Earlier Detection and Diagnosis of Breast Cancer:

A Report from It’s About Time! A Consensus Conference
Canadian Breast Cancer Foundation - Ontario Region

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The Canadian Breast Cancer Foundation - Ontario Region was founded in 1986 by a group of passionate and determined women who worked to reduce the stigma of breast cancer and fund groundbreaking research specifically addressing this disease.

Our founders’ legacy is one of leadership inspired with confidence that our vision of creating a future without breast cancer is achievable. Creating that future requires collaborating with other stakeholders on shared goals; advocating for policy change; and continuing to fund innovative research on all aspects of breast cancer.

All of these were brought to bear in October 2009, when the Foundation hosted It's About Time! A Consensus Conference on early detection and diagnosis of breast cancer. The recommendations arising from this conference provide solid evidence for advocating to ensure women have what they need to make informed decisions about breast cancer screening. Ultimately, this support will help reduce breast cancer mortality.

We are pleased to present the breast cancer screening recommendations and proceedings from It's About Time! A Consensus Conference. This report and position paper summarize the complex scientific evidence on earlier detection and final screening recommendations in clear, understandable terms, and provide insight into how the recommendations were reached. The report also provides the evidence to enable all of us to work towards advancing and improving screening practices and policies.

On behalf of the Foundation, we would like to extend our sincere gratitude to our sponsors, partners, donors and volunteers. Without their support, this work would not be possible. It is our hope that this work will bring us closer to a future without breast cancer.

Deborah Dubenofsky  
Chair, Board of Directors

Sandra Palmaro,  
CEO
The good news is we are beginning to make progress in the fight against breast cancer! Thanks to earlier detection and more effective therapies, fewer women are now dying of breast cancer. Since 1989 the mortality rate has fallen by about 2% per year. These benefits have come from careful research, which has then been incorporated into the delivery of breast health care.

As an active breast cancer researcher and director of a bold new initiative of the Ontario Institute for Cancer Research - a program to discover ways to detect and diagnose cancers earlier, to help further reduce death and suffering from breast cancer - I am excited about these opportunities. But, as I looked at the gap between the proven innovations that have come from past research and the actual availability of many of these benefits within our Ontario health care system, I became dismayed and frustrated. What is the point of doing research and obtaining successful results if those results aren’t implemented in a timely manner? Why should women be deprived of diagnostic tools that could help save their lives? And if people were made aware that these tools existed, would they not demand that they be made available?

Two particular examples of missed opportunities are very apparent to me. First, there is solid evidence that routine mammography screening of women in their 40s can reduce mortality from breast cancer by at least 24%, but Ontario still does not allow women in that age group into their breast screening program. Secondly, we now know that breast MRI is the most accurate method of detecting breast cancer early in women who are at high risk. This finding has been obtained in several independent studies, but little has been accomplished in implementing this knowledge clinically.

After much discussion with colleagues, there was general agreement that we needed to collect the current relevant information on the most effective ways to detect breast cancer earlier and to present this information to several audiences. Certainly we felt that women were often not receiving complete information as to how they could best avoid being diagnosed with advanced breast cancer. But, we also were concerned that many of the primary health care providers were not acquainted with the most up-to-date science. In fact, some of the advice presented on web sites and brochures did not reflect the latest understanding about breast cancer and how mortality could be reduced.

We thought that the best way to address these issues was through a forum at which we could bring the appropriate stakeholders together. I approached Beth Easton at the Canadian Breast Cancer Foundation - Ontario Region, because I knew that the Foundation has a strong interest in communicating knowledge about breast cancer and in advocacy; also, they know how to bring people together and activate them. I was impressed by their enthusiastic response and their energy as we worked together to create the It’s About Time conference. We then formed a Scientific Advisory Committee and identified experts who could provide us with the most reliable and up-to-date information.
Our two goals for the conference, as well as the publications arising from the conference presentations and recommendations, are straightforward. First, we want to ensure that all stakeholders are familiar with the most effective and appropriate methods to detect and diagnose breast cancer earlier and accurately through screening programs. Then, we seek to work with you to influence changes in health care policy.

Our collaborative efforts will help to ensure that these methods are available to women and their health care providers so that we can reduce the burden of breast cancer in our society.

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Introduction
Background

The Canadian Breast Cancer Foundation understands that participating in breast cancer screening is a woman’s choice. To support women to make informed choices about screening, in October 2009 in Toronto, Ontario, we held the It’s About Time consensus conference on breast cancer early detection and diagnosis. The goal of the conference was to improve screening practice in order to reduce breast cancer mortality. By reviewing screening science and making recommendations for practice, the conference undertook to demystify the evidence and to inform women, health care providers and public and non-profit decision-makers about how we can more effectively detect and diagnose breast cancer.

We called the conference It’s About Time because time is of the essence in breast cancer detection and diagnosis: earlier detection can result in better outcomes for women diagnosed with the disease. A current comprehensive review of the science was required to ensure that women fully benefit from all that can be done to effectively detect breast cancer. In Canada, federally issued recommendations on breast cancer early detection and diagnosis have not benefitted from a review or update since 2002, despite the emergence of new evidence on a range of relevant screening issues. Also, recommendations and guidelines from other Canadian non-profit and public bodies differ in some important areas. The It’s About Time conference sought to facilitate a fair interpretation and application of the evidence to achieve greater consensus and alignment amongst stakeholders, leading to clear, consistent information for the public.

We chose a consensus conference process to review screening evidence and make recommendations. Open, transparent, inclusive and accountable, consensus conferences bring together stakeholders representing different interests and perspectives who review evidence and reach agreements on what the science means and what actions are needed. Collaboration and open discussion lead to outcomes and recommendations that can be shared among stakeholders, helping to coordinate action and reduce areas of disagreement and difference. We believed that an open, collaborative process was needed to increase understanding and alignment in order to move screening practice beyond current debates and controversies.

Thus the It’s About Time consensus conference was different than other screening evidence review processes. It began with a public forum, broadcast live on the Internet, hosted by Beverly Thomson, a well-known national broadcast journalist and breast cancer survivor. By engaging the public we sought to increase their understanding about the issues and gain their input so that conference outcomes would address their interests. A poll was used to solicit input on key questions from both live and Internet audiences. A broad group of over 70 stakeholders was then invited to hear the 23 scientific presentations at the conference. Participants included breast cancer survivors, leading research scientists, health care providers, government and non-profit decision makers, educators and interested citizens.

A Scientific Advisory Committee was established and chaired by Dr. Martin Yaffe, whose distinguished career at Sunnybrook Research Institute has focused on the physics of breast cancer imaging. Under his leadership the committee drafted a collaborative paper reviewing the scientific research on screening that was then shared with participants and formed the bedrock of the consensus process. The committee also drafted an interim set of breast cancer screening recommendations based on their view of the best fit between scientific evidence and clinical practice. Experts who were able to address critical issues like age, increased risk and technical advances were invited from Canada, the United States and Europe to make presentations at the conference.

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. The proceedings of the entire event were digitally recorded, transcribed and subsequently summarized for this report. As not every participant was required to sign off on each recommendations, and because some participants had to leave the meeting before its conclusion, the Scientific Advisory Committee should
be considered the author of the recommendations.

The timing of the conference was critical for the province of Ontario. Its current policy and practice appear to be out of step with some of the evidence as well as policy in most other parts of Canada and a number of other countries. Ontario’s differences pertain to important areas of policy and practice, including the screening of women age 40 - 49 and the screening of high-risk women. The emergence of new evidence, including that from newer validated techniques not considered in previous provincial or federal reviews, meant there was a need for Ontario to step up to help guarantee that the best possible patient outcomes are realized.

What’s at Stake?

Early detection

Early detection has been the rallying cry of breast cancer from the outset of the response to the disease. While exact causes of breast cancer are not known, evidence suggests that a combination of inherited and environmental causes must be present for it to develop. Efforts to prevent breast cancer are hampered by the disease’s complexity and the limits of our current scientific knowledge. Many established risk factors for breast cancer, including being a woman, aging, breast density, family history, genetics, or a prior breast cancer diagnosis, cannot be modified.

On the upside, evidence demonstrates that the risk of developing breast cancer can be reduced by maintaining a healthy body weight, being physically active, eating well and limiting alcohol consumption. However, because personal risk reduction is still no guarantee, early detection has been the ballast of hope and action for breast cancer. Until we are able to effectively prevent breast cancer, early detection will remain our leading strategy for reducing mortality and illness due to the disease.

Early detection means using an approach that aims to diagnose breast cancer earlier than might otherwise occur. Breast cancer screening, sometimes referred to as secondary prevention, is the routine testing of individuals without symptoms that aims to detect breast cancer at its earliest stages so effective treatment can be offered. Since breast cancer screening began in Canada in the late 1980s, it is attributed with helping reduce breast cancer mortality by an estimated 25 - 30 percent.

Different services and unclear choices

Women can access screening through provincially run organized programs or through on-demand facilities that require a doctor’s referral, a process called “opportunistic screening.” With the exception of Nunavut, all Canadian provinces and territories offer organized breast screening programs through regional health authorities. These programs are considered the best approach to screening, helping to improve patient outcomes with targeted invitations, quality standards, and measures for effective follow-up when abnormalities are found. By contrast, opportunistic services lack the quality assurance standards and outcome monitoring provided by organized programs.

Many women who choose screening do not screen within organized provincial programs for several reasons. Some women are unaware of the differences in services that could inform their decisions about which service to choose. Also, organized programs are not available in some communities, meaning some women do not have ready access to an organized program and its benefits. Other women, including those in Ontario aged 40 - 49, are not eligible to participate in organized programs and cannot be screened within provincial programs even with a health care provider’s referral.
INTRODUCTION

Organized programs can result in better patient outcomes than on-demand, opportunistic screening. Of considerable concern is that women who could benefit from screening within organized programs do not select or are unable to access them. The consensus conference reviewed evidence relevant to these issues to respond to these inequities and limitations.

Gains, confusion and difficult questions

Overall, increased awareness about the benefits of earlier detection and participation in breast cancer screening has meant that more breast cancers are detected at earlier stages, contributing to more women surviving breast cancer. The success of early detection in helping to reduce mortality and illness is an important achievement in women’s health. However, anyone remotely familiar with the field will recognize that screening is not without limitations, challenges and controversies.

Who should be screened? At what age? Using what methods? How frequently? Do the potential benefits outweigh the potential limitations and harms? These questions resist simple answers and often lead to disagreements and debate.

Thanks to at least 25 years of increased awareness and public engagement, women of all ages have been alerted to breast cancer and the idea of early detection and diagnosis. We have been inundated with a vast amount of information and varying perspectives on the topic from friends, family, media, the Internet, health organizations and care providers. Public interest and media attention mean that relevant early detection and diagnosis debates regularly take place in public arenas, yet often lead to more questions than answers.

When women seek information to make decisions about breast cancer screening, they are apt to discover differences between recommendations. Screening recommendations provide guidance for policy and practice and aim to reduce breast cancer mortality within the population. Typically they are developed by convening groups of experts who review current scientific evidence and make recommendations for policy and practice. Each group reaches its own interpretations and conclusions.

Different policies and messages

The uptake of recommendations for policy and practice may vary as well, influenced by factors such as competing health priorities and costs. Often variances are not addressed or explained, leaving people in the dark about why differences exist and what it all means. Furthermore, there is limited information enabling women to effectively weigh the potential benefits, limitations and harms of screening, a necessary step in informed decision making. Finally, recommendations are based on evidence about how to reduce mortality and illness in whole populations and do not always translate effectively to individuals, who understandably are primarily concerned with what screening might mean for them.

For the public which relies on the findings of science to provide clear, consistent, reliable direction, inconsistencies between recommendations and disconnections with screening practice can be confusing and make it hard for people to make sense of what they are told. Being told different things also begs important questions: Who is right? Who should I believe? Inconsistencies undermine public confidence in breast cancer screening and may influence people’s willingness to participate.

What do I do?

Although women have been told that breast cancer screening is the best method currently available to respond to the risk of
breast cancer, confusing information and conflicting recommendations complicate decisions about what to do. Disagreements about potential benefits, limitations and harms may make women wonder whether breast cancer screening will work for them and whether they need to bother. The ability to understand and feel confident about a breast cancer screening decision can be extremely challenging for a woman who may simply be trying to answer the very personal question: “What do I do?”

Very simply, the Canadian Breast Cancer Foundation - Ontario Region held It's About Time! A Consensus Conference to better enable women to effectively answer this basic question.

Conference outcomes and recommendations

How can they help?

This publication presents a detailed summary of the proceedings and recommendations of the It’s About Time conference. The accessible, lay summary of the Proceedings section provides a valuable overview of the scientific evidence, while Making Sense explains the consensus recommendations according to how they were informed by the science discussed at the conference. This report is a companion paper to the conference scientific paper drafted by the Scientific Advisory Committee and circulated to all participants at the conference. The scientific paper, called Earlier Detection and Diagnosis of Breast Cancer: Recommendations and Scientific Review from It’s About Time! A Consensus Conference, was finalized after the conference presentations and reflects input from participants. It is available at www.itsabouttimecbcf.ca.

A distinguishing feature of the It’s About Time screening recommendations is that they were developed by convening a wide group of stakeholders to create a consensus on what the recommendations would say. That broad consensus represents an achievement in its own right. The rigorous process used to reach it is ultimately what makes these recommendations distinct.

The screening recommendations are tailored to women of average, intermediate and high risk, and include criteria to define each category. These risk categories aim to help women understand which screening approaches might best apply to them, informed by a fair consideration of the potential benefits, limitations and harms.

The recommendations are also for health care providers who may be unclear about current evidence and confused by divergent and outdated recommendations. The It’s About Time recommendations will enable providers to become knowledgeable sources of up-to-date screening information, better able to support patient decision making. The recommendations offer cancer and public health organizations the opportunity to align and clarify their public messaging on early detection and diagnosis, addressing public confusion and concern. More critically, the It’s About Time recommendations better equip public sector decision-makers with needed evidence to guide policy and program priorities that can improve early detection and diagnosis through strengthened breast cancer screening practice, thereby reducing breast cancer mortality.

Acknowledgements

The Canadian Breast Cancer Foundation - Ontario Region is extremely pleased to share the It's About Time consensus conference recommendations, confident in their ability to support improved breast cancer early detection and reduced mortality from breast cancer. The work to arrive at these recommendations was long and involved. Planning commenced over 18 months ago and tremendous effort by many people who generously gave their time, intelligence and goodwill made the conference a success.
Martin Yaffe, Chair, Scientific Advisory Committee

Immense thanks and gratitude are owed to Martin Yaffe for his tremendous contributions. Martin approached us over two years ago asking if there was anything the Canadian Breast Cancer Foundation could do to help address the limitations of screening policy and practice. Unrelenting in his determination, energy and good nature, Martin provided critical leadership to all aspects of the conference, ensuring the quality and relevance of the proceedings and its outcomes. It was a testament to the respect he and his work garner that we were able to secure such an esteemed roster of participants and presenters. While we anticipated that Martin would be an able, expert partner, we didn’t anticipate how his profound commitment to breast cancer would so fortify and inspire us.

Scientific Advisory Committee

The conference benefitted invaluably from an extremely hard working, expert volunteer Scientific Advisory Committee. Members were Martin Yaffe, PhD (Chair); Roberta Jong, MD; Etta D. Pisano, MD; Kathleen I. Pritchard, MD; and Robert A. Smith, PhD.

The conference placed many demands on the committee members, who met them with grace and commitment. Not only was each member responsible for contributing to drafting and reviewing many versions of the scientific paper before and after the conference, but each also attended the full conference, gave presentations, moderated panels and participated fully in the lengthy and challenging discussions. The conference engendered tremendous debate and included both strong agreements and disagreements. Committee members are to be recognized for the critical role they played in the conference’s outcome, for they helped inform and facilitate discussion, assisting the group in moving, where possible, beyond impasse to greater understanding and agreement.

Presenters

The conference was enriched by the expertise and thoughtfulness of 21 presenters, including leading researchers, clinicians, decision makers and public health practitioners. Each presented evidence on key aspects of breast cancer early detection and diagnosis, opening their work and ideas to examination and discussion. As the conference stakes were high - the aim being to arrive at recommendations that could change policy and practice - at times presenters were on the hot seat. They rose to the occasion, giving thorough and measured consideration of the evidence, expertly informing group understanding and discussion. Their willingness to debate the issues with the broader group allowed ideas to be vetted by all, making the process truly collaborative and the outcomes stronger.

Participants

Sincere thanks is owed to all of the conference participants. Over 70 invited stakeholders gathered for two full days to discuss the evidence and develop screening recommendations. Stakeholders represented diverse perspectives and insights on the topic, with many holding differing views and opinions on conference questions. Participants included women who had been diagnosed with breast cancer, whose input and insights were derived from direct experience. The group was required to respond to a total of seven plenary sessions involving 23 presentations. They then were asked to collaboratively work through the draft recommendations line-by-line in a final four-hour session.

The demanding process challenged each participant to be open to learning something new and to having their understandings and views evolve. The nature of the work meant that there were times when participants broached strongly held differences.
That participants chose to remain engaged and to openly, respectfully challenge and respond to one another when differences arose testified to both their integrity and commitment to work to reach agreement where agreement was possible. Without this commitment, the conference would not have resulted in a set of recommendations that reflect the expertise and insight of a diverse group of relevant and knowledgeable stakeholders. A full list of the participants is provided in Appendix B.

**Staff Team**

I would also like to thank the Canadian Breast Cancer Foundation - Ontario Region staff team. Led by Meagan Cameira, the team included Sylvia Scarsella, Lesley James, Natalie Gierman and Alysha Kropf. Together they effectively managed the planning and implementation of the conference. Paying attention to every detail with remarkable stamina and good humor, they ensured that all presenters and participants were well supported and that the conference was a success. I would also like to thank Yulia Yerofeyeva, a program administrator working with Martin Yaffe. Her willing and capable support to a number of important conference activities made her an honorary member of the Foundation staff team, contributing to its overall success.

Terry Trussler contributed significantly to the conference as our scientific advisor. He participated in program planning, attended the conference, and later methodically summarized the complex scientific evidence and wrote the accessible Proceedings section of this report. He then analyzed and explained the science and recommendations in Making Sense of Breast Cancer Screening, helping to begin the translation of this important information to a broader audience. Over the duration of the work, Terry provided invaluable insights and guidance about what we were trying to do and how to make sense of it all.

**Sponsors and Funders**

The Foundation wishes to recognize the important contributions of the sponsors and funders who helped make the conference possible. We would like to sincerely thank our Presenting Sponsor, CIBC, and our Gold Sponsors, AstraZeneca, GlaxoSmithKline Oncology and Pfizer Oncology. We would also like to thank the Canadian Institutes for Health Research and the Ontario Institute for Cancer Research, who generously provided grant support for the conference.

