
55-59	10 444	1.3	266.4
60-64	9271	1.6	346.7
65-69	6806	2.0	420.2
70-74	5204	2.1	433.8
75-79	4155	2.0	443.3
80-84	3444	1.9	420.6
≥85	3826	2.5	354.4

[a] Source: Populations: Total US [Katrina/Rita Adjustment], 1969-2011 Counties. National Cancer Institute, Division of Cancer Control and Population Sciences, Surveillance Research Program, Surveillance Systems Branch. Released October 2012.

[b] Source: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 18 registries, National Cancer Institute.

The 5-year risk among women aged 45 to 49 years (0.9%) and women aged 50 to 54 years (1.1%) is similar, and greater than that for women aged 40 to 44 years (0.6%)

Figure 1. Breast Cancer Burden by Age at Diagnosis for the Period 2007-2011



A, Age distribution of invasive female breast cancer cases (n = 292 369). Source: Surveillance, Epidemiology, and End Results (SEER) 18 registries.
B, Distribution of breast cancer deaths by age at diagnosis (n = 16 789), with patients followed up for 20 years after diagnosis. Source: SEER 9 registries.
C, Distribution of person-years of life lost (PYLL) due to breast cancer by age at diagnosis (total = 326 560), with patients followed up for 20 years after diagnosis. Source: SEER 9 registries. The PYLL is based on the 2011 US Female Life Table.[28]

Figure 1A: the proportion of all incident breast cancers in the population is similar for ages 45-49 years and 50-54 years (10% and 12%), compared with women aged 40-44 years (6%)

Figure 1B: the distribution of breast cancer deaths by age at diagnosis (10% and 11%) is similar, compared with women aged 40-44 years (7%)

Figure 1C: the age-specific incidence-based person-years of life lost were similar for women aged 45-49 years and 50-54 years at the time of diagnosis (approximately 15%) and together accounted for 30%of all person-years of life lost at 20years of follow-up.

Supplementary Analyses and Evidence-II

In addition to the evidence review, the ACS commissioned the BCSC to update previously published analyses on the association between mammography screening intervals and tumor characteristics at diagnosis by age, menopausal status, and postmenopausal hormone use, to measure the outcomes related to screening intervals.

Multivariable analyses suggested that somewhat more favorable characteristics were associated with a shorter interval among women aged 40-49 years, but not among older women (>50 years), although the difference was not statistically significant.

Additional analyses indicated that these results likely were influenced by menopausal status.

Premenopausal women were more likely to have advanced stage (RR, 1.28; 95%CI, 1.01-1.63), larger tumor size (RR, 1.21; 95%CI, 1.07-1.37), and poor prognosis tumors at diagnosis (RR, 1.11;95%CI, 1.00-1.22) associated with a screening interval of 23 to 26 months compared with a screening interval of 11to 14 months.

The degree to which this observation is due to age, premenopausal status, or reduced sensitivity of screening in young women (or a combination of these factors) is uncertain.

Table 5. Comparison of Current and Previous American Cancer Society (ACS) Guidelines for Breast Cancer Screening in Women at Average Risk[a]

Population	Recommendations for Breast Cancer Screening[b]	
	ACS, 2015	ACS, 2003[5]
Women aged 40-44 y	Women should have the opportunity to begin annual screening between the ages of 40 and 44 years. (*Qualified Recommendation*)	Begin annual mammography screening at age 40 years.
Women aged 45-54 y	Women should undergo regular screening mammography beginning at age 45 years. (*Strong Recommendation*) Women aged 45 to 54 years should be screened annually. (*Qualified Recommendation*)	Women should have annual screening mammography.
Women aged ≥55 y	Women 55 years and older should transition to biennial screening or have the opportunity to continue screening annually. (*Qualified Recommendation*)	Women should have annual screening mammography.
	Women should continue screening mammography as long as their overall health is good and they have a life expectancy of 10 years or longer. (*Qualified Recommendation*)	As long as a woman is in reasonably good health and would be a candidate for treatment, she should continue to be screened with mammography.
All women	Clinical breast examination is not recommended for breast cancer screening among average-risk women at any age. (*Qualified Recommendation*)	For women in their 20s and 30s, it is recommended that clinical breast examination be part of a periodic health examination, preferably at least every 3 years. Asymptomatic women 40 years and older should continue to receive a clinical breast examination as part of a periodic health examination, preferably annually.
	All women should become familiar with the potential benefits, limitations, and harms associated with breast cancer screening.	Women should have an opportunity to become informed about the benefits, limitations, and potential harms associated with regular screening.

