

# International programs for the detection of breast cancer

Robert A Smith, PhD.<sup>(1)</sup>

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## Abstract

The benefit of early breast cancer detection is the foundation for programs around the globe to reduce morbidity and mortality related to breast cancer. These programs range from educational programs targeted to women and health professionals to organized or opportunistic screening programs that target specific age groups of women. Modern mammography programs tend to follow the protocols from the randomized clinical trials, but there is variation in key program elements such as the age groups invited to screening, the screening interval, performance indicators, and the uptake rate. Until recently, the emphasis on early breast cancer detection was limited to mammography, but the steady rise in incidence and mortality in low and medium resource countries, where mammography may be unaffordable, has led to a renewal in emphasizing the incremental value of downsizing palpable tumors through physical exams. There is consensus that programs should be designed based on disease burden and available resources, but that even in low resource countries there are opportunities to reduce breast deaths through earlier diagnosis and effective treatment. Screening programs are most effective when they are organized, and program planners should consider WHO criteria and local input data as a basis for tailoring screening programs to the needs of their population.

Keywords: early detection of cancer; breast neoplasms; early diagnosis

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## Resumen

El beneficio de la detección temprana del cáncer de mama es el fundamento para programas alrededor del mundo que buscan reducir la morbilidad y mortalidad relacionada con este padecimiento. Estos programas abarcan desde los de tipo educativo, orientados a mujeres y profesionales de la salud, hasta programas de monitoreo organizados u oportunistas que tienen como objetivo grupos específicos de edad. Los programas modernos de mastografía tienden a seguir protocolos para estudios clínicos aleatorios, pero hay una variación en elementos clave como los grupos de edad invitados a participar, el intervalo para el monitoreo, indicadores de desempeño, y la tasa de captación. Hasta hace poco, el énfasis en la detección temprana del cáncer estaba limitado a la mastografía, pero el incremento en la incidencia y mortalidad en países de recursos bajos a medios, donde las mastografías no son asequibles, ha llevado a un renovado énfasis en el valor de los exámenes físicos. Existe un consenso en cuanto a que los programas deben estar diseñados basándose en la carga de la enfermedad y los recursos disponibles, pero incluso los países con recursos más limitados tienen oportunidades para reducir las muertes de cáncer de mama a través de un diagnóstico oportuno y un tratamiento eficaz. Los programas de detección son más eficaces cuando están organizados, y los planeadores del programa deben considerar los criterios de la OMS y la información local como bases para ajustarlos a las necesidades de la población.

Palabras clave: detección precoz del cáncer; neoplasias de la mama; diagnóstico precoz

(1) Cancer Control Sciences Department, American Cancer Society, Atlanta, GA, USA.

In the mid-18<sup>th</sup> century, Henri François LeDran proposed that breast cancer originated as a localized disease that subsequently spread via the lymphatics to the general circulation.<sup>1</sup> The historical antecedents of the modern effort to control breast cancer derive from early awareness that breast cancer is a progressive disease that could be cured if surgery were performed early in the disease's natural history. In the early to mid-twentieth century, parallel efforts were underway to initiate treatment of breast cancer earlier. Public education programs focused on the promotion of breast self-examination (BSE), and professional education stressed the importance of routine, systematic clinical breast examination (CBE), each focused on detecting breast cancer in its earliest palpable phase.<sup>2</sup> During this same period, experimental work with x-rays demonstrated that occult breast cancer could be detected with imaging, thereby establishing the possibility for diagnosis before the earliest detection of a palpable tumor.<sup>1,3</sup> This potential for the detection of pre-symptomatic breast cancer led to the support for population-based randomized controlled trials (RCTs) of mammography screening,<sup>4</sup> and the subsequent demonstration that an invitation to screening was associated with a reduction in breast cancer mortality provided the scientific evidence to support the implementation of mammography screening programs.<sup>5-7</sup>

