

# Science, Politics and Mammography: An International Focus

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In developed nations around the world, breast cancer is the most common cancer among women (excluding non-melanoma skin cancers) and is the second leading cause of cancer deaths in women (after lung cancer).<sup>1</sup> While the incidence of breast cancer has been steadily increasing in all of the developed nations, breast cancer mortality rates have been declining significantly over the same time period. This decline in mortality is generally attributed to earlier detection and more effective treatments. Early detection increases the likelihood that the cancer will be identified at a more treatable stage rather than at a later stage when the likelihood of metastases, for example, is greater. Since mortality rates are directly related to the stage at which the cancer is detected, early diagnosis affords the individual a greater chance of long-term survival. When a cancer is confined to the breast, the five-year survival rate is close to 100%.<sup>2</sup>

Although the mechanisms of breast cancer development are not fully understood, many factors, such as age, ethnicity, heredity, diet and socioeconomic status are known risk factors for this disease. But,

having one or more of these risk factors does not necessarily mean that breast cancer will develop. The majority of women with breast cancer have no known risk factors, and many women who do have them are cancer-free. Risk is based on probability and population averages. It does not imply inevitability.

## **Mammography Screening**

Early breast cancer detection and mammography screening are synonymous in the public's mind. The purpose of a screening test, be it a chest X-ray, cholesterol testing, or mammography, is to distinguish between those with normal and abnormal test results. A screening test, however, is not a confirmation of disease. Those who test positive are sent for further evaluation to determine whether they do in fact have the disease. A basic premise of mammography screening, for example, is to detect breast cancer at an early stage so that treatment could be initiated with the hope of extending lives. Another goal of screening is to reduce mortality. Saving lives, after

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all, is another basic premise of early disease detection. All things being equal, there should be longer survival among those who are screened.

Although mammography has been shown to be a highly effective and cost-efficient method of early detection of breast tumors, it is technically one of the most difficult radiographic investigations to interpret. A cancerous lesion can be seen on mammogram only if it looks different from surrounding breast tissue. In some cases, the cancer is indistinguishable from normal tissue. Accuracy in detection is influenced by many factors including the age of the woman, the density of the breast, the time in the menstrual cycle that the mammogram is done and the proficiency of the radiologist in detecting cancers on mammography.

Neither the sensitivity nor the specificity of mammography is 100%. The overall sensitivity of mammography (the ability to detect cancer when it is present) ranges between 71.1-91.5%. Among women older than age 50, the sensitivity ranges between 85-90%. Sensitivity is lower among women younger than age 50 primarily because these women tend to have denser breasts, which makes it more difficult to detect cancer. Specificity (ability to correctly identify those without cancer) ranges from 30-65%. The specificity among younger women (<50 years) is not as robust as that for women over age 50.

The proportion of all mammograms that are false positives suggesting abnormalities that after further testing turn out to be benign is higher than one might think. A large-scale ten-year study based on 9,762 screening mammograms and 10,905 screening clinical breast examina-

tions found that, of the women screened, one-quarter had at least one false positive mammogram. Over ten years, one-third of the women screened had abnormal test results requiring additional evaluation even though no breast cancer was present.<sup>3</sup> The cost, emotional and financial, of additional testing can be significant.

While the objective of breast cancer screening is to detect a cancer at its early stage, some cancers grow so slowly that failure to detect them would not make a difference in overall survival. To what extent does mammography increase the likelihood that these cancers would be detected? Is it necessarily a good thing that these cancers are detected? What are the psychological consequences to the individual? Most would agree that the benefits of mammography outweigh the harms, but that the benefits may come at a cost. In some instances, breast cancer that is left undiagnosed does not affect survival. However, in the majority of cases, early detection can make a difference. Mammography screening affords a potentially large benefit for a small number of individuals, and a potentially small amount of "harm" for a much larger number. In recent years, this issue has become contentious, and discussions/arguments about the benefits of mammogram screening have been hotly debated in the literature.<sup>4-7</sup> The degree to which mammography reduces mortality is an important issue in the debate.