2015 Guideline Update From the American Cancer Society *JAMA*. 2015;314(15):1599-1614

The GDG chose to more carefully examine the evidence on disease burden and the efficacy and effectiveness of screening in narrower age groups, with particular emphasis on the age range (40-55 years) for which disagreements about the age to begin screening and the screening interval have persisted over the past several decades.

There also was greater scrutiny of the evidence on harms.

The GDG also judged women's values and preferences as having a more important role in decisions where the balance of absolute benefits and harms is less certain.

In this update, the absence of clear evidence that CBE contributed significantly to breast cancer detection prior to or after age 40 years led the GDG to conclude that it could no longer be recommended for average-risk women at any age.

European Code against Cancer, 4th Edition: Cancer screening☆

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"12. Take part in organized cancer screening programmes for:

- Bowel cancer (men and women)
- Breast cancer (women)
- Cervical cancer (women)."

Mammographic screening

Breast cancer screening:

- women starting at age 50 years and not before age of 40 years,
- and from then on, every 2 years until age 70–75 years.

European Code against Cancer 4th Edition: Process of reviewing the scientific evidence and revising the recommendations☆

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Cancer Epidemiology 39S (2015) S139–S152

The Code aims to provide information on medical interventions that, if followed, reduce the risk of developing or dying from specific cancers.

The supporting evidence for interventions requires evaluation of the efficacy and effectiveness of such defined actions.

Like any health intervention, preventive interventions may also have harmful effects.

Therefore, careful consideration is given to the balance between the potential benefit and the potential harm before an intervention can be recommended.

Working Groups (WGs) of independent scientific experts in different fields of cancer research and prevention were appointed by the European Code Against Cancer scientific secretariat at the International Agency for Research on Cancer (IARC).

In order to update the previous version of the European Code against Cancer by formulating evidence-based recommendations, a systematic search of the literature was performed according to the methodology agreed by the Working Groups (WGs) involved in the project

Methods

A literature group composed of experts in systematic reviews was appointed to identify and assess the scientific literature relevant for the Code, adopting the following process

The Screening WG defined clinical questions according to the PICOS (population, intervention, control, outcome, study design) methodology

Systematic bibliographic searches were performed on the Cochrane Library, Medline, Embase, and PsycINFO from January 1st 2000 to January 31st 2013. Articles suggested by experts in the field were also considered. If a large amount of literature for a given topic was retrieved, preference was given in the first instance to recently published (since 2007) systematic reviews.

If updated systematic reviews addressing the PICOS questions were retrieved, the search for primary studies was limited to those studies published after the last search date of the most recently published systematic review.

The methodological quality of retrieved systematic reviews and primary studies was assessed using criteria extracted from published and validated checklists.

For each clinical questions, evidence tables and summary documents with the most relevant clinical information and the level of evidence were prepared.

Finally, the evidence collected was presented and discussed within the Screening WG. Recommendations were made based on consensus agreement obtained within the group.

The evidence was graded according to the levels reported.

Table 1
Grading of levels of evidence.

Level	Type of studies retrieved
I	Multiple randomized controlled trials (RCTs) of reasonable sample size, or their systematic reviews (SRs)
II	One RCT of reasonable sample size, or three or fewer RCTs with small sample size
III	Prospective or retrospective cohort studies or their SRs; diagnostic cross-sectional accuracy studies or their SRs
IV	Retrospective case–control studies or their SRs; time series analysis
V	Case series; before–after studies without a control group, cross-sectional surveys
VI	Expert opinion

Note: when results on side effects and/or benefits were derived from observational studies nested in RCTs, the level of evidence was not reported.

3.2.2.1. Effectiveness. Is mammography screening effective in reducing breast cancer mortality in the general female population at average risk of breast cancer?

Three meta-analyses of RCTs [84–86] found a statistically significant reduction in breast cancer mortality when women of all age ranges between 40 and 74 were considered together (RR, 0.81; 95%CI: 0.74–0.87, nine trials included [84]; RR, 0.82; 95%CI: 0.74–0.91, nine trials included [85]; RR, 0.80; 95%CI: 0.73–0.89, nine trials included [86]). Different meta-analyses include different trials, durations of follow-up, and definitions of outcome. Nevertheless, there is general agreement in their estimates of an approximate 20% reduction in relative risk of breast cancer mortality from invitation to screening (level of evidence: I).