The importance of early breast cancer diagnosis is the foundation for formal programs around the globe to reduce morbidity and mortality related to breast cancer. These programs range from simple public education programs targeted to women by civil society, advocacy groups, and public health institutions to organized screening programs that provide mammography to targeted age groups of women. Until recently, the emphasis on early breast cancer detection was limited to mammography, but the steady rise in incidence and mortality in low- and medium- resource countries,<sup>8</sup> where mammography may be unaffordable, has led to a renewal in emphasizing the incremental value of downsizing palpable tumors.<sup>9</sup> These programs, and in particular mammography screening, may be opportunistic or organized, with the latter having the greater potential to reduce breast cancer mortality. However, depending on program resources and population acceptability of screening, in some instances opportunistic screening may achieve higher participation rates than are achieved in organized screening.<sup>10</sup>

### Modern breast cancer detection programs

The decision to screen an asymptomatic population for preclinical disease is based on well-established criteria

that relate to the disease in question and the characteristics of applicable screening tests.<sup>11</sup> The disease should result in significant morbidity and mortality, and diagnosis and treatment early in its natural history should offer advantages in end-results compared with detection and treatment of symptomatic disease. The test should have acceptable accuracy and benefits should outweigh harms. Finally, testing should be affordable, and acceptable to the target population and referring clinicians.<sup>11</sup> In the context of breast cancer screening, these criteria are met for most high resource countries, and today the decision to implement mammography screening in medium and high resource countries principally is based on the level of disease burden, cost-effectiveness, competing health priorities, and capacity.

### Organized vs. opportunistic screening

Where mammography is available, screening may be organized, opportunistic, or available to the population in some combination to the two approaches. In the context of achieving the fullest potential of population screening, the distinction between organized and opportunistic screening is important.

The primary distinction between organized and opportunistic breast cancer screening is the manner in which invitations to screening are extended. In an organized breast cancer screening program, invitations are issued from centralized population registers. In opportunistic screening, invitations to screening depend on the individual's decision to undergo screening or on encounters with health care providers where screening may be recommended. Thus, opportunistic screening depends on a coincidence of interests and encounters between individuals and health care services, since generally mammography screening is not accessed without a referral. There are other distinctions (Table I). Organized screening programs tend to have centralized responsibility for other key elements of screening, such as eligibility requirements, quality assurance (QA), follow-up of positive test results, and program evaluation. Although organized and opportunistic approaches to breast cancer screening can yield similar uptake rates, organized programs have greater potential to reduce breast cancer mortality because of the use of central registers for invitation, and the centralized commitment to QA, monitoring, and evaluation. An organized approach to screening likely will also result in a more cost-effective program due to the central attention to quality, and the greater protection against the harmful effects of screening, including over-screening.

**Table I**  
**SIMILARITIES AND DIFFERENCES BETWEEN ASPECTS OF ORGANIZED AND OPPORTUNISTIC SCREENING**

<i>Aspect of screening</i>	<i>Organized screening</i>	<i>Opportunistic screening</i>
Screening method for a particular type of cancer (e.g., FOBT* vs. FS‡)	Fixed: chosen by government/health department	Variable: chosen by individual and individual health care provider
Aim	Reduce cancer incidence/morbidity/mortality at the population level	Reduce cancer incidence/morbidity/mortality at the individual level
Sensitivity of test	The most sensitive test may not be chosen for a nationwide program. Sensitivity targets for practitioners and programs are established and monitored.	Most sensitive test usually chosen. Sensitivity at the practitioner and program level not generally monitored
Specificity of test	High specificity important to reduce avoidable cost from unnecessary workup of false positives and associated adverse effects	High specificity less important at individual level
Screening interval	Fixed: chosen to maximize population benefit at reasonable cost	Variable: chosen to maximize individual's protection against cancer morbidity/mortality; usually more frequent than in organized programs
Available financial resources	Limited at the population level in relation to policies of health spending, taking into account all aspects of health care	Limited at the level of the individual, and health plan level decisions. Primarily depends on finances and insurance status of the individual
Health technology assessment	Must have been shown to do more good than harm	Efficacy does not necessarily have to be demonstrated
Quality assurance	Set targets are to be met, and are monitored	Targets may be set, and may or may not be monitored
Target uptake rates	Specified, monitored and lower rates result in organized efforts for improvement	May or may not be specified (i.e., by health plans or health agencies), monitored, and few opportunities for systematic applications for population based improvement
Invited	Fixed: all persons within a specified age range	Variable: persons in contact with health care professionals who recommend screening; those in particular jobs where health care coverage may include reimbursement for screening; anyone exposed to direct-to-consumer marketing
Invitation strategy	Active: everyone in the eligible population invited	Passive: no consistent strategy
Aim for equality of access	Equality of access built into the organization of the program	Equality of access is desired, but resource allocation limits the potential of outreach efforts.
Relation to risk of having cancer	Not necessarily persons at highest risk, but the age group most likely to receive greatest benefit from screening	Not necessarily persons at highest risk; may lead to overscreening of low-risk and underscreening of high-risk persons
Benefits	Maximized for the population within available resources	Maximized for the individual
Harms	Minimized for the population within available resources	Not necessarily minimized

