

Final Key Questions and Background

Appropriate Imaging for Breast Cancer Screening in Special Populations

Background

It is estimated that about one in eight women in the United States will develop invasive breast cancer in her lifetime; breast cancer is also the second-leading cause of cancer death among women, behind only lung cancer (BreastCancer.org, 2014). Some women have an elevated risk of breast cancer, including those who have a personal or family history of the disease, genetic abnormalities (particularly carriers of the BRCA1 and BRCA2 gene mutations), previous instances of chest radiation therapy, or the presence of denser breast tissue.

Early detection is widely considered essential to reduce the risk of breast cancer mortality. Population-based screening with x-ray mammography is considered the standard of care for women over 40 in the United States. Mammography has evolved from film-based to full field digital, which has resulted in improved visual precision and better sensitivity (Pisano, 2005). However, even digital mammography results in some missed cancers and requires some women to be “recalled” for additional diagnostic imaging to rule out cancer. Despite diagnostic imaging, some women also must undergo needle biopsy, most of whom are ultimately judged not to have cancer (i.e., false positives). In 2011, the FDA approved the use of digital breast tomosynthesis (DBT), an advanced application of digital mammography that has the promise of improved cancer detection and lower recall rates in comparison to conventional digital mammography (Friedewald, 2014). DBT produces detailed views of the breast by taking images at multiple angles; because of the detail available, the procedure is sometimes known as “3D mammography”.

In addition, the FDA’s recent approval of specialized imaging software has eliminated the need to generate conventional planar (i.e., mammography) and DBT images separately, which in effect doubled the radiation dose to the patient. Now, planar images can be generated directly from DBT data, and recent study suggests that equal-dose results are comparable to the older double-dose procedure (Zuley, 2014). Despite this promise, however, questions remain about DBT’s performance over the long-term, whether the use of this procedure lowers breast cancer mortality, whether the additional cancers detected by DBT represent appropriate targets for treatment (versus tumors that are not likely to progress), and DBT’s relative utility in specific patient subpopulations.

Women who are at an increased risk of developing breast cancer (as described above) often undergo supplemental screening to allow a second opportunity to identify tumors. Imaging technologies used for this purpose typically include magnetic resonance imaging (MRI), as well as

ultrasonography. Traditional ultrasounds are performed using a handheld wand, but a relatively new variant on this technology involves use of an automated transducer that produces three-dimensional images (Kelly, 2011). As with DBT, there are also questions about the impact of these supplemental screening approaches on cancer detection, recall rates, and unnecessary biopsy as a result of false-positive imaging.

Policy Context

There are two major policy considerations surrounding the use of advanced imaging approaches in breast cancer screening. The first is the potential for DBT to replace digital mammography as a frontline screening tool in asymptomatic women. Because this is a new technology, the evidence base is expected to be limited, particularly with respect to long-term patient outcomes.

The other major consideration relates to the use of supplemental screening among women with a normal mammogram (i.e., no abnormalities detected) but with dense breast tissue that might obscure an abnormality. Breast density is subjectively assessed by the radiologist (based on the likelihood that a cancer might be masked by dense tissue) into one of four possible letter designations: (a) almost entirely fatty, (b) scattered areas of fibroglandular density, (c) heterogeneously dense, which may obscure small masses; or (d) extremely dense, which lowers the sensitivity of mammography (BI-RADS, 2013). The term “dense breast tissue” has primarily been applied to categories (c) and (d).

Supplemental screening is a generally-accepted practice among women with very strong risk factors for breast cancer, such as BRCA mutations or significant family history of the disease. However, these represent a small proportion of screened women. In contrast, dense breast tissue is present in nearly 50% of screening-age women (BI-RADS, 2013). While the presence of dense breast tissue has also been acknowledged as an independent (although modest) risk factor for breast cancer and denser tissue may mask tumors on standard mammography, little is known about the potential impact of supplemental screening if it were to be expanded to all women with dense breast tissue regardless of overall breast cancer risk.