Beth Easton  
Vice President, Allocations and Health Promotion  
Canadian Breast Cancer Foundation, Ontario Region  
Toronto, Canada  
July, 2010
The Breast Cancer Screening

Recommendations
The breast cancer screening recommendations from the Canadian Breast Cancer Foundation - Ontario Region’s It’s About Time! A Consensus Conference are summarized here. Supporting evidence is provided in Appendix A. The criteria for risk categories (average, intermediate, high) are documented in Appendix A. They are based on scientific evidence, primarily from the randomized controlled trials of screening and observational studies of service screening.

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.  
   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. **Screening 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  
   d. **Evidence:** Appendix 2,3,4

3. **Screening 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 density is at least heterogeneous  
   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.  
   d. **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.  
   e. **Interval:** annually  
   f. **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.  
      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.  
   g. **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.

   a. **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 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.

   a. **Evidence:** Appendix 6

### 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 breast cancer screening recommendations consider the scientific evidence but 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 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.
Making Sense:

Explaining the Evidence
Introduction

This segment of the report presents a snapshot summary of the It’s About Time conference while adding up the scientific evidence behind the most important outcome - the screening recommendations. As we look closely at the specifics of the recommendations, we show how they were supported by specific research presentations delivered at the conference. The presentations were based upon the evidence presented in the conference scientific paper. This paper and its evidence is cited in Appendix A.

Like the conference itself, one of the main goals of this section is to demystify screening science for non-scientists, making the ideas of advanced research accessible to everyone - in short, to explain the science behind the screening recommendations. Because the interpretation of scientific language can skew meaning inadvertently, each of the presenters had an opportunity to review the summary of their conference paper for technical accuracy prior to publication.

In these ways this report stands as a gateway to the scientific evidence supporting breast cancer screening. Making Sense draws the individual conference papers into one big picture, showing how they relate and how they informed the consensus that developed in the It’s About Time Breast Cancer Screening Recommendations. The summarized conference papers themselves follow Making Sense. Each presentation summary provides more detail on specific issues mentioned in Making Sense and in turn offers a portal into the scientific literature on specific topics.

Through this exhaustive vetting process, the It’s About Time Breast Cancer Screening Recommendations have become the consensus of scientific evidence, clinical practice and public experience that the Canadian Breast Cancer Foundation hoped would develop by holding the conference. You can review the Breast Cancer Screening Recommendations in detail on page 19.

Explaining the Evidence

Ultimately, participating in breast cancer screening is a personal decision that everyone must make for themselves. Scientific evidence may indicate it, recommendations might suggest it, your health care provider may prescribe it, but in the end, you decide. Yet, as clear and compelling as our screening recommendations may be, they can realistically provide direction only about when and how to participate. Here we will help you review the screening consensus recommendations step-by-step to show how they have been supported by scientific evidence reviewed at the conference and how they inform the personal decision every woman should consider. Making a well-informed decision you feel confident about will send you sifting through the evidence that supports it - no small challenge, even for the experts.

The first thing you will notice is that the recommendations are separated into three “risk” groups. Most women fit the “average risk” profile and only small portions of the population are at intermediate or high risk. The differences between average and high risk are significant, however, so it will be important to assess yourself by what science and best practice suggests for each case. Later, we will re-examine the evidence on risk explored at the conference.

Age is still considered the most important risk factor, as Dr. Andrea Eisen reminded us at the conference. So the next thing to notice about the recommendations is that they specify the ages to begin and discontinue screening for each risk category. The age to start breast cancer screening is, however, one of its most controversial and debated points. An enormous amount of research and clinical experience, much of it reviewed at the conference, went into specifying age 40 to begin screening for women of average risk. We will review what was said at the conference and evidence assessed by the scientific committee to support screening at age 40.

The third point to notice in the recommendations is that they recommend the modality or the specific technology that
should be used to screen for breast cancer for each level of risk. The most commonly used imaging tool for detection of breast cancer is mammography, which examines the breast by an X-ray image on film. One of the key points made at the consensus conference was that newer technologies have been steadily improving the quality of images and their capacity to detect cancer early. Many of the technical advances have greatly improved sensitivity to finding cancer in higher risk women.

The fourth point to notice may well be the most important: the interval or the suggested frequency for screening. One of the key research findings raised by Dr. Robert Smith at the consensus conference was that the time it takes for a tumour to become visible to mammography is shorter in younger women, making a shorter interval between screenings critical. After menopause, tumour growth slows down, so a longer two-year interval between screenings is usually all that is required.

To be sure, considerable debate about the value of mammography, especially in women 40 - 49, continues to exist among certain scientists and physicians. All screening technologies have their limitations, and debates about screening largely centre on the limitations and their potential for harm. We will review the Scientific Advisory Committee's observations on limitations and harms.

But before getting deeper into the evidence for screening, some clarification of the term is in order. Screening for a disease simply involves the use of a medical test on a population of individuals without symptoms. The goal is to detect the disease earlier, before symptoms emerge. The benefit is that fewer people die and more easily tolerated therapies can be used in treatment. When the activities of population screening are organized by the health care system, we refer to this as a "screening program."

In Canada breast cancer screening programs are under provincial control. As Gregory Doyle pointed out at the conference, provinces vary by age of inclusion: some start screening at age 40 while others, like Ontario, start at age 50. Health administrations in each province have developed their own policies based on any number of factors, including scientific evidence, but often leaning toward the cost-effectiveness bottom line. Whatever their differences, most provinces fund on-demand screening facilities in addition to organized programs.

Of course, mammography is also used in a diagnostic setting to assess women with symptoms of a possible breast cancer. This use is known as "diagnostic screening." In some cases, women without symptoms receive mammograms after being referred by their primary health care provider. Known as "opportunistic screening," this option can help cancers be detected earlier, but lacks important features of an organized screening program, which can contribute to better patient outcomes.

### Public opinion poll:
How satisfied are you with the information available from Ontario's health care system to help make an informed decision about participating in breast cancer screening?

**Response:**
- A Very Satisfied 5%
- B Satisfied 28%
- C Don't know / Can't decide 17%
- D Unsatisfied 36%
- E Very unsatisfied 14%
Since mammography is generally available to anyone who needs it, you might wonder why screening programs are so controversial. The inclusion factor, especially of women aged 40 – 49, is one of the key points of debate. The Scientific Advisory Committee considered a mass of evidence about this age group and came to the conclusion that not only is 40 the age to begin mammography, but more importantly, that this group should be included in screening programs. Because screening programs include invitations and return notification for screening at regular intervals, quality assurance, performance reviews and onward referrals, they are considered a superior option to “opportunistic screening.” However, screening programs are costly and best practice often competes with economics in decisions about whom to include.

Dr. Martin Yaffe pointed out in his introduction to the conference that breast cancer screening may eventually become as easy as walking through the security gate at an airport. That vision is still in the distance, so we have to live within current limitations. Screening technology, however, has been improving incrementally, often to the point where the science has surpassed existing health policy. Several presentations delivered at the conference demonstrated these advances by showing immense improvements in image quality that exist now compared to the earlier days of mammography. Such improvements have increased the accuracy of experts’ interpretations and thus their capacities to identify cancer or dismiss it by what is visible on screen.

Risk Factors, Risk Groups

Since the recommendations use three risk groups to sort out differences in screening routines, you may be wondering how you fit the risk profile. Some people would consider just being a woman to be the most common risk factor for breast cancer. While men do get breast cancer, women are about 100 times more likely to get it. Thus the vast majority of women (at least 80%) are considered “average” risk. The prevalence of breast cancer increases with age, which makes advancing age the most commonly recognized risk factor. The median (middle) age for a breast cancer diagnosis is 61.

After age, the risk of breast cancer increases significantly with family history, certain benign lesions, breast density, a history of previous breast cancer and hormonal factors. According to Dr. Eisen, only about 20% of women who have had breast cancer have had a first or second degree relative who also had it. About 5% of women with breast cancer have a very strong family history of the disease, and about a quarter of high-risk cases are due to known genetic mutations such as BRCA1 and BRCA2. That leaves about three quarters of familial risk unexplained, possibly due to environmental factors, but more likely genetic factors yet unidentified.

An array of other risk factors have been explored. Some lifestyle factors like obesity, particularly in postmenopausal women, can increase risk. A specific diet to reduce breast cancer risk has been hard to pin down, but women who exercise regularly and vigorously may decrease their risk. Alcohol is a known risk factor. Low Vitamin D is also a possible risk factor.

Reproductive factors also affect breast cancer risk. Both early menarche (the age of first menstruation) and late menopause are associated with increased risk. Breast cancer risk also increases with nulliparity (having no full-term births) or having a first birth at a later age. According to Dr. Eisen, it was common over the past century for women to start families in their twenties and to continue giving birth well into their 30s. Today, women are more likely to have a first birth in their 30s. So it is possible that the social trend of having families later may be increasing breast cancer risk.

Exposure to estrogen is an important risk factor for breast cancer because hormones stimulate tumour growth. Women who are menopausal and obese have higher circulating estrogen. Excess estrogen can also be ingested with birth control pills, or hormonal replacement therapy after menopause. After 2001, breast cancer incidence appeared to decrease with a substantial drop in prescriptions after hormone replacement therapy was recognized as a possible breast cancer risk.
The **density of breast tissue**, a more recently recognized risk factor discussed at the conference, is related to the amount of estrogen in circulation. According to Dr. Norman Boyd, hormone levels vary with the proportion of dense and non-dense tissue in the breast. Excess estrogen in dense breasts is believed to accelerate tumour growth. Breast density risks apply mostly to premenopausal women, which is what makes the 40 - 49 age group, even up to age 55, so important. As Dr. Boyd pointed out, after menopause the proportion of dense tissues in the breast begins to diminish. The tissues become more fatty and produce less estrogen.

The question is how to combine all these possible risk factors to assess your personal risk. Several different assessment tools have been developed. There are two different types. One type, such as the Gail model (www.cancer.gov/bcrisktool), assesses the absolute risk of developing breast cancer. Another type assesses your likelihood of carrying a gene mutation such as BRCA1 and BRCA2. The output of the tools produces a percentage lifetime risk that can tell you which screening risk group most fits your personal profile.

Extremely dense breasts help define the group considered at “intermediate risk” in the recommendations. Women in this category may also have had a personal history of breast cancer but are not BRCA mutation carriers, have had a prior high-risk lesion but are not on chemoprevention, or have an intermediate family history of breast cancer with a 15 - 25% lifetime risk. If you believe you fit the intermediate risk profile, the recommendations suggest beginning screening annually at age 40. Your first appointment will confirm breast density and the appropriate follow-up. For those who do fit the category, ultrasound is recommended in addition to mammography, or MRI (Magnetic Resonance Imaging) may if available replace ultrasound.

Family genetic factors are the main criteria defining the screening group at “high risk” for breast cancer: women with a BRCA1 or BRCA2 mutation; women who have a first-degree relative with a BRCA mutation (even if you have yet to test yourself); and women with a 20 - 25% or greater risk of breast cancer based on risk assessment tools, which include family history. The recommendations suggest starting screening at age 30 or earlier but not under age 25.

**Starting Age**

The age to begin screening has been the source of much of the controversy surrounding mammography over the last decade. To make matters more complicated, provincial screening programs and various other health policy advisory bodies vary by their designation of the screening starting age: some say 40 and others 50. The Ontario Health Technology Advisory Committee recommends 50, while the Canadian Task Force on Preventive Health Care claims there is insufficient evidence to warrant inclusion or exclusion of women in their 40s. In the United States, the American Cancer Society recommends 40, as does one of the nation’s leading cancer treatment facilities, the MD Anderson Cancer Center, but the US Preventive Services Task force has recently revised its recommendation upward to age 50. To understand why these differences have arisen requires a rough guide to the history of screening research and how the findings have been interpreted.

Much of the research to support screening mammography from age 40 rests on the foundation of a particular type of study known as the Randomized Control Trial (RCT). The study protocol divides research participants into two groups and compares their outcomes after a period of time: one group gets treated (screening) and the other gets standard health care. Better outcomes (fewer deaths) in the screened group would show that screening is effective in reducing cancer mortality. Among many types of clinical research, the RCT is considered the most reliable. Strength, however, is also the RCT’s weakness. Screening trials usually involve very large samples - in excess of 100,000 participants - who are followed for at least a decade or more. The large samples and length of time involved in these studies make RCTs difficult to set up, troublesome to manage and very expensive.
If it was not for the expense and difficulty of running them, RCTs would be the preferred method for evaluating new advances in screening, but the costs are so high that these studies are rare and may never be replicated. For this reason the data from RCTs tend to be highly valued for analysis in secondary studies looking at specific technical issues. As Dr. Andrew Coldman pointed out at the Conference, differences in findings from the RCTs, depending on the specific focus of the researcher, have a tendency to touch off the debates we see in the media.

According to Dr. Coldman, when people look at the trials and try to summarize them, they have different objectives in mind: assessing imaging effectiveness or screening in general, or studying a specific age group. Different authors have come to different decisions about which RCTs to include in their analysis and how to summarize the RCTs’ overall results.

The costs of RCTs also affect their usefulness in different ways. Some of the trials that began in the 1960s will never be repeated, even though much has changed. As treatments have improved, for example, the mortality gap between early and late-stage cancer detection has been narrowing. Later cancers can now be treated more effectively than they used to be. Nonetheless, as Dr. Coldman noted, the best estimates we have from real world implementation suggest that the effectiveness of screening is actually better than the results achieved in the randomized trials.

As Dr. Robert Smith pointed out, interest in age 40 as the starting age for screening began with an RCT known as the HIP trial. Researchers noted that 20% or 1 in 5 of all breast cancer deaths were in women age 35 - 49. Because of their relative youth, the years lost to breast cancer are greater in this age group, accounting for a third (34%) of all life years lost to breast cancer.

Dr. Smith also pointed out an important bias existing in debates about screening that can skew understanding about breast cancer. In the context of screening, the most important measure of disease is not the death rate in an age group, but the death rate stemming from a woman’s age at diagnosis. Age at diagnosis matters more than age of death because diagnosis occurs at a time when there may be an opportunity to prevent death. Many women diagnosed in their 40s actually die in their 50s. Between 2005 and 2006, deaths attributable from breast cancer diagnosed in women in their 40s accounted for about 16.5% or 1 in 6 of all breast cancer deaths.

Since the mid-1990s, it has been common to pool the data from several RCTs using a technique called meta-analysis to get a combined estimate of overall effectiveness. Yet one particular meta-analysis might have shown significant mortality reductions in women age 39 - 49 except that a particularly large trial in the group had negative results. For some scientists, this result revealed a problem with meta-analysis itself in attempting to demonstrate the effectiveness of screening younger women. The one large trial showing no effect weakened the overall effect that could be observed in younger women.

Many such issues have come to light. The RCT data can arise from older methods and older equipment. Discoveries found in other forms of clinical research on screening have since had a major impact on screening practices, but are not reflected in prior trials. One of the key findings affecting women 40 - 49 was a discovery that the “tumour sojourn time” - the time it takes for a tumour to become detectable by screening - is shorter in younger women. According to Dr. Smith, when screened every 24 months, women under 50 were more likely to have worse tumours and higher “interval” rates - where cancer emerges between screenings. To successfully screen women under the age of 50 then, the intervals had to be shorter: between 12 - 18 months and really not any longer.

Another key problem is that the randomized screening trials in RCTs do not necessarily have adequate representation of women in their 40s in the first place. At the conference, Dr. Susan Moss presented the findings of the most recent trial specifically set up in the 1990s to assess the screening age recommendations for women in their 40s in the United Kingdom. The aim of the trial was to estimate the effect on breast cancer mortality of starting mammographic screening at ages 40 - 41.
compared with age 50. The trial included 160,921 women aged 40 - 41. Of those, about a third (53,914) were randomly selected for the screening arm, where they were offered annual mammography to age 48, from 1991 - 1997.

The results showed a 17% mortality reduction among women invited to screen. However, this effect was considered statistically non-significant - meaning the result could have happened by chance. When the research team looked at the women who actually turned out for screening, adjusting for those who did not, they found a more significant, 24% reduction in deaths. The mortality reduction was .04 per 1,000 women, or in other words, 2,512 women would have to be invited to screen to save one life from breast cancer - about four times the number to save one life for women 50 or over.

Several problems in this trial's procedures may have weakened its findings. The study never reached its planned recruitment target of 190,000, which diminished the likelihood of a significant finding. As well, the team decided not to use two-view mammography after the first screen, and this too diminished the observed effectiveness. In the end the team concluded that screening may be effective in this age group, but the absolute benefit would be less than in older women, and more frequent screening would be necessary. The trial did not seem to make the case that the study team had hoped for.

While the results of the UK trial lacked the confident outcome that was desired, the findings were somewhat similar to other screening trials. As Dr. Smith pointed out at the conference, “Screening in women younger than 50 represents a different challenge compared to women over age 50, and that is primarily the need for high-quality screening at shorter intervals.”

So now that you know about the research, what does it say about an individual woman's decision to participate in screening? Unfortunately, not enough. While the trials and other clinical studies of screening tend to stir up great debates about effectiveness, almost all the talk is about effects that can be seen in the population and not so readily in individuals. This point is rarely raised in the debates, leaving individual women confused about the issue, with little help to inform their personal decisions.

Public opinion poll:
In your opinion, do the benefits of breast cancer screening women 40 - 49 outweigh the limitations and risks?

Response:
A Much more benefit than risk 49%
B More benefit than risk 39%
C Equal benefit and risk 8%
D More risk than benefit 2%
E Much more risk than benefit 2%
As many physicians and scientists noted at the conference, the real issue is not so much about age 40 or 50 anyway. After all, age is only an arbitrary cut point. The stage of women’s development around menopause is what really matters. Changes in the breast prior to, during and after menopause - fatty tissues replacing dense tissues - affect the development of tumours. Since the arrival of menopause is not the same in every woman and therefore not exactly predictable, screening recommendations default to an age range. To acknowledge this in the UK, official policy moved to include women starting at age 47.

As you might have surmised from reading the array of potential risks, breast cancer tends to arise spontaneously and randomly even among those who reduce their risk factors. Screening is one of the few options available to get ahead of random chance and detect a tumour early. In most cases, the earlier treatment begins the better the prognosis. When it comes down to a personal decision to screen, it is individual likelihood that is at stake, not what happens to the rest of the female population. The recommendations address this problem by showing you what you can do, when to start and how to approach screening depending on your level of risk.