\* FOBT: Fecal occult blood test

‡ FS: Flexible sigmoidoscopy

Source: Reference 10. Reprinted with permission

### *Mammography screening programs*

The International Cancer Screening Network (ICSN), which is supported by the Applied Research Branch of the U.S. National Cancer Institute (NCI), periodically

conducts a survey of participating country representatives to ascertain details about their cancer screening programs.<sup>12</sup> Results from previous surveys are available on the ICSN website (<http://appliedresearch.cancer.gov/icsn/>). While the inventory of

breast cancer screening programs is not inclusive of all breast cancer screening programs in the world, and some notable long-standing organized programs are not represented (i.e., Sweden, Netherlands, etc.), the results of these surveys highlight the diversity of program designs.

The most recent survey of ICSN members was conducted in 2007-2008, and includes breast cancer screening program descriptions from North America, Latin America, Europe, and Asia.<sup>13</sup> Most of these programs were initiated in late 1980s and early 1990s, following favorable results from the early RCTs,<sup>14,15</sup> and it is evident that the RCT results have had lasting influence on program design. For example, while the Health Insurance Plan of Greater New York (HIP) RCT evaluated the combination of CBE and mammography screening with general purpose x-ray equipment, the Swedish Two-County RCT evaluated mammography screening alone, but with the a new generation of dedicated mammography equipment that showed more favorable performance. Most modern screening programs did not include CBE at initiation, and the number that have maintained CBE in combination with mammography has declined likely due to the complexity of adding CBE screening to a mammography program, the low cancer detection rate, and the lack of sufficient evidence that CBE results in a significant contribution to program sensitivity.<sup>16</sup> In contrast, more than half of the programs reported the integration of digital mammography into the screening program.<sup>13</sup>

The influence of the early results of the RCTs also is evident in the age-groups invited to screening. Most RCTs included women who were 40 and older, while upper ages in the randomized groups ranged from 64-74.<sup>17</sup> However, based on early age-specific findings from the RCTs that were unfavorable to a policy of screening women under age 50, as well as the lower prevalence of breast cancer in this age group, a majority of countries represented in the survey begin screening at age 50, with others starting at age 40 or 45.<sup>13</sup> Only a small number of countries have modified the age range of women invited to screening since the inception of the program, and these modifications have included both lowering the initial age and raising the upper age for eligibility. The screening interval also has changed very little since the inception of most breast cancer screening programs, and ranges from between 1 and 3 years, with most countries inviting women to mammography every 2 years. Based on the age-specific interval cancer rate observed in the Swedish RCTs,<sup>18</sup> and subsequent estimates of age-specific mean sojourn times,<sup>19</sup> the Swedish Board of Health and Welfare sets age-specific screening intervals based on age, with women ages 40-54 being invited to

mammography every 18 months, and women ages 55 and older being invited every 24 months.<sup>20</sup>

The importance of mammography QA is well-established, and all countries reported that their programs had QA guidelines. While few specific details on the content of the QA programs were available, it appears that most programs follow either the QA recommendations of the American College of Radiology,<sup>21</sup> the European guidelines for QA,<sup>22</sup> or variants of each. In order to achieve the highest levels of quality imaging and interpretation in film and digital systems, QA guidelines address a broad spectrum of equipment and processing standards, monitoring and equipment testing recommendations, and personnel standards related to background training, credentialing, screening volume, and regular medical audits of performance.

