

# Earlier Detection and Diagnosis of Breast Cancer:

{ Recommendations and Scientific Review from  
It's About Time! A Consensus Conference }

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## { PREFACE }

Breast cancer screening has been playing a major role in reducing premature death in women, and scientific evidence supporting this contribution continues to emerge. Nevertheless, varying interpretations of the evidence by individuals and organizations have contributed to different policies and practices, in turn leading to inconsistent and confusing messages for the public.

Although the mortality attributable to breast cancer is gradually falling due to a combination of earlier detection and improvements in treatment, breast cancer continues to be a leading killer of North American women. However, our current health care policies do not allow all women to benefit fully from some of the newer techniques and therapies that have emerged from the latest research and been validated in recent years. This limitation is particularly evident in the area of breast cancer detection, where policies vary not only among countries, but also between Canadian provinces.

To address this situation, the Canadian Breast Cancer Foundation - Ontario Region convened the It's About Time scientific consensus conference and forum. The aim was to provide an opportunity to summarize the relevant scientific knowledge, balanced with a fair interpretation of its limitations, and conclude with clear recommendations for policy and action based on the current evidence.

A conference Scientific Committee was established to identify expert panel participants who could bring the most relevant and up-to-date information and insights to the meeting. They were also asked to develop a draft discussion paper with recommendations based on the research literature that would be circulated to all participants, which included breast cancer survivors, public health advisors, basic researchers, oncologists, clinical trial scientists, epidemiologists, medical imagers, family physicians and breast surgeons.

From October 21-23, 2009 the It's About Time scientific consensus conference convened investigators from Canada, Britain and the United States who spelled out the specific evidence from the scientific literature and from their own diverse research. They, along with decision-makers from the government and the community, reviewed the evidence and their discussion helped to further illuminate and clarify key issues, including what is known about the benefits of screening and whether they outweigh limitations and risks; who should be screened, over what range of age, and how often; how well screening programs perform; and the opportunities for further improvement.

By the conclusion of the conference the presented evidence and draft recommendations had been thoroughly reviewed and refined by the participants, and there was agreement among the majority of discussants on the recommendations presented in this paper. Nevertheless, as not every participant was required to sign off on each recommendation and because some participants had to leave the meeting before its conclusion, the Scientific Advisory Committee should be considered the author of the recommendations.

As many of the participants were breast cancer specialists who diagnose and treat breast cancer and work with patients on a daily basis, there was an opportunity to draw on their direct patient care expertise to inform the recommendations. Along with relevant insights and input from primary health care providers and breast cancer patients, their knowledge was valuable in helping to craft the recommendations in the limited number of instances where clinical trial data did not exist.

The conference proceedings were also documented, and the summary of the presentations and discussions, along with a discussion of the evidence and Recommendations, will be presented in a summary report and position paper authored by the Canadian Breast Cancer Foundation - Ontario Region. Copies of the Canadian Breast Cancer Foundation - Ontario Region report called *Earlier Detection and Diagnosis of Breast Cancer: A Report from It's About Time a Consensus Conference* are available for download at [www.cbcf.org/ontario](http://www.cbcf.org/ontario) or [www.itsabouttimecbcf.ca](http://www.itsabouttimecbcf.ca)

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We would like to thank the Canadian Breast Cancer Foundation - Ontario Region, the Lead sponsor and convener of the conference, as well as CIBC, the conference's Presenting sponsor and Gold sponsors AstraZeneca, GlaxoSmithKline and Pfizer. We would also like to thank the Canadian Institutes of Health Research and the Ontario Institute for Cancer Research for their generous financial support of the conference. And finally, a tremendous thanks to all of the participants for their thoughtful contributions to the discussion that led to this paper and its Recommendations for the Earlier Detection and Diagnosis of Breast Cancer.

## 1. Introduction

Breast cancer is a leading cause of premature death in North American women. While numerous risk factors associated with breast cancer have been identified, most have modest effects on increasing risk and are not practically modifiable. Furthermore, the mechanisms of breast cancer causation are not well understood, and thus a preventive strategy that can be applied to all women remains elusive. However, there is substantial evidence that a significant amount of death and disability caused by breast cancer can be avoided by early detection and appropriate treatment<sup>A</sup>.

Routine testing of individuals for the purpose of attempting to detect cancer before symptoms develop is referred to as **screening**. This report summarizes the best scientific information currently available on effective early detection of breast cancer. A great deal of information has already been written on this topic. The reader is referred to clear and comprehensive articles discussing breast cancer screening in general<sup>1,2</sup> and the age-specific issues of early breast cancer detection in particular.<sup>3</sup>

## 2. Risk of Breast Cancer

It is useful to define some concepts related to risk. In discussions about breast cancer, risk is commonly expressed in terms of incidence and mortality rates, and absolute and relative risks.

*Incidence rates* represent the estimated number of new cases of breast cancer diagnosed each year within a certain population (e.g., per 1,000 or 100,000 women). These rates can be expressed for the population as a whole, or for age-specific subgroups. Since the risk of breast cancer is influenced by age, rates for the population as a whole are *age-adjusted* to a standard population. Age-adjusting the overall breast cancer rate removes the influence of different age distributions in different populations or a changing age distribution in the same population over time, such as is occurring with the maturing of the post-World War II birth cohort. Because age-specific rates (e.g., the annual incidence of breast cancer in women ages 60-69) have a smaller age range, they are not age-adjusted. Age-specific breast cancer incidence rates for North American women are shown in **Table 1**.

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<sup>A</sup> *It is realized that by the time breast cancer can be detected by any practical method, the cells have already been growing for some time. Therefore, in this document the term "early" is intended to mean at a sufficiently early point that there is a reasonable expectation that treatment will reduce the likelihood of mortality, or will at least lead to improved quality of life.*

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*Absolute risk* is the risk estimate that a woman will develop breast cancer. This can be either over her lifetime, or during some other specified period of time. If we consider a group of 1,000 women, the *absolute lifetime risk* of breast cancer can be stated as the number of women per thousand who at some point in their natural lives will develop breast cancer. This estimate takes into consideration that from birth until death some women who might have developed breast cancer do not because they die of other causes. Thus, the actual estimate of the number of women who will be diagnosed with breast cancer is less than the number of women who *would have* been diagnosed with breast cancer if they did not die of other, competing causes of death. For North American women, the absolute lifetime risk of developing invasive breast cancer is 12.08% or about 1 in 8 women; the combined risk of developing either invasive or in situ cancer is 14.5% or about 1 in 7 women.<sup>4,5</sup>

Individuals are generally more interested in their risk in the near term. Thus, at any given time, we can also consider the incidence rates: the number of breast cancers per thousand women at each age that will be diagnosed per year. These rates are known as *age-specific incidence rates*. The 1 in 8 lifetime risk is derived from the aggregate of the accumulation of the age-specific incidence rates shown in **Table 1**. The incidence rates in **Table 1** are for the entire population and thus represent average rates for all women. Certain subgroups in the population, for example women with a significant family history of breast cancer, are at greater risk and within any specific age group would have a higher incidence rate.

**Table 1. Age-specific incidence of invasive breast cancer (per 1,000 women per year); SEER data.<sup>6</sup>**

Age Range	Incidence
35–39	.585
40–44	1.18
45–49	1.85
50–54	2.29
55–59	2.88
60–64	3.51
65–69	3.94
70–74	4.15
75–79	4.42
80–84	4.28
85+	3.42

This brings us to *relative risk*, which describes the higher or lower risk of breast cancer associated with a woman’s particular characteristics or behaviours, which might also be described as “exposures.” The risk of breast cancer varies in different countries (**Figure 1**),<sup>7</sup> being an overall reflection of the differences in underlying risk based on the prevalence of known risk factors in those regions. In Western societies, breast cancer is the most frequent form of cancer in women and is the second largest cause of cancer mortality (**Figure 2**). Risk (incidence) is clearly dependent on age (**Table 1**) and, as noted above, may increase or decrease depending on individual characteristics, life experiences or exposures called *risk factors*. **Table 2** shows the *relative risk* (risk associated with a woman possessing a risk factor compared to not possessing it) for some of these factors. Note that a relative risk greater than 1.0 indicates increased risk, while a value less than 1.0 indicates a reduction in risk compared to women without that factor. An example of an exposure that reduces breast cancer risk is the protective effect of lactation.

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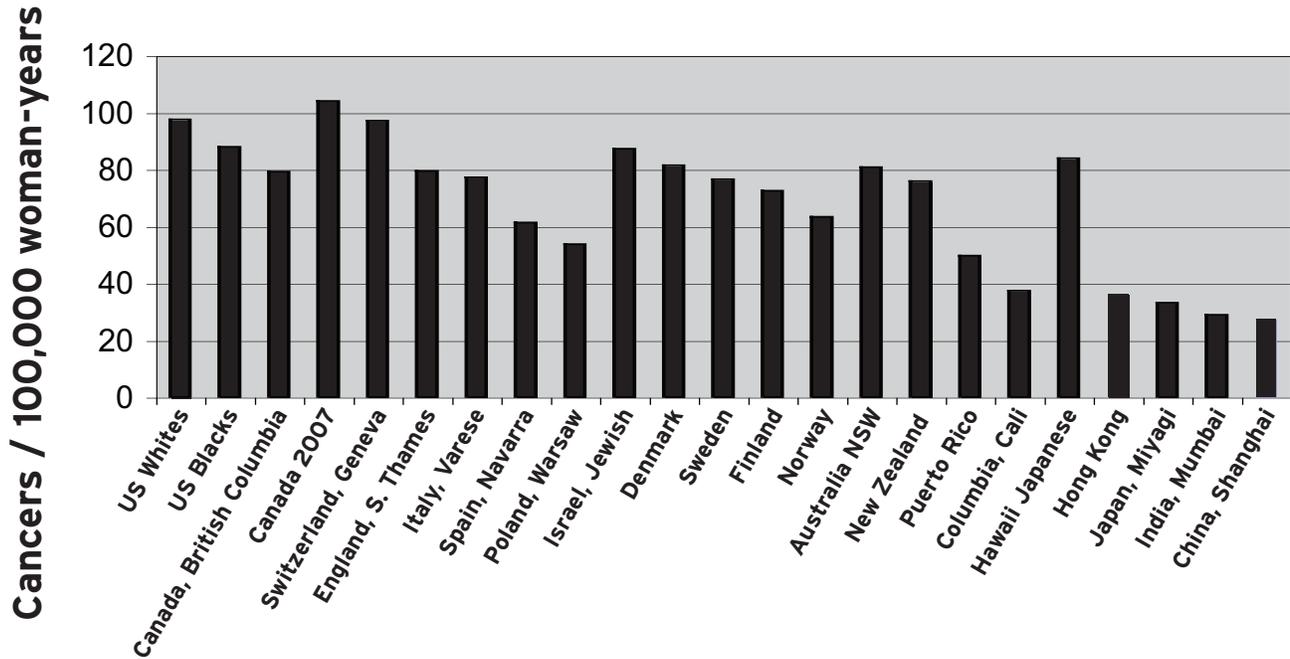


Figure 1. Geographic variation in breast cancer incidence.<sup>7</sup> Data are for the period 1993 to 1997. Value for Canada 2007 from the Canadian Cancer Society.<sup>8</sup> Here, incidence is expressed in terms of the number of cancers per year per 100,000 women in the population.