### **Mammography Controversy**

Recently, Danish researchers concluded that, based on their review of the data from

large-scale mammogram screening trials, screening for breast cancer with mammography does not decrease breast cancer mortality, and therefore screening should not be recommended. They dramatically concluded that screening for breast cancer with mammography is unjustified (their term), because there is no reliable evidence that it reduces mortality.<sup>8</sup> This strong anti-mammography screening stance created a furor. All recommendations regarding mammogram screening were based on data from the same trials included in the Danish reanalysis, and as flawed as these studies may be, all organizations and governments involved in setting screening recommendations felt that the benefits of screening far outweighed the negatives. The literature is consistent in advocating early screening and detection for breast cancer even though screening mammography does not detect all tumors nor prevent all deaths from breast cancer.

There have been numerous studies conducted in many countries that show significantly lower breast cancer mortality among those screened for breast cancer compared to those diagnosed pre-screening.<sup>9-13</sup> Australia, in particular, is an interesting case study. Breast cancer incidence and mortality there is similar to that in other developed countries.<sup>14</sup> One in 11 Australian women will be diagnosed with breast cancer before age 75. Overall, the incidence of breast cancer rose from 94.6 cases per 100,000 population in 1990 to 117.2 cases per 100,000 population in 2001.<sup>15</sup> Among the 50-69 year old cohort, in particular, there was a marked increase in breast cancer. Advocates of mammography screening strongly suggest that this increase was most likely due to the introduc-

tion of the national breast cancer screening program that started in 1992.<sup>16</sup>

## **BreastScreen Australia**

In 1992, Australia initiated an innovative population-based breast cancer screening program, BreastScreen Australia, that allows for the empirical assessment of the effectiveness of mammography on early detection and mortality. Each Australian State has its own breast screening program, funded by the federal and state governments, whose objective is to provide free mammography screening every two years to women between the ages of 50 and 69. For women between the ages of 40 and 49 and over age 70, free screening is available for those who so desire. Women under age 40 are not eligible for screening under this program. The proportion of women screened in all age groups increased substantially between 1988 and 1994. By 1994, approximately 70% of women in their 50s and 58% of women in their 60s had undergone an initial mammogram screen. Data also show that 54% of women in their 40s and 25% of those aged 70-74 and 6% of those 80 years and older had been screened at least once by 1994.<sup>17</sup>

Every citizen in Australia must register to vote, making the election rolls an excellent source from which to identify and locate individuals. Motor vehicle registration, for example, is not as complete since not everybody has a driver's license. BreastScreen Australia actively recruits women aged 50-69 years from the electoral roll. At age 50, each woman is sent a letter of invitation to have a mammogram free of charge. Appointments are scheduled and follow-up

letters are sent if necessary to those who did not respond to the first letter. After a woman receives her initial mammogram screening, an automatic reminder letter is sent out at two-year intervals to schedule subsequent mammograms.

BreastScreen Australia is heavily advertised with a significant marketing campaign (TV, radio, print media) to raise awareness of the program. Some of the State-based programs rely on famous Australian actresses to raise awareness of the importance of regular mammograms. In order to make the process more convenient for the individual, there is flexibility in the hours that mammogram centers are open; there are mobile vans that go into local communities on set schedules; there are numerous fixed sites in each city; for example, in Sydney, one of the fixed sites is located next to the intimate apparel section in a major downtown department store.

BreastScreen New South Wales, where Sydney is located, is one of Australia's largest mammogram screening programs. Population breast screening in NSW began in the late 1980s in pilot areas and full State coverage was in effect in 1996.<sup>18</sup> Whereas the incidence of breast cancer in New South Wales (representing one-third of Australian women) changed little from 1972 to 1983, there was a steady increase from 1984, and by 1995, the incidence was almost 50% higher than it was in 1983.<sup>19</sup> The greatest increase was in women in the target age group for mammography screening: those aged 50-69 years.

Data also show that there had been a significant drop in breast cancer mortality since the screening program started in 1992.<sup>20</sup> From 1991 to 2001, the breast cancer death rate declined by an average

of 2.2% per year. The observed increase in incidence is thought to be a result of screening. Thus, while more Australian women are being diagnosed with breast cancer, they are much less likely to die from the disease. Certainly, changing fertility, improved nutrition and advances in treatment have influenced trends in breast cancer mortality. Nevertheless, mammogram screening is viewed as a major contributor to this trend.