Among all countries surveyed by the ICSN, the primary method used to recruit women to mammography screening was a personal invitation. Some countries also rely on physician referral and media advertising to recruit women to screening. Despite similarities in recruitment strategies, considerable variation in uptake rates has been reported, with Japan reporting only 12% attendance and Finland reporting 87%.<sup>13</sup>

In some countries, such as the U.S. and Hong Kong, opportunistic screening is the principal pathway by which women obtain mammography. A number of European countries (France, Switzerland, Luxembourg, Austria, Hungary, etc.) have mixed systems, in which both organized and opportunistic screening co-exist.<sup>23</sup> In some instances, as was the case in Hungary, opportunistic mammography screening has been available and then nationwide organized screening has been introduced, resulting in a significant increase in the volume of both organized and opportunistic screening.<sup>24</sup> As noted above, opportunistic approaches to screening can compare favorably to organized systems in terms of the uptake rate and breast cancer mortality reductions.<sup>25,26</sup> However, across all program elements, opportunistic screening generally will not perform as effectively as organized screening due to the absence of centralized call-recall systems, on-going program evaluation, and attention to QA. An inventory of breast cancer screening programs based on data from the ICSN and other sources is shown in Table II.

#### *Breast cancer screening in low to medium resource countries*

The rising breast cancer mortality in the developing world is the result of rising incidence, and the low availability of early detection programs and wide capacity for state-of-the-art diagnosis and therapy. The Breast Health

**Table II**  
**CHARACTERISTICS OF SELECT BREAST CANCER SCREENING PROGRAMS BY REGION**

Región/country	Organizational level	Year initiated	Detection methods	Age groups	Screening interval (years)
<b>Europe</b>					
Austria	NS, O	2010	MM	40-69	1
Denmark	S	1991	MM, DM	50-69	2
Finland	N	1986	MM, DM	50-69	2
France	NS	1989	MM, CBE	50-74	2
Hungary	N	2002	MM	45-65	2
Ireland	N	2000	MM, DM	50-64	2
Italy	NS	2000	mm	50-69	2
Luxemburg	N	1992	MM	50-69	2
Netherlands	N	1989	MM	50-75	2
Norway	N	1996	MM, DM	50-69	2
Portugal	S	1990	MM, CBE	45-69	2
Spain	S	1990	MM	45-70	2
Sweden	NS	1986	MM, DM	40-74*	1.5 (40-54); 2 (55-74)
Switzerland	S, O	1999	MM	50-69	2
United Kingdom	N	1988	MM, DM	50-70 <sup>§</sup>	3
<b>North America</b>					
Canada	NS	1988	MM, DM, CBE	40-69	1 (40-49); 2 (50-69)
United States	O		MM, DM, CBE	40+	1-2
<b>Latin America</b>					
Brazil	NS	2000	MM, CBE	40-69	2
Mexico	NS, O	2002	MM, CBE	40-69	1-2 <sup>‡</sup>
Uruguay	N	1990	MM, CBE	40-69	2 (40-49); 1 (50-69)
<b>Middle East</b>					
Israel	N	1997	MM	50-74	2
Jordan	O	2006	MM, CBE	40+	1-2 (40-49); 2 (50+)
<b>Asia/Pacific</b>					
Australia	NS	1991	MM	50-69	2
Japan	N	2002	MM, DM, CBE	40-75	2
Korea	N	2002	MM	40-75	2
New Zealand	N	1998	MM, DM	45-69	2
Taiwan	N, O	2004	MM	45-69	2

Source: Adapted from references 12, 13, 25, 27

Organizational level: N, National screening policy; NS, National screening policy with state/provincial/regional implementation; S, State/provincial/regional implementation; O, Opportunistic screening

Mammography (MM), Digital Mammography (DM), Clinical Breast Examination (CBE), Breast Self-examination (BSE)