**Technology and Modalities**

The recommendations suggest specific technologies for each of the three risk groups. Digital or film mammography is specified for average-risk women, digital supplemented by ultrasound in intermediate-risk women, and digital supplemented by MRI in high-risk women. The differences in technologies are related to differences in breast density and tumour characteristics in higher-risk women. Some imaging systems are better than others for detecting cancer or dismissing it given certain characteristics of an individual woman’s breasts.

At the conference, standard film mammography was often described as the foundation of screening programs and the basis for most of our knowledge of screening effectiveness. As Dr. Wendie Berg observed at the conference, mammography is still the only screening test that has been shown to reduce deaths due to breast cancer, almost entirely by the decrease in size of cancers detected. A 25% mortality reduction is the most widely accepted result of the screening trials.

While newer technologies have developed, they have not necessarily surpassed mammography in their overall effectiveness. The reason, according to Dr. Yaffe, is that since all tests have limitations, there is always a technical trade-off between sensitivity to abnormalities and specificity about whether they are cancer or something else. Newer technologies, however, may one day change the landscape of breast cancer screening.

Digital mammography is a case in point. While digital mammography is visibly superior than film to the eye, it has not proven to be more effective than film for screening women of average risk, according to Dr. Etta Pisano. Dr. Pisano presented the findings of a clinical trial known as DMIST at the conference. The study recruited 42,000 women at 33 sites in the US and Canada to evaluate the efficacy of digital versus film mammography. All participants received both digital and film mammography randomized by order. Some women received digital first while others received film first.

Overall, it turned out that there was no significant difference in diagnostic accuracy between digital and film mammography when applied to most women in the population. Digital mammography, however, showed significantly better diagnostic accuracy than film when applied to specific subgroups: women with dense breasts, under age 50 and pre- or perimenopausal. Ultimately, cost-effectiveness analysis showed that the best use of digital mammography was targeted screening to these subgroups, but there were not sufficient health gains to discontinue film or recommend digital for all women.

Nonetheless, digital technology has largely replaced film in most contexts today. Some screening facilities will eventually find it difficult to keep both film and digital systems going. The important point is that if the closest screening facility to
you still use film, the results are equally valid for women of average risk. Your first screening will indicate if breast
density is an issue, along with an assessment of other risk factors.

As the superior imaging capabilities of digital mammography find their best use in higher-risk women, so do, it turns out,
the other imaging modalities mentioned in the recommendations: ultrasound and MRI. The conference also heard presenta-
tions on advanced imaging technologies under development that may revolutionize breast cancer screening in the future.

Dr. Wendie Berg presented the findings of a study known as the ACRIN trial exploring ultrasound as an additional screening
technology in subgroups that do not benefit as much as others from mammography, such as women with dense breasts. Dense
fibrous tissue produces an image that is too detailed to read accurately with standard mammography. Tumours can sometimes
remain hidden behind normal tissue. Breast ultrasound can image tissue at different angles to overcome the limitations of the
one-dimensional image produced by mammography.

In the ultrasound trial, all study participants had at least 25% dense breast tissue: 20% were high risk; 53% had a prior history
of breast cancer; and the remainders were intermediate risk. Each had a mammogram plus ultrasound every year for three years.
In the first year, half the cancers were found by mammography, but an additional 30% were found only by ultrasound. Over the
three years of the study, there was an absolute increase in invasive cancer detection of 34%.

According to Dr. Berg, the ACRIN study proved the value of ultrasound, providing reasonably strong evidence for its use
as supplemental screening in addition to mammography in high-risk women who cannot tolerate MRI; intermediate-risk
women with a prior history of breast cancer; and women with extremely dense breasts or a high proportion of dense
tissue. The screening recommendations of the Scientific Advisory Committee specify supplemental ultrasound for
women at intermediate risk and as an alternative to MRI in high-risk women.

Magnetic Resonance Imaging (MRI) uses a completely different technology than mammography to produce what is visible
on screen, and its full capabilities in breast cancer screening are still under study. As Dr. Roberta Jong described at the
conference, there are so many advantages to MRI that women often wonder why it has not replaced mammography. One
of the most appealing attributes of MRI is that it requires no breast compression, the most common complaint with
mammography. There is also no radiation, and its sensitivity to finding abnormalities is very high.

Nonetheless there are drawbacks with MRI that diminish its appeal as a mass screening technology, at least for the time
being. Standard MRI equipment is very expensive and additional parts needed for breast imaging only add to the cost. The
imaging time is much longer than mammography (30 minutes), so screening is slower for the individual and fewer women
can be processed by the facility. MRI also requires an injection of a contrast agent that helps enhance abnormalities on screen.
Some women find the machine noisy and confining and it has size and weight limits. Among other limitations MRI also has
lower specificity - the ability to rule out cancer - because normal tissues and benign abnormalities can sometimes become
conspicuous and cause “false alarms.”

High-risk women who may begin screening as early as 25 have the advantage with MRI of reduced lifetime accumulation
of radiation, along with other benefits. As Dr. Don Plewes explained at the conference, one of the main benefits is bilateral
imaging (both breasts at once), a fundamental advantage over other systems imaging one breast at a time. Early breast MRI
required two separate scans, needing two imaging sessions, sometimes on different days. Now, with bilateral imaging, both
breasts are imaged at once with only one injection of contrast agent.

The image capabilities of MRI are what make this technology so useful in screening higher-risk women. The most recent
development displays a 3D image showing the spatial positioning of the breast’s internal structures that is viewable from any angle - a virtual “fantastic voyage” that was once only science fiction. If a suspicious mass is found, MRI imaging also assists with studying the lesion’s size, shape, position and even the extent of disease, all of which promotes more effective treatment and ultimately better outcomes.

Screening Intervals

The recommendations prescribe the frequency of visits for each of the risk categories. After menopause most women over 50 should return for screening every two years. Younger women and those at higher risk should screen more regularly: every year. As we pointed out earlier, research has shown that shorter intervals are critical to successful screening in younger women. Tumours grow faster in women who have not gone through menopause, and the objective is to remove cancers as new and small as possible.

Experience has shown, though, that distorted perceptions of time between intervals can often mean that women show up too late for screening. The result is advanced tumours, more complicated procedures and greater risk to life. Screening programs often include invitations to return for a next appointment at the correct interval, which is what makes organized programs so valued. Even with regular routine visits, tumours can emerge between screenings. These are known as “interval cancers” and are reason enough for maintaining your screening schedule. As Dr. Rene Shumak pointed out at the conference, women benefit from routine screening because cancer is found early. With interval cancers women lose that benefit because their cancer is found later. The need to keep on top of the potential for cancer to emerge between appointments makes committing to routine screening and sticking to your schedule so important.

Cancers that emerge between visits are one of the ways that screening programs evaluate the quality of their work. A client’s previous screening and diagnostic films are reviewed to determine whether an abnormality was not actually there, missed, or benign at the time. The results determine whether the interval cancer was a “true interval” (arising spontaneously between screenings) or a cancer “missed at screening” or “missed at diagnosis.” True intervals usually appear more frequently than the others combined in a well-run screening program.

Public opinion poll:
How satisfied are you that Ontario’s health care system keeps up with the state of the art in cancer detection, treatment and care?

Response:
A Very satisfied 4%
B Satisfied 20%
C Don’t know/Can’t decide 23%
D Unsatisfied 40%
E Very unsatisfied 13%
According to Dr. Shumak, the best way to improve on “true intervals” is to improve on the screening equipment, and to ensure that radiologists and technologists are well trained and highly experienced. Avoiding cancers “missed at screening” requires greater scrutiny by the radiologist. It is also critical that suspicious findings from the screening examination are not later missed in the diagnostic assessment that follows. This is why it is considered so valuable to have a close linkage between a screening centre and a high quality, comprehensive diagnostic assessment facility that includes further imaging, biopsy and pathology evaluation.

**Targeting and Participation**

Even in urban centres where screening facilities are within reach, women often experience difficulties with getting to screening appointments. Child care, transportation and time off work can all be barriers to routine screening. Some women have more barriers than others, however. The conference heard about research and community action with specific groups of women: First Nations, the physically disabled and immigrants.

Dr. Jan Angus described a community-based study of breast cancer screening in women with disabilities. Women with disabilities often have a difficult time with breast screening right from the start: just having their doctor acknowledge its importance. Most screening facility waiting areas or change rooms are not designed to accommodate wheelchairs or other assistive devices. Mammography equipment that requires women to stand for extended periods is a significant obstacle. Social barriers are presented by staff, who may not be responsive to the needs of clients with a range of possible disabilities. And if the appointment takes longer because of these issues, the client’s link with wheelchair transportation may get missed. Obviously disabled women need more and better adapted facilities.

First Nations women who live in remote rural areas experience both distance and cultural barriers with breast screening. At the conference, Dr. Bruce Minore described research into the fears and anxieties that First Nations women experience. They wonder why they have to fly hundreds of kilometers south to a strange community for a medical appointment when they are not sick. Separation from family turns out to be their major barrier. First Nations women said that it was important to recognize their cultural circumstances when inviting them into screening. Not only do they need to understand the screening process themselves, but so do their families and communities.

Immigrant women living in urban areas can often be isolated by gulfs of language and culture. Linda Ferguson presented a report on Toronto Public Health’s efforts to reach and encourage such women to participate in breast cancer screening. Many immigrant women do not know about either the importance of screening, the recommended frequency, or the concept of prevention, and lack access to primary care physicians. Fatalistic attitudes pervade many immigrant communities: “If it’s going to happen, it will happen.” The main outreach strategies in use are personal skill building, education and awareness raising. Translated materials and ads appear in the media of 11 different ethnic communities. Volunteers set up presentations and displays in a variety of community settings, especially ethnic shopping malls.

**Quality Assurance**

One of the virtues of participating in a screening program is that service quality standards are monitored and reviewed. Dr. Rebecca Smith-Bindman described studies in the United States that found wide variation in the interpretation of mammograms depending on the institution where they were performed. According to Dr. Smith-Bindman, the accuracy of mammography is no worse than other imaging tests, but mammography still needs to improve. It can improve by standardizing interpretation and having clear performance parameters. Higher volumes seem to improve quality in institutions, as does staff experience and specialized training. According to Dr. Smith-Bindman, as a widespread screening test, the performance of mammography is unlikely to be improved upon in the near future. Nonetheless, the future is unfolding now.
The Future

At the conference several other technologies were introduced that are still under study and only available in research settings. Digital Breast Tomosynthesis (DBT) eliminates the super-imposition of internal breast structures, making it possible to identify subtle abnormalities which may be otherwise hidden in conventional mammography. As Dr. Jong explained, both 2D and 3D images are visible simultaneously and a movie function can image a virtual “fantastic voyage” inside the breast.

Dr. John Boone introduced another screening device, breast computed tomography (CT). Using this technology the radiologist can see virtual 3D slices of the inside of the breast, which eliminates the super-imposition issue. The device is also designed to maximize the comfort of screening while lying face down with breasts suspended. The main point with these newer technologies is that the science of breast cancer screening is still very much in motion and improving cancer detection capabilities dramatically.

Eventually, though, breast cancer screening will reach Dr. Yaffe’s vision of a test that is as easy as passing through the security gate on your next flight. Dr. John Valliant presented that future in research being conducted now. As Dr. Valliant pointed out, the detection of cancer has been dominated by methods that image anatomy. It is now possible to use a molecular imaging probe, an agent that seeks out and emits a signal from the site of disease, to visualize its biochemical processes.

Changes in biochemistry precede the physical manifestation of cancer, giving molecular imaging the ability to find tumours earlier and provide the physician with more information about treating them. A number of chemical probes are currently under development that address some of the limitations of existing imaging techniques. Their greatest value may lie not only in early detection, but in guiding the choice of therapy. With chemical probes the physician will actually be able to observe what happens to a tumour in the presence of a chemotherapy. If the treatment does not appear to diminish the tumour, the physician can switch to another therapy.

Manual Detection and Breast Cancer Screening

You might wonder where all this leaves simpler forms of early cancer detection like your own self-exam and clinical breast exams. As the recommendations state, the evidence is reasonably clear that self-examination is an unreliable breast cancer screening method for detecting cancers early and reducing mortality. While it is always good practice to be aware of your body, cancers found by self-examination are likely to be much larger than those found by mammography. However, whether or not breast self-examination can be shown by science to be effective at early cancer detection, it seems very likely that personal vigilance - being aware of changes in your breast - can help you identify changes that might warrant follow-up with a health care provider. This watchfulness also affirms most women’s desire to be an active agent in their own breast health.

CBE in conjunction with screening mammography was also reviewed at the conference. According to Dr. Anna Chiarelli, CBE has been shown to detect a small number of cancers missed by mammography, but at the cost of a steep increase in false positive results. In reviewing these findings the Scientific Advisory Committee felt that women should get information about the risks and benefits of having a CBE in addition to mammography.

Limitations and Potential Harms

While the conference clearly demonstrated that mammography is effective in detecting cancer early, that it is effective in women 40 - 49 at one-year intervals using digital imaging technologies, and that newer screening technologies are incrementally improving on these benefits, some limitations associated with all screening tests are worth thinking
about. The appearance of cancer between screening appointments suggests that some tumours can be missed in screening. At the conference, such “false negatives” were shown to be relatively rare cases even among interval cancers. Keeping to your regular screening schedule is the best way to stay on top of that potential.

False alarms are also possible. High sensitivity to abnormalities can trigger “false positives.” Suspicious results will send you to another level of screening, for more views possibly with ultrasound or MRI. More often than not “false positives” are ruled out with additional images, but sometimes a biopsy may be needed. Many women find these additional tests unnerving; however, most also realize their ultimate worth.

Some of the controversy surrounding breast cancer screening has framed these limitations as potential harms. The emotional reverberations of false alarms are one concern. Excessive use of biopsies is another concern. Quality assurance and well-managed screening programs help to minimize both false alarms and unnecessary biopsies. To find out how women feel about these concerns, we polled our public forum participants about screening preferences: Test A - always finds cancer, but 1 out of ten are false alarms; or Test B - has no false alarms, but finds 1 in 3 cancers.” As many as 90% of participants said they would prefer Test A that always finds cancer, even at the cost of false alarms.

Another problem featured in recent controversies concerns “overdiagnosis”: cancers found through screening that would not have become a health problem if they were never found. Some tumours may be malignant but slow growing or non-progressive - a problem more prevalent in diagnosing prostate, bowel and uterine cancer. A key issue is distinguishing between threatening and non-threatening tumours. Presentations at the conference demonstrated that imaging technologies are already able to visualize the rate of tumour growth, which may be one way this problem will be eliminated. While acknowledging that overdiagnosis is a concern, the Scientific Advisory Committee estimated that the current occurrence of overdiagnosis in breast cancer is less than 10 percent.
Your Decision

One of the main points of the conference was to explore the scientific evidence on breast cancer screening in a way that would help ordinary women decide what to do for themselves. Overwhelmingly, conference participants felt that women should start thinking about what to do at much earlier ages than the entry age of Ontario’s Breast Screening Program. Despite the controversies over inclusions in screening programs, women have themselves, their risks and their own personal histories to consider. Screening is the one thing you can do for yourself to get ahead of risk. The recommendations spell out your best plan.
It’s About Time! A Consensus Conference

Proceedings
Introduction

This section provides the key points for each paper delivered at the conference followed by more in-depth summaries. The summaries have been interpreted for non-scientists and each presenter has had a hand in writing them. Reading through the entire Proceedings will give you an even broader perspective on the science of screening than what is covered in Making Sense.

If you would like to go further, you can read Earlier Detection and Diagnosis of Breast Cancer: Recommendations and Scientific Review from It’s About Time! A Consensus Conference, written by the Scientific Advisory Committee, or reference its bibliography found in Appendix A which will take you on to the scientific literature itself.

Plenary 1: Current Status
What do we know about the current effectiveness of screening?

MODERATOR:
Robert A. Smith, PhD
Director of Cancer Screening, American Cancer Society

1.1 Performance of Mammography Screening

Andrew Coldman, PhD
Leader of Population and Preventive Oncology, British Columbia Cancer Agency
Head of Surveillance and Outcomes Unit, British Columbia Cancer Agency

Key Points
• Random Control Trials - set up to measure breast cancer mortality—demonstrated that screening had the potential to reduce mortality by 25–35%.
• Different authors have applied varying criteria to select and summarize results of the trials so that there is no single summary of results that is used by all authors. Thus, a range of summaries and interpretations appear in the scientific literature.
• More recent observational studies have suggested that the implementation of mammography screening has actually achieved or exceeded the benefit suggested in the trials.

Presentation Summary
Screening for breast cancer with mammography is recommended in all Canadian provinces. Each has established a program to deliver screening mammography. All provincial programs include women aged 50 - 69, but vary in their coverage of younger (40 - 49) and older (70+) women.

These programs came about as knowledge grew about the benefits of screening. The programs did not develop simultaneously. Start-ups ranged between 1988 and 1998 depending on the province. The evidence to create these programs primarily came from randomized trials that started two decades earlier during 1960 - 80.

Randomized trials are difficult to conduct. In order to measure mortality reductions they must be large, including tens of thousands of subjects, and take a long time, since they need to wait for cancer development and subsequent death. Thus, randomized trials are expensive and rare.
Consequently, breast screening trials are often quite unique. They use the following:

- Different interventions (mammography with/without physical exam)
- Different screening frequencies
- Different numbers of screening rounds
- Different age groups
- Different randomization units
- Different comparison groups
- Different amounts of follow-up post-screening

When people look at the collectivity of trials and try to summarize them, they may have different objectives in mind, e.g., imaging effectiveness, screening in general, or a specific age group. Different authors have come to different decisions about what trials to include in their analysis and how to summarize their overall results. Factors that influence these decisions include perceived quality measures, interventions and age inclusions. Thus, a range of summaries and interpretations appear in the scientific literature.