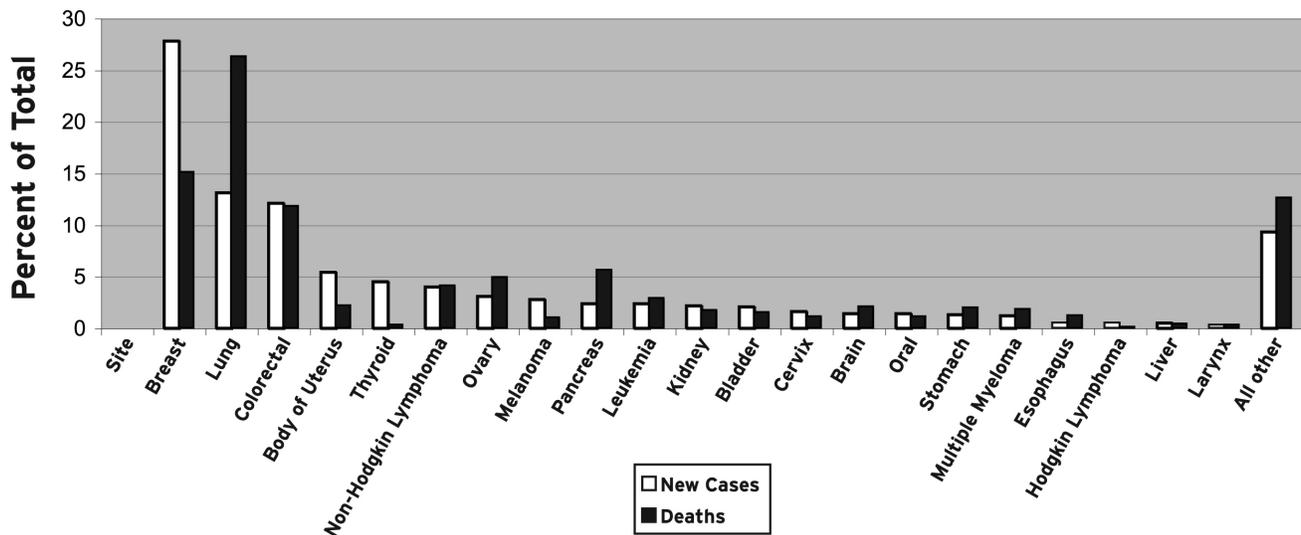


Figure 2. Distribution of new cases and deaths among cancer types. Canadian data.<sup>8</sup>

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**Table 2. Selected risk factors for breast cancer. The right-hand column indicates the strength of the effect on risk associated with having the corresponding factor in the left-hand column. "Strong" indicates relative risk factors of > 3 times, "Medium" 1.5-3 times and "Weak" 1.1-1.5 times. Note that these risk factors do not add to give a risk score. Adapted from the Susan G Komen web site.<sup>9</sup>**

Established Factors linked to breast cancer		Effect on Risk
Increasing Age		Very strong increase in risk
Being female		Very strong increase in risk
BRCA1 or BRCA2 gene mutation		5 - 14 times
Family history of breast cancer		
	Two immediate family members diagnosed with breast cancer	3 - 4 times
	Mother diagnosed before age 60	2 - 3 times
	Mother diagnosed after age 60	1.1 times
High breast density		3 - 6 times
Hyperplasia (benign breast condition)		
	Atypical	2 - 4
	Usual	1.5 - 1.9
Lobular carcinoma in situ (LCIS)		7 - 10
Personal history of cancer (including breast cancer, DCIS, Hodgkin's disease and other cancers)		2 - 6
Radiation exposure or frequent x rays during youth		
	Risk for breast cancer being diagnosed at age 40	11
	Risk for breast cancer being diagnosed at age 60	3.6
Childbearing:	Not having children (compared with having 1st child before 35)	1.3
High levels of blood androgens (pre- and postmenopausal)		2.2
High levels of blood estrogens (postmenopausal)		2
First period before age 12		1.2 - 1.3
Age at menopause 55 or older		2
Alcohol consumption (2 - 4 drinks / day)		1.4
Ashkenazi Jewish heritage		1.1
Birth control pills (current or recent use)		1.1 - 1.3
Being tall		1.2
High socioeconomic status		1.2 - 1.8

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Postmenopausal hormone use (current or recent use for 5 or more years)	Estrogen + progestin	1.3 – 2
Overweight/ weight gain		1.2 – 1.5
Not breastfeeding		1.1 – 1.2
High bone density		2
Lack of exercise		1.2

Mortality rates from breast cancer are expressed in the same way as incidence rates, and risk of death can also be expressed in terms of a lifetime risk or a relative risk. The lifetime risk of dying from breast cancer is considerably less than the risk of developing breast cancer, since most women diagnosed with breast cancer do not die from the disease due to improvements in diagnosis and treatment. We can think about breast cancer mortality in two ways: 1) First, what is the risk of dying from breast cancer? 2) Second, if a woman dies from breast cancer, how much earlier will this death occur compared to if she had not developed a fatal breast cancer? **Since, ultimately, all of us will eventually die from one cause or another, the more important measure of disease burden is how many years of potential life are lost at the time of death.** For example, for the year 2000, it has been estimated that in the U.S., 526,508 women-years of life have been lost in women less than 65 years of age due to breast cancer, and 267,769 women years in women over 65 at a total cost to society of \$121 billion USD.<sup>10</sup> Breast cancer is the leading cause of premature mortality in women due to death from cancer. On average, a U.S. woman who dies from breast cancer dies 19 years earlier than she would have if she had not died from breast cancer. While statistics are not available specifically for Canada, it is expected that they would be similar.

### 3. Breast Cancer Detection

Like most cancers, breast cancer has a long period of growth prior to reaching a size when a woman experiences symptoms from the tumour or when it is detected during a physical exam. There is a period prior to the tumour becoming symptomatic when it is detectable by a mammogram. This period is known as the detectable preclinical phase or the sojourn time, and it is generally between one and several years in length, depending on a woman's age and breast density. Since breast cancer is a heterogeneous (i.e., diverse) disease, some breast cancers may spread to other parts of the body before they would be large enough to produce symptoms, while other breast cancers may not spread until the tumour becomes quite large. There is currently no way to determine with certainty whether a woman will or will not develop breast cancer, and if she does, how aggressive that breast cancer might be. Thus, regular screening to detect breast cancer early, when most breast cancers have not begun to spread and can be cured, is recommended by most organizations. If breast cancers are detected when they are very small, the large majority of patients can be cured of their disease.

#### 3.1. Delivery of Screening: Opportunistic and Organized Screening

Screening can be provided to a population of women in different ways. In opportunistic screening, women choose to go to a facility where testing is available based on advice from a health care provider, friends or the popular media. That facility might provide a variety of different tests whose efficacy and quality can vary considerably, and the interval at which a woman is tested can be regular or sporadic. Provided that the appropriate tests are available, their quality is high and the woman presents herself for screening at appropriate intervals, opportunistic screening can be quite effective. Nevertheless, its effectiveness depends on all of these factors being in place.

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The alternative screening delivery process is referred to as organized screening. An organized program is designed to maximize the probability that all quality elements are in place,<sup>11</sup> including the following:

- a system for identifying the eligible population to be screened
- a means for advertising the availability and potential benefits of the program
- a mechanism for the invitation of eligible participants and re-invitation at the appropriate regular intervals
- a comprehensive quality assurance system that includes
  - maintenance of standards for qualifications,
  - requirements for training and continuing education of personnel,
  - standards for safety,
  - standards for equipment and its maintenance, and
  - regular review of performance measures;
- a means for directing those women who have suspicious findings on screening to appropriate workup or assessment

### **3.2. Benefits, Limitations and Harms Associated with Breast Cancer Screening**

**Benefits:** The main benefit of early detection through screening is the reduction in mortality due to breast cancer. Other benefits include avoiding or minimizing the possible negative outcomes associated with a diagnosis of advanced breast cancer, which include more aggressive surgery (mastectomy v. lumpectomy) and chemotherapy, and if treatment is not successful, years of disability, reduced years of life and the loss for dependents, family and friends of those who die of breast cancer. There is also a great cost to society in treating the disease and losing a productive member of society.

If death from breast cancer is not prevented outright by earlier detection, then at least a delay in death is possible. As well, earlier detection allows for the employment of therapies that are more easily tolerated and may be less costly for breast cancer patients, and for other improvements to the quality of life.

**Limitations and harms:** No screening test is perfect, and mammography, the imaging test most widely employed for the detection of breast cancer, has a range of known limitations. “Limitations” refer to human, technical, and host-related factors that cause the performance in detecting cancer to be less than perfect and are distinguished from “harms,” which are negative consequences that can befall an individual. Limitations can result in harms unless those limitations are recognized and informed decisions are made with the knowledge that those limitations exist.

**Limitations of mammography screening:** Regular screening will not identify all breast cancers, although it will identify most of them. Technical and human limitations contribute to the failure to detect some breast cancers at the time of screening. These “misses” are referred to as *false negatives*, i.e., the exam is interpreted as normal when in fact the patient has breast cancer. It also is the case that mammography is less accurate in some women, leading to a failure to detect a breast cancer at the time of screening. On the other hand, the accuracy of mammography can be limited by the appearance of abnormalities in the breast that are interpreted as positive detections, but ultimately are determined to not be breast cancer. These results are called *false positives*. The large majority of false positive results are quickly ruled out by doing additional imaging of the breast. However, some positive results cannot be resolved without a biopsy to determine if the abnormality is cancer.

**Harms associated with mammography screening:** Although the benefits of mammography are well established, certain downsides associated with regular screening are commonly expressed as “risks” or “harms.” These harms include the pain that some women experience during the examination, the consequences of the inaccuracy of mammography and the exposure to ionizing radiation during the examination. At some point the distinction between limitations and harms can become an exercise in semantics. For example, if a suspicious screening examination prompts a needle biopsy procedure that determines that

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no cancer is present, some would consider the “unnecessary” biopsy experience to be a limitation of an imperfect screening test while others would think of it as a harm. The distinction might be made on the basis of how frequently such negative biopsies occurred. On the other hand, if a surgical biopsy (a much more elaborate procedure requiring an anaesthetic) were carried out and no cancer was found this would almost certainly be thought of as a harm. The trade-off between benefits and harms will be discussed later.