\* Countries determine whether to invite beginning at age 40 or 50

‡ Invitations and/or intervals vary by risk assessment

§ Target population expanding to 47-73

Global Initiative (BHGI) has endorsed tiered strategies that have common denominators at all resource levels (i.e., diagnostic and treatment services), but endorses the implementation of different early diagnosis strate-

gies based on factors such as disease burden and level of resources.<sup>28</sup> These strategies are based on the well-established association between tumor size and long-term survival, indicating that the benefits of smaller

tumor sizes represent a continuum that includes both occult and palpable tumors.<sup>9</sup> The observation that the average size of palpable tumors in the world's regions is highly variable suggests the potential for successful interventions in the absence of screening mammography. For example, as proposed by the BHGI, at the most basic level detection methods are limited to clinical history and CBE, whereas in the next resource tier, i.e., countries with limited resources, diagnostic breast ultrasound, with or without mammography in women with a positive CBE should be feasible, as well as screening mammography in select higher risk groups.<sup>29</sup>

The observation that breast cancer incidence can vary between rural and urban areas, and vary across socioeconomic groups, suggests that there is value in tailoring the BHGI guidelines selectively within a country based on the level of disease burden and available resources. The assessment, planning and initiation of several research programs and screening programs in Asia and Latin America illustrate this potential.

Cazap and colleagues surveyed 100 breast cancer experts from 12 Latin American countries in 2006 to assess the current state of breast cancer treatment in this region, including some questions on access to screening and patterns of detection from which some inferential conclusions can be drawn. While respondents reported that approximately two-thirds of the population had access to mammography, they also stated that among approximately 80% of cases the initial suspicion of breast cancer was prompted by the patient, suggesting mammography availability principally was for diagnostic services.<sup>30</sup> Respondents also reported differential access to services in their country as a whole vs. the community where their cancer center was located. A second manuscript described medical care standards (MCS) in 12 Latin American countries, with most respondents reported guidelines for physical examinations and mammography, although the perception at both the country and cancer center level was that most breast cancer was detected initially by women themselves.<sup>31</sup>

In response to the growing burden of breast cancer in Mexico, a considerable volume of research has been undertaken in the descriptive epidemiology of breast cancer,<sup>32-35</sup> assessing capacity for diagnosis and treatment,<sup>36</sup> and estimating the cost-effectiveness of screening programs.<sup>37</sup> Rodríguez-Cuevas and colleagues reported initial results of the Mexican Foundation for Education in Prevention and Opportune Detection of Breast Cancer (FUCAM)'s first mammography screening program in Mexico.<sup>38</sup> In 2005-2006, approximately 97 000 mammograms were performed through mobile units in local communities, and the findings are consistent with what would be expected with the introduc-

tion of breast cancer screening to a largely unscreened population. Approximately 1 in 4 women presenting for mammography screening was determined to be symptomatic, accounting for about one-third of all abnormal mammograms in the program. The breast cancer detection rate was 2.1 per 1 000 women screened and the distribution of tumor characteristics was consistent with the expected contribution of mammography to the detection of earlier stage breast cancer. However, an indication of a challenge that will need to be addressed was the lack of further evaluation among 1 in 5 women with an abnormal mammogram, despite additional attempts at personal notification.<sup>38</sup>

In Mumbai, where mammography screening is judged to not be feasible, 150 000 women are participating in an RCT comparing CBE, breast self examination (BSE), and breast awareness education with breast awareness education alone.<sup>39</sup> As of now, there is inferential, but no direct evidence of the value of CBE-only screening based on the demonstrated association between tumor size and prognosis. An earlier trial of CBE screening in the Philippines had demonstrated the potential for favorable rates of detection of palpable masses, but had to be stopped due to very low rates of follow-up of positive CBE.<sup>40</sup>