What follows is a summary taken from the IARC Breast Screening Handbook with the results from the UK Age Trial included.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Enrollment</th>
<th>Age Range at Entry</th>
<th>Mean FU</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIP (New York)</td>
<td>1963 - 66</td>
<td>40 - 64</td>
<td>18.0</td>
<td>0.78</td>
</tr>
<tr>
<td>Malmo 1</td>
<td>1976 - 78</td>
<td>45 - 70</td>
<td>19.2</td>
<td>0.81</td>
</tr>
<tr>
<td>Malmo 2</td>
<td>1978 - 90</td>
<td>43 - 49</td>
<td>9.1</td>
<td>0.65</td>
</tr>
<tr>
<td>2 County Kopparberg</td>
<td>1976 - 78</td>
<td>40 - 74</td>
<td>20.0</td>
<td>0.59</td>
</tr>
<tr>
<td>Ostergotland</td>
<td>1978 - 81</td>
<td>40 - 74</td>
<td>17.4</td>
<td>0.89</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>1978 - 81</td>
<td>45 - 64</td>
<td>12.6</td>
<td>0.78</td>
</tr>
<tr>
<td>Canadian NBSS 1</td>
<td>1980 - 85</td>
<td>40 - 49</td>
<td>13.0</td>
<td>1.06</td>
</tr>
<tr>
<td>Canadian NBSS 2</td>
<td>1980 - 85</td>
<td>50 - 59</td>
<td>13.0</td>
<td>1.02</td>
</tr>
<tr>
<td>Stockholm</td>
<td>1981 - 83</td>
<td>40 - 64</td>
<td>14.9</td>
<td>0.90</td>
</tr>
<tr>
<td>Goteborg</td>
<td>1982 - 84</td>
<td>40 - 59</td>
<td>13.3</td>
<td>0.78</td>
</tr>
<tr>
<td>Finland</td>
<td>1987 - 89</td>
<td>50 - 64</td>
<td>4.4</td>
<td>0.76</td>
</tr>
<tr>
<td>UK - Age</td>
<td>1991 - 97</td>
<td>39 - 41</td>
<td>10.7</td>
<td>0.83</td>
</tr>
</tbody>
</table>


Randomized trials summarized by a forest plot: The boxes measure the relative mortality results. A value of 1 represents no effect. Less than 1 represents a mortality lower in the screened group than the comparison group. There is a range of ages at entry. There is also a range of effects, but most are clearly less than one. The confidence intervals (lines extending across the boxes) measure the statistical accuracy of the result, usually spanning one. There is a systematic pattern of evidence showing that breast cancer is reduced in the trials.
The value of screening results from the capacity to advance the time of diagnosis and find cancer at an earlier stage. However, the trials were conducted many decades ago. Conditions have changed and the benefits of screening may also have changed. As the public is more aware of signs and symptoms, screening may not offer as much advantage as in the past because this heightened awareness leads to earlier diagnosis. The reduction in breast cancer mortality from screening relies on the better outcomes of earlier stage cancer. As treatments improve, the gap in outcomes between early and late-stage cancer may be narrowing. Later cancers can now be treated more effectively than they used to be.

There is thus an interest in and need to examine outcomes of mammography screening in more current, real world settings in order to confirm that expected outcomes are being achieved.

That is, to examine the current effectiveness of breast cancer screening with mammography. Designs of observational studies aimed at doing this are varied:

- Case-control studies: typically use deaths from breast cancer as the outcome, with retrospective analysis of screening use
- Cohort analysis: follows groups using mammography (exposed) and not (unexposed)
- Time trend analysis: breast cancer mortality before and after commencement of screening
- Population modeling: fitting models of screening and treatment to observed mortality rates

<table>
<thead>
<tr>
<th>Location</th>
<th>Enrollment Period</th>
<th>Age</th>
<th>FU Date</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navarre (Spain)</td>
<td>1990 -</td>
<td>45 - 65</td>
<td>2004</td>
<td>0.65</td>
</tr>
<tr>
<td>Copenhagen (Denmark)</td>
<td>1999 -</td>
<td>50 - 69</td>
<td>2001</td>
<td>0.75</td>
</tr>
<tr>
<td>British Columbia (Canada)</td>
<td>1988 -</td>
<td>40 - 79</td>
<td>2003</td>
<td>0.76</td>
</tr>
<tr>
<td>Ostergotland &amp; Dalarna (Sweden)</td>
<td>1978 -</td>
<td>40 - 69</td>
<td>1997</td>
<td>0.59</td>
</tr>
<tr>
<td>Utrecht (Netherlands)</td>
<td>1974 -</td>
<td>50 - 64</td>
<td>1989</td>
<td>0.52</td>
</tr>
<tr>
<td>Florence (Italy)</td>
<td>1970 -</td>
<td>40 - 70</td>
<td>1986</td>
<td>0.53</td>
</tr>
<tr>
<td>Guildford (UK)</td>
<td>1979 -</td>
<td>45 - 64</td>
<td>1989</td>
<td>0.51</td>
</tr>
<tr>
<td>Malmo (Sweden)</td>
<td>1976 -</td>
<td>45 - 69</td>
<td>1988</td>
<td>0.42</td>
</tr>
</tbody>
</table>


The best estimates we have from real world implementation suggest that the effectiveness of screening is actually better than the results achieved in the randomized trials. We should not be worried that the current implementation of screening will not live up to the promise of the randomized trials. Less effectiveness measured in the trials is potentially due to a number of factors:

- Compliance and contamination issues lessening the measurable effects
- Limited screening rounds in trials
- Improvements in the management of early disease in more recent times
- Biases associated with self-selection in observational studies

Studies of screening mammography started almost 50 years ago. Randomized trials demonstrated that screening had the potential to reduce the mortality risk by 25 - 35%.
More recent observational studies have suggested that the implementation of mammography screening has achieved or exceeded the benefit suggested in the trials.

1.2 The Contribution of Clinical Breast Examination (CBE) to Breast Cancer Screening

Anna M. Chiarelli, PhD
Lead Scientist, Population Studies and Surveillance, Cancer Care Ontario
Associate Professor, Dalla Lana School of Public Health, University of Toronto

Key Points
- Although CBE has been shown to detect a small number of cancers missed by mammography, it is at the cost of a steep increase in false positive results.
- 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.

Presentation Summary
Since 1998 the Canadian Task Force on Preventive Health Care has recommended that women aged 50 to 69 years undergo screening for breast cancer by mammography and clinical breast examination (CBE) every one to two years. The reason: because the relative contribution of mammography and CBE have not been determined, both are recommended.

In 2002, using more recent data, the US Preventive Services Task Force (USPSTF) recommended screening mammography, with or without CBE, every one to two years for women aged 40 or older. Their reason: the task force could not determine whether the potential benefits of routine CBE outweigh the potential harms. And they could not determine the added benefit of CBE with mammography.

An evaluation conducted by the International Agency for Research on Cancer (IARC) in 2002 showed there is inadequate evidence that breast screening with CBE, either alone or in addition to mammography, can reduce mortality from breast cancer. IARC noted 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.

No randomized trial of screening mammography has compared CBE alone with no screening, but four trials included CBE in addition to mammography. Two studies (Kerlikowski et al., 1995; Humphrey et al., 2002) looking at the evidence from all the trials found that the decrease in breast cancer mortality in the four trials including CBE in addition to mammography was similar to those in trials including mammography only.

However, another way to look at the effectiveness of CBE is to look at sensitivity and specificity indicators: a pooled analysis of the RCTs showed that CBE had a sensitivity (finding cancer) of 54% and a specificity (showing there is no cancer) of 94%. This study also showed that longer examinations using standardized procedures had greater accuracy.

Three studies in community settings have looked at the contribution of CBE in addition to mammography for women 50 to 69 years of age. A US study (Bobo et al., 2000) found an additional 2.6 cancers per 10,000 mammography screenings. A Canadian study (Bancej et al., 2003) found an additional three cancers per 10,000 screenings. And an Ontario study (Chiarelli et al., 2009), using highly trained nurses, found an additional 4 cancers per 10,000 screened. However, achieving these results comes at a cost as there would be an additional 219 false positives found.
The evidence that supports the effectiveness of CBE in reducing mortality is indirect, as no randomized controlled trial has studied CBE alone without mammography compared to no screening. Although CBE has been shown to detect a small number of cancers missed by mammography, it is at the cost of a steep increase in false positive results.

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.

1.3 Evidence on Age Range and Interval for Screening

Robert A. Smith, PhD
Director of Cancer Screening, American Cancer Society

Key Points
- A significant portion of all women who die from breast cancer each year were diagnosed in their 40s.
- Since the goal of screening is to detect tumours in the pre-clinical phase, i.e., before symptoms emerge, women ages 40 - 49 are an important group to consider for screening.
- Screening women under the age of 50 is a larger challenge, but we have learned a lot about how to do it and the differences are not as dramatic as has been historically highlighted by the randomized trials.

Presentation Summary
The classic criteria by which we think about whether or not to offer screening, developed by Wilson and Jungner for the World health Organization (WHO) back in the 1960s, can also be applied to specific age groups within a screening program. How significant is the disease burden; what is the relative balance of benefits and harms; is the screening test effective and acceptable to the age group? This approach can be applied to determine an age to begin screening and an age to stop screening.

What was the origin of beginning screening at 40? When the planners of the HIP Trial were determining which age groups to include in their landmark study, they observed that
- 20% of breast cancer deaths occurred in women aged 35 - 49;
- 41% of all person-years of life lost (PYLL) due to breast cancer was associated with cases diagnosed between ages 35 - 49; and
- 34% of all PYLL due to breast cancer was associated with breast cancer diagnosed between ages 40-49.

Age of death is a common measure of disease burden. But in the context of screening, the most important measure of disease burden is not the death rate within an age group, but death rate associated with the age group in which breast cancer was diagnosed. As a measure of disease burden, age at diagnosis matters more than age of death because diagnosis occurs at a time when there may be an opportunity to prevent death.
Breast cancer has been shown to be a leading cause of premature death in women, which means it also is a leading cause of years of life lost. Why? The median age at diagnosis and the occurrence of death is much younger with breast cancer than with the majority of other adult cancers. For example, significantly fewer years of life are lost (less than half) due to prostate cancer in men because the disease typically occurs at older ages. Interestingly, in the years between 2005 and 2006, deaths from breast cancer attributable to a diagnosis in the 40s accounted for about 16.5% of all breast cancer deaths. This percentage has been fairly persistent over time - ranging from about 15% to 19% - and it is influenced by underlying population dynamics. As this large number of “baby-boom” women get older they are now accounting for a growing percentage of breast cancer deaths attributable to a diagnosis in the 50 - 59 age group.

Since the mid-1990s, it has been common to examine the randomized trial data with meta-analysis, where results of all studies are pooled to get a combined estimate of the effectiveness of screening. In the analysis below (see forest plot) we see mortality reductions in women age 39 - 49 (with some statistically significant) except in one large trial that had
negative results (large square crossing 1.0). While meta-analysis has its values, it also has costs, in that the effect size will be influenced by the largest trial, which in this case showed no benefit. Many issues come to light with the trials themselves. For example, they miss the benefit of scientific and technological advances that have occurred over a 45 year time frame.

In addition to demonstrating the efficacy of mammography, data from the randomized trials have provided other important insights that guide screening protocols. For example, data from the Swedish Two County Trial showed that the “interval cancer” rate was higher in younger women. Interval cancers occur between screenings, so this suggested that screening intervals need to be shorter in younger women: every year instead of every two years. The reason, it turns out, is that tumour sojourn time (the length of time that it takes for a cancer to become detectable) is shorter in younger women: 1.5 years in women aged 40 - 49, but 2.8 years in women age 50 - 59 and 3.3 years in women aged 60 - 69. This observation also suggested that the smaller effect size in the women randomized in their 40s was influenced by a screening interval that was too long.

Not all key questions have been satisfactorily answered by the trials, and new questions arise, yet the potential for new trials to answer them is low. Still, where the trials leave questions, valuable lessons have been learned from service screening - studies of screening in real-world conditions rather than research settings. For example, we now know the tumour sojourn time is shorter in younger women. We now use two-view mammography rather than one view. We appreciate the importance of high rates of participation at the right screening interval for the specific age group. We know there is a benefit to double reading or computer-aided diagnosis. We also appreciate the importance of quality monitoring. The evaluation of service screening can examine the influence of the improvements in screening protocols that have evolved since the trials were conducted, and also determine the effectiveness of modern programs in reducing breast cancer morbidity and mortality.

In order to better understand the effects of modern service screening and the effects of mammography in the community setting (and because Sweden actually has excellent data systems), we created the Swedish Organized Service Screening Evaluation Group. The first analysis we did was an evaluation of service screening in seven Swedish counties.

The goal of mammography is to detect asymptomatic breast cancer during the pre-clinical but detectable phase. What we have seen is that when screening every 24 months, women under the age of 50 are more likely to have worse tumour characteristics and more likely to have higher interval cancer rates. This tells us that to successfully screen this age group - women under the age of 50, perhaps even women under the age of 54 - the screening intervals should be between 12 - 18 months and really not any longer. We also have seen mortality reductions in modern service screening that are as good, and often exceeding the mortality reductions observed in the randomized trials. These reductions in deaths are observed in women ages 40 - 49 at diagnosis and are similar to the mortality reductions observed in women ages 50+.

There is a great deal of interest in the harms that are associated with mammography, which include missed cancers; false-positives with imaging and biopsy; and even the possibility of 59 overdiagnosis (treating cancers that need no treatment). However, the data from the Breast Cancer Surveillance Consortium are very telling. There is little value in comparing women ages 40 - 49 on these issues with all women over 50. Instead, when you compare the screening results of women aged 40 - 49 with women aged 50 - 59, the differences are not dramatically different.

We do see that screening sensitivity is somewhat lower in women ages 40 - 49, but the effectiveness of screening improves with age in all age groups.
1.4 Population Breast Cancer Mortality Reductions: Screening or Treatment?

Donald A. Berry, PhD
Professor and Division Head, Frank T. McGraw Memorial Chair for Cancer Research
Chair, Department of Biostatistics, University of Texas MD Anderson Cancer Center

Key Points
- Statistical models showed that screening and therapy have a roughly equal impact on breast cancer mortality.
- The effect of screening in statistical models was similar to the mortality benefit shown in the randomized trials.
- Simulations have shown the potential for a “rebound” in breast cancer mortality in future years that can be offset only by additional improvements to either screening technology or cancer treatment.

Presentation Summary
Headline: “Statistical Blitz Helps Pin Down Mammography Benefits”
New York Times Editorial: “What seems most important is that each team found at least some benefit from mammograms. The likelihood that they are beneficial seems a lot more solid today than it did four years ago, although the size of the benefit remains in dispute.”

What caused the 24% dip in breast cancer mortality in the nineties? Many want to claim “It was me.” So what was it? Was it screening? Was it Tamoxifen? Was it chemotherapy? Or was it something else?

In the modeling study seven research groups worked on their own independent models and then compared them. Data was provided by the National Cancer Institute and the Centers for Disease Control. Input data considered features such as who gets screened; what therapies are applied; estrogen receptor status; stage of disease at diagnosis; and age. The focus was on the relative attribution of screening versus therapy on breast cancer mortality.
Model W showed the impact of screening and treatment on breast cancer mortality was about the same.

Model W showed what would happen without screening or therapy - a 30% increase in mortality. What would cause this? Hormone replacement therapy (HRT) was being more widely prescribed then and increasing the rates of cancer, but it is not clear what impact it had on breast cancer mortality. Screening only and treatment only each contributed about a 20% dip in mortality. The model showed that the contributions of screening and treatment were about the same.

What about both together? My hypothesis was that there would be synergy, i.e., that women who have a screen-detected tumour and therapy would be better off than those receiving only the sum of each contribution alone. That turned out not to be true. The modeling suggests that the effects of the two factors are additive.

Comparing the models showed a remarkable similarity in results:
- Screening lowering breast cancer mortality
- Population treatment benefit similar to clinical trials
- Little evidence for synergy from screening and therapy
- Some model differences
- Overall robustness across models
A more recent simulation study has looked at the question, “Are we going to achieve NCI’s (National Cancer Institute) healthy people targets?” This model looks at various contributions such as aromatase inhibitors and taxanes in the treatment of the disease. It indicates that without additional improvements in therapy or screening, breast cancer mortality is going to rebound. However, and now reflecting an optimistic view the future, additional improvements are coming, at least in therapy.

1.5 The Effectiveness of Mammographic Screening in Young Women

Sue Moss, PhD
Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research

Key Points
- UK Age Trial results showed a reduction of 17% in breast cancer mortality in the 40 - 49 age group at 10 years of follow-up.
- The use of two-view mammography throughout might have increased the effectiveness of the intervention.
- Other factors such as contamination in the control group did not seem to have a large impact on the results.

Presentation Summary
Many of the randomized screening trials did not have adequate representation of women in their 40s. Women in their 40s were invited into the trials, but most were also screened after age 50. So the UK Age Trial was set up specifically to look at inviting women starting at age 40.

The aim of the trial was to estimate the effect on breast cancer mortality of starting mammographic screening at ages 40 - 41 compared with age 50. The trial included 160,921 women aged 40 - 41. Of those, about a third (53,914) were randomly selected for the intervention arm, where they were offered annual screening to age 48. The remainder went to the control arm where they received standard care. Participants from both arms became eligible for the national screening program at age 50.
When setting up the trial we decided to use two-view mammography on the first screen and only single view on subsequent screens. At the time we were concerned about radiation exposure. In retrospect, given what we know now, the intervention would be likely to have been more effective if we had used two views throughout.

In 2006 we first published the results of the trial after a ten-year follow-up. The results showed a 17% mortality reduction in the women invited to screening, considered statistically “non-significant.” When we looked at the women who actually attended screening, adjusting for non-attenders, we found a 24% reduction in mortality, again not quite reaching “significance.”

In measuring the absolute benefit of screening in the trial, we found a mortality reduction of .04 per 1,000 women. Another way of looking at it is that we would have to invite over 2,512 women to save one life from breast cancer - about four times the number in the UK to save one life in women age 50 and over.

When we published these results we felt the effect of screening might have been underestimated. The effect of later screens in the trial would not have been evident at the time of our measurement (10 years from the first screenings). Two-view mammography throughout the trial would have increased sensitivity. There was lower than expected uptake in the screening arm than in the national program because there was little publicity about the trial. Also, women who moved from the trial centres were lost to the intervention arm and no longer invited to screening. Finally, it was evident that there might have been some screening going on in the control arm (contamination) that would have diluted the effect of the intervention, although any effect of this appears to have been small.

We have now updated our results, looking at another three years of follow-up. As can be seen (see plot) the lines do not appear to be diverging greatly. At 14-year follow-up the mortality reduction was 14% in the intervention arm, 19% among those who actually screened. The absolute reduction was .46 per 1,000 women invited or 2,167 women invited to save one life.
We looked at potential harms from screening in the trial. The effects of radiation do not appear to be an issue. About 27% of women in the intervention arm had a false positive result over ten screenings - much higher than seen in older women in the randomized control trials. We also found little evidence of overdiagnosis in the trial.

Conclusions

- Results showed a reduction of 15 - 17% in breast cancer mortality in the 40 - 49 age group, consistent with estimates from meta-analyses of the other trials.
- Use of two views and re-invitation of all women might have increased efficacy.
- Current evidence suggests little overdiagnosis as a result of screening from age 40.
- False positive mammograms did not impact on subsequent screening uptake.
- Contamination in the control arm is unlikely to have had a large effect.