Results from observational studies considering women invited to screening (intention-to-treat analysis) pooled in meta-analyses confirmed the effectiveness of screening in reducing breast cancer mortality [87,88]. The pooled mortality reduction among invited women in seven incidence-based mortality studies was 25% (RR, 0.75, 95%CI: 0.69–0.81), and in seven case–control studies it was 31% (OR, 0.69; 95%CI: 0.57–0.83) [87]. When only women who actually received mammography screening were included in the analysis (per-protocol analysis), the estimate of mortality reduction was significantly higher. Among those actually screened, the pooled mortality reduction in the incidence-based mortality studies was 38% (RR, 0.62; 95%CI: 0.56–0.69) and in the case–control studies it was 48% (OR, 0.52, 95%CI: 0.42–0.65), when adjusted for self-selection [87]. When trend studies were considered, 12 of the 17 trend studies retrieved by Broeders et al. [87] quantified the impact of population-based screening on breast cancer mortality. The estimated reductions in breast cancer mortality ranged from 1% to 9% per year in studies reporting an annual percentage change, and from 28% to 36% in those comparing post- and pre-screening periods over study time periods ranging from 15 to 30 years. [87] (level of evidence: III–IV).

GRUPPI DI ETA' E INTERVALLI DI SCREENING

PICOS: la fascia d'età ottimale in cui effettuare la mammografia di screening per il carcinoma mammario, e qual è l'intervallo di tempo ottimale per tale screening?

•Tutte le meta-analisi sia di RCT sia di studi osservazionali sull'invito allo screening mammografico hanno rilevato una **riduzione statisticamente significativa nella mortalità per carcinoma mammario, considerando tutti i gruppi di età compresi nella fascia 40-74 anni** - LIVELLO DI EVIDENZA: I–III

•La riduzione è stata **maggiore per la fascia d'età 60-69 anni** – LIVELLO DI EVIDENZA: I

•Per i gruppi d'età **40–49 e 50–59**, la riduzione della mortalità si è mostrata **statisticamente significativa anche se in misura minore** che per la fascia 40-74 anni– LIVELLO DI EVIDENZA: I

•Per le donne di età **70–74** anni, i risultati indicanti una riduzione nella mortalità per carcinoma mammario si sono mostrati al limite della significatività statistica - LIVELLO DI EVIDENZA: I

Armaroli et al, 2015

From available evidence from RCTs on breast cancer mortality, when considering the age range 40–49 years, one RCT estimated a significant reduction in mortality for an interval <24 months. For the age range 50–69 years, a significant reduction in mortality was observed for an interval of 24–33 months, and for the age ranges from 39–69 when the interval was <24 months [85] (level of evidence: I–II).

- What are the other benefits, for example in terms of life years gained, reduced risk of mastectomy, rate of cure, incidence rates of advanced cancer, of mammography screening?

- What is the frequency of mastectomy and breast-conserving surgery for women after mammographic breast cancer screening?
- What is the risk of overdiagnosis in the screening process (by age range) within a population-based programme or with opportunistic screening?
- What is the (cumulative) rate of false positive in the screening age period (by age range)?
- What about the other harms/negative side/adverse effects (e.g. radiation, psychological effects, overtreatment) of mammography screening within a population-based programme or with opportunistic screening?
- What is the risk of radiation-induced breast cancer in women at average risk undergoing mammographic screening?

Systematic review: AMSTAR checklist. This is a checklist which assesses the quality of conduct of a systematic review (Shea, 2007)

'a priori' design provided in a protocol**:**
duplicate study selection
duplicate data extraction
comprehensive literature search
status of publication not used as an inclusion criterion
list of studies (included and excluded) provided
characteristics of the included studies provided
scientific quality of the included studies assessed and documented
scientific quality of the included studies used in formulating conclusions
methods used to combine the findings of studies appropriate
likelihood of publication bias assessed
the conflict of interest included

Yes to every question:

high quality sistematic review

Annals of Internal Medicine

CLINICAL GUIDELINE

Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement

Albert L. Siu, MD, MSPH, on behalf of the U.S. Preventive Services Task Force*

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Recommendations: The USPSTF recommends biennial screening mammography for women aged 50 to 74 years. (B recommendation)