Taiwan can be described as a country with low- to medium-breast cancer risk, but also with a trend of rising incidence rates. From 1995-2004, breast cancer screening evolved through the evaluation of three programmatic strategies, each carefully designed based on epidemiologic data and evaluated in demonstration projects according to conventional criteria for program performance. Initially women who were 1<sup>st</sup> degree relatives of breast cancer cases were invited to breast cancer screening with mammography, ultrasound, and CBE.<sup>41</sup> The design of this program was based on the estimation that population-based mammography screening was too costly, but that screening women at high risk based on family history could be cost-effective. Program planners also estimated the mean-sojourn time for women with a family history, and consistent with other investigations,<sup>42</sup> observed that it was shorter (1.9 years) compared with women without a family history. Based on modeling of surrogate endpoints, annual screening was estimated to confer a 33% reduction in breast cancer mortality in this group, with a marginal cost per year of life saved of \$4 851.<sup>41</sup> Subsequently (1999-2001), a demonstration project of population-based screening with CBE was launched. In 23 counties (365 health centers) women ages 35 years and older were offered CBE by public health nurses. Invitation was by mass media campaigns and word of mouth, and approximately 900 000 asymptomatic women attended screening and

completed a risk factor questionnaire.<sup>27</sup> Based on the low-yield of physical exams, a third demonstration project was initiated in 2002 to evaluate a two stage screening program in which women completed a risk factor questionnaire, and those at moderate to high risk were offered mammography.<sup>27</sup> Of the 218 822 women who completed the questionnaire, 117 550 were invited to mammography screening. Wu and colleagues summarized the findings of the three demonstration projects and concluded that the two-stage program was the most cost-effective, had the highest detection rate of DCIS or stage T1 tumors (71%), node-negative tumors (63%), and the highest positive-predictive value (14%).<sup>27</sup> While the study had demonstrated an effective risk based strategy, in 2004 the Bureau of National Health Insurance began subsidizing biennial mammography screening for women ages 50-69, and in 2010 expanded the program to include women ages 45-69. However, the incremental approach taken by Taiwan policy makers illustrates the importance and value of careful consideration of local key factors relevant to the design of a screening program, i.e., the underlying burden of disease, the ability to identify higher risk subgroups, clinical capacity (human resources and equipment), awareness and acceptability of the target population, costs, and affordability.

#### *Current issues in the design and evaluation of breast cancer screening programs*

Before the availability of breast imaging, the control of breast cancer relied entirely on treating symptomatic breast cancer. Today, breast cancer control is significantly influenced by the opportunity to diagnose breast cancer at a more favorable stage, due both to increased mammography utilization as well as increased awareness among women of the importance of reporting new symptoms promptly to a clinician.<sup>43-45</sup> While strategies to prevent breast cancer should be pursued, for the foreseeable future early detection and appropriate treatment will remain the cornerstone of the disease control strategy for breast cancer in average and high risk women.

In the presence of a growing global burden of breast cancer, early detection is increasingly being regarded as representing a continuum, from the detection of occult breast cancer with mammography and other imaging technology to earlier diagnosis of symptomatic breast cancer when mammography is not available. Insofar as the benefits of treating breast cancer early in its natural history are well established, decisions about whether or not to implement breast cancer screening, the age groups to invite, and the technology to utilize can be

made by following the remaining WHO principles and practices for screening.<sup>11</sup> Indeed, the application of the WHO principles overall, and for specific age subgroups, oblige us to consider the entirety of the evidence that is relevant to screening policy decisions.

The BHGI has emphasized the importance of breast awareness as a strategy to insure prompt reporting when a woman first detects breast symptoms.<sup>9,28</sup> In most of the world's regions, the first indication that a woman has breast cancer comes from her own awareness of a change in her breast. In Western countries, the promotion of BSE was intended to be a simple, low-cost strategy to help downsize palpable tumors. While guidelines commonly emphasize that there is no evidence that BSE is effective, it also can be stated that there is not persuasive evidence that it is ineffective.<sup>46</sup> In reviewing the results of the Shaingai Trial of BSE instruction, Thomas and colleagues pointedly noted that the equivocal results of the trial should not be interpreted as evidence that BSE didn't work, but rather that BSE instruction was not associated with a reduction in breast cancer deaths among Shainghai women, a population that already appeared to respond early to the first indication of breast changes.<sup>47</sup> In their judgment, it was possible in a setting where women commonly presented with much larger, more advanced tumors that BSE could be beneficial if women adhered to a systematic regimen at regular intervals.<sup>47</sup> It also may be the case that BSE instruction is an effective strategy to increase breast awareness even if women do not subsequently practice routine, systematic BSE. The evidence does show that BSE instruction results in an increase in benign breast biopsies, but in the Shanghai trial this increase appears to have been limited to a short period following instruction. If BSE instruction increases awareness over the life-course, then short period of elevated risk for benign biopsy may be a cost-effective trade-off. This is an area in need of further evaluation.