**Overdiagnosis:** Overdiagnosis is the diagnosis through screening of treatable disease (in situ and invasive breast cancer) that would never have given rise to clinical symptoms during a person’s lifetime. In other words, if screening had not taken place, the disease would never have been identified and would not have caused death in the patient’s lifetime.

The term “overdiagnosis” is commonly applied to circumstances that, although quite disparate, result in the same lack of benefit from early detection. First is the theoretical possibility of diagnosis of lesions that have no biological propensity to progress; in other words, they are histologically neoplastic, but biologically benign. Overdiagnosis must be understood as a statistical phenomena because it is impossible to determine if any malignancy is truly non-progressive. Overdiagnosis is quite prevalent in screen-detected, pre-malignant lesions of the uterine cervix or adenomas in the large bowel and quite possibly in some cancers of the prostate. Estimates of the rate of overdiagnosis of invasive malignant lesions of the breast vary, but most careful estimates are less than 10%, with a benefit-risk estimate that is clearly favourable to screening.<sup>12,13</sup> Likewise, there is a larger proportion of in situ lesions with dubious potential for progression, but non-progressive lesions still are likely to be a minority of DCIS (ductal carcinoma in situ) cases.

The second circumstance pertains to the early diagnosis and treatment of a cancer that would not have been life threatening without detection by screening before a patient died from some other cause. This kind of overdiagnosis is of greatest concern when screening is offered to individuals who have very limited longevity due to life-limiting, co-morbid conditions with little possibility of benefiting from any preventive health measure. While it is commonly included in definitions of overdiagnosis, the proper definition refers only to those malignancies that would not have progressed to become symptomatic cancers. The true limitation of screening in this case may be related to the kind of specificity currently available in the pathology diagnosis, rather than the actual detection of an abnormal imaging finding.

### 3.3. Test Performance

**Types of screening errors:** Although many of the screening tests for cancer are quite accurate, none is 100% accurate. As discussed above, detection tests are susceptible to two types of errors. Some cancers that are present can be missed (a *false-negative* result), or there can be false alarms (*false positives*) when the test suggests that cancer is present when it is not. The first type of error causes a delay in diagnosis that in some cases can be detrimental to the patient. This delay may also be lengthened by a false sense of reassurance given by the false negative; for example, a woman may ignore a lump because of her “normal” mammogram. On the other hand, the false-positive type of error causes stress in the patient and her family until the uncertainty of her positive finding is resolved, most often by additional imaging procedures; as well, the false positive may trigger performance of additional test procedures that are harmful, such as surgical biopsies. The detection method itself may also have associated negative aspects or risks, such as discomfort due to compression of the breast, exposure to X-rays, the need to undergo the injection of a contrast agent, etc.

**Attributes of a good screening test:** It is generally accepted that in order to detect breast cancer early enough to make a difference in mortality or quality of life, detection should take place before symptoms of the disease are evident. Applying a test routinely to women without symptoms is known as *screening*.

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A technique that is used for screening should have several key properties:

1. It should be sensitive in detecting the disease, i.e., there should be few false negatives. *Sensitivity* is the probability of finding a cancer if it is present in the breast. For example, if 5 women who have cancer are tested and cancer is found in 4 of them, then the sensitivity is  $4 / 5$  or 80%.
2. It should be specific. *Specificity* is the probability of determining that there is no cancer when, in fact, no cancer is present, thereby avoiding a false-positive finding. If 200 women without cancer are examined and 190 are correctly told that they don't have cancer (while the other 10 have further examination), then the specificity is  $190/200$  or 95%.

An important analogous concept is *positive predictive value* (PPV). This is the probability that when a positive test result occurs, cancer is actually present; PPV is given by  $PPV = TP / (TP + FP)$  with TP being the number of true positive test findings (cancers correctly detected). The PPV approaches 1.0 as the number of false positive findings is reduced, so it depends on both the specificity of the test and the number of people in the screened population who do not have cancer.

Another related statistic is the recall rate, which is simply the fraction of individuals tested who receive a positive test result and therefore will require additional testing (possibly including biopsy), i.e.,

$$\text{Recall rate} = (TP+FP) / (TP+FP+TN+FN)$$

This rate, which is often expressed as a percentage, can be minimized by minimizing the number of false positive test results, but as discussed below (regarding the Receiver Operating Curve), beyond a certain point this will only be accomplished with a loss of sensitivity (i.e., cancers will be missed).

3. It should be safe. If radiation is used, doses should be as low as possible.
4. It should be affordable.
5. It should be accessible.

**How the performance of a screening test is evaluated: the Receiver Operating Characteristic (ROC):** Most medical tests don't have a single sensitivity or specificity. Instead, these can be varied according to how the test is performed or interpreted, and based on the performance of the test in a population over consecutive years of screening, i.e., *program* sensitivity and specificity. However, one graphic way of describing the performance characteristics of a test is through what is known as its *receiver operating characteristic* or ROC. The idea is illustrated in **Figure 3**, where the sensitivity versus specificity of two different tests are plotted. A perfect test, represented by the dot in the upper right hand corner of the graph, would find all cancers (100% sensitivity) and create no false positives (100% specificity).

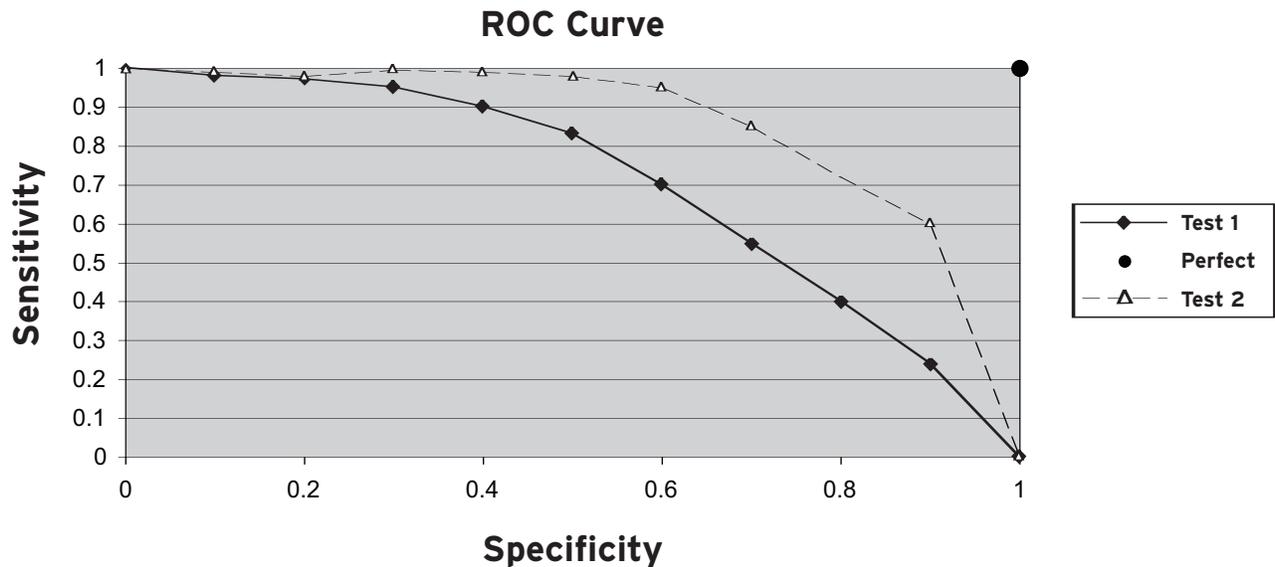


Figure 3. ROC curve. Test sensitivity is plotted versus specificity. Test performance improves as the curve approaches the upper right-hand corner of the graph.<sup>B</sup>

A real test such as Test 1 does not do as well, and a point describing its performance falls below and to the left of the upper right-hand corner. That said, usually a test cannot be described by a single point because its sensitivity and specificity will depend on how it is performed. Therefore, the performance of the test is described by multiple points, i.e., a ROC curve for that test.

Let's say that as a test is being performed, it achieves a sensitivity of 70% and a specificity of 60%. By interpreting the data from this same test more aggressively, the cancer detection rate can be increased to 80%, but for this test, the improvement would be accomplished at the expense of a drop in specificity to about 54% (i.e., for 46% of the examinations, the test would yield a false positive result). Therefore, there is a trade-off between sensitivity and specificity; as one increases, the other falls.

When radiologists perform imaging tests for cancer, their accuracy is described by curves such as this one. In their work, they attempt to achieve the highest sensitivity at an acceptable false positive rate, i.e., at an acceptably high specificity. Where they are able to operate on the curve depends on factors such as their experience, the prevalence of disease in the population being imaged (e.g., are they at normal or high risk?), and also on the consequences of a missed cancer or a false positive result.

The ROC for a different test, Test 2, is also shown in **Figure 3**. This is a better test than Test 1 because at any level of specificity, higher sensitivity is obtained so that the curve lies closer to the upper right-hand corner of the graph. Therefore, superior cancer detection can be obtained if this test replaces Test 1. Note, though, that even for Test 2, a range of sensitivities (each with an associated specificity) is possible depending on how the test is performed. It is also important to recognize that

<sup>B</sup> Frequently ROC curves are plotted instead as a graph of true positive fraction versus false positive fraction, i.e., sensitivity versus 1-specificity, so that a perfect test would be represented by a dot in the upper left-hand corner. In this document both conventions will be used.

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the actual levels of performance illustrated by the ROC curve for a test can only be achieved if the test is conducted with the proper equipment and technique, and is interpreted by an appropriately trained and skilled individual.

**Choice of an operating point:** The choice of the operating point on the ROC is important and, as discussed above, varies for different reasons. For example, in North America, screening a group of 1,000 women in their 50s with mammography typically yields a positive test result in 8% to 12% of examinations<sup>13</sup>. Most of these women will not have breast cancer, so the specificity of screening (percentage of false positives) will be in the range of 88-92%. This false positive rate is influenced by a strong desire to avoid missing cancers; in other words, some specificity is lost in order to obtain higher sensitivity. On the other hand, in Europe, where there is a stronger emphasis on maintaining high specificity, false positive rates are typically kept below 4% (96% specificity), presumably at the cost of some reduced sensitivity. It must be mentioned that such comparisons are simplistic because a proper comparison must also consider the actual size and stage of cancers at the point of diagnosis, rather than simply whether they are detected or not.

Some of the techniques that have been evaluated for screening and are currently being used, or are being studied and considered for this purpose, include clinical manual breast examination (palpation), film mammography, digital mammography, ultrasound, breast MRI, tomosynthesis, breast computed tomography, and nuclear medicine imaging procedures such as single photon emission computed tomography (SPECT) and positron emission tomography (PET). Information on the performance of these techniques in screening is provided in the Appendices, with examples of ROC performance wherever available.