The decision to start screening mammography in women prior to age 50 years should be an individual one. Women who place a higher value on the potential benefit than the potential harms may choose to begin biennial screening between the ages of 40 and 49 years. (C recommendation)

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening mammography in women aged 75 years or older. (I statement)

The USPSTF concludes that the current evidence is insufficient to assess the benefits and harms of digital breast tomosynthesis (DBT) as a primary screening method for breast cancer. (I statement)

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of adjunctive screening for breast cancer using breast ultrasonography, magnetic resonance imaging (MRI), DBT, or other methods in women identified to have dense breasts on an otherwise negative screening mammogram. (I statement)

Appendix Table 1. What the USPSTF Grades Mean and Suggestions for Practice

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer/provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer/provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer/provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

These recommendations apply to asymptomatic women aged 40 years or older who do not have pre-existing breast cancer or a previously diagnosed high-risk breast lesion and who are not at high risk for breast cancer because of a known underlying genetic mutation (such as a *BRCA1* or *BRCA2* gene mutation or other familial breast cancer syndrome) or a history of chest radiation at a young age.

Methods: The USPSTF reviewed the evidence on the following: effectiveness of breast cancer screening in reducing breast cancer–specific and all-cause mortality, as well as the incidence of advanced breast cancer and treatment-related morbidity; harms of breast cancer screening; test performance characteristics of digital breast tomosynthesis as a primary screening strategy; and adjunctive screening in women with increased breast density. In addition, the USPSTF reviewed comparative decision models on optimal starting and stopping ages and intervals for screening mammography; how breast density, breast cancer risk, and comorbidity level affect the balance of benefit and harms of screening mammography; and the number of radiation-induced breast cancer cases and deaths associated with different screening mammography strategies over the course of a woman's lifetime.

REVIEW

Annals of Internal Medicine

Effectiveness of Breast Cancer Screening: Systematic Review and Meta-analysis to Update the 2009 U.S. Preventive Services Task Force Recommendation

Heidi D. Nelson, MD, MPH; Rochelle Fu, PhD; Amy Cantor, MD, MPH; Miranda Pappas, MA; Monica Daeges, BA; and Linda Humphrey, MD, MPH

REVIEW

Annals of Internal Medicine

Harms of Breast Cancer Screening: Systematic Review to Update the 2009 U.S. Preventive Services Task Force Recommendation

Heidi D. Nelson, MD, MPH; Miranda Pappas, MA; Amy Cantor, MD, MPH; Jessica Griffin, MS; Monica Daeges, BA; and Linda Humphrey, MD, MPH

Systematic review: AMSTAR checklist. This is a checklist which assesses the quality of conduct of a systematic review (Shea, 2007)

'a priori' design provided in a protocol**:**
duplicate study selection
duplicate data extraction
comprehensive literature search
status of publication not used as an inclusion criterion
list of studies (included and excluded) provided
characteristics of the included studies provided
scientific quality of the included studies assessed and documented
scientific quality of the included studies used in formulating conclusions
methods used to combine the findings of studies appropriate
likelihood of publication bias assessed
the conflict of interest included

Yes to every question:

high quality sistematic review

Key questions:
For women aged ≥40 years older*:
1. What is the effectiveness of routine mammography screening in reducing breast cancer–specific and all-cause mortality, and how does it differ by age, risk factor†, and screening interval?
2. What is the effectiveness of routine mammography screening in reducing the incidence of advanced breast cancer and treatment-related morbidity‡, and how does it differ by age, risk factor†, and screening interval?
3. How does the effectiveness of routine breast cancer screening in reducing breast cancer–specific and all-cause mortality vary by different screening modality§?
4. How does the effectiveness of routine breast cancer screening in reducing the incidence of advanced breast cancer and treatment-related morbidity‡ vary by different screening modality§?

* Excludes women with preexisting breast cancer; clinically significant *BRCA1* or *BRCA2* mutations, Li-Fraumeni syndrome, Cowden syndrome, hereditary diffuse gastric cancer, or other familial breast cancer syndromes; high-risk lesions (ductal carcinoma in situ, lobular carcinoma in situ, atypical ductal hyperplasia, atypical lobular hyperplasia); or previous large doses of chest radiation (≥20 Gy) before age 30 y.
† Risk factors include family history; breast density; race/ethnicity; menopausal status; current use of menopausal hormone therapy or oral contraceptives; prior benign breast biopsy; and, for women aged >50 y, body mass index.
‡ Morbidity includes physical adverse effects of treatment, quality-of-life measures, and other measures of impairment.
§ Screening modalities include mammography (film, digital, tomosynthesis), magnetic resonance imaging, ultrasonography, and clinical breast examination (alone or in combination).