BreastScreen New South Wales currently consists of ten screening and assessment centers. Their services are closely evaluated with respect to quality and outcomes. Trained radiographers are located at each site, be it a fixed location or a mobile van. Contracts are made with radiology practices to read the mammogram films, and two radiologists read each mammogram. The radiologists are paid a set rate per mammogram. Within two weeks, the results of the mammogram are sent by mail to both the patient and her doctor, unless the individual requests otherwise. In New South Wales, approximately one in 20 women are asked to come back for further tests because of an abnormal finding. These women are asked to go to an assessment center for further testing, which is also free of charge.

Some women undergo mammography outside of the BreastScreen New South Wales program through Medicare, the Australian government-funded universal health insurance scheme. Under Medicare, mammography is partially refundable if it is clinically indicated, but Medicare does not pay for routine screening. These individuals need to obtain a physician referral for a mammogram. Research has shown that women who receive screening outside

of the BreastScreen New South Wales program are generally of higher socioeconomic status, have a higher level of education, have a family history of breast cancer and appear to be influenced by referral patterns of their physician.<sup>21</sup>

In order to assess the impact of mammography, studies have examined temporal trends in the incidence of breast cancer as compared with trends in mammography in New South Wales. Findings showed an increase in the incidence of breast cancer that coincided with an increase in mammography after the introduction of the statewide breast cancer screening program. Specifically, the increases in incidence of breast cancer in NSW women are most pronounced in the screening age group 50-69. Sharp increases occurred in 1991, which coincided with a sharp increase in the number of mammograms. The second peak in incidence occurred in 1994-96, and corresponds to the full-scale operation of BreastScreen NSW.<sup>22</sup>

Australian researchers also found that the incidence of ductal carcinoma in situ (DCIS) in women aged 50-69 increased, primarily as a result of the screening program. DCIS is the most common type of non-invasive breast cancer and is considered a precursor to or potential marker for invasive ductal carcinoma. These pre-invasive lesions originate within the ducts of the breast and can be detected at an early stage by screening mammography. DCIS is usually not felt or detected primarily because the cells are too small to have formed a lump. More than half of the Australian women diagnosed with DCIS were between 50 and 69 years of age, with a mean age at diagnosis of 59 years.<sup>23</sup> The high incidence of DCIS provides another reason

for women to have regular mammography screening.

## Evidence from Other Countries

There have been numerous case-control studies and randomized clinical trials, involving nearly half a million women, which compare mortality rates of those who were screened to those who were not. There have been hundreds of opinion pieces and editorials commenting on their findings. Based on the empirical evidence, there is a general consensus that screening mammography for women aged 50-69 is beneficial. However there is no clear agreement regarding recommendations for women in their 40s or in their 70s.

Of all the large trials, only one, the Canadian National Breast Screening Study, found that annual mammography screening had no appreciable impact on breast cancer mortality. It was the only study to show no beneficial effect of mammography, regardless of age.<sup>24</sup> What makes the Canadian study findings so different from those of other trials? Why was this study the only one to find no beneficial effect from mammography? Rather than delve further to address these questions, most public and private organizations as well as medical associations chose to ignore the Canadian findings and continued to advocate for mammography screening. Many feel that there is compelling evidence to show that mammography has benefits and that it is time to move on.<sup>25</sup>

In an update review of the Swedish randomized trials, researchers extended the follow-up and analyzed the age-specific

and trial-specific effects on breast cancer mortality.<sup>26</sup> In a thoughtful analysis, the Swedish researchers concluded that there is a statistically significant reduction in breast cancer mortality and that the effect of mammography screening on mortality persists after long-term follow-up. In their opinion, the data confirm that screening mammography has a real but modest effect on mortality from breast cancer, although this effect varies with age. The reduction in breast cancer mortality is greatest among those 60-69 at entry to the study, and there were statistically significant effects in the age groups 55-59, 60-64 and 65-69. There was a small effect among those 50-54. That is, the benefits of screening became statistically significant beginning at age 55. Among women in the 55-64 age category, there were 27% fewer deaths among those who were screened than among those who were not. Similarly, deaths were reduced by 14% in the 45-54 age group.