UK Screening Policy Postscript

Screening policy in the UK is changing to include women below age 50, but not directly because of the age trial results:

- women age 47 - 73 invited with full coverage as of 2012
- women to receive their first invitation before age 50 (47 - 49)
- invitation to centres where digital mammography has been implemented
- batch randomization currently being piloted to compare inclusion of younger versus older women

Plenary 2: Policy Perspectives

Where does Canada stand?

MODERATOR:

Martin Yaffe, PhD

Senior Scientist in Imaging Research at Sunnybrook Health Sciences Centre
Consultant Physicist for the Ontario Breast Screening Program
Professor, Departments of Medical Biophysics and Medical Imaging, University of Toronto

2.1 Policy and Programs in Breast Cancer Screening in Canada

Gregory Doyle

Chair, National Committee, Canadian Breast Cancer Screening Initiative (CBCSI)
Program Director, Breast Screening Program for Newfoundland and Labrador

Key Points

- All Canadian provinces offer mammography programs, but each varies by their inclusion of the 40 - 49 age group.
- Four provinces include the 40 - 49 age group with annual recall.
- Mammography is generally available opportunistically to women of all ages outside of provincial programs.

Presentation Summary

In Canada, breast cancer is the second-most common malignancy and second leading cause of cancer-related death. A Canadian woman has about a one in nine chance of developing breast cancer and a one in 27 chance of dying from it over the course of her lifetime. In 2009, there were 22,600 diagnosed cases of breast cancer in Canada, 3,600 among women age 40 - 49 (16%) and 11,700 among women aged 50 - 69 (52%).
The effectiveness of screening as demonstrated by the randomized control trials is well accepted in Canada and there is significant public demand for screening services. Organized screening programs are widely available, but there is also a significant volume of opportunistic screening occurring outside of these programs. The advantage of organized screening programs is that they are subject to considerable health service monitoring and evaluation.

Prior to screening, most women presented to health care with symptoms of breast cancer. Self-examination, clinical breast exams and diagnostic mammography were all that was available. With screening programs, mammography is promoted in the population. Invitations and facilitated referrals are used systematically to recruit and recall women of screening age. Mammography is the principal modality of screening, and in some provinces it is complimented with a clinical breast examination. Screening programs coordinate further diagnostic work, and all aspects of care are monitored with electronic data bases.

Organized screening in Canada began in British Columbia in 1988 and proceeded across the country over the next decade. Canada’s provincially organized program is somewhat unique among nationally organized programs in the UK, Australia, New Zealand and Europe. Most of those programs target women for screening beginning at age 50, except for Hungary, which begins at age 45 (note: the UK has proposed a policy age of 47).

Mammography is generally available to all women in Canada, regardless of age, outside the organized programs.

**Provincial programs accepting women aged 40-49**

- British Columbia
- Yukon
- Northwest Territories
- Alberta (with referral)
  - Saskatchewan
  - Manitoba
  - Ontario
  - Quebec
  - New Brunswick
- Nova Scotia
- Prince Edward Island
- Newfoundland

The Canadian Community Health Survey collects self-reported data on participation in any form of mammography. On average about 25% of Canadian women age 40 - 49 report having had a mammogram in the last 12 - 24 months, compared to 35% in provinces where programs exist. Among women age 50–69, about 63% self-report having had a mammogram over the same period.

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A Since April 2009, women can self refer to the Prince Edward Island provincial breast screening program starting at age 40.
Women's participation in screening programs varies across Canada. However, by combining screening records and fees for services paid at diagnostic facilities, it has been determined that at least 70% of women in the 50 - 69 age group had a mammogram over a 30-month time frame. Where screening programs accept women age 40 - 49, participation is robust. In British Columbia, for example, approximately 33% of screening program capacity is used by women age 40 - 49.

### 2.2 Policy and Programs in Breast Cancer Screening in Canada

**Jay Onysko**  
Manager, Screening and Early Detection, Chronic Disease Management Division  
Centre for Chronic Disease Prevention and Control, Public Health Agency of Canada

Every time a woman participates in an organized screening program, her data - screening episodes, diagnostic tests and results, cancer staging - flow to a national database in a systematic way. This allows the performance of screening programs to be compared so that the provinces and territories can learn from each other's successes and challenges.

One thing that is inconsistent is the performance of mammography across age groups. The abnormal recall rate decreases with age: 13.4 per 1,000 screens in women age 40 - 49; 12.6 in women aged 50 - 59; 10.5 in women aged 60 - 69; and 9.0 in women over 70. On the other hand, the cancer detection rate increases with age: 2.1 per 100 screens in women age 40 - 49; 4.0 in women aged 50 - 59; 7.4 in women aged 60 - 69; and 10.8 in women over 70. Consequently, the “positive predictive value” of the screening increases with age.
Given relative limitations of screening performance in the 40 - 49 age group, and a number of critical meta-analyses of breast screening studies that challenge the value of screening, the Public Health Agency of Canada undertook to develop a Decision Aid for breast cancer screening. While screening programs strive to maximize benefits and minimize harms, they all have limitations. It is felt that women’s involvement in weighing the potential benefits and harms of screening will empower more informed health care choices.

The Decision Aid is a booklet featuring information on breast cancer and screening that every woman should consider: risk factors; age group differences; what happens in screening; potential benefits and harms; and a personal planning worksheet.

Conclusion
• Screening program age-based acceptance policies vary across the country.
• Age-based acceptance policies appear to influence utilization.
• Screening program performance varies substantially with age.
• Understanding the potential benefits and limitations of mammography empowers women to make informed health care choices.

| Selected indicators by age group for women participating in Canadian screening programs |
|---------------------------------|----------------|----------------|----------------|----------------|
|                                  | 40-49 years    | 50-59 years    | 60-69 years    | 70+ years      |
| Abnormal Call Rate on Initial Screen | 13.4 | 12.6 | 10.5 | 9.0 |
| Cancer Detection Rate (per 1000 screens) | 2.1 | 4.0 | 7.4 | 10.8 |
| In-Situ Cancer Detection Rate (per 1000 screens) | 1.0 | 1.1 | 1.8 | 1.5 |
| Positive Predictive Value (%) of Initial Screen | 2.3 | 4.0 | 8.9 | 13.8 |
| Positive Predictive Value (%) of Rescreen | 2.6 | 6.0 | 9.1 | 13.4 |
MODERATOR:

Etta Pisano, MD
Vice Dean for Academic Affairs, Kenan Professor of Radiology and Biomedical Engineering,
Director of the University of North Carolina Biomedical Research Imaging Center

3.1 Digital Mammography: What We Learned from DMIST (Digital Mammographic Imaging Screening Trial)

Etta Pisano, MD
Vice Dean for Academic Affairs, Kenan Professor of Radiology and Biomedical Engineering,
Director of the University of North Carolina Biomedical Research Imaging Center

Key Points

• Digital mammography has not been shown to be more accurate than film in diagnosing all women in the population.
• Where digital mammography has shown to be significantly more accurate is in testing women with dense breasts, women under 50 and pre- or perimenopausal women
• Converting to digital mammography may not be warranted by test accuracy. Digital costs more; however, it also costs more to maintain two types of equipment in an technological environment where film use is declining.

Presentation Summary

Digital mammography has been in use since 1992. A large clinical trial (DMIST) involving at least 42,000 women at 33 sites in the US and Canada was used to evaluate the efficacy of digital versus film mammography. All participants received both digital and film mammography. The exams were randomized by order. Some women received digital first while others received film first. Two separate readers read every woman’s mammogram, one for film, the other digital. Every site had at least three readers.

The study found overall that there was no significant difference in diagnostic accuracy between digital and film mammography when applied to all women in the population, as measured by difference under the ROC (relative operating characteristic) curve (p=0.182). The study did not use mortality as an endpoint because this would have added more cost to an already expensive trial. It was assumed that if we found cancer with digital at the same rate as film, mortality would be affected in a similar way. We also assumed that if we found additional, potentially deadly cancers that mortality would be affected in a positive way.
However, digital mammography showed significantly better diagnostic accuracy than film (p <0.0033) when applied to specific subgroups of women:
- Dense breasts (p=0.003)
- Under age 50 (p=0.023)
- Premenopausal and perimenopausal (p=0.022)

A ROC curve (relative operating characteristic) is used to plot the results of a diagnostic test. The horizontal line (1.0) represents a perfect test. The area under the curve (AUC) is expressed as a value that is a measure of test accuracy. The red line and the blue line closely parallel each other, indicating very little difference in test results between digital and film when used in the whole population.

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- Under age 50 (p=0.023)
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The curves are widely separated in this ROC plot. The blue line approaches the horizontal line (1.0) while the red line drops below, indicating more accuracy from digital mammography than film in pre- and perimenopausal women.
Overall, 65% of the women participating in DMIST were in at least one of three groups that could benefit from the improved diagnostic accuracy of digital mammography: those with dense breasts (46%); those under age 50 (33%); and those who are pre- or perimenopausal (38%). The evidence suggests that the majority of women would benefit from digital instead of film mammography. Why?

Consider that 40% of women over 50 have dense breasts. Age is an arbitrary cut point and breast density appears to be the driver behind DMIST results. The reason digital outperforms film in such conditions is its ability to enhance image contrast to see subtle objects on a dense background. The image contrast of digital mammography can actually be adjusted, unlike film. Thus the improvement in accuracy with digital mammography does not depend on readers or any other factor, but the improved quality of the diagnostic image itself.

Is it reasonable to adopt digital mammography for all or some women? Cost-effectiveness analysis in the DMIST study showed that its best value was in targeted screening, but there were not sufficient health gains to warrant its use in all women. Targeting women according to age rather than breast density might be feasible.

Moving to increase the use of digital mammography is not directly supported by efficacy data from the DMIST study. As well, maintaining both film and digital mammography equipment at a diagnostic facility might not be feasible because of the increased costs involved. On the other hand, it may be wise to invest in digital for reasons beyond potential health gains, such as the declining use of film technology in general.

3.2 Screening Breast Ultrasound

Wendie A. Berg, MD, PhD
Assistant Professor, Department of Radiology, Johns Hopkins University
Study Chair, American College of Radiology Imaging Network

Key Points
- Ultrasound is useful as an additional screening technology to overcome the limitations of mammography.
- Some women benefit less than others from mammography: those of high and intermediate risk, or with dense breasts.
- The ACRIN 6666 study showed that adding screening ultrasound to mammography resulted in a statistically significant absolute increase in cancer detection of 29% compared to mammography alone, and a 34% absolute increase in invasive cancer detection.

Presentation Summary
Five years after beginning a randomized trial of screening using breast ultrasound, we now have final results from ACRIN 6666.

Mammography is still the only screening test that has been shown to reduce deaths due to breast cancer: a 40% reduction of mortality among those actually screened (Tabar et al. 2003 (1)). The mortality reduction is almost entirely attributable to the decrease in the size of cancers detected with screening (Tabar et al. 2000 (2)), and only trials that show an increase in detection of node-negative cancers show a decrease in breast cancer mortality (R Smith 2004 (3)).

It stands to reason that, if we are looking at a new technology to consider for screening, we would demand that it find small (median size 1 cm) invasive cancers that are node negative at detection. It is reasonable to infer that a technology that can show such cancers would achieve even further reductions in mortality than mammography. However, mortality in screening beyond mammography has not been studied, and it is unlikely to be studied because of the cost of the research.
Still, there are subgroups of women who do not benefit as much as others from mammography, such as those with dense breasts. Should we consider supplemental screening in addition to mammography with these women? Alternative screening methods that detect small (< 1-2 cm), node-negative cancers could provide additional reduction in mortality. What about ultrasound?

There is particular interest in studying high-risk women: BRCA mutation carriers and their first-degree relatives, those with a high lifetime risk or a previous history with breast cancer. They have more cancers to find. They tend to be at a younger age at diagnosis, so there is potential for greater years of life saved. As well, they often have dense breast tissue where there is a known limitation with mammography. And, they are more motivated. Thus annual MRI in addition to mammography is appropriate for screening high-risk women (Saslow 2007 (4), Berg 2009 (5)).

Women of intermediate risk are also of interest, representing from 15 to 30% of the screening population: those with LCIS (lobular carcinoma in situ), a personal history of breast cancer, previous atypical biopsy, a lifetime risk of 15 to 20% by models that evaluate family history, and/or women with dense breast tissue. The evidence is insufficient for or against screening with MRI in this group (4). These women represent a relatively large group to consider for ultrasound.

There is also a significant group of high-risk women who may not want MRI for other reasons. As many as 42% of eligible women declined MRI in the study, 25% due to claustrophobia (Berg 2010 (6)). Body implants such as a pacemaker or aneurysm clip and concerns over screening agent injections accounted for another 14%.

Prior to the ACRIN trial, there were single-centre ultrasound studies that showed fairly consistent results of detecting 3.5 cancers per 1,000 women screened, found only on ultrasound (Berg 2004 (7)). The vast majority of the patients screened with ultrasound had dense breasts. Ninety-five percent of the cancers were invasive, 70% were under 1 cm and the vast majority were node negative. So ultrasound at least meets the criteria for an alternative screening technology.

In the ACRIN trial, 20% of the women studied were high risk; 53% had a prior history of breast cancer, and the remainder were intermediate risk (Berg 2008 (8)). All study participants had at least 25% dense breast tissue confirmed by a previous mammogram. Each had a mammogram and ultrasound every year for three years. The exams were independently performed by separate radiologists.

In the first year of the study, half of the cancers were found by mammography, but another 30% were found only by ultrasound (Berg 2008 (8)). The area under the ROC curve (AUC) increased significantly with ultrasound. There were 5% false positives; however, most of the patients found an ultrasound-guided biopsy easier than going to the dentist.
Overall we saw an absolute increase in invasive cancer detection of 34%, and only one node-positive cancer out of 31 invasive cancers seen only on ultrasound, over three years of the study.

At this point we have reasonably strong evidence for the use of supplemental screening ultrasound in addition to mammography in specific groups of women: high-risk who cannot tolerate MRI; intermediate risk due to prior history of breast cancer; those with extremely dense breasts; and those with an intermediate family history and at least heterogeneously dense breasts (Berg 2009 (5)). Facilities offering screening ultrasound must have trained personnel and the ability to biopsy lesions seen only on ultrasound.

3.3 The Role of MRI (Magnetic Resonance Imaging) in Breast Cancer Detection

Roberta Jong, MD
Associate Scientist, Sunnybrook Research Institute
Division Head of Breast Imaging, Department of Medical Imaging, Sunnybrook Health Sciences Centre
Associate Professor, Department of Medical Imaging, University of Toronto

Key Points
• The advantages of MRI are that there is no ionizing radiation, no breast compression, it’s not affected by breast density and it provides greater than 90% sensitivity.
• The problems with MRI are largely related to the cost of the equipment, the need for an intravenous injection of a contrast medium and the longer time required for imaging. Specificity is lower because with MRI normal tissues and benign abnormalities can be enhanced.
• MRI is also useful to guide biopsies and to show the response of cancers to neoadjuvant chemotherapy.

Presentation Summary
MRI is one of multiple imaging modalities that we have for detecting cancer.

Who should be doing MRI of the breast? The American College of Radiology publishes guidelines on-line (www.acr.org).
People who are doing breast MRI should be expert in breast disease and breast imaging. They need to be able to perform imaging-guided interventions using ultrasound or MRI. In addition, they need strong feedback links with pathology to correlate the imaging and biopsy results and fine-tune their diagnostic abilities.

What are the advantages of MRI for screening? There is no ionizing radiation, so it is good for younger women and repeated examinations. There is very little breast compression and discomfort. It is unaffected by dense tissue and has extremely high (>90%) sensitivity for finding invasive cancer. Still, it is not a perfect test.

What are the problems with MRI screening? They are largely related to the high cost and limited access to the equipment. As well, because it takes a lot longer to do a breast MRI examination than a mammogram or ultrasound, it’s not as efficient a screening procedure. It can also be awkward to get into the device, and some women who suffer from claustrophobia cannot tolerate it. The machine’s size and weight limits can be prohibitive, and patients with certain metal devices in the body cannot have an MRI. Finally, MRI requires an intravenous injection of a contrast agent, which excludes patients with impaired kidney function.

What are some of MRIs limitations? It has lower sensitivity for detecting DCIS (ductal carcinoma in situ) than invasive disease, but it can detect DCIS not detected by mammography. The converse is also true. One of MRI’s problems is its lower specificity, because normal tissues and benign abnormalities can be enhanced and obscure significant lesions. Consequently, it is necessary to time a screening MRI to the second week of the menstrual cycle in premenopausal women. Postmenopausal women may have to stop taking HRT to reduce this background enhancement.

Because abnormalities can be found that are not seen on mammography and ultrasound, it is absolutely necessary to be able to do an MRI–guided, vacuum-assisted biopsy and clip placement. That requires additional expertise and training in procedures and interpretation.

What are the indications for MRI? Screening high-risk women, whose lifetime risk of developing breast cancer is greater than 20%, has been recommended by the American Cancer Society and Cancer Care Ontario. There may be other groups for which screening MRI might be useful, such as those with intermediate risk, dense breasts or a personal history of breast cancer, but there are insufficient data on screening these groups.

MRI is also useful in evaluating the extent of malignancy, detecting 15 - 30% more disease. This information helps in making surgical decisions such as lumpectomy or mastectomy and may reduce the need for additional surgeries for residual disease. However, data do not exist that suggest that using MRI changes recurrence or mortality rates.

With MRI, we can also follow the response of women with locally advanced breast cancer who are receiving neoadjuvant chemotherapy to see whether the medication is working and to see how much residual disease is evident post-treatment. If there is no response, the drug might need to be changed. MRI is also useful in detecting cancers that may be present but undetected in the opposite (contralateral) breast.

Some of the lesions detected by MRI can be found in retrospect on ultrasound and mammography. But what we miss with mammography may be seen on MRI or ultrasound. Doing MRI effectively is a learning experience that requires correlating all modalities.
3.4 Breast MRI: Technical Issues and Basic Requirements

Donald Plewes, PhD
Senior Scientist, Imaging Research, Sunnybrook Research Institute
Professor, Department of Medical Biophysics, University of Toronto

Key Points
- One of the main benefits of MRI is bilateral imaging (both breasts at once), a fundamental advantage over other systems imaging one breast at a time.
- Breast coils, the apparatus added to MRI equipment specifically for breast imaging, are critical to the success of MRI in breast cancer detection.
- MRI is capable of high-resolution 3D images and capable of detecting tumours on the basis of angiogenesis through the use of diffusible contrast agents.
- MRI can be used to monitor the treatment of breast cancer through changes in diffusion, pharmacokinetics of contrast media uptake and tumour size.