Included randomized, controlled trials (RCTs); observational studies of screening cohorts; and systematic reviews that compared outcomes of women exposed to screening versus not screening.

Several meta-analyses were conducted to determine more precise summary estimates when adequate data were reported by trials rated as fair- or good-quality.

We assessed the aggregate internal validity (quality) of the body of evidence for each key question as good, fair, or poor by using methods developed by the USPSTF that are based on the number, quality, and size of studies; consistency of results between studies; and directness of evidence

Table 2. Summary of Evidence: Effectiveness of Breast Cancer Screening

Previous USPSTF Reviews	Studies in Update	Overall Quality	Limitations
Effectiveness of screening in reducing breast cancer–specific and all-cause mortality: differences by age, risk factors, and screening intervals			
Mammography screening reduced breast cancer mortality in RCTs for women aged 39–49 y (RR, 0.85 [95% CrI, 0.75–0.96]; 8 trials), those aged 50–59 y (RR, 0.86 [CrI, 0.75–0.99]; 6 trials), and those aged 60–69 y (0.68 [CrI, 0.54–0.87]; 2 trials); data were limited for women aged 70–74 y	3 RCTs provided updated data in addition to 5 previously published RCTs; 65 observational studies (57 included in 4 systematic reviews, plus 8 additional studies)	Fair	Trials have methodological limitations Observational studies used various methods that introduce potential bias

Consistency	Applicability	Summary of Findings
Results are consistent across types of studies	Most studies were conducted in Europe RCTs were based on technologies and treatments that have changed over time	Breast cancer mortality is generally reduced with mammography screening, although results of RCTs varied by age: 39–49 y (RR, 0.92 [95% CI, 0.75–1.02]; 9 trials), 50–59 y (RR, 0.86 [CI, 0.68–0.97]; 7 trials), and 60–69 y (RR, 0.67 [CI, 0.54–0.83]; 5 trials); data were limited for women aged 70–74 y Meta-analyses of observational studies indicated 25%–31% reduction in breast cancer mortality for women aged 50–69 y invited to screening Two observational studies of women in their 40s indicated 26%–44% reduction in breast cancer mortality All-cause mortality was not reduced with screening for any age Studies of risk factors and screening intervals were not available or were methodologically limited

BCSC = Breast Cancer Surveillance Consortium; CBE = clinical breast examination; CrI = credible interval; NA = not applicable; RCT = randomized, controlled trial; RR = relative risk; USPSTF = U.S. Preventive Services Task Force.

Previous USPSTF Reviews	Studies in Update	Overall Quality	Limitations
Effectiveness of screening in reducing the incidence of advanced breast cancer and treatment-related morbidity: differences by age, risk factors, and screening intervals			
Not included	5 RCTs of screening and cancer stage; 1 Cochrane review of 5 RCTs of treatment; 1 RCT of intervals; 14 observational studies	Poor (observational studies) to fair (RCTs)	Definitions of advanced breast cancer were heterogeneous Observational studies were not designed to determine effectiveness

Consistency	Applicability	Summary of Findings
Results are consistent across types of studies	Most trials were conducted in Europe RCTs were based on technologies and treatments that have changed over time	Mammography screening reduced cancer stage for women aged ≥50 y (RR, 0.62 [CI, 0.46–0.83]; 3 trials), but not for those aged 39–49 y Women randomly assigned to screening had more mastectomies, lumpectomies, and radiation therapy, and less hormone therapy, than controls Observational studies were inconclusive Studies of risk factors and screening intervals were not available or were methodologically limited

BCSC = Breast Cancer Surveillance Consortium; CBE = clinical breast examination; CrI = credible interval; NA = not applicable; RCT = randomized, controlled trial; RR = relative risk; USPSTF = U.S. Preventive Services Task Force.