### 4. Developing Rational Policy

The key questions relevant to policy and individual decisions about breast cancer screening are similar to those that would be asked in reference to any screening program:

1. Based on evidence, does cancer screening reduce mortality or contribute to increased years of life?  
For what age groups?
2. Does earlier detection contribute to improved quality of life?
3. Are some screening methods more appropriate for certain groups of women?
4. What is the optimum interval for screening?
5. What special provisions are required for women at high risk and for younger women?

### 5. Evidence of the Efficacy of Screening

Information provided through the ROC on the accuracy of a screening test represents only part of the total evidence needed to determine the efficacy of a screening program. The other components are usually addressed through various types of studies in which screening is actually performed.

Numerous research studies over the past forty years have provided useful information on the performance of different screening methods, and these studies have been conducted with different methodologies possessing varying strengths and weaknesses. These include randomized controlled trials (RCTs), case-control studies, observational studies of existing service screening programs and simulations of screening.

**Randomized controlled trial of screening:** In an RCT, a woman is randomly assigned to one of two groups: one that will be invited to screening (the intervention group), or one that will not be invited to screening (the control group). The end point (usually the number of deaths due to breast cancer) is compared between the groups or *arms* of the study after several rounds of

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screening and a number of years of follow-up. The strength of an RCT lies in the elimination of different biases known to influence screening studies such as self-selection, lead-time bias and length bias.<sup>14</sup> These biases can contribute to incorrect conclusions regarding the performance of screening. They are eliminated when the arm of the trial in which a woman participates is determined by random chance. While counterintuitive, it is customary to analyze results of RCTs according to the *assignment* of individuals to one arm or the other regardless of whether or not the individual has actually complied with the study protocol. For example, some individuals in the intervention group may have refused to receive the intervention, and others in the control group, desiring to partake in the intervention, have sought and received it outside the study. This *crossover* will tend to weaken the apparent effect of an intervention. While RCTs are the strongest form of evidence of the efficacy of screening, they are very costly and take many years to complete. Given the increasingly rapid pace of technology and the evolution of our understanding of the best use of the technology at hand, RCT results often represent outcomes based on outmoded protocols. This, in combination with comparing deaths in the entire experimental group and control group regardless of whether the screening exposure was received or not, can artificially lower the estimate of the true benefit.

**Retrospective case control study:** The case control study is a design that can provide additional evidence on screening effectiveness. The advantage of this approach is that it is a low-cost strategy that may provide evidence more quickly than RCTs when the screening procedure is already in clinical use.<sup>15</sup> Although mortality reduction can be an end point measured in these studies, case-control studies are also subject to bias and confounded by uncontrolled factors. In a case control study, the screening histories of subjects who have died from the cancer of interest (cases) are compared with living controls matched according to age and other characteristics. The methodology of these studies is complex because the definition of exposure to screening may inadvertently add bias to the findings in favour of the cases or controls. Furthermore, even the process of age-matching, which is seemingly straightforward, may introduce bias if there is interplay between the age to begin screening, the interval for screening, and whether chronological age or birth year(s) is used.<sup>16</sup> Thus, it is not uncommon for medical literature to contain case control studies that reach different conclusions about the efficacy of exposure to screening.

**Evaluation of service screening:** Although there have been many ad hoc judgments about the influence of screening on breast cancer mortality when examining population trends, the evaluation of service screening is complex due to the need to isolate screened and unscreened cohorts when comparing trends in end results. In the evaluation of service screening, a comparison is made between various end results (mortality, the incidence rate of advanced disease, etc.) in a group that has been invited to screening or is actually receiving screening and the group that has not yet been invited to screening, or that has rejected the invitation to screening.<sup>17</sup> The advantage of these studies is that they evaluate not only the effects of breast cancer screening in the community, but also the impact of screening on women who are exposed and not exposed to screening. In addition, the evaluation provides a better opportunity to examine the age-specific benefits of screening, whereas RCTs are limited to age at randomization. However, as with case control studies, these studies are observational and can thus be subject to the biases mentioned above, although the evaluation of modern service screening has demonstrated that adjustments for known biases can be made based on findings from the RCTs.<sup>18</sup> For example, there is the bias of “self-selection,” in that women themselves have chosen to be screened or not, rather than being allocated randomly into either a group that is invited to screening or one that receives usual care. Women who choose to be screened may have different characteristics than those who do not, which may also affect the nature of their breast cancer, how it is treated and whether they die from this disease. In some cases, during the analysis, corrections can be made for these biases. A major advantage of the data from service screening programs is that they do represent the real-world delivery of screening and, unlike RCTs, the groups that are compared represent women who have *actually received* the intervention and those who have not.

**Simulation of screening:** This study is used for a purpose other than screening or in a group without a comparable reference group. Various surrogate indicators of performance of the screening test are measured in one group and used to infer what effect could be achieved in a screening population. For example, a test may be used for diagnostic purposes (i.e., women have

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already demonstrated an increased probability for having breast cancer, perhaps by having symptoms) on a number of women. Sensitivity and specificity of the test can be measured on these women. Since their risk is high and several cancers are likely to be discovered, the test can be evaluated with statistical significance in a relatively small population. The results could then be translated to draw an inference on how the test would perform in a screened population of individuals at lower risk. While this approach is attractive, there is a risk that performance measured this way would not be representative of what would be attainable in the screening setting. For example, if the physician interpreting the image is aware that there will be a relatively large number of cancers in the population, he or she may operate at a higher sensitivity point on the ROC curve than they would with a screening population where the cancer incidence will be lower.

### **6. Recommendations: Considerations and Limitations**

The scientific review resulted in evidence-based recommendations on breast cancer screening for women of average, intermediate and high risk. The recommendations are based on evidence from the randomized control trials of screening and observational studies of service screening. Where evidence did not exist, or where there were gaps in recommendations, additional information and assessments were provided by experienced specialists who diagnose and treat breast cancer as there was an opportunity to draw on their direct patient care expertise to inform the recommendations.

For example, while no studies have been carried out on screening women who are at intermediate risk (15% to 25% lifetime risk) for breast cancer, it was considered that those in this category required more intensive surveillance than women at average risk. Based on the understandings of experienced specialists of the sensitivity and specificity of different imaging modalities, they proposed a hybrid between the regimens for average-risk and high-risk screening as a reasonable approach to address the needs of this group.

The recommendations do not consider other factors that influence decisions about breast cancer screening policy and practice, including those related to health economics, public policy priorities and issues, as well as political issues. These can all play a role in determining how recommendations based on scientific evidence may or may not be engaged. Given that there are always competing priorities for finite resources and there may be other causes of mortality and morbidity considered to be more pressing at a particular time, not all worthy initiatives can be funded. Recognizing that these factors, along with scientific evidence, influence decisions helps to ensure increased transparency about the decision making process.

Several presentations at the It's About Time Consensus Conference discussed the important issue of geographic, cultural and social barriers to women benefitting from the most effective approaches to detection and diagnosis of breast cancer. Presenters considered the factors causing poor participation in screening in some socio-demographic groups. The issues are sufficiently critical that it was felt that the time available at the conference did not allow for an adequate discussion to take place, and that further refinement and additional input were necessary before recommendations in this area could be framed. Therefore, while recognizing the importance of these barriers and the urgent need to develop strategies to overcome them, we will not attempt to provide such recommendations here. Some of the evidence that motivates additional effort in this area is presented in Appendix 7.

Shortly after the conference and the discussions that led to this document, the U.S. Preventive Services Task Force released its recommendations.<sup>19</sup> This report sparked great controversy because it largely reverses some of the recommendations of this same committee that were published in 2002. Some comments regarding this report and the differences between its recommendations and those arising from the It's About Time conference are presented in Appendix 8.

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## Recommendations

The breast cancer screening recommendations of the Scientific Advisory Committee for the Conference on the Earlier Detection and Diagnosis of Breast Cancer, October 21–22, 2009, Toronto, Canada are summarized here.

The Scientific Advisory Committee, chaired by Dr. Martin Yaffe, drafted an interim set of breast cancer screening recommendations. At the end of the conference, all participants had an opportunity to review and revise the draft Recommendations, in a point-by-point discussion, followed up by email.

Supporting evidence is provided in the Appendices. The criteria for risk categories (average, intermediate, high) are documented in Appendix 1.

### 1. Screening of women at average risk:

- a. **Age to begin:** Eligible at approximately 40 years old.
- b. **Modality:** high-quality digital mammography (preferred) or film mammography. Delivered within an organized program (see above).
- c. **Interval:** annually between ages 40 and 55 (or the onset of menopause, whichever occurs earlier); every one to two years thereafter, based on risk factors and breast density. Women in BIRADS 3 and 4 density categories should be screened annually, preferably with digital mammography.
- d. **Age to terminate screening:** generally, screening is recommended for women who have at least a 10-year life expectancy, taking into consideration current health status.
- e. **Targeting:** special efforts to encourage women to participate in screening should be used for the age group 50-73.
- f. **Evidence:** Appendix 2.

### 2. Surveillance of women at intermediate risk (15–25% lifetime risk):

- a. **Age to begin:** 40 years old, or after a diagnosis with breast cancer or high-risk lesion.
- b. **Modality:** digital mammography and ultrasound. MRI may be appropriate, and if performed would replace ultrasound. Delivered within an organized program.
- c. **Interval:** annually.
- c. **Evidence:** Appendix 2, 3, 4.

### 3. Surveillance of women at high risk (over 25% lifetime risk):

- a. **Age to begin:** by 30, but not before age 25.
- b. **Age to terminate and rejoin normal screening stream:** 60 years old, unless the breast is at least heterogeneously dense.
- c. **Modality(ies):** contrast-enhanced breast MRI special breast technical protocol, plus digital mammography. Ultrasound could be used if MRI is not available. Delivered within an organized program. Modality is identified by an initial process of multi-disciplinary risk assessment. This assessment could take place through a tool for self-identification such as the Gail or BRCAPRO model (this could be available on a web site) or in discussion with the primary care provider and referral to an organized high-risk clinic.
- d. **Interval:** annually.
- e. **Special issues:**
  - i. Due to radiation concerns for young women (under 30 years of age) at high risk, it is suggested that, prior to age 30, the required useful information regarding the presence of breast microcalcifications could be obtained from a one-time only, single-view screening mammogram.

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- ii. Use of MRI may not be possible due to metallic implants, claustrophobia or susceptibility to nephrogenic systemic fibrosis (NSF). In such cases, digital mammography plus ultrasound could be considered as alternatives.