Their conclusion, that the advantageous effect of breast screening on breast cancer mortality persists after long-term follow-up, directly challenges the Danish critique. The Swedish overview focuses on issues of randomization methodology and selection of participants, concerns raised by the Danish researchers. The Swedish study was, in many ways, a methodologically more robust meta-analysis.<sup>27</sup>

For most cancer screening programs, there is only a relatively brief age range during which screening is worthwhile. Breast cancer is rare among very young women, below age 35, for example. Hence, only the very small number of individuals who potentially would benefit from screening would be outweighed by the much larger number of women who

potentially could be “harmed” by regular screening; e.g., inconvenience, cost, or false negative readings. As the incidence of breast cancer increases with age, the benefit of screening increases to the point where the harms might outweigh the benefits. That is, the older the woman, over age 69, for example, the fewer the years in which breast cancer can cause symptoms or death, because there are competing factors such as heart disease or cardiovascular diseases that could lead to death before the cancer. Additionally, it is possible that a screening program for older women would detect more cancers, which would never be clinically important. In this situation, the benefits of screening would be outweighed by the harms.

Mammogram screening is generally considered worthwhile between the ages of 50 and 69 years. In order to quantify when the harms outweigh the benefits, the size of the mortality benefit from screening should be calculated as well as the potential harms of screening such as unnecessary work up for false positive results. Unfortunately, this is not a simple task.

### **The Younger Woman**

The extent of the benefit women in their 40s receive from mammography is a subject of ongoing debate. Mammograms fail to detect up to 25% of breast cancer in women in their 40s compared to 10% for women aged 50 and older.<sup>28</sup> It is well accepted that mammograms of younger, premenopausal women are more difficult to read. Among this cohort, there are more false positive readings, which entail further testing. The overwhelming major-

ity of these cases end up not having cancer, but the discomfort, anxiety and cost of undergoing tests must be factored into the equation. Additionally, there are more false negative readings among this cohort compared to women over age 50. Further complicating the matter, women in their early 40s are biologically different from those in their late 40s. All of these factors must be considered when determining a screening program for women below the age of 50.

There have been several meta-analyses on breast cancer screening among women aged 40-49. A major difficulty with interpreting the evidence from these analyses, however, is that the trials on which they are based either enrolled women aged 40-49 or 45-49, but not women aged 40. This begs the question, "What is the incremental benefit of beginning screening at age 40 rather than at age 50?"

Based on eight randomized clinical trials, a large demonstration project, case-control studies and meta-analyses, there is general consensus that overall, the results showing mortality reduction among women aged 40-49 are mixed, mortality is reduced for the 40-49 cohort, For the most part the benefit of screening women in their forties can be attributed to screening that occurs after age 50. Irwig and colleagues, in their review of the evidence about the value of mammography screening in 40- to 49-year-old women, concluded that approximately 2,600 women aged 40-49 would need to be screened to prevent one death from breast cancer 13 years later.<sup>29</sup> Applying their model to a hypothetical cohort of 10,000 women who were offered screening every two years from age 40, the expected benefit would be a sav-

ing of seven lives after 13 years per 10,000 women invited to begin screening at age 40 rather than at age 50. Of these 10,000 women, 2,000 would have an abnormal mammogram and would be recalled for further assessment. The overwhelming majority of these women will not have breast cancer. Of the 2,000 with abnormal mammograms, 230 would require biopsies of which 100 invasive cancers would be diagnosed. The researchers conclude that the evidence to date shows a modest benefit of initiating screening from age 40 rather than age 50. Any benefit, however, would not be apparent until eight years after the commencement of screening. Further, to be considered against these benefits are the increased rates of false positives and false negatives that will occur among this cohort.

The Irwig et al. model assumed that the 40-49 year old cohort was similar, but it could be argued that the benefit of screening would be greater in the older 45-49 group rather than in the younger 40-44 group. Age, however, is not the only risk factor for breast cancer. Those with a family history or identification of genetic mutations could gain a greater absolute benefit by screening in their forties. At this time, there are no trials that test whether screening would be beneficial for women at high risk of breast cancer. Intuitively, those who are at highest risk could expect to benefit more from screening.

Because the detectable preclinical phase for breast cancer is shorter in younger women than in women 50 years and older, a key issue that remains unresolved concerns the choice of an appropriate screening interval. Should there be annual screening or would a 24-month screening interval be

sufficient? The National Cancer Institute in the United States suggests that women in their 40s have screenings every one to two years, depending on individual risk factors.<sup>30</sup> However, given the evidence, a universal recommendation for mammography for women in their 40s is difficult to make. The most prudent course of action is for the individual to decide for herself, in consultation with her physician, whether and when to initiate mammogram screening. This decision should be based on the individual's risk factors for breast cancer as well as her perceptions of risks and benefits of screening.