Previous USPSTF Reviews	Studies in Update	Overall Quality	Limitations
Effectiveness of screening in reducing breast cancer–specific and all-cause mortality by screening modality			
Not included	No studies evaluated this question	NA	NA
Effectiveness of screening in reducing the incidence of advanced breast cancer and treatment-related morbidity by screening modality			
Not included	2 observational studies	Poor	No RCTs; comparability of groups not known

Consistency	Applicability	Summary of Findings
NA	NA	NA
Results are consistent	High clinical relevance	No differences in cancer size or node status between screening with mammography alone vs. mammography and tomosynthesis

BCSC = Breast Cancer Surveillance Consortium; CBE = clinical breast examination; CrI = credible interval; NA = not applicable; RCT = randomized, controlled trial; RR = relative risk; USPSTF = U.S. Preventive Services Task Force.

Key Questions:

For women aged ≥40 y*:

1. **What are the harms† of routine mammography screening, and how do they differ by age, risk factor‡, and screening interval?**
2. **How do the harms† of routine breast cancer screening vary by screening modality§?**

* Excludes women with preexisting breast cancer; clinically significant *BRCA1* or *BRCA2* mutations, Li-Fraumeni syndrome, Cowden syndrome, hereditary diffuse gastric cancer, or other familial breast cancer syndrome; high-risk lesions (ductal carcinoma in situ, lobular carcinoma in situ, atypical ductal hyperplasia, or atypical lobular hyperplasia); or previous large doses of chest radiation (≥20 Gy) before age 30 y.

† False-positive and false-negative mammography results, biopsy recommendations due to false-positive mammography results, overdiagnosis and resulting overtreatment, anxiety, pain, and radiation exposure.

‡ Family history; breast density; race/ethnicity; menopausal status; current use of menopausal hormone therapy or oral contraceptives; prior benign breast biopsy; and, for women aged >50 y, body mass index.

§ Mammography (film, digital, or tomosynthesis), magnetic resonance imaging, ultrasonography, and clinical breast examination (alone or in combination).

Included recently published systematic reviews; randomized, controlled trials (RCTs); and observational studies of prespecified harms. When available, studies providing outcomes specific to age, risk factors, screening intervals, and screening modalities

Studies meeting criteria for high quality and with designs ranked higher in the study design–based hierarchy of evidence were emphasized because they are less susceptible to bias (for example, RCTs were chosen over observational studies).

When possible, we assessed the aggregate internal validity (quality) of the body of evidence for each key question (good, fair, or poor) by using methods developed by the USPSTF based on the number, quality, and size of studies; consistency of results between studies; and directness of evidence

Table 3. Summary of Evidence

Primary Findings From Previous USPSTF Reviews	Number and Type of Studies in Update	Overall Quality	Limitations	Consistency	Applicability	Summary of Findings
False-positive and false-negative results						
Younger women had higher rates of false-positive mammography results per screening cycle. Cumulative 10-y rates for false-positive mammography results were 49% overall and 56% for ages 40–49 y; cumulative 10-y rate of biopsies due to false-positive mammography results was 19% (based on 1 observational study).	2 observational studies of women screened in the United States	Good	Not all risk factors were examined.	Consistent	Good	10-y cumulative rates of false-positive mammography results and biopsies were higher with annual vs. biennial screening (61% vs. 42% and 7% vs. 5%, respectively) and for women with heterogeneously or extremely dense breasts, those aged 40–49 y, and those using combination hormone therapy.

Table 3. Summary of Evidence

Primary Findings From Previous USPSTF Reviews	Number and Type of Studies in Update	Overall Quality	Limitations	Consistency	Applicability	Summary of Findings
Overdiagnosis						
Estimates of overdiagnosis ranged from 0% to 50% (based on 1 systematic review and 8 studies).	1 meta-analysis of 3 trials; 1 systematic review of 13 studies; 18 individual studies	Poor	No established definition or method to determine overdiagnosis; studies were highly heterogeneous, and estimates varied depending on the analytic approach.	Inconsistent	Poor	Estimates of overdiagnosis ranged from 0% to 54% overall and from 11% to 22% in randomized trials.
Anxiety and distress						
Many women have anxiety with mammography, but it is generally transient and is not a deterrent to future screening (based on 2 systematic reviews of 77 observational studies).	2 systematic reviews of 24 studies; 10 observational studies	Fair	Studies used different outcome measures and thresholds; effects based on age, risk factors, and screening intervals were not determined.	Consistent	Fair	Women with false-positive results had more anxiety, distress, and breast cancer–specific worry than those with negative results, particularly those who had biopsies, fine-needle aspirations, and early recall; distress persisted for some women but was transient for others. Some women with false-positive results did not return for screening, although some studies showed no differences in reattendance.

