SPECIAL REPORT

Breast-Cancer Screening — Viewpoint of the IARC Working Group

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In November 2014, experts from 16 countries met at the International Agency for Research on Cancer (IARC) to assess the cancer-preventive and adverse effects of different methods of screening for breast cancer. (The members of the working group for volume 15 of the IARC Handbook are listed at the end of the article; affiliations are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) This update of the 2002 IARC handbook on breast-cancer screening[1] is timely for several reasons. Recent improvements in treatment outcomes for late-stage breast cancer and concerns regarding overdiagnosis call for reconsideration. The definition of what constitutes the best implementation of mammographic screening programs (e.g., which age groups should be screened and with what frequency) needs to be revisited in light of the results of recent studies. New studies on clinical breast examination and self-examination warrant the reevaluation of these screening practices, and imaging techniques other than mammography, which were not evaluated in the 2002 handbook, now warrant rigorous scientific evaluation. Finally, the screening of women at high risk for breast cancer requires a thorough reassessment, particularly in the context of the improved data that are now available on possible alternative screening methods.

In preparation for the meeting, the 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. (For details on the process used and on the evaluation criteria, see the working procedures on the IARC handbooks website.[2]) This article briefly summarizes the evaluation of the scientific evidence reviewed at the meeting (Table 1). The full report is presented in volume 15 of the IARC Handbooks of Cancer Prevention.[3]

Breast cancer is the most frequently diagnosed cause of death from cancer in women worldwide,[4,5] the second leading cause of death from cancer in women in developed countries,[4,5] and the leading cause of death from cancer in low- and middle-income countries, where a high proportion of women present with advanced disease, which leads to a poor prognosis.[6] Established risk factors for breast cancer include age, family or personal history of breast cancer or of precancerous lesions, reproductive factors, hormonal treatment, alcohol consumption, obesity (for postmenopausal breast cancer only), exposure to ionizing radiation, and genetic predisposition.[7]

Screening for breast cancer aims to reduce mortality from this cancer, as well as the morbidity associated with advanced stages of the disease, through early detection in asymptomatic women. The key to achieving the greatest potential effects from this screening is providing early access to effective diagnostic and treatment services. Comprehensive quality assurance is essential to maintaining an appropriate balance between benefits and harms.[8]

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
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
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	

Table 1. (Continued.)

Method	Strength of Evidence†
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

* For the complete evaluation statements, see International Agency for Research on Cancer[2] or the IARC Handbooks of Cancer Prevention website (http://handbooks.iarc.fr). MRI denotes magnetic resonance imaging.
† For detailed information on the evaluation criteria, see the working procedures section of the IARC Handbooks of Cancer Prevention website (http://handbooks.iarc.fr/workingprocedures/index.php).
‡ 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.
‖ An interval cancer is a cancer that develops in the interval between routine screenings for that particular cancer.

The most common means of screening women for breast cancer is standard mammography (film or digital), offered either by organized programs or through opportunistic screening. Organized screening programs are characterized by invitations to join a target population at given intervals, systematic recalls for the assessment of detected abnormalities, and delivery of test results, treatment, and follow-up care, with regular monitoring and evaluation of the program and a national or regional team responsible for service delivery and quality. Opportunistic screening typically provides screening to women on request and coincidently with routine health care.

As a consequence of the results of randomized, controlled trials that showed a reduction in breast-cancer mortality several decades ago,[1] mammographic screening has been implemented to a great extent in high-income countries and regions and less so in countries in Central and Eastern Europe, through either opportunistic or organized screening. Most countries in Latin America have national recommendations or guidelines, including those calling for mammographic screening combined with clinical breast examination and breast self-examination. In other low- and middle-income countries, breast-cancer screening is promoted primarily by advocacy groups and periodic campaigns to promote breast-cancer awareness.

In 2002, on the basis of findings from randomized, controlled trials, the previous IARC Handbook Working Group concluded that the evidence for the "efficacy of screening by mammography as the sole means of screening in reducing mortality from breast cancer" was sufficient for women 50 to 69 years of age, limited for women 40 to 49 years of age, and inadequate for women younger than 40 or older than 69 years of age.[1] We carefully reviewed the results of all available randomized, controlled trials and reaffirmed the findings from the previous evaluation of the efficacy of mammographic screening in women 50 to 69 years of age; the evidence of efficacy for women in other age groups was considered inadequate.

The working group recognized that the relevance of randomized, controlled trials conducted more than 20 years ago should be questioned, given the large-scale improvements since then in both mammographic equipment and treatments for breast cancer. More recent, high-quality observational studies were considered to provide the most robust data with which to evaluate the effectiveness of mammographic screening. The working group gave the greatest weight to cohort studies with long follow-up periods and the most robust designs, which included those that accounted for lead time, minimized temporal and geographic differences between screened and unscreened participants, and controlled for individual differences that may have been related to the primary outcome. Analyses of invitations to screenings (rather than actual attendance) were

considered to provide the strongest evidence of screening effectiveness, since they approximate the circumstances of an intention-to-treat analysis in a trial. After careful consideration of the limitations of case–control studies in the evaluation of effectiveness, these studies were also considered to provide information that was relevant to organized screening programs and to other venues, such as opportunistic screening, for which cohort data were not available. Among ecologic studies, only those that controlled for time- and treatment-related factors in design or analysis were considered to be informative.