Presentation Summary
Several studies have shown the benefit of breast MRI in high-risk screening populations. Each study is different in the details of recruitment and techniques, but the results are consistent: MRI is a robust breast screening modality with 2.5 to 3 times more sensitivity than mammography. Though the basic techniques of breast MRI are well established, optimizing its capabilities is still a complex and evolving science.

MRI does not detect breast cancer without the use of a gadolinium-based contrast agent (GBCA). The contrast agent reflects tumour angiogenesis: the altered growth and architecture of blood vessels that mark malignancy. So, an intravenously injected contrast agent is critical to the success of cancer imaging with MRI.

MRI displays images in both two- and three-dimensional formats. The two-dimensional format, most common in North America, displays a sagittal image of the breast as seen from the side. In Europe, the more commonly used axial orientation displays both breasts at once from above. The most recent development in MR imaging is the isotropic format, which displays a 3D image showing the spatial positioning of the breast’s internal structures viewable from any angle.

Bilateral imaging was an important development. Early breast MRI required two separate sagittal scans, needing two imaging sessions, sometimes on different days. Now, with bilateral imaging, both breasts are imaged at once, which requires only one injection of contrast agent. This is a fundamental advantage of MRI over PET or other imaging procedures where one breast is imaged at a time, each time requiring an injection of contrast agent.

Follow-up examinations of suspicious lesions can be performed with MRI using high-speed pulse sequences to study the pharmacokinetics of the lesion - the uptake of contrast agents, for example. High-resolution sequences may be used for morphologic assessment: studying the lesion’s size, shape and position. Currently evolving is the use of hybrid combinations of both high speed and high resolution in a single pulse sequence.

The image presentation is a key advantage of MRI. Three-dimensional MIP (Maximum Intensity Processing) images allow a view through the breast, which can be useful in assessing the effect of the contrast agent. Isotropic resolution imaging permits a view of the inside of the breast from multiple directions or orientations, which assists in defining the extent of disease.
To date, studies of breast MRI have been performed at a field strength measure of 1.5 Tesla. Now, MRI is performed at double the field: 3 Tesla. At this greater field signal quality increases, which permits imaging of chemicals and chemical shifts in the breast but at the expense of other limitations. Both 1.5T and 3T systems are acceptable for breast MRI, but 3T is preferred for spectroscopy or chemical shift imaging in studying the uptake of therapies.

Fat suppression is another advantage and prerequisite of breast MRI. A contrast agent allows for easier detection of tumours against a fatty background. However, the effect can be greatly sharpened by imaging with and without contrast agent and subtracting one data set from the other. In the resulting image tumours appear against a more uniform surround. Other methods of fat suppression involve chemical shift imaging and fat saturation techniques, but can be somewhat more time consuming.

Breast coils, the apparatus added to MRI equipment specifically for breast imaging, are critical to the success of MRI in breast cancer detection. Breast coils improve the image signal by varying degrees depending on the manufacturer. Several systems are available with differing features including set-up, patient comfort and access for MRI-guided biopsy. Good breast coils are a less expensive upgrade for MRI than an increase of field strength from 1.5 to 3T.

A gadolinium-based contrast agent is safe for healthy patients. The use of macro-cyclic formulations have a substantially lower risk of complications in patients with renal failure.

### Plenary 4: High Risk

**What challenges are involved in screening higher-risk women?**

**MODERATOR:**

**Kathleen Pritchard, MD**
Senior Scientist, Sunnybrook Research Institute
Chair, Breast Cancer Site Group, Odette Cancer Centre
Professor, Departments of Medicine and Public Health Sciences, University of Toronto
Clinical Director, Ontario Clinical Oncology Group

#### 4.1 Identification of Women at High Risk

**Andrea Eisen, MD**
Head, Preventive Oncology, Odette Cancer Centre
Chair, Greater Toronto Area Cancer Prevention and Screening Network

**Key Points**
- A wide range of factors have been shown to increase or decrease the risk of breast cancer in the population.
- Good models exist for identifying women at high risk.
- More work needs to be done on the “usability” of risk assessment models, aligning recommendations with levels of risk.

**Presentation Summary**
The most commonly recognized breast cancer risk factors include the following:

- age  
- family history  
- certain benign lesions  
- breast density  
- previous breast cancer  
- hormonal factors
Age is likely the most important risk factor. The median age for a breast cancer diagnosis in Canada is 61. Benign breast lesions like lobular carcinoma in situ (LCIS) increase the risk of breast cancer. Breast density is also an established risk factor for breast cancer. Previous history with one breast cancer increases the risk of developing another one. The risk of developing cancer in the opposite breast is 0.5 to 1% per year for the average woman.

Lifestyle factors like obesity, particularly in postmenopausal women, increase risk. By contrast, women who exercise regularly decrease their risk. A specific diet affecting breast cancer risk has been hard to pin down. The consumption of alcohol is increasingly recognized as a risk factor. Low Vitamin D is also a possible risk factor.

Research on modifiable risk factors from the Canadian Community Health Survey (2009) shows the extent of lifestyle risks in the population. It is self-reported data, but despite the messaging, 20% of women still report smoking; 15 - 18% describe themselves as obese; and at least 10% say they drink more alcohol than the recommended guidelines. Less than half of women report having the recommended amount of fruit and vegetables in their diet and even fewer exercise regularly.

Reproductive factors also affect breast cancer risk. Early menarche (the age at first menstruation) and late menopause are both associated with increased risk. Breast cancer risk also increases with nulliparity (having no full-term births) or having a first birth at a later age. Fertility studies show that it was common over the past century for women to be giving birth in their late 30s and early 40s, but today they are more likely to be having a first birth at that age. So this social pattern may be increasing breast cancer risk.

Exposure to estrogen is an additional risk factor for breast cancer. Exposure can be endogenous, arising from within. For example, women who are menopausal and obese have higher circulating estrogen. Excess estrogen can also be exogenous, taken in the form of birth control pills or hormonal replacement therapy (HRT) after menopause. After 2001, breast cancer incidence appeared to decrease when hormone replacement therapy was recognized as a possible cancer risk and HRT prescriptions decreased (Ravdin et al. 2007).

Family history and genetics is also an established breast cancer risk factor. Only about 20% of women who have had breast cancer have had a first- or second-degree relative who also had it. About 5% of women with breast cancer have a very strong family history of the disease, and about a quarter of these familial cases are due to known genetic mutations such as BRCA1 and BRCA2. That leaves about three quarters of familial risk unexplained, possibly due to environmental factors, but more likely genetic factors as yet unidentified.

The question is, how do we combine all these possible risk factors to advise an individual woman who feels she might be at risk? Several different models have been developed that can predict the risk of developing breast cancer. There are two different types. One type assesses the absolute risk of developing breast cancer, for example the Gail and IBIS models. Another type assesses the likelihood that a woman carries a gene mutation such as BRACAPRO (Parmigiani et al.)

Gail Model: www.cancer.gov/brickstool
International Breast Cancer Intervention Study: ibis@cancer.org.uk
BRACAPRO: www4.utsouthwestern.edu/breasthealth/cagene

Risk prediction tools on the Internet
The difficulty with breast cancer prediction models is applying them to individual women. Models are calibrated by the whole population, so how well do they discriminate between those who develop cancer and those who don’t? How accurate is their prediction? The Gail model, for one, shows a high degree of overlap between predicted and actual breast cancer.

4.2 Mammographic Density—Why Does It Increase Breast Cancer Risks?

Norman Boyd, MD
Senior Scientist, The Campbell Family Institute for Breast Cancer Research, Ontario Cancer Institute

Key Points
- Breast density is a strong risk factor for breast cancer (1).
- Emerging tumours are affected by hormone levels that vary with the proportion of dense or non-dense tissue in the breast.
- Detection by screening is likely to be improved if tailored to the breast tissue characteristics of individuals.

Presentation Summary
Studies show a consistent trend of decreasing risk of interval cancers with increasing amounts of non-dense area of the breast. Why might this be?

The tissues that give rise to density are collagen, fibroblasts and epithelial cells. The non-dense, lucent areas are adipocyte, or fat cells. All of these tissues are related in one way or another. For example, collagen is the product of stromal fibroblast cells. Stromal fibroblasts and epithelial cells communicate with each other, producing hormones and growth factors that influence both themselves and surrounding tissues. Adipocytes are produced by differentiation of stromal fibroblasts known as pre-adipocytes (2).

All of these processes are under the influence of several factors, including age, menopausal status and genes. Menopause increases the proportion of fatty tissue and reduces dense tissues in the breast. About two thirds of the variance in breast density is believed to be related to genetic factors. Greater amounts of density are associated with circulating levels of...
insulin-like growth factor and prolactin, both of which have been shown to be related to increased breast cancer risk (2).

These biological properties of breast tissue may explain the effects that dense and non-dense tissue have on the detection of breast cancers and their growth rates. Aromatase activity, which converts male hormones into estrogen, is a property of the pre-adipocyte. Tumours emerging in the presence of high density develop in the presence of high levels of hormone production, while tumours arising in the presence of fatty tissue may be exposed to lower levels of hormones (3).

There are several imaging problems that may contribute to interval cancers in women with dense breasts. Problems with the mammogram may arise from radiological noise caused by the presence of dense tissues in the breast, making it difficult for the radiologist to see a tumour. It is also possible that radiological signs of breast cancer are not present in a mammogram because they are concealed behind dense structures in the breast. Or it is possible that radiological signs were not present at the time of screening because of rapid tumour growth that emerges shortly after screening. Double reading or alternative imaging modalities may address these issues, but more frequent imaging may also be required.

We now have compelling evidence that mammographic density is a strong risk factor for breast cancer, increasing the risk of both screened and interval cancers. Dense and non-dense tissues each contribute independently to the risk of interval cancer. Thus breast cancer detection will likely improve if tailored to the breast tissue characteristics of individuals. More research is needed to define measures of tissue density, optimal imaging modalities and the frequency of screening. Further research is required to verify the biological mechanisms of the increased cancer risk with dense breasts.

4.3 Comparison of Modalities

Ellen Warner, MD
Associate Professor of Medicine, University of Toronto
Department of Medical Oncology, Odette Cancer Centre

Key Points
• MRI has the highest sensitivity of all cancer detection modalities and is especially superior to mammography in women with dense breasts.
• Mammography alone misses approximately half of the tumours found by MRI in women with dense breasts.
• Annual MRI and mammography from age 30 is now standard of care for high-risk women.

Presentation Summary
The overwhelming majority of women enrolled in high-risk screening are in one of three groups:
• carrying a BRCA gene mutation
• being an untested, first-degree relative of someone with BRCA mutation
• having a 25% or greater lifetime risk of breast cancer based on family history

Women in this category are usually given two options: double mastectomy with breast reconstruction or screening. At least 75% opt for screening in hope of detecting a cancer at a stage when it is still curable.

In the mid 1990s, following the discovery of BRCA, high-risk women who opted for screening had all of the following: yearly mammography, starting at age 25 - 30; clinical breast exam every six months; and breast self-examination every month. No data existed beyond general screening guidelines so there was little else to offer.
But it quickly became clear that this strategy was not going to work. Half of their tumours were being missed by mammography. Half of those that were found were larger than 1 cm, and 30% were node positive. Clearly something else was needed.

Most of these women tended to be young with dense breasts, so mammography could not be expected to be very effective for them. We looked for screening modalities that seemed to work best with breast density - MRI and ultrasound - and launched the Toronto High Risk Screening Study (1997). In this study we aimed to compare the sensitivity and specificity of four screening modalities: clinical breast exam, mammography, ultrasound and MRI.

We enrolled 580 high-risk women in the study; 82% were BRCA-mutation carriers. Over the nine-year study we found 52 cancers, confirming the high-risk status of this group. Only one interval cancer was found during the study. Comparing all the screening modalities by their sensitivity to finding these cancers, MRI was the overwhelming winner.

MRI found 89% of the cancers but mammography only 25%

98% of the cancers were found by one of the screening modalities but, without MRI, almost half of the cancers would have been missed
The study showed that 98% of the cancers were found by all combined screening modalities, but if we had left out either mammography or ultrasound, sensitivity would have dropped only marginally to 94%. If we left out MRI, sensitivity would have dropped by almost half.

This showed us just how much we needed MRI in screening high-risk women. The price for this sensitivity, though, was false positives. As many as 18% of women we studied had to return for biopsies in the first year. That dropped to 8% in the next years, but MRI clearly generates more false positives than other modalities.

Policy change would be unlikely on the basis of this one study; however, there have now been 11 prospective studies of high-risk women, combining MRI with mammography, with surprisingly similar results. Our meta-analysis of these studies indicated that the sensitivity of mammography was 32% and MRI 75%, but with both modalities it was 84%. Since these studies, the sensitivity of MRI has improved to nearly 98%. We concluded that the best strategy for screening high-risk women was a combination of mammography and MRI.

Since MRI is expensive and scarce we wanted to know if we could eliminate any high-risk subgroups. We looked for likely candidates among BRCA carriers, younger and older age groups and women with low versus high breast density. It would have been wrong to eliminate any of them. MRI had the best sensitivity overall.

Would MRI screening reduce breast cancer mortality in high-risk women? It seems likely because there is an extremely good correlation between larger tumours and node positivity and mortality - what early screening tries to avoid. However, a randomized control study is unlikely. Our data was so strong that we thought it would be unethical to offer regular mammograms to a control group of high-risk women. Instead we are currently conducting a cohort study, and though there is no mortality data yet, so far, the results are very encouraging.

### Plenary 5: Quality and Capacity

**What are the challenges and limitations of screening program delivery?**

**MODERATOR:**

**Claire Holloway, MD, PhD**  
Associate Scientist, Sunnybrook Health Sciences Centre

#### 5.1 The Diagnostic Assessment

**Rene Shumak, MD**  
Radiologist-in-Chief, Ontario Breast Screening Program  
Department of Medical Imaging, University of Toronto

**Key Points**

- Interval cancers often expose inaccuracies in mammographic screening and diagnostic work-up.
- Interval cancer reviews can determine whether the interval cancer is a “true interval” arising spontaneously between screenings - or cancer “missed at screening” or “missed at diagnosis.”
- The best way to improve on “true intervals” is by upgrading and optimizing the equipment. Those “missed a screening” require greater scrutiny by the radiologist. “Diagnostic misses” demonstrate why we need diagnostic assessment centres.
Presentation Summary

In order to maximize the benefits of screening for breast cancer, avoiding inaccuracies associated with inefficient diagnostic workups is very important. You can go through the screening and find the abnormality - a tiny little thing that is going to turn out to be a small invasive cancer - that is still easily treatable. But the whole thing can fall apart without a careful work-up.

With screen-detected cancers a woman benefits from screening because cancer is found early. With interval cancers a woman does not benefit from screening because cancer is found later, between screenings. A screening episode involves not only the mammogram, but all work-up imaging related to it.

The Ontario Breast Screening Program reviews all cancers found prior to a woman’s next screening appointment. Screening and diagnostic films are reviewed in these cases to determine whether an abnormal screen was missed, or an abnormal screen was found to be negative or benign following work-up. The results of the reviews determine whether the interval cancer was a “true interval,” arising spontaneously between screenings, or a cancer “missed at screening” or “missed at diagnosis.”

Case 1:
A 63-year-old woman was sent for ultrasound to investigate an abnormality on a mammogram. Ultrasound reported “normal glandular tissue” and suggested screening in the next year. A year later a huge tumour (> 3.5 cm) was found. What went wrong? The screening mammogram and report were not reviewed properly by the radiologist who did the ultrasound. Correlation between ultrasound and screening mammography is essential. In this case the interval cancer was “missed at diagnosis”: 3.5 cm invasive ductal carcinoma, node negative.

When additional modalities enter a screening episode, they must be correlated adequately with the initial mammogram.

Case 2:
A 55-year-old woman had an obvious abnormality on her screening mammogram. The screening report described it as a large “spiculated mass” - quite worrisome. Ultrasound was requested. But the ultrasound report said it was “probably benign” and suggested “BI-RADS 3 follow-up in six months.” Six months later the abnormality had grown. What went wrong? Even though the screening mammogram had been suspicious, the ultrasound was less worrisome. The most concerning imaging should have determined the course of action. The result: “missed at diagnosis,” a 1.3 cm invasive ductal carcinoma, node positive.

In such cases great finds on the screening mammogram are being lost at the work-up. “BI-RADS 3” is a commonly made request for a short-term follow-up. But a BI-RADS 3 request should only be made when there is a less than 2% chance that the abnormality found in screening will become malignant.
In looking at interval cancers, OBSP (Ontario Breast Screening Program) has found that the best way to improve on “true intervals” is to improve on the equipment. Those “missed at screening” require greater scrutiny by the radiologist. The diagnostic misses show the need for diagnostic assessment centres that could provide accurate correlation with the screening facility. We are developing more of them with OBSP, but it is very important to follow these cases carefully and provide feedback to the staff when errors are made so they can learn from them.

Suggestions:
• Ensure careful scrutiny of prior screenings
• Examine screening images prior to further work-up
• Decide follow-up based on the most concerning image
• Use BI-RADS 3 cautiously, only if < 2% probability of cancer
• Combine all modality reports into a single report
• Give clear instructions for follow-up

5.2 Mammography Quality

Rebecca Smith-Bindman, PhD
Associate Professor in Residence, Department of Radiology, University of California, San Francisco

Key Points
• Studies have found wide variation (30 - 40%) in the accuracy of mammographic interpretation between physicians.
• Similar results have been found among facilities, and those serving vulnerable populations have a 30% lower cancer detection rate of good-prognosis tumours.
• Comparing mammography between the UK and US shows that the UK is performing at a higher level with similar cancer detection rates, but at half the recall rate.

Presentation Summary
If mammography is to have maximum benefit, it needs to be of highest quality, meaning it finds cancers early. Is the quality of mammography as high as it can be? Is access to high-quality mammography uniform across the population? How would we measure the quality of mammography to find out? Is sensitivity an adequate measure? Answering these questions has shown where mammographic screening in the US needs improvement.
Mammography, even when done well, is an imprecise test. Not all cancers are found (the rate is only 50 - 75%), and not all cancers that are found are important (i.e., there can be overdiagnosis). Many women without cancer get abnormal mammography results. In the US, of 1,000 women screened, 150 will be recalled for additional tests - diagnostic mammograms, ultrasounds, biopsies and surgical biopsies - that will finally lead to the detection of about five cancers. The limitations, even when mammography is done well, show how much quality needs to be maximized in every possible way.