There also is little direct evidence supporting the value of CBE, although there is sufficient inferential evidence to support demonstration projects to determine whether or not it is a cost-effective strategy in settings where mammography screening is not feasible, or not yet feasible.<sup>9</sup> While the CBE is taking place there also is an opportunity for health care professionals to provide women with information about early breast cancer detection and to answer any questions they may have about breast health. There are data that show that when mammography screening programs are in place, CBE provides only small incremental advantages in terms of increased sensitivity.<sup>16</sup> If CBE is included in a mammography screening program, it is programmatically advantageous to conduct CBE before mammography

so that if a palpable mass is detected, the patient can bypass screening and proceed to the evaluation of the symptom.

Breast cancer screening, in particular mammography screening, is not without its detractors.<sup>48-51</sup> Like any screening test, physical exams and imaging exams have limitations and less than perfect accuracy. Not all women participating in a program will have their cancer detected early, and a significant fraction of women will have to undergo further evaluation for symptoms or signs on imaging that ultimately are determined to be normal. The early conclusion that mammography was not beneficial in women under age 50 still has a faithful following of devoted skeptics,<sup>52,53</sup> despite (1) clear, evidence-based explanations for why the early trials showed differential age-specific results;<sup>7,17,54</sup> (2) results from second-generation RCTs showing statistically significant or near significant mortality reductions in women in their forties invited to screening;<sup>55-57</sup> and (3) evaluations of modern service screening showing similar breast cancer mortality reductions in women screened in their 40s compared with women ages 50+.<sup>58-60</sup> Rather than rely on historic debates and legacy policies, the growing literature on age-specific benefits is worthy of consideration when designing screening programs.

An additional source of on-going debate pertains to the estimate of the effectiveness of mammography, and the balance of benefits and harms. While an RCT may be the sine qua non of experimental evidence in the evaluation of screening, an intention-to-treat analysis may significantly underestimate the true effectiveness of screening due to non-adherence with the randomization assignment. Moreover, when all RCTs are combined to produce a weighted estimate of benefit, the true estimate of effectiveness is further degraded. Given the consistency of the strong association between the relative risk of being diagnosed with an advanced breast cancer and the relative risk of dying from breast cancer across the RCTs,<sup>17</sup> it is counterintuitive to regard each of the RCTs as contributing equivalent value in estimating the benefit of breast cancer screening in meta-analyses.<sup>17,60</sup> Further, evaluation of modern mammography, which can be based on the age-specific benefits of exposure to screening (vs. age at randomization) consistently shows benefits as good or better than the results of the most effective trials.<sup>61</sup> In this respect, program planners can benefit from several decades of scientific literature from which to model the anticipated effects of a screening protocol on long-term outcomes in their population. Finally, a common attempt to evaluate the benefits of screening is to compare breast cancer death rates before the introduction of screening with breast cancer death rates after the introduction of screening. While this sort

of comparison is perhaps the most intuitively straightforward, there are a number of methodological pitfalls that lead to incorrect conclusions about the effectiveness of screening. Some errors are simple, but they can have a significant effect on the estimate of benefit and should be part of the "checklist" for evaluating these evaluations. For example, in 1999, Sjonell and Stahle<sup>62</sup> argued that, despite results from the RCTs showing lower breast cancer mortality associated with an invitation to mammography, widespread screening in Sweden had not demonstrated that same benefit. However, Sjonell and Stahle's analysis (1) did not correctly identify when counties initiated screening; (2) did not adjust for the duration of time that it takes (usually several years) to invite an entire population to screening after the program begins; (3) did not adjust for the proportion of the population that may already be undergoing opportunistic screening; (4) did not adjust for the proportion of new breast cancer cases that already will be advanced at the time of the first mammogram; and (5) most important, did not distinguish screened and unscreened cohorts among the deaths from breast cancer after the beginning of the program.<sup>63</sup> In a hypothetical 10-year period after screening has been initiated, more than half of the deaths from breast cancer will be among women who were diagnosed before the beginning of program began.<sup>20</sup>