Some 20 cohort and 20 case–control studies, all conducted in the developed world (Australia, Canada, Europe, or the United States) were considered to be informative for evaluating the effectiveness of mammographic screening programs, according to invitation or actual attendance, mostly at 2-year intervals. Most incidence-based cohort mortality studies, whether involving women invited to attend screening[9-13] or women who attended screening,[14-17] reported a clear reduction in breast-cancer mortality, although some estimates pertaining to women invited to attend were not statistically significant.[12,13] Women 50 to 69 years of age who were invited to attend mammographic screening had, on average, a 23% reduction in the risk of death from breast cancer; women who attended mammographic screening had a higher reduction in risk, estimated at about 40%. Case–control studies that provided analyses according to invitation to screening were largely in agreement with these results. Evidence from the small number of informative ecologic studies was largely consistent with that from cohort and case–control studies. A substantial reduction in the risk of death from breast cancer was also consistently observed in women 70 to 74 years of age who were invited to or who attended mammographic screening in several incidence-based cohort mortality studies.[17-19] Fewer studies assessed the effectiveness of screening in women 40 to 44 or 45 to 49 years of age who were invited to attend or who attended mammographic screening, and the reduction in risk in these studies was generally less pronounced.[20-23] Overall, the available data did not allow for establishment of the most appropriate screening interval.

The most important harms associated with early detection of breast cancer through mammographic screening are false positive results, overdiagnosis, and possibly radiation-induced cancer. Estimates of the cumulative risk of false positive results differ between organized programs and opportunistic screening. The estimate of the cumulative risk for organized programs is about 20% for a woman who had 10 screens between the ages of 50 and 70 years.[24] Less than 5% of all false positive screens resulted in an invasive procedure. Owing to differences in health systems and quality control for screening performance, recall rates for additional investigation tend to be higher in opportunistic screening (e.g., in the United States)[25] than in organized screening programs. Overall, studies show that having a false positive mammogram has short-term negative psychological consequences for some women.[26]

Overdiagnosis can be estimated on the basis of data from observational studies conducted in organized programs or through statistical modeling. There is an ongoing debate about the preferred method for estimating overdiagnosis. After a thorough review of the available literature, the working group concluded that the most appropriate estimation of overdiagnosis is represented by the difference in the cumulative probabilities of breast-cancer detection in screened and unscreened women, after allowing for sufficient lead time. The Euroscreen Working Group calculated a summary estimate of overdiagnosis of 6.5% (range, 1 to 10%) on the basis of data from studies in Europe that adjusted for both lead time and contemporaneous trends in incidence.[27,28] When the same comparators were used, corresponding estimates of overdiagnosis in randomized, controlled trials after a long follow-up period from the end of screening were similar (4 to 11%).[29,30] Similar non-European and more recent European observational studies have led to higher estimates of overdiagnosis.

Radiation-induced breast cancer is a concern in women who are offered screening. The estimated cumulative risk of death from breast cancer due to radiation from mammographic screening is 1 to 10 per 100,000 women, depending on age and the frequency and duration of screening. It is smaller by a factor of at least 100 than the estimates of death from breast cancer that are prevented by mammographic screening for a wide range of ages.[31]

After a careful evaluation of the balance be-

tween the benefits and adverse effects of mammographic screening, the working group concluded that there is a net benefit from inviting women 50 to 69 years of age to receive screening. A number of other imaging techniques have been developed for diagnosis, some of which are under investigation for screening. Tomosynthesis, magnetic resonance imaging (MRI) (with or without the administration of contrast material), ultrasonography (handheld or automated), positron-emission tomography, and positron-emission mammography have been or are being investigated for their value as supplementary methods for screening the general population or high-risk women in particular.

Evidence for population screening with other imaging techniques is based solely on data from observational studies. The use of adjunct ultrasonography in women with dense breasts and negative results on mammography may increase the detection rate of cancers, but it also increases false positive screening outcomes.[32] As compared with mammography alone, mammography with tomosynthesis increases rates of detection of both in situ and invasive cancers and may reduce false positive screening outcomes[33]; however, evidence for a reduction in breast-cancer mortality was inadequate (Table 1) and the radiation dose received with dual acquisition is increased.

Clinical breast examination is a simple, inexpensive technique. In three trials in which women were randomly assigned to receive either clinical breast examination or no screening, breast cancers detected at baseline and in the early years of the trials tended to be of a smaller size and less advanced stage in the former group of women than in the latter.[34-36] Results on breast-cancer mortality have not yet been reported. In addition, five observational studies, conducted mostly in the 1970s, reported that clinical breast examination combined with mammographic screening increased the breast-cancer detection rate by 5 to 10 percentage points as compared with mammography alone.[1]

As has been previously reported,[1] the available data from randomized, controlled trials and observational studies generally did not show a reduction in breast-cancer mortality when breast self-examination was either taught or practiced competently and regularly (Table 1). Overall, surveys in general populations have shown that the numbers of women who report practicing breast self-examination are probably too few to have had an effect on mortality from breast cancer.

Women with a family history of breast cancer, with or without a known genetic predisposition, are at increased risk for breast cancer and therefore may benefit from intensified monitoring, with a combination of methods, from an earlier age and possibly at shorter intervals than women at average risk. However, high-risk women may be more sensitive to ionizing radiation,[37] and screening from an earlier age increases the risk of radiation-induced cancer. A number of observational studies have evaluated the sensitivity, specificity, incremental rate of breast-cancer detection, and false positive outcomes associated with various imaging techniques in high-risk women (Table 1). There is abundant literature showing that the use of MRI as an adjunct to mammography significantly increases the sensitivity of screening in women with a high familial risk and a *BRCA1* or *BCRA2* mutation as compared with mammography alone, but the addition of MRI also decreases the specificity[38]; data for other high-risk groups were fewer and provided weaker evidence.[39] The sensitivity of ultrasonography was found to be similar to or lower than that of mammography and was consistently lower than that of MRI.[40] The evidence regarding other screening techniques was too sparse to allow any conclusions.

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