Table 3. Summary of Evidence

Primary Findings From Previous USPSTF Reviews	Number and Type of Studies in Update	Overall Quality	Limitations	Consistency	Applicability	Summary of Findings
Pain						
Many women have pain with mammography, but it is generally transient and is not a deterrent to future screening (based Pain could be reduced by providing information to patients or using breast cushions (based on 1 systematic review of 7 trials of interventions to reduce pain).	1 systematic review of 20 observational studies of pain	Fair	Studies used different outcome measures and thresholds; effects based on age, risk factors, and screening intervals were not determined.	Consistent	Fair	Although many women had pain during mammography (1% to 77%), the proportion of those experiencing pain who did not attend future screening varied (11% to 46%).
Radiation exposure						
No studies	2 modeling studies of radiation exposure	Poor	No studies directly measured associations between radiation exposure from mammography screening and breast cancer incidence and death.	Consistent	Poor	Models estimated 2 to 11 deaths per 100 000 women due to radiation-induced cancer from screening with digital mammography, depending on age and screening intervals.

Primary Findings From Previous USPSTF Reviews	Number and Type of Studies in Update	Overall Quality	Limitations	Consistency	Applicability	Summary of Findings
Harms of screening, by modality						
Not included	5 observational studies of tomosynthesis and 1 of clinical breast examination combined with mammography	Poor	No randomized trials; comparability of groups was not reported; biopsy rates and outcomes were not uniformly reported.	Consistent	Fair	A U.S. study found that tomosynthesis plus mammography resulted in a decrease of 16 recalls and an increase of 1.3 biopsies per 1000 women compared with mammography alone. A Canadian study found that mammography plus clinical breast examination resulted in an increase of 55 recalls per 10 000 women compared with mammography alone.

How Often to Screen

No clinical trials compared annual mammography with a longer interval in women of any age.

Available observational evidence evaluating the effects of varying mammography intervals found no difference in the number of breast cancer deaths between women aged 50 years or older who were screened biennially versus annually

Table 4. Lifetime Benefits and Harms of Annual Versus Biennial Screening Mammography per 1000 Women Screened: Model Results Compared With No Screening*

Variable	Ages 50–74 y, Annual Screening	Ages 50–74 y, Biennial Screening
Fewer breast cancer deaths, *n*	9 (5–10)	7 (4–9)
Life-years gained	145 (104–180)	122 (75–154)
False-positive test results, *n*	1798 (1706–2445)	953 (830–1325)
Unnecessary breast biopsies, *n*	228 (219–317)	146 (121–205)
Overdiagnosed breast tumors, *n*	25 (12–68)	19 (11–34)

* Values reported are medians (ranges).

Benefit and Harms of Screening and Early Treatment

The USPSTF found adequate evidence that mammography screening reduces breast cancer mortality in women aged 40 to 74 years.

The number of breast cancer deaths averted increases with age;

women aged 40 to 49 years benefit the least and women aged 60 to 69 years benefit the most.
Direct evidence about the benefits of screening mammography in women aged 75 years or older is lacking.

The USPSTF found adequate evidence that screening for breast cancer with mammography results in harms for women aged 40 to 74 years.

The most important harm are overdiagnosis and overtreatment.
False-positive results are common and lead to unnecessary and sometimes invasive follow-up testing, with the potential for psychological harms (such as anxiety). False-negative results also occur and may provide false reassurance. Radiation-induced breast cancer and resulting death can also occur, although the number of both of these events is predicted to be low.

Benefit and Harms of Screening and Early Treatment -II

The USPSTF found inadequate evidence on the benefits and harms of DBT as a primary screening method for breast cancer.

The USPSTF found inadequate evidence on the benefits and harms of adjunctive screening for breast cancer using breast ultrasonography, MRI, DBT, or other methods in women identified to have dense breasts on an otherwise negative screening mammogram.

In both cases, while there is some information about the accuracy of these methods, there is no information on the effects of their use on health outcomes, such as breast cancer incidence, mortality, or overdiagnosis rates.

Conclusioni

- Le posizioni tra i due Oceani si avvicinano molto
- Sistematic review of the evidence of high quality
- Inclusion of observational studies in the assessment of the effectiveness
- Balance between benefit and harms
- Great attention to women <50years
- Role of women's values and preferences and informed consent

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Grazie per l'attenzione!