**f. Evidence:** Appendices 3 and 4.

**4. Clinical breast examination (CBE):** Where organized screening programs using mammography, ultrasound and / or breast MRI are available, women should be informed of the risks and benefits of having a CBE in addition to mammography for breast screening. If CBE is offered as a screening test, standards for training, performance and tracking should be established as for mammography. The evidence that supports the effectiveness of CBE in reducing mortality is indirect, as no randomized controlled trial has studied CBE alone without mammography. While clinical breast examination by a trained health professional can contribute slightly (approximately 5-10%, i.e., 2.5-4 cancers per 10,000 screening examinations) to the cancer detection rate achievable with mammography alone in an organized screening program, CBE sharply increases the number of false positive examinations and the cost and complexity of offering screening.

**Evidence:** Appendix 5.

**5. Breast self-examination (BSE):** There is insufficient evidence that breast self-examination, a standardized technique of self-examining breasts, contributes to the reduction in mortality due to breast cancer, but also insufficient evidence that it does not. Women should neither be encouraged nor discouraged from practising BSE. There may be some benefits from women being aware of changes in their breasts and discussing these with a health care provider.

**Evidence:** Appendix 6.

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## Appendix 1: Identification of Risk Categories

The MD Anderson Cancer Center in Texas has provided helpful guidelines for estimating risk categories for individuals to assist in identifying the appropriate strategy for screening. The material here has been adapted from those guidelines. These categories are intended to be used for individuals without symptoms of breast cancer. Those with symptoms should consult their health care provider without delay.

### Risk Categories

#### Average Risk

Women at average risk of breast cancer are those who have the following:

- No history of radiation treatment to the chest
- No genetic mutations, including an abnormality in the BRCA 1 or BRCA 2 genes, Li-Fraumeni Syndrome, CDH1, Cowden's Syndrome or Bannayan-Riley-Ruvalcaba Syndrome
- No history of lobular carcinoma in situ
- A five-year risk of breast cancer less than 1.7% for women age 35 or older, as defined by a Gail Model calculation. A risk calculator based on this model is available at [www.cancer.gov/bcrisktool/Default.aspx](http://www.cancer.gov/bcrisktool/Default.aspx).
- A lifetime risk of breast cancer less than 15%, as defined by models dependent on family history.<sup>c</sup> Women with a strong family history of breast cancer should consider speaking with a genetic counsellor to learn more and to have their risk determined.

#### Intermediate Risk

Women at intermediate risk of breast cancer are those who have the following:

- Extremely dense breasts or at least heterogeneously dense breast tissue and one of the following conditions:
  - i. Personal history of breast cancer, but not known or suspected to be a carrier of the genetic mutations, including an abnormality in the BRCA 1 or BRCA 2 genes, Li-Fraumeni Syndrome, CDH1, Cowden's Syndrome or Bannayan-Riley-Ruvalcaba Syndrome
  - ii. Prior high-risk lesion (ADH, ALH, LCIS, atypical papilloma) and not currently on chemoprevention
  - iii. Intermediate family history of breast cancer with lifetime risk of 15-25%

#### High Risk

Women at high risk include those who have the following:

- A history of radiation treatment to the chest
- Genetic mutations, including an abnormality in the BRCA 1 or BRCA 2 genes, Li-Fraumeni Syndrome, CDH1, Cowden's Syndrome or Bannayan-Riley-Ruvalcaba Syndrome
- A history of lobular carcinoma in situ
- Five-year risk of breast cancer 1.7% or greater at age 35 or older, as defined by a Gail Model calculation. A risk calculator based on this model is available at <http://www.cancer.gov/bcrisktool/Default.aspx>.

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<sup>c</sup> The MD Anderson guidelines state 20%; however, we have defined an additional "intermediate risk" category that extends between 15% and 25%.

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- A lifetime risk of breast cancer 25% or greater, as defined by models dependent on family history. Women with a strong family history of breast cancer should consider speaking with a genetic counsellor to learn more and to have their risk determined.

In addition, for the purposes of identifying candidates for routine screening by breast MRI the American Cancer Society (ACS) includes the following factors: <sup>46</sup>

- First-degree relative of BRCA carrier, but untested
- Lifetime risk of ~20% to 25% or greater, as defined by the BRCAPRO model or other models that are largely dependent on family history

Notably, this document differs from the MD Anderson or ACS Guidelines in that here the transition from intermediate risk to high risk occurs at 25% lifetime risk of breast cancer, while the US guidelines consider high risk to be above 20%.

### Appendix 2: Performance of Screening Mammography

**Tables 3** and **4** list the international performance trials of breast cancer screening. The performance of the trials is relatively consistent, although there was a range of outcomes in terms of observed mortality reductions. The differences are due to several factors, including the number of screening rounds and the duration of follow-up; differences in the screening protocol, including the screening interval and number of mammographic views; and differences in sensitivity. Sensitivity depends on such factors as the density of the breast, the size and type of the cancer, the equipment and exposure techniques used, the interval between screens, and perhaps most importantly, the experience and skill of the technologist and the radiologist. Reports of the sensitivity in historical trials of mammography screening will vary enormously because of differences in these factors. However, despite these differences, individual trials and meta-analyses show statistically significant breast cancer mortality reductions in the group invited to screening versus the group randomized to usual care (see **Table 4** below). Also consistent is the strong association between the magnitude of the mortality reduction and the magnitude of the reduction in the incidence rate of advanced breast cancer in the group invited to screening.

**Table 3. Sensitivity of mammography in various historical screening trials. From Humphrey et al.<sup>33</sup> and Tabar et al.<sup>26</sup>**

Study	Age range	Screening period (approx.)	Sensitivity (%)
HIP	40 - 64	1963 - 1967	39
Malmö	45 - 49	1976 - 1986	73
	50 - 59	1976 - 1986	71
	60 - 69	1976 - 1986	85
Swedish 2-County	40 - 49	1977 - 1989	82.4
	50 - 59	1977 - 1989	91.4
	60 - 69	1977 - 1989	93.5
Stockholm	40 - 49	1981 - 1985	64
CNBSS-1	40 - 49	1980 - 1985	61
CNBSS-2	50 - 59	1980 - 1985	66

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Data are also presented for the performance of more modern mammography<sup>21</sup> The sensitivity overall is considerably higher than it was in the earlier time period over which the RCTs were conducted.

**Table 4. Performance measures for 3,603,832 screening mammography examinations from 1996 to 2006 by age.**<sup>21</sup>

	Sensitivity (%)	Specificity (%)	PPV (%)	Recall(%)
Overall	80.2	91.4	4.3	8.9
Age 40–49	70.8	89.8	1.5	10.3
45–49	74.3	89.8	2.3	10.3
50–54	78.4	90.9	3.3	9.2
55–59	81.6	91.5	4.6	8.8
60–64	80.0	91.9	5.4	8.4
65–69	82.5	92.4	6.3	8.0
70–74	82.9	93.1	7.9	7.3
75–79	84.5	93.6	9.8	6.9

Note that a specificity of 91.4% indicates that 91.4% of the women screened who do not have breast cancer will be correctly told that they do not have the disease, while 8.6% will be asked to undergo further assessment. This rate for assessment of suspicious findings on screening is probably higher than optimal for the most practical sensitivity; the consequence is increased stress, costs and morbidity for women who eventually undergo biopsy. It is certainly desirable to reduce this rate while still maintaining high sensitivity. Nevertheless, most women, when made aware that false positives are one of the “costs” for detecting small, node-negative breast cancer if it is present, readily accept this reality of an imperfect test.<sup>22</sup>

In the Digital Mammography Imaging Screening Trial (DMIST)<sup>23</sup> whose results were published in 2005, the sensitivity for film mammography overall was 66%, whereas it was only 55% for women with dense breasts. The specificity was 92% overall and 90% for women with dense breasts. The reader should understand that the authors chose an algorithm for estimating sensitivity that was much more conservative than the methods conventionally used.<sup>D</sup>

### **Mortality Reduction**

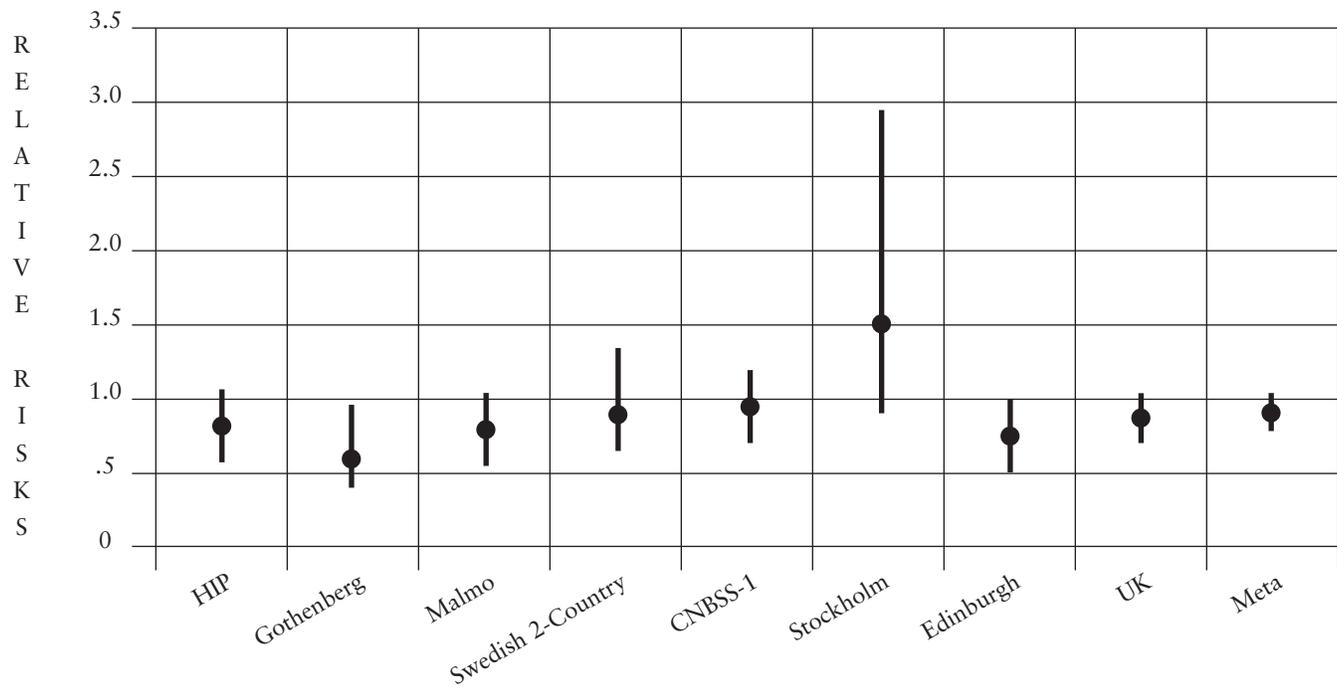
Screen-film mammography is the **only** imaging technique that has been directly demonstrated to contribute to reduced mortality from breast cancer. Nine randomized controlled trials (RCTs) have been conducted.<sup>24,25,26,27,28,29,30,31,32</sup> During the period over which these trials were conducted and since that time, enormous technical improvements have occurred in mammography involving the technology, the exposure technique and the image interpretation process. Therefore, measurement of the performance of screening has to be thought of as a moving rather than a static target. Each study had its own strengths and weaknesses. Some trials showed a mortality benefit of mammography screening, while others did not.

