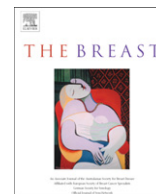




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Original article

## Risk assessment, screening and prevention of breast cancer: A look at cost-effectiveness

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## A B S T R A C T

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Recent suggestions by the United States Preventive Task Force to change the longstanding guidelines for screening mammography have raised the issue of cost-effectiveness in regards to breast cancer detection. Given the enormous number of women who have had, or who will be diagnosed with breast cancer, it is essential to maintain the quality of care that has been achieved here in the United States while utilizing a cost-effective approach. The following review attempts a close examination of current methods available for risk assessment, screening and prevention programs. These programs must be carefully considered and analyzed prior to implementing cost-saving changes to current clinical standards that have proven successful in decreasing the mortality from breast cancer throughout the world.

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## Introduction

Breast cancer continues to take a tremendous toll throughout the world. In the United States, over 200,000 women are diagnosed with the disease each year, and more than 40,000 will die as a result of its diagnosis. Thus, we cannot ignore the impact that breast cancer has on each and every one of us. We often hear of the importance of finding cancer early, particularly in regards to decreasing the mortality rate. However, it is not often that the financial impact of finding breast cancer at its earliest stages is studied and/or discussed. These issues are critical to an understanding of the financial implications of the complex, multi-modality treatment of breast cancer, and the impact this has on the overall health care costs to our society.

Given that later stage disease is much more difficult, complex and thus more costly to treat, one must consider many factors when examining the “cost of breast cancer”. Important aspects include both direct and indirect costs. Direct costs would include the cost of screening mammography, biopsy, surgery, pathology examination, hospital fees, etc. But there are a myriad of indirect costs as well which are much more difficult to quantify—such as

time away from work for the patient and family members, impact of co-morbid medical conditions, etc. These insidious costs create an unknown financial burden to our health care system and society. For example, when women with co-morbid medical conditions undergo treatments for cancer, the course of treatment overall can be much more costly due to unexpected complications. Whereas women who maintain a healthy lifestyle and follow screening guidelines, in the long run, will cost the system less. Thus, it soon becomes obvious how difficult it is to actually assess the true “costs” of breast cancer, which may be why this topic is often avoided.

Yet, clinicians who have been intimately involved in the care of breast cancer patients over the span of the last 40 years understand and have seen the evolution of how early detection can change many things, such as greater selection of treatment options, and minimizing the need for adjuvant therapies as well. While looking at any small piece of this puzzle may not reveal obvious cost savings, evidence in the literature firmly supports the notion that early detection and treatment proves to be more cost-effective than not. In fact, some of the most important scientific works of this past century have shown the benefits of screening mammography programs, specifically in regards to improvement in mortality rates which directly correlates to stage of disease at the time of diagnosis. Many clinicians agree that a focus on risk assessment, along with screening and prevention programs, will help decrease the “costs” associated with breast cancer over time. We feel an examination of these issues is a timely and valuable subject indeed.

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In this brief overview, we will review current practices of risk assessment, screening modalities, possibilities for preventive interaction, and the potential cost-effectiveness of these interventions.

### Risk assessment

Many physicians and the general public continue to believe the myth that a strong family history accompanies the majority of patients who present with newly diagnosed breast cancers. In fact, this is not at all the case, since we know that over 80% of all breast cancers occur in women with no family history of the disease whatsoever. So, community and physician education are paramount to developing an understanding and a mechanism for determining better methods to assess a woman's risk of developing breast cancer.

The longstanding art of a thorough medical and family history goes a long way in an initial assessment of risk for most women. Table 1 illustrates known factors that play a role in a woman's lifetime risk of developing breast cancer. Each of these factors should be considered in a patient's history, and some factors are clearly accepted as indicators of a greater risk than others. You will note that these risk factors are grouped according to various issues. Some are controllable by an alteration in lifestyle (i.e., obesity, smoking, etc.) while others may require clinical intervention (i.e., genetic predisposition). Once a woman is identified as having one or more of these risk factors, she can be triaged for close clinical monitoring, and she can choose to modify her lifestyle so that she herself can help decrease her risk of developing cancer.