Nevertheless, within the last 5 years, 18 states have passed legislation requiring physicians to notify women if they have dense breast tissue, largely as a result of patient advocacy efforts fueled by situations of missed cancer on mammography (Are You Dense Advocacy, 2014). Some of these mandates also require insurers to cover supplemental screening in such women. Many patient advocacy groups have commended these efforts, stating historically poor communication between the medical community and patients about the limitations of mammography (Lee, 2013). Others are concerned that such mandates are premature, as the current literature does not provide evidence of the benefits of supplemental screening in such a large and diverse population (D’Orsi, 2012). Advocates for DBT have also stated that the three-dimensional visualization may obviate the need for supplemental screening in women with dense breast tissue, but there are questions about whether there is sufficient evidence to support this claim. Payers and policymakers alike are concerned about the level of benefit that might be gained from supplemental screening in this population relative to the potential harms of patient anxiety, overdiagnosis and overtreatment, and false-positive findings.

Project Scope

This review will involve an evaluation of the evidence within two distinct constructs: (a) use of digital breast tomosynthesis versus digital mammography as a frontline general population screening tool; and (b) use of automated and handheld ultrasound as well as magnetic resonance imaging for supplemental screening in women with dense breast tissue. This project will be an expansion of a previously-conducted systematic review of the published literature on supplemental screening for women with dense breasts (ICER/CTAF, 2013). Specific details on the proposed scope of the updated literature search (Population, Intervention, Comparators, and Outcomes, or PICO) are detailed in the following sections.

Populations

As described above, the population of interest for the assessment of DBT will include all asymptomatic women age 40-74 who are candidates for screening mammography (while women age ≥ 75 do receive breast cancer screening, most large studies of screening mammography have not included these women and observational data show lower rates of screening in elderly women [BCSC, 2014]). In addition, available studies will be stratified by screening interval (e.g., annual vs. biennial) to allow for appropriate comparisons of test performance.

The target population for the comparison of supplemental screening modalities will include women with dense breast tissue and a normal mammography result. We will examine clinical trials and observational studies that include women in the BI-RADS categories of “c” (heterogeneously dense) or “d” (extremely dense) (BI-RADS, 2013). Importantly, the method of classification of breast density will be abstracted for each study, as the approach to classifying density is now based on the potential for masking of cancer vs. the previous standard of assessing the volume of dense tissue. Both populations will be stratified by a number of other important characteristics as the available evidence allows, such as age, race/ethnicity, overall breast cancer risk, and others.

Interventions

We will evaluate the effectiveness, costs, and cost-effectiveness of magnetic resonance imaging (MRI), handheld ultrasonography (HHUS), automated ultrasonography (ABUS), and digital breast tomosynthesis (DBT). Data on these technologies will be collected regardless of manufacturer, imaging protocol, or other test characteristics. Note that, while the focus of attention on supplemental screening technologies will be findings in women with dense breast tissue, overall results from major clinical studies will also be abstracted to provide context for test performance.

Comparators

The comparator of interest for frontline screening with DBT will be digital mammography. Studies that use film mammography as the primary screening tool will be excluded, as nearly 95% (12,790/13,523) of all US mammography machines accredited by the U.S. Food and Drug Administration are now full-field digital (FDA, 2014). We will evaluate supplemental screening technologies against each other, and individually against additional follow-up (with any method) or no follow-up examination in women with dense breasts. In addition, we will consider studies utilizing clinical breast examinations (CBEs) or self-exams as comparators.

Outcomes

Specific outcomes of interest will be focused on the test characteristics of the modalities of interest, including rates of sensitivity and specificity, positive predictive value, recall, and biopsy. Where available, we will also collect data on the impact of screening modality on breast cancer mortality and health-related quality of life. Finally, potential harms of interest will include unnecessary biopsy as a result of false-positive imaging, overdiagnosis and overtreatment, missed cancers, and radiation exposure.