<sup>D</sup> In the DMIST, sensitivity was calculated as the number of cancers detected as a result of the screening divided by the total number of cancers discovered clinically or at a one-year mammogram over a follow-up period of either 365 days or 455 days. Here, the data for 365 days are quoted to be consistent with data reported in other studies. Nevertheless, these sensitivities will be lower than seen from other studies because a cancer detected in a mammogram one year after the screen would be normally considered as an incident cancer, rather than a missed cancer as was done in the DMIST.

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To improve the overall statistical power of these studies to demonstrate an effect (if one exists), it is common to perform a meta-analysis, essentially, a pooling of the data from all studies. Such an analysis carried out by Humphrey et al.<sup>33</sup> demonstrated a mortality reduction of 16% for women over the full range of ages studied (40-74), i.e., a relative risk of 0.84 (95% CI, 0.77 to 0.91), equivalent to a number needed to screen (NNS) of 1,224 to prevent one breast cancer death. For women in the age range 40-9, the summary relative risk<sup>E</sup> was 0.85 (CI, 0.73 to 0.99) after 14 years of observation, and it was estimated that the NNS was 1,792 women (CI, 764 to 10,540) to prevent one death from breast cancer. The authors also analyzed the trials with the exclusion of the Canadian women in the 40-49 age group (CNBSS-1 in **Figure 4**) because these women had been pre-screened by a nurse clinical examiner before entry to the study; the authors found that the summary relative risk fell to 0.80 (CI, 0.67 to 0.96), i.e., a 20% mortality reduction. This corresponds to a number needed to invite (NNI) to screening of 1,385 (CI, 659 to 6,060) women to prevent one death from breast cancer. Note that the NNI is a poor proxy for the NNS, which reflects actual exposure to the screening intervention.

**Figure 4. Outcome, shown as relative risks (RR) of breast cancer mortality of various RCTs for mammography screening of women in their 40s.**



<sup>E</sup> The authors excluded the Edinburgh trial for having been of poor quality.

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Tabar et al. examined the impact of service screening in Sweden by comparing mortality rates in women before screening was introduced with those in screened and unscreened women after the introduction of screening.<sup>34</sup> Corrections were made for self-selection bias and for the change in breast cancer incidence rates between the two periods. The investigators found evidence for a statistically significant mortality reduction of 41% associated with 40-49 year old women who underwent screening compared to those who did not. In the overall group in the age range 40-69 years, the mortality reduction was 44%.

Coldman et al. compared mortality due to breast cancer between women who participated in mammography screening in the British Columbia Breast Screening Program<sup>35</sup> and those who did not. They found a mortality ratio (relative risk) associated with being screened of 0.61, i.e., a mortality reduction of 39%, with similar values for women aged 40-49 and those over 50. After excluding the effects of mortality associated with cancers diagnosed after age 50 in women for whom screening started in their 40s, and correcting for self-selection bias, the mortality ratio for both age groups was 0.76, a mortality reduction of 24%.

Moss et al.<sup>36</sup> carried out a randomized trial of film mammography screening of women in their 40s in the UK with breast cancer mortality as an endpoint. This study had some limitations in that, contrary to modern practice, after the initial screen with two mammographic views per breast, subsequent screens were performed with only a single view. Nevertheless, in the authors' report in 2006, which had involved 10.7 years of follow-up, for women who were actually screened the study found a mortality reduction of 24% (RR = 0.76) that just missed statistical significance (CI = 0.51-1.01).

Recent meta-analyses have been performed by Nelson et al.<sup>37</sup> and Smith et al.<sup>38</sup> These include the results of the UK Age Trial and show benefits of screening similar to those found by Humphrey et al.<sup>33</sup>

### **Digital Mammography**

In digital mammography, the film used to record the mammogram is replaced by a sensitive digital detector. The detector provides an electrical signal that is digitized, stored in a computer and displayed on a monitor. Unlike film, where the image characteristics are fixed, in digital mammography, the displayed image can be adjusted during viewing to enhance visibility of anatomical information. Digital mammography was developed with the intention of improving performance of mammography in dense breasts.

No performance study with mortality as an end point has been done (or is likely to be done) with digital mammography. However, in the DMIST study,<sup>23</sup> the performance of digital mammography was compared to film mammography in terms of meaningful surrogate measures that included sensitivity and specificity. While overall the sensitivity of digital mammography was not significantly better than that of film (70% versus 66% for film), the study demonstrated that in women with dense breasts, digital mammography had substantially higher sensitivity (70%) than film mammography (55%) with no loss in specificity (~90% for both). This finding strongly suggests that in these women, digital mammography should contribute more strongly than film mammography to reducing mortality through earlier detection.

### Appendix 3: Breast MRI

As breast cancers grow, they ensure their blood supply by sending out signals that recruit the development of new blood vessels, a process referred to as tumour angiogenesis. These vessels are poorly formed and are leaky. If an intravenous injection of a chelated Gd contrast agent is performed, the agent that leaks from these vessels will pool in the extravascular space and then wash out. Breast MRI produces three-dimensional images that allow the pattern of leakage and washout to be monitored. The conspicuity of lesions can also be enhanced by subtracting images acquired prior to injection of the contrast agent from those produced at various times after the injection. The amount of uptake of the contrast agent, the shape of the enhancing areas and the kinetics of uptake provide information that allows very high sensitivity in detecting breast cancers and distinguishing them from non-cancerous structures in the breast. Cancers seen on an MRI tend to have shapes similar to those seen in a mammogram. They often show a rapid high concentration of the contrast agent, but this tends to wash out more quickly than for benign structures.

Several groups have studied the performance of breast MRI in high-risk women - those who carry one of the breast cancer gene mutations or who have strong family histories of breast cancer. Six major studies conducted on a total of 3,818 high-risk women in the Netherlands, the UK, Germany, the US, Canada and Italy (**Table 5**) all showed superior sensitivity of MRI for breast cancer detection (77-100%) compared to 16-40% for mammography or ultrasound.<sup>39,40,41,42,43,44</sup> Recently, Warner et al. performed a systematic review of the results of the major studies of breast MRI for screening high-risk women.<sup>45</sup> Specificity varied among the different studies between 81 and 99%. **Figure 5** is from the work of Warner et al.<sup>40</sup> It demonstrates that for this group of women, breast MRI is much more sensitive than any of the other modalities that have traditionally been used for breast cancer detection. It also shows that excellent sensitivity can be obtained when breast MRI is combined with mammography and / or ultrasound. Corresponding ROC curves for individual and combined modalities are shown in **Figure 6**.

<b>Published Breast MRI Screening Study Results</b>						
	<b>The Netherlands</b>	<b>Canada</b>	<b>United Kingdom</b>	<b>Germany</b>	<b>United States</b>	<b>Italy</b>
<b>No. of centers</b>	6	1	22	1	13	9
<b>No. of women</b>	1,909	236	649	529	3909	105
<b>Age Range</b>	25 - 70	25 - 65	35 - 49	≥30	≥25	≥25
<b>No. of cancers</b>	50	22	35	43	4	8
<b>Sensitivity (%)</b>						
<b>MRI</b>	80	77	77	91	100	100
<b>Mammogram</b>	33	36	40	33	25	16
<b>Ultrasound</b>	n/a	33	n/a	40	n/a	16
<b>Specificity (%)</b>						
<b>MRI</b>	90	95	81	97	95	99
<b>Mammogram</b>	95	>99	93	97	98	0
<b>Ultrasound</b>	n/a	96	n/a	91	n/a	0

n/a = not applicable.

**Table 5. Performance of various imaging modalities in studies evaluating MRI for screening high-risk women. From Saslow et al.<sup>46</sup> See also reference<sup>45</sup>.**

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**Sensitivity by Modality (n=19)**

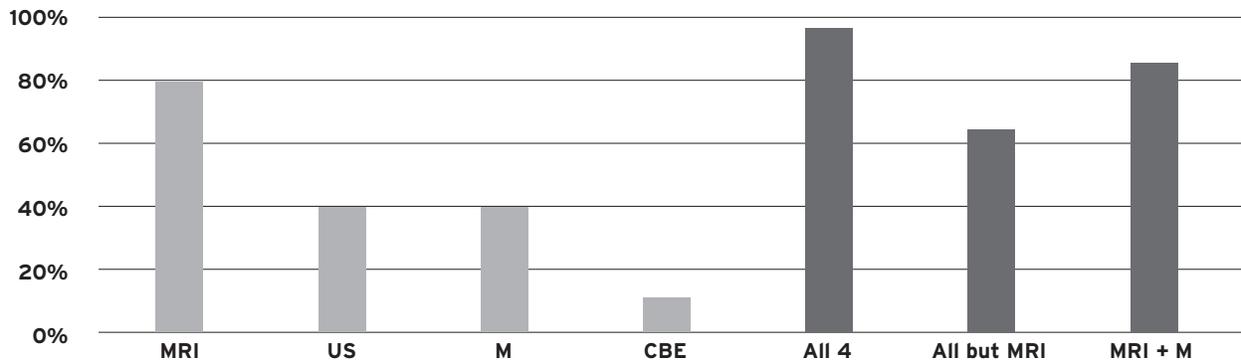


Figure 5. Sensitivity of individual and combined screening modalities in detecting breast cancer in high-risk women. US = ultrasound, m = mammography, CBE = clinical breast exam. From Warner et al.<sup>40</sup>