We know that age and breast density affect the quality of mammography, as does the quality of equipment. What about physician characteristics? Are some physicians better at mammography than others? And what about the delivery of services? Are some mammography sites better than others?

While the quality of many medical tests is difficult to measure, mammography is less so because it is widely used to screen an asymptomatic population with known risk factors. We conducted a cross-sectional study of 209 physicians who interpreted 1.2 million screening mammograms as part of the Breast Cancer Surveillance Consortium 1995 - 2000 (Smith-Bindman et al. 2005). The study included mammography data from four US states. We assessed physician characteristics associated with accuracy: age, year since medical school graduation, average annual volume, ratio of screening to diagnostic exams.

The result was that we found wide-ranging variation in mammographic accuracy among physicians. Their average sensitivity was 77%, but the range was exceedingly wide, from 29% to 97%. Their average false-positive rate was 10%, but again the range was dramatic: anywhere from 1% to 29%. The results pointed to an unacceptable variation in performance of physicians doing mammography.

Such dramatic differences in accuracy among physicians could not be explained by differences in the patient mixture of each site. The more experienced, high-volume physicians had lower recall rates, but we could not find physician characteristics associated with sensitivity. There was wide variation among physicians but little evidence about why. We could not distinguish physicians who were good at interpretation because they did more mammograms from those who did more because they were good at it.
Very similar results were found in a study of diagnostic mammography (Migloretti, 2007). The study involved 123 radiologists from 72 facilities, and 35,895 mammograms, ordered to investigate a problem, were evaluated. The median sensitivity among these physicians was 79%, but again there was wide variation from 27% - 100%. Overall the false positive rate was 4%, but the range was 0 to 16%.

Radiologists at academic medical centers did somewhat better with sensitivity, but at the cost of increased false positives. Radiologists having more time for imaging, those with more recent training and those with biopsy experience outperformed others in terms of patient recall.

Variation in mammography quality occurs not only at the physician level but also at the facility level. Several recent papers have shown variations in the quality of mammography among facilities (Taplin, 2008; Jackson, 2009). Because there are large differences in breast cancer outcomes by race and economic status in the US, we questioned whether the quality of mammography may differ where such patients receive care, contributing to worse outcomes. We assessed the quality of mammography at 158 facilities that serve vulnerable populations, reviewing 1.7 million mammograms primarily using cancer detection rates. We thought sensitivity as a measure might mask true differences. The results showed a lower detection rate of small, good-prognosis cancers in facilities that serve vulnerable versus non-vulnerable populations. For each measure of vulnerability we used, we found there was a much lower rate of cancer detection at facilities serving these populations.

So it seems we find a great deal of variation in the quality of mammography among physicians and facilities in the US. Can the US improve on its mammography quality overall? In previous work, we compared mammography between the US and UK in a cross-sectional study of screening mammograms from 1996 - 1999 (Smith-Bindman, 2003). The results showed that, while cancer detection rates were similar, recall rates in the UK were half of the US rate. In the UK mammography performs at a much higher level.

I believe the primary difference is in quality assurance and education. The UK has nationally set and monitored quality standards linked to continuing education activities. Underperforming programs and physicians are subject to review, aiming to meet standards. By contrast the US has no nationally set standards and physician education is limited and in need of a complete overhaul.

While the accuracy of mammography may be no worse than other imaging tests we use - it’s just been scrutinized more than other tests - it still needs to improve, largely because it can improve. Efforts at improving mammography should focus on standardizing interpretation and setting clear performance parameters. While the data on volume remains inconclusive, higher volumes of screenings seem to improve quality, as do experience and specialized training. As a widespread screening test, the performance of mammography is unlikely to be improved upon in the near future by other tests such as ultrasound or MRI. As such it would be better to try to improve patient outcomes by improving the accuracy of the test we have: mammography.
6.1 Navigating Systemic and Institutional Barriers

Jan Angus, PhD, RN
Associate Professor, University of Toronto, on behalf of the “Gateways” project team: Nancy Barry, Linda Muraca, Sharmini Fernando, Fran Odette, Samira Chandani, Julie Devaney and Lisa Seto

Key Points

- Mammography equipment and institutional architecture are designed based on normative assumptions about women’s bodies and abilities. This results in significant barriers for women with physical disabilities.
- Participation in breast cancer screening is not just a physiological, health-related concern, but also a social process that can be marginalizing for those who do not conform to normative assumptions.
- Mammography equipment needs to be adapted, but so do the architectural features of screening centres and the readiness of their personnel to provide appropriate care.

Presentation Summary

To improve participation, we must first understand the kind of process we are asking women to participate in. Breast cancer screening involves bodily monitoring for a significant personal health issue, but it is also a social process that is institutionally organized and technologically driven. For those who do not conform to the assumptions on which screening is based, the institutional context of breast cancer screening can be so marginalizing that it becomes a barrier to participation in itself.

Our community-based participatory research study of breast cancer screening in women with disabilities revealed that, although there were many physical barriers in set-up and equipment, the one-size-fits-all expectations of care providers could be equally difficult to navigate. The study was based on extensive outreach to women with disabilities, encouraging community discussion about breast, cervical and colorectal cancer screening. We gathered our research material from five peer-led focus groups involving the experiences of 24 women with physical disabilities.

From this research, we learned that women with disabilities have a difficult time with breast screening right from the start: having their doctor acknowledge its importance. Disabled women, we learned, spend much of their lives dealing with health care and information. They have to confront assumptions everywhere, and one of them is primary care providers’ overemphasis on health issues related to their disabilities. This may lead to neglect of breast screening.

Breast screening is yet another health care challenge for many disabled women who already spend a great amount of their time arranging and attending health-related appointments. A first issue is the location and distance of the screening centre and access to it. As it turns out, wheel trans services may not drop women off in time for screening appointments. Then, delays and waits at the screening centre may mean women miss the scheduled pick-up time for the ride home. Furthermore, some women may need to arrange for an attendant to assist them throughout the appointment. Both wheel trans and attendant care operate independently of one another and are separate from the health care system. Thus, women with disabilities do considerable work to coordinate health visits.
The screening facility represents other barriers for women with disabilities. Waiting areas or change rooms are often not designed to accommodate wheelchairs or other assistive devices. Mammography equipment that requires women to stand may represent a significant obstacle. Social barriers are presented by staff, who may not be astute to the needs of clients with a range of possible disabilities. A woman who played a key role in the study describes being reduced to tears by a radiological technician’s inept handling whilst attempting to get her to stand for her mammography.

Focus group participants were also full of suggestions for how to make breast cancer screening more accessible to them. Certainly, the mammography equipment needs to be adapted, but so do the architectural features of the facility. When booking appointments, women could be offered an opportunity to identify additional requirements so a facility could prepare in advance with adaptations (including a longer time interval) and attendants.

An adapted “barriers free” facility that widely publicized such services would very likely attract a loyal following among disabled women. However, disabled women also need to see themselves in screening education messages if only to support self-advocacy with their physicians. So yes, we can improve screening participation for disabled women in these ways, but we will have to aim for an inclusive process if that is to be achieved.

6.2 Barriers and Personal Choices: Screening in Ontario First Nations

Bruce Minore, PhD
Research Director, Centre for Rural and Northern Research, Lakehead University

Key Points
• Anxiety and fear are a common reaction to breast cancer screening among women living in remote northern communities.
• Cultural, community and family obligations also compete against personal concerns like early detection.
• Culturally appropriate screening promotion should address the attitudes and beliefs of the community, not only target-aged women.

Presentation Summary
“They’re scared to go.” This was what one of the participants in our study of 91 First Nations women answered when we asked why so many from her community had failed to keep their breast screening appointments. In a neighboring community, another woman said, “They wonder why they have to fly hundreds of kilometers south to a strange community for a medical appointment when they’re not sick.” Another woman told us that, although she had been taught breast cancer self-examination, she did not do it because she was afraid of what she might find.

These women are giving expression to a shared anxiety that turns out to be the key reason why so many women from remote communities in the North do not participate in breast cancer screening. But anxiety is just one of the reasons. As well as fear, the context in which care is being delivered needs to be appreciated, as well as how much they know about breast cancer, the effects of cultural beliefs on their decisions, and the impact of their personal circumstances.

The Canadian Breast Cancer Foundation funded this study to better understand the beliefs, attitudes and experiences of women toward mammography and breast self-examination in northern communities. We also wanted to learn what suggestions these women might have about improving breast screening participation.

The Northwest Region of the Ontario Breast Screening Program provides a coach service to road-accessible northern communities. Women from more remote communities are flown in for fixed appointments. However, many eligible women miss
the opportunity: 14.5% fail to show altogether and a further 16.5% need to rebook missed appointments. This represents a costly, lost opportunity for early detection.

We found that little was known about breast cancer in these communities except that it is “something you die from,” which is what makes it so significant in their experience. They do not want to know and they do not want others to know because of stigma about being branded by the diagnosis. Consequently, these women do not know who else may have been diagnosed in the community - potential sources of mutual support. They are fatalistic: “If it’s going to happen, it will.”

They associate the causes of breast cancer with their change of diet from fresh game foods to store-bought foods and the abandonment of traditional breast feeding for the baby’s bottle. They also suppose that breast cancer may be caused by injury, which makes them suspicious of the breast compression involved in mammography.

Northern women were aware of mammography and its purpose but less so about the screening process and referrals. One woman felt that since there were nine seats on the screening plane, they just find nine women to go. There are stories of painful mammography experiences and little culturally appropriate promotion of screening participation to motivate them.

When we probed why women choose not to participate, one of the issues mentioned was the flight south. However, it was the separation from family that turned out to be the major barrier. Even though the screening flight involves only one day, competing family demands such as help with traditional food gathering and child care often intervene. Some fear getting lost in an English speaking “southern” town.

Among suggestions for improving participation, northern women said that it was important to recognize their cultural circumstances. Not only do women need to understand the screening process, but so do their families and communities. Attitudes need to be addressed beyond just the clinical information about screening and breast cancer. Importantly, they felt that a dedicated screening worker could help northern communities to deal with cultural barriers and establish local screening strategies.

6.3 Cancer Prevention and Screening in the Community

Linda Ferguson, RN
Manager, Healthy Living Service, Chronic Disease Prevention Program, Toronto Public Health

Key Points
- The profile of women not participating in breast cancer screening is not unique to Toronto: having a lower economic status, being an immigrant, not having a personal physician.
- Many immigrant women do not know about the importance of screening, nor the recommended frequency, nor the concept of prevention.
- We facilitate communities in identifying their health issues and in building solutions through multi-stakeholder participation.

Presentation Summary
Under-participation in public health programs is an issue in Toronto, especially among immigrant and marginalized women. Toronto Public Health’s main role in breast screening is promotion: increasing awareness, education, persuasion and reducing barriers to access.
What we do well is community engagement. We facilitate communities in identifying their health concerns and in building solutions through multi-stakeholder participation. We build community capacities to take control of the issues that affect their health. We use a solution-focused approach, training peer health educators to provide cultural and language interpretation in their own communities.

The profile of women not participating in breast cancer screening is not unique to Toronto: having a lower economic status, being an immigrant, not having a personal physician. Many immigrant women do not know of the importance of screening nor the recommended frequency, nor the concept of prevention. Fatalism pervades in many of the communities we serve.

Both having access to and knowing how to access screening are issues. As one of the world’s most diverse, multicultural cities, Toronto has multiple barriers of language, cultural values and socioeconomic status. Culturally scripted modesty needs and a preference for a female physician are common issues non-participating women have with screening facilities. Fear and anxiety towards and past negative experiences of institutional settings are also common.

We are mandated by Ontario Public Health Standards (2008) to collaborate with community partners in promoting Ontario’s cancer screening programs and the awareness of the benefits of screening. We adapt existing national and provincial communication strategies or develop unique local ones. In linking with the Ontario Cancer Plan we are striving to achieve 70% participation in breast cancer screening by 2010. We currently have about 60%. Cancer 2020, a longer-term planning framework, is aiming for 90% participation. So we still have far to go. The main strategies we use are personal skill building, education and awareness raising. We have presentations and displays in a variety of settings. We provide training and support to community agencies to help them build breast screening awareness into their activities and programs. We offer workplace programs: white collar, blue collar and pink collar.

We also use social marketing. Our current message campaign is a series of post cards reminding women to “Take the Time: Get checked for breast cancer.” We have translated our materials and place ads in the media of 11 different ethnic communities. We are currently reaching out to Toronto’s Somali community. We found that the key to the door of this community was the retailers in a mall that is popular among Somali women.
Toronto Public Health sees a strong link between cancer screening and prevention even when prevention means early detection. While we collect information about the numbers of people we work with, further research and evaluation are certainly needed. Knowing more about which interventions work well and which do not could well improve our strategies.

Plenary 7: The Future
How will technology improve the future of cancer detection?

MODERATOR:
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7.1 Digital Breast Tomosynthesis

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Division Head of Breast Imaging, Department of Medical Imaging, Sunnybrook Health Sciences Centre
Associate Professor, Department of Medical Imaging, University of Toronto

Key Points
- Digital Breast Tomosynthesis (DBT) eliminates the superposition of internal breast structures, making it possible to identify subtle abnormalities that may be otherwise hidden in conventional mammography.
- Studies have shown that DBT can achieve a 30% increase in specificity over digital mammography with no loss of sensitivity.
- Ultimately, DBT could be used for screening, especially in women with dense, “busy” breasts.

Presentation Summary
Mammography is the only screening modality shown in randomized controlled trials to decrease breast cancer mortality, but it is nonetheless limited, especially in women with dense breasts: 20% of cancers are missed and 10% of mammograms are recalled, most of these being false positives. One of the main reasons is that mammography produces a two-dimensional summation image with the superposition of structures within the breast. As the X-ray passes through the breast it goes through multiple different structures, but with superposition, tumours may remain hidden by other structures in the final image. Thus the small subtle abnormalities we are trying to find are obscured.

The DMIST trial showed that digital mammography is more accurate than film for women less than 50 years old and with 50% or more dense tissue. Are there other technologies that could do even better?

To address the limitations of mammography caused by superposition and breast density, we have been investigating Digital Breast Tomosynthesis. The prototype is a modified digital mammography unit that we use for research purposes only. The radiation source rotates in an arc over the breast, taking multiple images. The principle is that structures at varying distances from the detector appear in different locations on the projection images. These images are used to create a set of thinly sliced images through the full thickness of the breast. The total radiation dose is less than with two-view mammography.
On the workstation we can see both 2D and 3D images simultaneously and, as in a movie, review the whole set of images through the breast. There is also a slab option so we can view “thicker slices” of the breast. Or we can use the mouse to scroll slowly through the images at any speed. Like any digital image these can be adjusted for clarity.

The result is that much clearer, adjustable images are produced by tomosynthesis than by conventional mammography. True tumours that were obscured in mammography can be made more visible by tomosynthesis, and images that appeared to be suspicious with conventional mammography can be eliminated as tumours with tomosynthesis.

We have conducted a small pilot study to compare conventional mammography with Digital Breast Tomosynthesis (DBT) in a diagnostic setting. There were 24 women with 25 lesions enrolled in the study. We found a statistically significant improvement in specificity with DBT over mammography. Malignant lesions tended to look more suspicious on DBT and false lesions tended to look less conspicuous.

We concluded from this small study that focal asymmetries that we see on regular mammograms can clearly be distinguished as being spurious or true masses with DBT. We think this would mean fewer call backs for false findings if DBT alone was used for screening. The suspicious features of malignant masses were also more conspicuous, but more research is needed on malignant calcifications.

Studies in the literature have shown that DBT combined with digital mammography could decrease the recall rate, with no change in sensitivity, by 30% or as much as 10% if used alone (Gur et al. 2009). Another study found a high correlation between breast density measured by digital mammography and in the central DBT projection image, which could lead to a better way to measure breast density (Bakic et al. 2009). Saunders et al. found through simulation that DBT could achieve the same lesion conspicuity with reduced breast compression (2009). Finally, another study found DBT superior to digital mammography for imaging masses and asymmetries but inferior for calcifications (Poplack et al. 2007).

So what can we expect from DBT? Tomosynthesis can provide lesion localization with increased clarity due to the elimination of superposition. The margins of masses and architectural distortions are more visible. Sensitivity is maintained while specificity (recognizing normal structures) increases significantly with DBT. That means fewer call backs and additional imaging for false positives. DBT might also increase cancer detection rates.
Ultimately, DBT could be used for screening, especially in women with dense, “busy” breasts. DBT would also be useful for diagnostic problem solving. It might have a role in finding multi-focal cancers that are not seen on conventional mammography. In the future, the use of contrast enhancement with DBT may be able to simulate what is currently done with breast MRI.

7.2 Breast Computed Tomography

John M. Boone, PhD
Professor and Vice Chair (Research) of Radiology; Professor of Biomedical Engineering,
University of California Davis Medical Center

Key Points
- The idea of breast computed tomography (CT) is that the radiologist can see a virtual 3D slice of the breast that eliminates the superposition issue.
- One goal with this device is to improve the comfort of screening because breast compression is such a common complaint with mammography.
- Overall, breast CT outperforms mammography with greater sensitivity for any size of lesion while retaining equal specificity.

Presentation Summary
The issue with mammography is that it is a 2D imaging technique for a 3D breast. Imaged tissues are summed up and lesions can be obscured behind normal tissue. The idea of breast computed tomography (CT) is that the radiologist can see a virtual 3D slice of the breast that eliminates the superposition issue.

With breast CT the patient lies face down on the device with breasts “pendant.” There is no breast compression. One goal with this device is to improve the comfort of screening because breast compression is such a common complaint with mammography. We conducted a survey among women undergoing screening to assess the comfort of breast CT compared to mammography. According to their assessment, CT was a significant improvement. We feel breast screening will improve if we can improve the comfort of screening.
Currently there are two breast CT scanners under study, one at the University of California, Davis, and another UC Davis scanner that was relocated to the University of Pittsburg as part of a collaboration there. At UC Davis we have scanned 210 patients scheduled for biopsy. Some of those have received additional tests to compare breast CT with and without contrast enhancement and to compare breast CT images with breast PET and tomosynthesis.

The radiation dose of CT is equal to two-view mammography. CT increases the energy of X-rays for greater penetration of the breast, but with less radiation dose left in the patient. Due to the very thin, tomographic images, the radiologist can see a lesion on 20 - 30 images, which builds confidence about what is being seen.

We believe that breast CT may be a candidate for screening. But we are also interested in using contrast-enhanced CT in diagnostic assessment. With contrast-enhanced CT, breast lesions “light up” vividly.