The shortcomings of Sjonell and Stahle's analysis represent important lessons related to measuring the effectiveness of service screening. The failure to distinguish screened and unscreened cohorts also applies to the evaluation of population trends in breast cancer incidence, stage at diagnosis, and mortality after screening has been introduced. In 2009, Esserman et al argued that in the U.S. screening should have produced a rise in breast cancer incidence rates, followed by a fall in rates, and then a return to prescreening rates with a more favorable stage distribution.<sup>51</sup> In this theoretical scenario, the introduction of screening would result in an increase in incidence (due to lead time), which would then be followed by a decline in the expected incidence rate because in subsequent years cancers that had would have been detected already have been detected by screening. Eventually, there should be a return to the pre-screening incidence rate, but with a much more favorable stage distribution due to the down-staging influence of screening. Esserman, et al. noted that breast cancer screening in the U.S. with mammography has not produced that trend, but instead has led to an increase in localized disease, without a decline in advanced disease. Without reconciling these observations with the results from the RCTs, they concluded that screening is not very effective at altering the natural history of aggressive disease, and mostly detects less



aggressive and indolent (i.e., overdiagnosed) cases. However, the absence of the theoretical rise and fall of incidence rates with an accompanying stage shift is easily explained by a number of factors that are unique to screening programs in general, but also breast cancer trends in the U.S., not the least of was a long period of rising incidence rates until 1999 due to the underlying epidemiology of the disease.<sup>64</sup> But the more common error in evaluating the effectiveness of screening through population trends is failure to recognize that the entire population is different from the potentially screened population, the ever-screened population, and the occasionally and regularly screened populations. In any population, incidence rates include cancers detected in adults who: (1) are not eligible for screening based on age or co-morbidity, (2) have no or limited access to screening due to geography and/or social class; (3) are eligible, but refuse screening, or are irregularly screened; (4) are screened but did not have their early stage disease detected (interval cancers); (5) are screened positive, but are lost to follow-up; and (6) those who enter the screening cohort for the first time, of which the latter group will manifest the characteristics of a prevalent screening round. In the USA, with rising incidence rates, and a significant proportion of the population attending screening, it is expected that much of that excess incidence will be measured in rising incidence rates of early stage disease. The conclusion that much of the excess of early stage disease represents significant overdiagnosis may be explained by the short period of observation, a trend in rising incidence rates, and the expected effect of lead time. Short term evaluations of population surveillance data are not a sound basis for judging the effectiveness of screening, and policy makers should be cautious when these sorts of evaluations challenge the consistency of evidence from RCTs and carefully conducted observational studies of women exposed to screening. The Swedish Organized Service Screening Evaluation Group (SOSSEG) has done a number of before-after comparisons that provide good examples of how lessons learned from the evaluation of the RCTs can be applied to service screening evaluations.<sup>65</sup>

The design of a breast cancer screening program should be a strictly evidence-based process, one that addresses the needs of women in the community where the program will be established. Too often planners uncritically embrace guidelines and program designs from other countries without careful consideration of the historical and idiosyncratic factors that led to those policy decisions. In addition, the age-incidence curve, and burden of disease as measured by premature mor-

ality, may suggest different target groups for screening than are targets in other countries. Guidelines should not be static, but rather should be periodically reconsidered in light of new epidemiological evidence, detection technology, and advances in therapy. Following a careful, evidence-based process, combined with regular evaluation and feedback on program performance, will insure the most cost-effective delivery of services, and the confidence of the target population and health care workers.

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