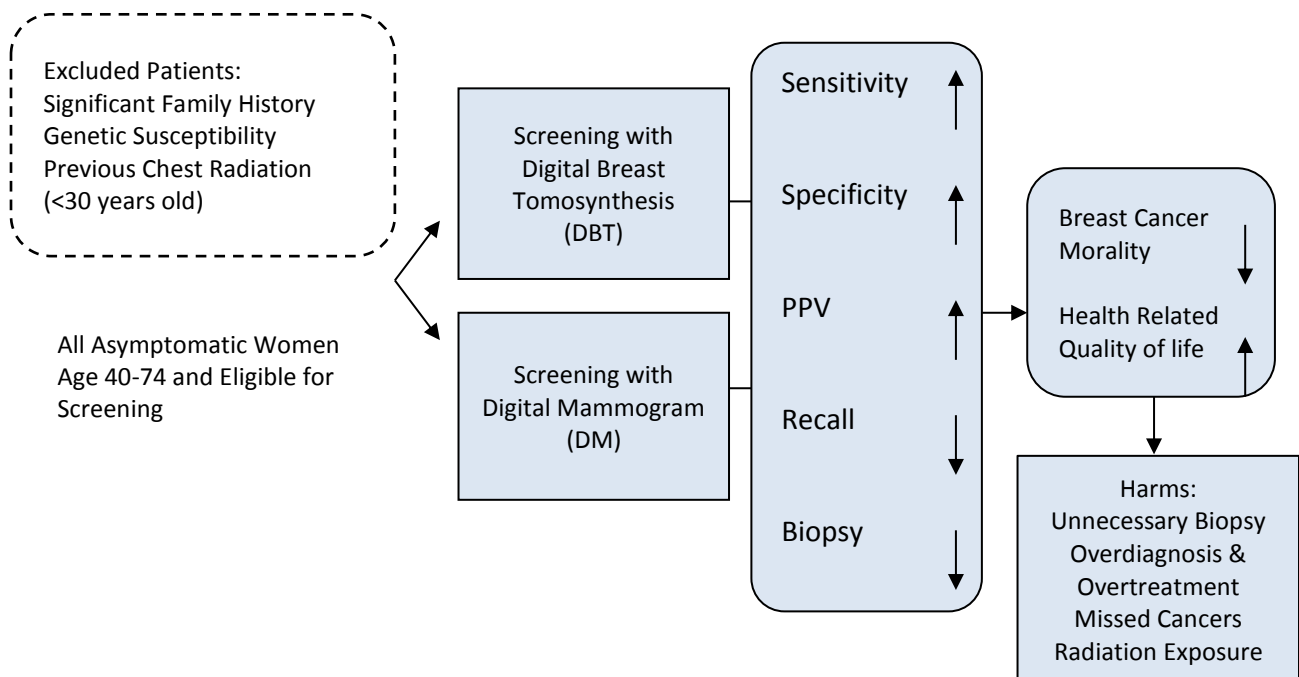
Information on the costs and cost-effectiveness of each screening method will also be collected where available.