Compared to breast tomosynthesis the radiologist has greater control of anatomical “slices,” making soft tissue lesions more visible with breast CT. Comparing with MRI, breast CT can achieve similar imaging results at much lower cost without the worries about metal implants or claustrophobia.

Overall, breast CT outperforms mammography in regards to soft tissue lesions with greater sensitivity for any size of lesion while retaining equal specificity. Non-contrast Breast CT is not yet as good as mammography for identifying microcalcifications, an early warning sign of breast cancer; however further development efforts may improve this situation.

### 7.3 Molecular and Biomarker Imaging

**John Valliant, PhD**  
Associate Professor and Acting Director, Chemistry and Medical Physics,  
The McMaster Institute of Applied Radiation Sciences

**Key Points**

- Molecular imaging probes are used to make biochemical processes and molecular targets visible. They seek out sites of disease and emit a signal that is detected and converted into an image of biology as opposed to only structure.
- Molecular imaging tools that are specifically designed for detecting breast cancer are emerging as a new class of tools to address the high false-positive rates associated with existing screening methods. These techniques include Positron Emission Mammography and Molecular Breast Imaging.
• A number of novel probes for the early detection of breast cancer and for addressing some of the limitations of existing imaging techniques are currently under development. Their greatest value may in fact lie not in early detection, but in guiding the choice of therapy.

Presentation Summary
The non-invasive detection of cancer has been dominated by methods that show anatomy. It is now possible to use a molecular imaging probe, a compound that seeks out and emits a signal from the site of disease, to visualize biochemical processes. Changes in biochemistry precede the physical manifestation of cancer, giving molecular imaging the ability to find tumours earlier and provide the physician with more information about their propensity to spread and be treated.

Ultimately, the imaging field aims to combine imaging modalities used in cancer detection. A functional image looking at biochemistry will be fused together with an anatomical image such as MRI to exploit the advantages of both strategies. These types of technologies that include the recently reported PET-MRI are available today.

At the Centre for Probe Development and Commercialization (CPDC), which was funded by the federal and provincial governments (www.imagingprobes.ca), we are developing and validating new imaging probes and making them available for preclinical and clinical studies. Clinicians are interested in using probes in development as well as those routinely used in clinics in Europe and the United States, few of which are approved in Canada. The Centre was created to make it feasible for physicians to access these agents and to move new discoveries from the lab to the clinic.

The CPDC, for instance, is currently studying “dedicated” breast imaging technologies (Molecular Breast Imaging - MBI) in concert with developing new probes for assessing the aggressiveness of breast cancers. In addition, the CPDC has developed the capacity to produce agents for Positron Emission Tomograph (PET) and Mammography (PEM) for use in clinical trials to monitor new therapies. The interest in MBI and PEM stems from their higher resolution, shorter imaging times and lower cost versus whole body imaging systems. An additional feature of breast PET systems is that it is possible to integrate the instruments’ imaging capabilities with biopsy. This way, tissue sampling will be based on biological activity (i.e., sites that seem the most aggressive) and not necessarily simply based on abnormal structures.

There is a major push in Ontario around PET because of its unique ability to detect cancer and because there are a number of radiopharmaceuticals available for breast cancer detection and staging. The most common probe, “FDG,” looks at glucose metabolism, but a number of newer probes aim to take this technology further. There is a PET agent for evaluating estrogen receptor status. Another agent measures cell hypoxia: how oxygen starved the tumour may be.

The CPDC is participating in a clinical trial using a PET probe called FLT, which measures the “proliferative status” or the aggressiveness of tumours. The uptake of FLT is dependent on the type of breast cancer, providing a way for physicians to delineate the type of tumour prior to treatment and / or biopsy. For example, there is some FLT uptake with lobular carcinoma, but much more in a primary ductal carcinoma and much less in an inflammatory breast carcinoma. Uptake also varies in areas of the tumour itself. FLT does not get confused with areas of inflammation to the same extent as other probes, and there is a close correlation between the PET images using this agent and pathology stains in the lab.

FLT is an attractive agent for drug development, in particular for gaining an early assessment of a tumour’s response to therapy. In a mouse model we can see the early effects of a drug on a tumour. The uptake of FLT gradually decreases, showing that the tumour has stopped spreading even though the size of the tumour remains the same.

Novel probes address some of the limitations of existing imaging techniques, but their greatest value may be in guiding the
choice of therapy. While a patient is under treatment, molecular imaging can be used to follow biochemical changes in the cancer that would not be evident with conventional imaging methods. Many of the newer therapies are specific to subpopulations of cancer patients, so an agent that targets a specific site will help to select the best candidates for a specific drug. This feature offers an important cost-saving strategy in addition to improving treatment outcomes.

Molecular Breast Imaging is another technique in development with a capability of imaging very small lesions that are obscured using other imaging technologies. There are only two agents available to use with the MBI camera, and none of them target specific proteins associated with breast cancer, so further development is needed.

The Valliant group is therefore currently developing an insulin-derived molecular imaging probe because insulin receptors are up-regulated in breast cancers: about 6.5 times higher than in normal breast tissue and 20 times higher than levels found in fat tissue. The CPDC is in the process of developing this agent and a “menu” of PET probes for use with conventional and dedicated breast imaging systems. A new generation of molecular imaging probes for breast cancer is emerging that will change the way in which breast cancer patients are identified, prescribed treatment and monitored during and after therapy.

7.4 Future Breast MRI

Donald Plewes, PhD
Senior Scientist, Imaging Research, Sunnybrook Research Institute
Professor, Department of Medical Biophysics, University of Toronto

Key Points
• Novel breast MRI techniques currently under development have a common goal of increasing specificity.
• Alternative methods of image reconstruction exploiting recent advances in mathematical estimation methods can produce sharper images with less data, thus reducing scan time requirements.
• Several MRI techniques are under exploration that measure different features of the cellular and molecular microenvironment; these may aid in distinguishing malignant from benign lesions, thereby increasing specificity.

Presentation Summary
Several novel Breast MRI methods are under development, all of which have a common goal: to improve the specificity of MRI, correctly distinguishing benign lesions from cancer. These methods make use of new forms of digital image reconstruction, novel contrast agents and MRI without a required contrast agent.

We have been developing methods of dynamic imaging in “adaptive mode” where one can take a data set of an MRI and choose “after the fact” to reconstruct very high resolution images or very fast images to look at the kinetics of substance uptake. Recent advances in the mathematics of information theory introduced only three years ago are now being applied to assist in the reconstruction of highly detailed images from MRI.
Compressed Sensing uses the same data as standard MRI, but an alternative method of digital image reconstruction to create a high quality picture with less acquired data and thus with a shorter imaging time. This new approach, destined to affect the future of imaging science, is now being applied to breast cancer.

Diffusion MRI measures water diffusion through cell tissue. Unlike standard, contrast-enhanced MRI, diffusion imaging requires no contrast agent injection. This addresses one of the key challenges of MRI for some patients: the potentially negative effects of gadolinium-based contrast agents. It turns out that cancers that are made up of compacted cells have “low ADC” (Apparent Diffusion Coefficient) compared to benign cells, which have “high ADC.” Measuring diffusion differences in this way assists in identifying malignant from benign lesions, improving specificity. This technique is less effective on some cancers such as DCIS, and it is also restricted to use on lesions greater than 1 cm.

Sodium-Based MRI can image the proton spin of sodium in cells - undetectable with standard MRI. The images reflect sodium concentrations inside and outside of cell tissues. With cancers there are changes in metabolism that affect sodium pump activity around cell linings. In the presence of cancer, the pumps break down and sodium levels rise inside the cells. Malignant lesions then have a high sodium uptake relative to benign lesions. The difference can be readily seen in sodium-based MRI images, consequently increasing their specificity over standard MRI.
Proton Spectroscopy looks at the resonance of proton spins in tissues. This has shown that invasive cancers like lobular and ductal carcinomas as well as DCIS resonate elevated levels of choline, which is not present in normal tissues. Thus, measuring the resonance of choline substantially improves the specificity of proton spectroscopy over standard MRI, also when combined with standard MRI. While there is much interest in this technique, several limitations, including low signal strength from choline, makes it less effective for imaging very small tumours. Another limitation is that imaging time increases up to 30 minutes when proton spectroscopy is combined with standard MRI.

Pyruvate elicits lactate and alanine resonance but decays rapidly after injection.
Pyruvate elicits lactate and alanine resonance but decays rapidly after injection. Hyperpolarization is an exciting new method to deal with the problem of low signal strength. Using this technique, the signal strength of an injection agent, pyruvate, can be increased ten thousand times by magnetizing it at very low temperature, - 271 °C, while applying a gigahertz radiofrequency exposure. Magnetic resonance in tissue is very low with standard MRI at room temperature. But when this hyperpolarized agent is re-warmed, it is like injecting a liquid magnet material that can be detected by standard MRI equipment. Once injected, the pyruvate is converted to lactate via normal or abnormal cellular metabolism. The resulting lactate level can be detected separately from the injected pyruvate. Higher levels of lactate are associated with cancer, while lower levels tend to be associated with normal tissue - another way of increasing specificity.

The future suggests that many of these methods can be hybridized with standard MRI to increase specificity. Alternative image reconstruction will facilitate this effort by making imaging sessions faster and by making it easier to combine results into one diagnostic output. All of these techniques need further testing and are active ongoing subjects of research.
Presentation References

Plenary 1

Andrew Goldman presentation


**Anna Chiarelli Presentation**


**Robert Smith Presentation**


**Donald Berry Presentation**


**Sue Moss Presentation**


**Plenary 2**

**Gregory Doyle and Jay Onysko's Presentation**


**Plenary 3**

**Eta Pisano Presentation**


Wendie Berg Presentation


**Roberta Jong Presentation**


**Donald Plewes Presentation**


**Plenary 4**

**Andrea Eisen Presentation**


3. Links to risk prediction models:
   Gail Model: www.cancer.gov/bcrisktool
   IBIS: ibis@cancer.org.uk
   BRCAPRO: www4.utsouthwestern.edu/breasthealth/cagene
Norman Boyd Presentation


Plenary 4

Ellen Warner Presentation


**Plenary 5**

**Rene Shumak Presentation**


3. Data also used from the results of the interval cancer reviews conducted by Cancer Care Ontario/Ontario Breast Screening Program.

**Rebecca Smith-Bindman Presentation**


**Plenary 6**

**Jan Angus Presentation**


**Bruce Minore Presentation**


**Linda Ferguson Presentation**


Appendix A:

Excerpt from Earlier Detection and Diagnosis of Breast Cancer:

Recommendations and Scientific Review from It’s About Time! A Consensus Conference
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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.
- A lifetime risk of breast cancer less than 15%, 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.

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 www.cancer.gov/bcrisktool/Default.aspx.
- A lifetime risk of breast cancer 25% or greater, as defined by models dependent on family history.

EXCERPT FROM RECOMMENDATIONS AND SCIENTIFIC REVIEW

The MD Anderson guidelines state 20%; however, we have defined an additional “intermediate risk” category that extends between 15% and 25%. 

VII
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: 27

- 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 1* and *2* 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 Figure 1). 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 1. Sensitivity of mammography in various historical screening trials. From Humphrey et al. and Tabar et al.**

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

Data are also presented for the performance of more modern mammography. The sensitivity overall is considerably higher than it was in the earlier time period over which the RCTs were conducted.
Table 2. Performance measures for 3,603,832 screening mammography examinations from 1996 to 2006 by age.²

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

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.³

In the Digital Mammography Imaging Screening Trial (DMIST)⁴ 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.⁵

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.⁶,⁷,⁸,⁹,10,11,12,13 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.

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.⁴ 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 - 49, the summary relative risk⁵

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³ 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.

⁵ The authors excluded the Edinburgh trial for having been of poor quality.
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 1) 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.

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.15 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 Program16 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%.

Figure 1. Outcome, shown as relative risks (RR) of breast cancer mortality of various RCTs for mammography screening of women in their 40s.
Moss et al.\textsuperscript{17} 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.\textsuperscript{18} and Smith et al.\textsuperscript{19} These include the results of the UK Age Trial and show benefits of screening similar to those found by Humphrey et al.\textsuperscript{14}

\textbf{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,\textsuperscript{4} 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.

\textbf{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 (\textbf{Table 3}) all showed superior sensitivity of MRI for breast cancer detection (77 - 100\%) compared to 16 - 40\% for mammography or ultrasound.\textsuperscript{20,21,22,23,24,25} Recently, Warner et al. performed a systematic review of the results of the major studies of breast MRI for screening high-risk women.\textsuperscript{26} Specificity varied among the different studies between 81 and 99\%. \textbf{Figure 2} is from the work of Warner et al.\textsuperscript{21} 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 \textbf{Figure 3}.
## Published Breast MRI Screening Study Results

<table>
<thead>
<tr>
<th></th>
<th>The Netherlands</th>
<th>Canada</th>
<th>United Kingdom</th>
<th>Germany</th>
<th>United States</th>
<th>Italy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of centers</td>
<td>6</td>
<td>1</td>
<td>22</td>
<td>1</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>No. of women</td>
<td>1,909</td>
<td>236</td>
<td>649</td>
<td>529</td>
<td>3909</td>
<td>105</td>
</tr>
<tr>
<td>Age Range</td>
<td>25 - 70</td>
<td>25 - 65</td>
<td>35 - 49</td>
<td>30</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>No. of cancers</td>
<td>50</td>
<td>22</td>
<td>35</td>
<td>43</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

**Sensitivity (%)**

<table>
<thead>
<tr>
<th></th>
<th>MRI</th>
<th>Mammogram</th>
<th>Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>80</td>
<td>33</td>
<td>n/a</td>
</tr>
<tr>
<td>Mammogram</td>
<td>77</td>
<td>36</td>
<td>33</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>77</td>
<td>40</td>
<td>n/a</td>
</tr>
</tbody>
</table>

**Specificity (%)**

<table>
<thead>
<tr>
<th></th>
<th>MRI</th>
<th>Mammogram</th>
<th>Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>90</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>Mammogram</td>
<td>95</td>
<td>&gt;99</td>
<td>91</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>81</td>
<td>93</td>
<td>n/a</td>
</tr>
</tbody>
</table>

n/a = not applicable.

Table 3. Performance of various imaging modalities in studies evaluating MRI for screening high-risk women.

From Saslow et al.\(^27\) See also reference.\(^26\)

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## Sensitivity by Modality (n=19)

![Sensitivity by Modality](image)

Figure 2. 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.\(^21\)
Recently, the American Cancer Society (ACS) published guidelines for the use of breast MRI for screening 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 4 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 4. Recommendations for breast MRI screening as an adjunct to mammography. From Saslow et al.27

<table>
<thead>
<tr>
<th>Recommend Annual MRI Screening (Based on Evidence*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA mutation</td>
</tr>
<tr>
<td>First-degree relative of BRCA carrier, but untested</td>
</tr>
<tr>
<td>Lifetime risk ~20 to 25% or greater, as defined by BRCAPRO or other models that are largely dependent on family history</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommend Annual MRI Screening (Based on Expert Consensus Opinion†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation to chest between age 10 and 30 years</td>
</tr>
<tr>
<td>Li-Fraumeni syndrome and first-degree relatives</td>
</tr>
<tr>
<td>Cowden and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Insufficient Evidence to Recommend for or Against MRI Screening‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime risk 15 to 20%, as defined by BRCAPRO or other models that are largely dependent on family history</td>
</tr>
<tr>
<td>Lobular carcinoma in situ (LCIS) or atypical lobular hyperplasia (ALH)</td>
</tr>
<tr>
<td>Atypical ductal hyperplasia (ADH)</td>
</tr>
<tr>
<td>Heterogeneously or extremely dense breast on mammography</td>
</tr>
<tr>
<td>Women with a personal history of breast cancer, including ductal carcinoma in situ (DCIS)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommend Against MRI Screening (Based on Expert Consensus Opinion )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women at &lt;15% lifetime risk</td>
</tr>
</tbody>
</table>

* 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.28 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 4, taken from Berg et al.,28 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.
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.\(^\textsuperscript{29}\) in 1995 and Humphrey et al.\(^\textsuperscript{14}\) 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.\(^\textsuperscript{30,31,32}\) 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 5). Chiarelli\(^\textsuperscript{32}\) 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 5. Performance of CBE in a community setting. Age range studied is shown in parentheses.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bobo et al.(^\textsuperscript{30}) (n=589,048)</td>
<td>36.1% (≥40)</td>
<td>96.2% (≥40)</td>
</tr>
<tr>
<td>Oestreicher et al.(^\textsuperscript{33}) (n=61,688)</td>
<td>20.0-22.8% (40-49)</td>
<td>97.4-98.6% (40-49)</td>
</tr>
<tr>
<td>Kolb et al.(^\textsuperscript{34}) (n=11,130)</td>
<td>27.6% (≥40)</td>
<td>99.4% (≥40)</td>
</tr>
<tr>
<td>Fenton et al. 2005(^\textsuperscript{35}) (n=485)</td>
<td>21.6% (40-65)</td>
<td>99.4% (40-65)</td>
</tr>
<tr>
<td>2007(^\textsuperscript{36}) (n=1,427)</td>
<td>26-27% (rescreen, 50-69)</td>
<td>97-98% (rescreen, 50-69)</td>
</tr>
<tr>
<td>Chiarelli et al.(^\textsuperscript{32}) 2009 (n=290,23)</td>
<td>32-47% (initial, 50-69)</td>
<td>96% (initial, 50-69)</td>
</tr>
<tr>
<td></td>
<td>26-27% (rescreen, 50-69)</td>
<td>97-98% (rescreen, 50-69)</td>
</tr>
</tbody>
</table>
As seen in Table 6 below, very few cancers were detectible by CBE alone, and these tended to be larger and less likely to be node negative than those detectible 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. 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.

Table 6. Characteristics of mammography and CBE detection in ten years of OBSP screening (from Chiarelli et al.37)

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

In its 1998 report, The Canadian Task Force on Preventive Health Care 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. 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, 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 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 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.

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. 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. Barriers have been defined as the conditions that inhibit individuals from carrying out a recommended behaviour.

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. However, despite the increase in eligible women attending screening, several barriers impede uniform access across populations.

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. 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 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.

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

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. Since 2005, the use of mammography among women at the lowest income level has declined.

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. 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.

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, 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.15

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.

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.
REFERENCES FOR APPENDICES 1-8


2. NCI-funded Breast Cancer Surveillance Consortium co-operative agreement (U01CA63740, U01CA86076, U01CA86082, U01CA63736, U01CA70013, U01CA69976, U01CA63731, U01CA70040). Downloaded June 9, 2009 from the Breast Cancer Surveillance Consortium website: http://breastscreening.cancer.gov/.


Appendix B:
It’s About Time! A Consensus Conference
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