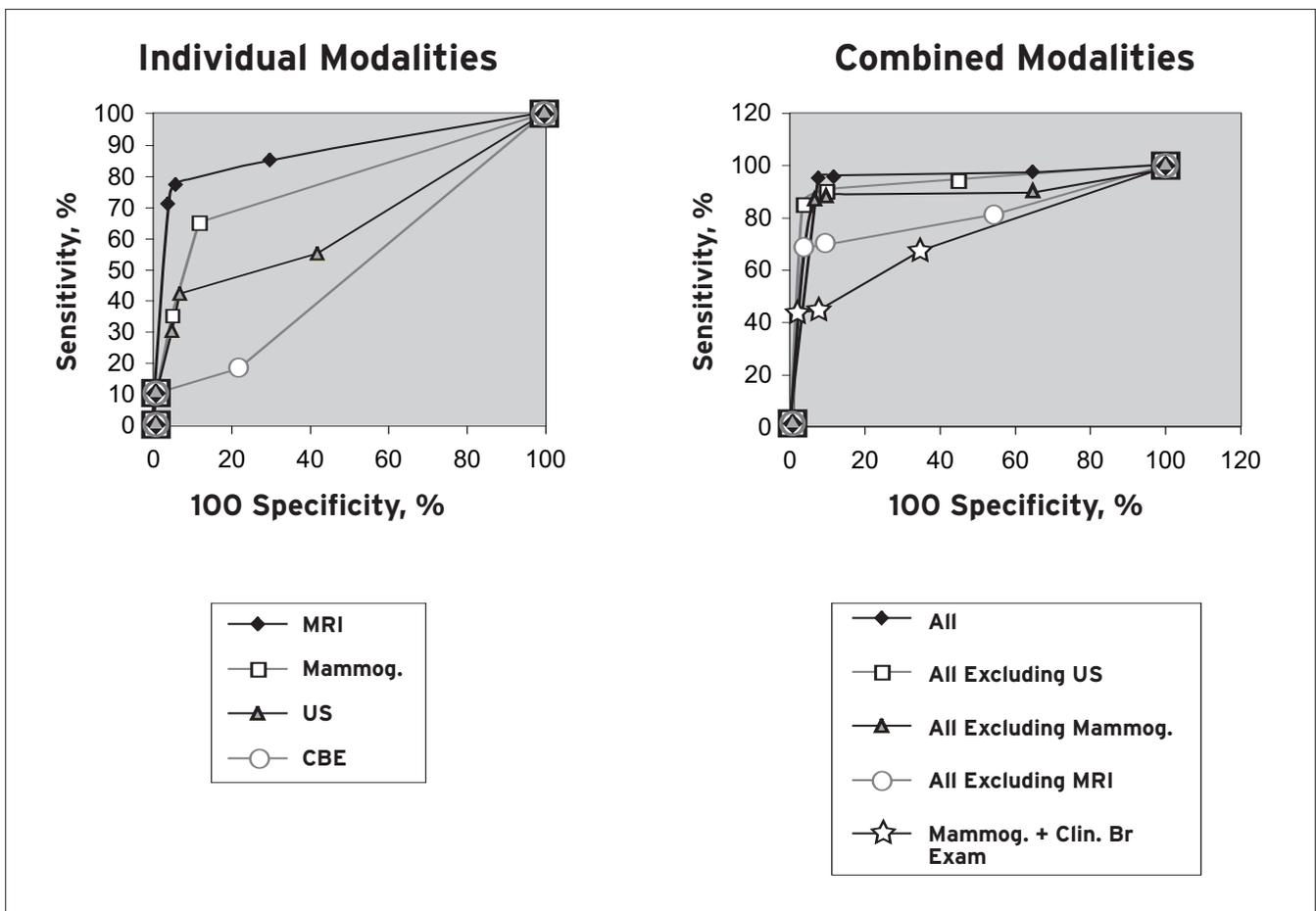


Figure 6. ROC curves for imaging modalities evaluated for screening high-risk women. From Warner et al.<sup>40</sup> (CBE = clinical breast examination, US = ultrasound)

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Recently, the American Cancer Society (ACS) published guidelines for the use of breast MRI for screening<sup>46</sup> women at elevated risk for breast cancer. The evidence on performance characteristics of breast MRI screening was reviewed and the recommendations are framed for women according to their defined levels of risk. In particular, screening MRI plus mammography is recommended for women with an approximately 20-25% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women who have been treated for Hodgkin's disease. The main recommendations are summarized in **Table 6** and also identify certain risk subgroups for whom, at the present time, the ACS considers that there was insufficient evidence to recommend for or against screening with breast MRI. The guidelines emphasize the need for specialized breast coils and pulse sequences for the MRI examination. The guidelines also discuss approaches to help identify risk based on genetic testing, family history or clinical indicators of risk.

**Table 6. Recommendations for breast MRI screening as an adjunct to mammography. From Saslow et al.<sup>46</sup>**

<b>Recommend Annual MRI Screening (Based on Evidence*)</b>
BRCA mutation
First-degree relative of BRCA carrier, but untested
Lifetime risk ~20 to 25% or greater, as defined by BRCAPRO or other models that are largely dependent on family history
<b>Recommend Annual MRI Screening (Based on Expert Consensus Opinion†)</b>
Radiation to chest between age 10 and 30 years
Li-Fraumeni syndrome and first-degree relatives
Cowden and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives
<b>Insufficient Evidence to Recommend for or Against MRI Screening‡</b>
Lifetime risk 15 to 20%, as defined by BRCAPRO or other models that are largely dependent on family history
Lobular carcinoma in situ (LCIS) or atypical lobular hyperplasia (ALH)
Atypical ductal hyperplasia (ADH)
Heterogeneously or extremely dense breast on mammography
Women with a personal history of breast cancer, including ductal carcinoma in situ (DCIS)
<b>Recommend Against MRI Screening (Based on Expert Consensus Opinion )</b>
Women at <15% lifetime risk
* Evidence from non-randomized screening trials and observational studies.
† Based on evidence of lifetime risk for breast cancer.
‡ Payment should not be a barrier. Screening decisions should be made on a case-by-case basis, as there may be particular factors to support MRI. More data on these groups is expected to be published soon.

### Appendix 4: Breast Ultrasound

Ultrasound is widely used for breast imaging as a tool for assessment of symptoms or signs that increase the suspicion of malignancy. Ultrasound technology is relatively inexpensive and widely available. It is particularly useful for investigating mass lesions and distinguishing whether they are cystic, solid or suspicious of malignancy. Recently, a study investigated the role of screening ultrasound as an adjunct to mammography in women who were at enhanced risk for breast cancer.<sup>47</sup> The study found that the addition of ultrasound to the screening procedure increased the breast cancer detection rate from 7.6 per thousand to 11 per thousand. The sensitivity also increased from 50% to 77.5%. Many of the additional cancer findings were small, invasive cancers with negative nodes. **Figure 7**, taken from Berg et al.,<sup>47</sup> shows the ROC curves of mammography alone, ultrasound alone and the two used together. The authors pointed out that because of its relatively low specificity for cancer detection, the addition of ultrasound does result in a substantial increase in the number of false positive results.

Unlike MRI, breast ultrasound does not require the injection of a contrast agent. Ultrasound is well tolerated by patients and does not expose them to ionizing radiation. As well, ultrasound is a reasonable alternative to MRI for women who would otherwise be eligible for MRI examination, but who either cannot or are not willing to have an MRI examination. However, ultrasound has limited value in the fatty breast due to lack of contrast.

In terms of challenges, because ultrasound is a labour intensive procedure, it is currently not considered practical for a physician to perform the scans in the screening setting.

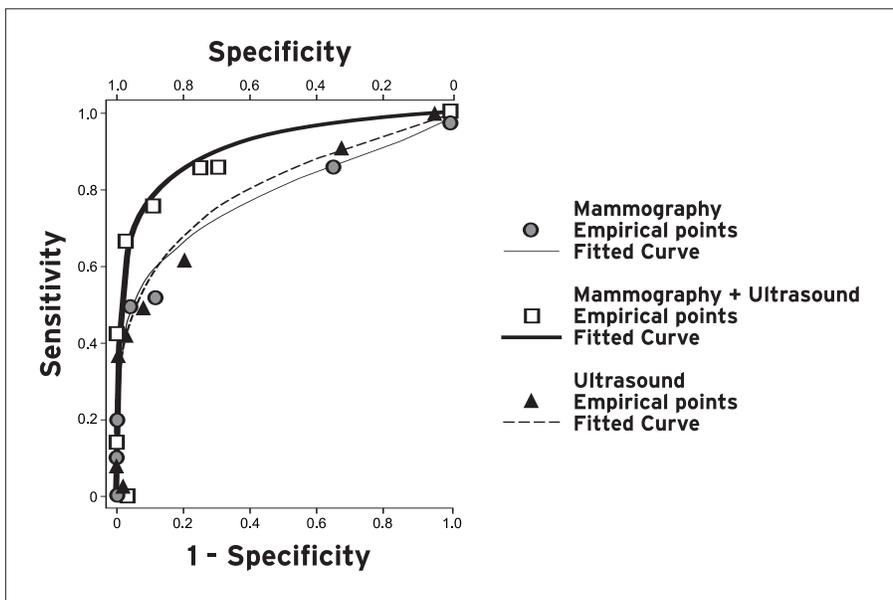


Figure 7. ROC performance of ultrasound, mammography and their combination for screening high-risk women. From Berg et al.<sup>47</sup>

## Appendix 5: The Contribution of Clinical Breast Examination (CBE) to Breast Cancer Screening

There have been two published meta-analyses of randomized control trials of CBE: Kerlikowske et al.<sup>48</sup> in 1995 and Humphrey et al.<sup>33</sup> in 2002. These found that CBE in addition to mammography did not decrease breast cancer mortality beyond the reduction achieved by mammography alone. There have also been several observational studies of the performance of CBE in service screening.<sup>49,50,51</sup> Typically, these found that in women 50-69 years of age, the contribution to breast cancer detection from CBE alone ranged from 2.5-4 additional cancers per 10,000 examinations, about 10% of the detection rate achievable by mammography alone. In addition, the sensitivity of CBE is low (see Table 7). Chiarelli<sup>51</sup> compared the accuracy of screening among Ontario Breast Screening Program (OBSP) centres that offered CBE and mammography with centres that offered mammography alone in 290,230 women. Her study found that standardized CBE provided by highly trained nurses resulted in a higher CBE sensitivity of 32-47% on initial screens and 26-27% on rescreens. She observed that in the OBSP context, the addition of CBE would lead to the detection of breast cancer in only 4 women in 10,000 screens and lead to false positive results for an additional 219 women.

**Table 7. Performance of CBE in a community setting. Age range studied is shown in parentheses.**

Authors	Sensitivity	Specificity
Bobo et al. <sup>49</sup> (n=589,048)	36.1% ( $\geq 40$ )	96.2% ( $\geq 40$ )
Oestreicher et al. <sup>52</sup> (n=61,688)	20.0-22.8% (40-49)	97.4-98.6% (40-49)
	19.4-24.7% (50-69)	96.9-98.3% (50-69)
Kolb et al. <sup>53</sup> (n=11,130)	27.6% ( $\geq 40$ )	99.4% ( $\geq 40$ )
Fenton et al. 2005 <sup>54</sup> (n=485)	21.6% (40-65)	99.4% (40-65)
2007 <sup>55</sup> (n=1,427)		
Chiarelli et al. <sup>51</sup> 2009 (n=290,23)	32-47% (initial, 50-69)	96% (initial, 50-69)
	26-27% (rescreen, 50-69)	97-98% (rescreen, 50-69)

As seen in **Table 8**, very few cancers were detectable by CBE alone, and these tended to be larger and less likely to be node negative than those detectable by mammography alone. In addition, the positive predictive value (related to specificity) was much lower for CBE, and many more negative biopsies were carried out on the basis of CBE-only findings. The study by Bancej et al.<sup>50</sup> had similar conclusions.