### **The Older Woman**

Almost half of new cases and nearly two-thirds of deaths from breast cancer occur in 13% of the female population 65 years and older. However, compared to younger women, women over age 65 are less likely to have ever had a mammogram or to have had a recent mammogram in the past one to two years. In addition, older women who are diagnosed with breast cancer are often at a late stage of the disease, limiting both the treatment options and the chances of survival. Mammography can result in detection of earlier stage breast cancer among older women, thus increasing the odds of increased survival, but there are risks inherent in advocating screening for all elderly women.<sup>31</sup>

The over-65 cohort is also heterogeneous. Women in their 70s, for example, are different from those between 65 and 69, and thus, blanket recommendations should not be made. A recent systematic review designed to assess the benefits, harms

and costs of screening mammography in women age 70 and older found that the benefit of screening women 70-79 years is 40%-72% of that achieved in women age 50-69 years and declines further with increasing age. The life expectancy benefit of screening mammography in older women diminishes with increasing age.<sup>32</sup> From an economic point of view, the central question is whether it would be valuable to extend mammography screening beyond age 69. Given the uncertainty, older women, in consultation with their physician, may want to decide for themselves whether or not to continue with mammography screening. Such choices will vary depending on the degree to which each individual values the possible benefits and risks.

Nevertheless, some organizations recommend screening mammography for women aged 70 and older despite the lack of clear evidence of benefit.<sup>33</sup> Although the data are limited, it is generally agreed that mammograms after age 69 offer little benefit with regards to gains in life expectancy.<sup>34</sup> Especially in this cohort, one needs to take into account the potential harms of mammography. Most of these women have co-morbid conditions such as hypertension, heart disease, respiratory disease and the like, which will affect survival. Regardless of the stage at diagnosis of breast cancer, death from other causes is far more likely within 3-5 years. With reduced life expectancy to begin with, screening mammography will not likely affect overall mortality, but may indeed influence quality of life. That is, diagnostic work up of an abnormal mammogram must be taken into account, especially since the vast majority of these abnormal results would not represent cancer.


One could support the idea of targeting healthy older women rather than those with multiple health problems. For this group of women, screening may be beneficial, as early detection of breast cancer could result in reduced mortality. Nevertheless, a woman's preference for a possible small gain in life expectancy must be weighed against the potential harms of screening. For most women over age 70, perhaps a clinical breast exam would be more appropriate.

## **So, Now What?**

The mammogram debate is far from settled, and many questions remain to be answered. Is screening mammography an effective means of early detection for breast cancer given that it neither detects all tumors nor necessarily increases survival? Researchers reviewing and analyzing the same data sets disagree not only about the age at which mammogram screening should be recommended, but also whether the benefits of mammography outweigh the risks in the first place. Policymakers are equally confused and are perhaps reluctant to publicly state that mammography may not be valuable. While the current debate assumes an either-or decision, the issue is far more complex than that. For instance, the magic cut-off age of 50 years is arbitrary. How does one differentiate a 48-year-old woman from one who is 51 years old? Weighing the costs against the benefits of mammography screening as well as taking into account the psychological impact of false positive screening results must all be considered.

The body of evidence, however, does in-

dicating that mammography is beneficial for women aged 50-69. After age 69, mammography screening offers minimal gains in life expectancy and there are potential harms associated with screening that might outweigh the potential benefits. But, what should be done for women between 40 and 49? For this cohort, the evidence that mammography reduces mortality from breast cancer is weak and the absolute benefit of screening is smaller than it is for older women. Proponents and critics adhering to their position continue to enrich the debate. All the while, it is important to note that their recommendations are based on population statistics derived from studies inherently flawed in methodology. Although some have arrived at strikingly different conclusions about the benefits of mammography screening, the evidence, in my opinion, can support guidelines that recommend breast cancer screening beginning at age 40 or 50.

In truth, choosing whether to undergo mammography largely depends on the circumstances of each individual. For instance, genetic and hereditary risk factors that might predispose a woman to breast cancer must be taken into account. Furthermore, individual risks, including comfort level, as well as associated emotional and financial costs, need to be considered. While not every cancer will lead to death, physicians cannot predict which ones are dangerous and which ones are not. From the woman's perspective, one question remains: how much harm is she willing to accept for an uncertain benefit? 

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