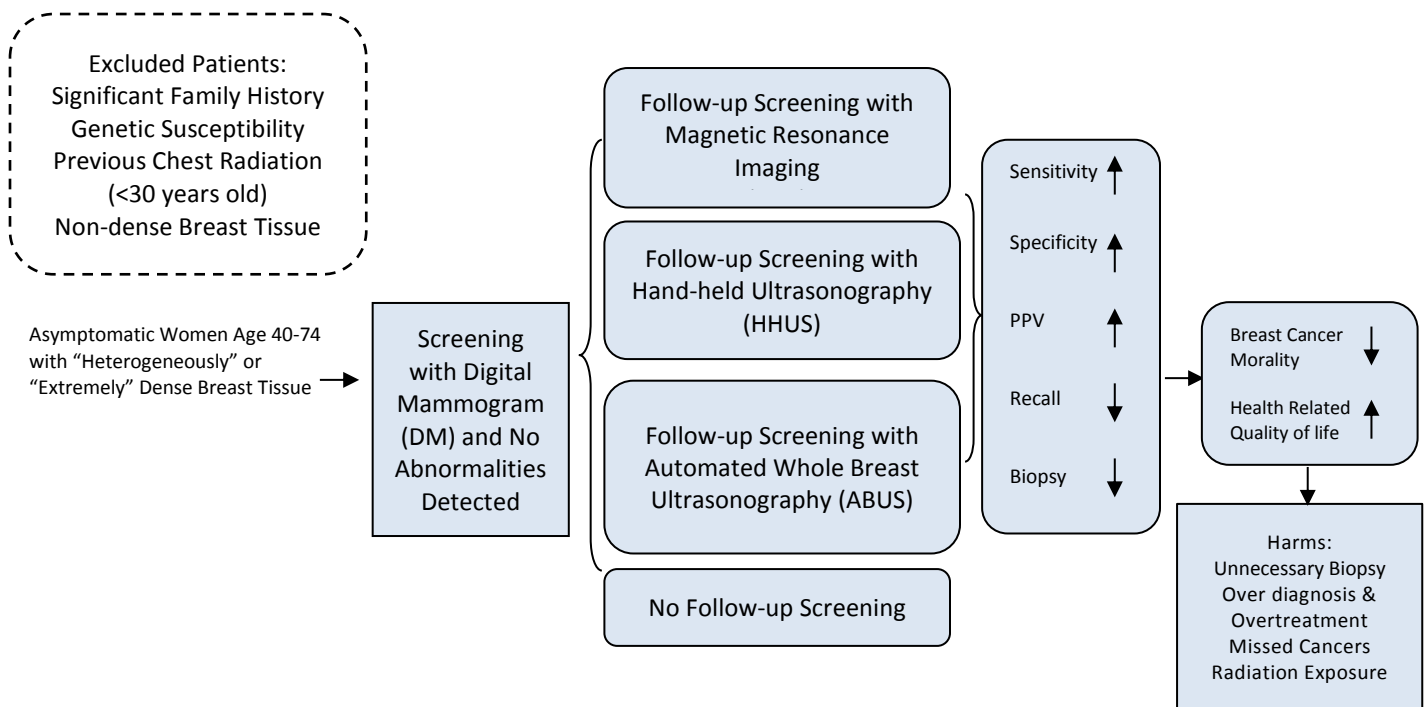
Analytic Framework

The proposed analytic frameworks for this project are depicted on the following page. As is the case for many screening or diagnostic tests, it is expected that data linking screening modalities to direct patient outcomes will be limited, requiring instead a series of conceptual links between test characteristics and the major outcomes of interest.

Analytic Framework: Breast Cancer Screening

Search A



Search B**Key Questions**

A number of key questions are felt to be of importance for this project. Each question is listed below, along with the type of evidence that will be examined.

- 1) What is the effectiveness of screening with digital breast tomosynthesis (DBT) vs. digital mammography among women aged 40-74 who are candidates for screening mammography?
- 2) What is the comparative effectiveness of handheld ultrasonography, automated ultrasonography, and magnetic resonance imaging when used as supplemental screening modalities in women with dense breast tissue and a negative mammogram or negative DBT result?
- 3) What are the documented and potential harms associated with these imaging tests, including overdiagnosis and overtreatment, unnecessary biopsy as a result of false-positive imaging, patient anxiety, and radiation exposure?
- 4) What is the differential effectiveness and safety of the tests of interest according to such factors as age, race or ethnicity, comorbidities, BMI, method of breast density classification, overall breast cancer risk, scan vendor, and imaging protocol (e.g., whether ultrasound is performed by a radiologist, technologist, or some combination of the two)?
- 5) What are the costs and cost-effectiveness (e.g., cost per cancer detected) of the imaging modalities of interest?

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For more information about this technology review and the Washington State Health Technology Assessment program, visit www.hca.wa.gov/hta.