The OBSP study concluded that women should be informed of the risk and benefits of having a CBE in addition to mammography for breast screening. If CBE is offered as a screening test, standards for training, performance and tracking should be established as for mammography.

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**Table 8. Characteristics of mammography and CBE detection in ten years of OBSP screening (from Chiarelli et al.<sup>56</sup>)**

Criterion	Mammography Only	CBE Only
Invasive cancer detection rate (per 1,000) - Initial Screen	3.3	0.3
Re-screen	2.6	0.3
In situ cancer detection rate (per 1,000) - Initial Screen	0.8	0.1
Re-screen	0.7	0.0
Positive predictive value (%) - Initial Screen	5.0	0.7
Re-screen	7.0	1.0
Benign to malignant surgical biopsy ratio - Initial Screen	1.7 : 1	9.9 : 1
Re-screen	0.9 : 1	6.1 : 1
Tumour size $\leq$ 10 mm (%) - All Screens	53.2	27.2
Positive lymph nodes (%) - All Screens	16.8	34.4
Diagnostic interval (% diagnoses completed within 7 weeks if surgical biopsy) - All screens	48.4	35.7

In its 1998 report, The Canadian Task Force on Preventive Health Care<sup>57</sup> recommended that women aged 50 to 69 years undergo screening for breast cancer by mammography and clinical breast examination every one to two years. Their rationale for this recommendation was that the relative contributions of mammography and CBE had not been ascertained. The 2002 recommendations of the U.S. Preventive Services Task Force take a rather different perspective. They recommend screening mammography, with or without CBE, every one to two years for women aged 40 or older. Their reasoning is that at that time they could not determine whether the potential benefits of routine CBE outweighed the potential harms, nor did they have adequate evidence on the incremental benefit of adding CBE to mammography. In 2002, the International Agency for Research on Cancer (IARC) stated that there is inadequate evidence that breast screening with CBE, either alone or in addition to mammography, can reduce mortality from breast cancer.<sup>58</sup> The IARC do suggest, however, that CBE may be important in countries where there are insufficient resources for mammography or where disease is usually at an advanced stage at the time of diagnosis.

## Appendix 6: Breast Self-examination

Breast self-examination (BSE) usually refers to a standardized technique of self-examining breasts in a particular way. This usually involves following a prescribed pattern (such as a grid or clock pattern) of touching the breast on a specific monthly schedule. BSE is typically promoted as a way of screening for breast cancer, with the implication being that it will reduce breast cancer mortality. However, there is insufficient evidence to support any of the specific BSE methods or the assertion that BSE reduces breast cancer mortality rates within the population.

There have been two recent reports of results of trials of breast self-examination for breast cancer screening, one in Russia, the other in Shanghai. Findings from the two studies were similar. In an otherwise unscreened population in St. Petersburg<sup>59</sup> offered instruction in routine breast self-examination, there was a subsequent increase in the number of breast cancers that were detected and improved survival in the women who received instruction, but no difference in all-cause mortality (i.e., death due to any cause). Although all-cause mortality is an inappropriate endpoint for a disease-specific intervention, the results of the St. Petersburg trial were not suggestive of a significant benefit from the intervention.

In the Shanghai<sup>60</sup> study, similar results were observed. In both studies there was an approximate doubling in the number of benign breast biopsies for the women who received instruction in BSE, with the majority of these procedures taking place in the year after instruction. No significant difference in mortality between the experimental and control group was observed. A U.S. retrospective study<sup>61</sup> found that women who practiced BSE for longer periods of time and more frequently were more likely to have diagnostic mammography or ultrasound examinations, but no increase in the rate of benign biopsies was observed. Similarly, meta-analyses of small trials have not shown a mortality benefit associated with BSE.<sup>62,63</sup>

Nevertheless, it is possible that by noticing a change in her breast, a woman could find a breast cancer before it would otherwise be detected without her having had a heightened sense of awareness. Therefore, it is suggested that **breast awareness** is a reasonable health practice, especially for younger women who do not receive mammograms. Information provided to the public about this health practice should clarify that it is not necessary to use a specific method in checking the breasts and underarms, but to be familiar with how they look and feel; if any differences or changes are noticed other than those that occur normally during the monthly cycle, they can be reported to a health care provider. Finding such changes doesn't necessarily mean that cancer is present, but occasionally one will be detected.

## **Appendix 7: Underserved Populations**

This section focuses on *underserved populations* that have been identified within the context of Canadian provincial organized screening programs. For the purpose of this paper, “underserved” refers to groups who are at higher risk of poor health outcomes because of particular characteristics associated with barriers to receiving adequate health care.<sup>64</sup> For these groups, there is also the increased incidence of receiving less or a lower standard of care; experiencing differences in treatment by health care professionals; or receiving care or treatment that does not recognize their distinct needs.<sup>65</sup> Barriers have been defined as the conditions that inhibit individuals from carrying out a recommended behaviour.<sup>66</sup>

In Canada, organized screening programs exist in all of the provinces and territories with the exception of Nunavut. All of the provinces and territories in Canada offer screenings for women aged 50-69. The eligibility for women outside of this age group varies from province to province and may require a doctor's referral.

User trends of organized screening programs from 1990 to 2008 indicate that in 1990 fewer than half (40%) of women aged 50-69 reported that they had had a mammogram in the past two years. As organized screening has become well established, this rate had increased to 72% in 2008.<sup>67</sup> However, despite the increase in eligible women attending screening, several barriers impede uniform access across populations.<sup>67,68,69</sup>

As of 2009, the types of socio-demographic data collected through provincial organized screening programs vary by region. The Canadian Breast Cancer Screening Database (CBCSD) exists to evaluate and assess Canadian organized breast cancer screening programs through the use of standard performance indicators<sup>67</sup>. These indicators do not currently include formal socio-demographic data collection that could determine user and non-user profiles and do not provide the data needed to document the extent of disparities among populations accessing screening programs. These data are needed to develop evidence-based policies and interventions to remove barriers to access.

### **Characteristics of underserved populations in Canada**

Statistics Canada recently published *An Update on Mammography Use in Canada*<sup>67</sup> using data from the 2008 Canadian Community Health Survey to identify several characteristics associated with non-users, including low socio-economic status (SES); being an immigrant; not having a regular medical doctor; not having contacted a general practitioner or family doctor in the past year; and being a smoker.<sup>67</sup>

These characteristics are similar to factors most associated with overall health disparities in Canada, which also include Aboriginal identity, gender and geographic location.<sup>70</sup> Several Canadian studies have also identified numerous barriers to access for older women<sup>71</sup> and women with disabilities.<sup>72</sup> The consequences of health disparities are recognized to be most pronounced in the lowest 20% of the SES scale and for Aboriginal peoples.<sup>70</sup>

Higher SES groups are more likely to make use of some preventive services such as cancer screening, while lower SES groups are less likely to adopt preventive behaviours even when these are recommended by a health care practitioner.<sup>73</sup> Since 2005, the use of mammography among women at the lowest income level has declined.<sup>67</sup>

In the US context, similar underserved populations have been identified, but additional barriers to screening exist that are distinct to the current US health care system, including lack of health insurance, state funding for screening programs and differences in quality among screening facilities.<sup>74</sup> Developing and lower-resource countries also face the same barriers, compounded by a lack of health care resources, lack of data, lack of awareness and education, and country-specific cultural barriers.<sup>75</sup>

## **Appendix 8: U.S. Preventive Services Task Force (USPSTF) Screening for Breast Cancer Recommendation Statement**

This report, which was issued in 2009, reverses several of the recommendations published by the same task force in 2002. This is surprising, because in some cases no new scientific evidence supported a change of recommendations, while in others there was new evidence to support the existing policy in the U.S., but that evidence was ignored by the committee. Because some of the new recommendations disagree with the recommendations presented in this document, some discussion is justified.

1. Contrary to its 2002 recommendations,<sup>33</sup> the 2009 USPSTF report recommends against routine screening mammography of women in their 40s. However, as discussed in Appendix 2, data from randomized trials and observational studies of mammography screening in the real world (Sweden and British Columbia) demonstrate a breast cancer mortality reduction of 25-45% in women whose breast cancers were detected by mammography screening in their 40s. Similarly, in the Netherlands, the death rate in health care districts continued to rise despite the introduction of new therapies, and only when screening was introduced did the death rates begin to decline. These data have been ignored in the current report and, based on meta-analysis of all RCTS, the USPSTF has chosen instead to emphasize an artificially low value of 15% mortality reduction attributable to mammography screening. The USPSTF also concluded that the NNI to save one life (n=1904) was unreasonably high for the small benefit estimated by meta-analysis. However, NNI as a measure of cost-effectiveness not only is an imprecise concept due to the fact that it obscures the actual screening rate, but is especially imprecise when derived from eight RCTs with different rates of adherence to the randomization assignment and different years of follow-up. This is not a trivial issue, since these methodological decisions led to the elimination of a recommendation for screening for women in their forties. In fact, when the more proper estimate of benefit, i.e., number needed to screen (NNS) is estimated for women aged 40-49 from a single population, the NNS 5-6 times over a 10 year period to prevent one breast cancer death after 20 years of follow-up was estimated to be 726, less than half the number estimated by the USPSTF.<sup>34</sup>
2. The USPSTF report also indicates that “The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account, including the patient’s values regarding specific benefits and harms.” While all decisions of this sort are individual, and patients deserve to be given factual information regarding benefits, limitations and possible harms of any procedure, this recommendation is not particularly useful in that the main risk factor for breast cancer is being a female over 40 years of age. While there are other well-established risk factors for breast cancer, most breast cancers occur in women without those factors. Furthermore, it is widely accepted that because of the faster growth rate of cancers in younger women, if screening is to be performed in women in their 40s, it should be done annually.

The USPSTF has used modelling to determine that a screening interval of two years, rather than annual screening, be employed for women over 50. While modelling can be helpful when no direct data are available, as is the case in this situation, modelling must be distinguished from “evidence” and used carefully. In particular, there is reason to believe that if there is a natural transition point between annual and biennial screening, it should occur following menopause, which generally occurs somewhat later than age 50.

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The USPSTF also stated that there was insufficient evidence to recommend for or against use of clinical breast examination (CBE) in screening programs. When this statement is considered in conjunction with the USPS recommendations against routine mammography screening of women in their 40s (where we disagree) and against the teaching of breast self-examinations, this position leaves women with no actions that they can take on their own to avoid dying of breast cancer. While CBE is generally less sensitive and less specific in detecting small, earlier breast cancers, it is certainly more sensitive than no screening whatsoever, and in countries where mammography is simply not available, would be a preferable alternative to doing nothing.

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