Another common belief focuses on breast cancer as a disease of the aging female. Numerous, well-controlled studies have proven the benefits of annual mammographic screening in women over the age of 40, which is why most screening programs begin at this age. These studies clearly illustrate a decrease in mortality from breast cancer in women within this demographic category when compliance with annual screening is accomplished. While studies clearly support the increased incidence of breast cancer with increasing age, we cannot ignore the fact that younger women can be afflicted with the disease as well. In addition, because the incidence in younger age groups is relatively low, and the diagnosis may be more elusive in younger women, there is often a significant delay in diagnosis of these women, and their outcomes tend to be worse than their older counterparts.

Since screening mammography does not routinely start until age 40, clinicians have long looked at other methods of testing that might help clarify how to best determine a "younger" woman's risk. Stratifying young women according to risk factors is easy when there is a strong family history, but what about those women who are asymptomatic and who are not easily stratified by their potential genetic risk?

First, we must examine what we mean by "risk assessment". Simply stated, "risk" is the ability of the clinician to determine which of our patients are most likely to develop a disease, in this case, breast cancer. Clinicians have utilized various mathematical models such as the Gail model, the BRCAPro model, Tyrer–Cuzick model, etc. to try and determine an individual's risk. However, these tools were devised in order to determine risks in large populations of women, and they prove less helpful when trying to determine risk on an individual basis.

In light of the shortcomings inherent in using qualitative clinical history and mathematical models, breast specialists have tried for many years to devise a simple tool that might provide a reliable clinical test to help determine risk. Many risk assessment specialists are drawn to the concept of using tissue or cellular collection to try and aid with risk assessment. This stems from the fact that atypical hyperplasia and cellular atypia are both common denominators of known "historical risks".

Perhaps even more convincing is the fact that atypical hyperplasia is a powerful predictor of tamoxifen effectiveness. This was clearly demonstrated in the NSABP P-01 trial that showed that use of tamoxifen resulted in a relative risk reduction of 86% in women with a history of atypical hyperplasia.<sup>1</sup> Taken together, these two factors yield a very effective tool for risk assessment. So powerful, that this discovery fueled the birth of a new research agenda—the active pursuit of atypia.

Although directed core biopsies are sometimes considered as a possible approach in the pursuit of histologic atypia, investigators usually look to more practical approaches using cytologic atypia as a marker of increased risk for breast cancer. Often misunderstood as a diagnostic test for breast cancer, these strategies are actually meant to focus on risk stratification, i.e. identifying patients who are at a higher probability for developing breast cancer than the general population, even when no historical risks have been identified. For those with known historical risks, cellular atypia can serve as an additional stratifier, more accurately placing patients into clinical algorithms for additional monitoring.<sup>2</sup>

This concept of actively seeking cellular atypia was not widely appreciated until the introduction of ductal lavage.<sup>3</sup> However, research on cellular atypia had preceded ductal lavage by several decades, complete with relative risks for various findings. Random final needle aspiration (FNA) for cytologic atypia was introduced by Fabian et al. in the early 1990s, then later used with the Gail model to identify women at very high short-term risk for the development of breast cancer, i.e., a 5-fold risk, comparable to histologic ADH.<sup>4</sup> Earlier still, beginning in the 1970s, studies began that now have greater than 20 years of follow-up.<sup>5,6</sup> These studies indicate a doubling of breast cancer risk simply through the retrieval of normal and hyperplastic epithelial elements found in nipple aspirate fluid (NAF). Another study that included 2701 women and had a mean follow-up of 12.7 years, showed that cellular atypia in NAF

**Table 1**  
Recognized risk factors for breast cancer.

General risk factors	Medical risk factors	Genetic risk factor
First menstrual period prior to age 12	Personal history of breast cancer	1 or more 1st-degree relative with breast CA prior to age 50
Nuliparous	Atypia (ADH/ALH or cellular atypia)	1 or more 1st-degree relative with breast CA after age 50
1st full-term pregnancy after age 35	LCIS (lobular carcinoma in situ)	2 or more 2nd-degree relatives same side of family (maternal or paternal) with breast CA prior to age 50
Menopause after age 55	Nipple Aspirate Fluid (NAF) with epithelial/atypical cells	1 or more 2nd-degree relative with breast CA prior to age 50
Post-menopausal Obesity	History of multiple breast biopsies (2 or more)	
Significant alcohol use (>1 drink/day)	Hormone replacement therapy >10 years	
Smoking	Dense breast tissue on mammography	
	Chronic cystic change on breast imaging studies	
	Chest wall radiation exposure prior to age 30	

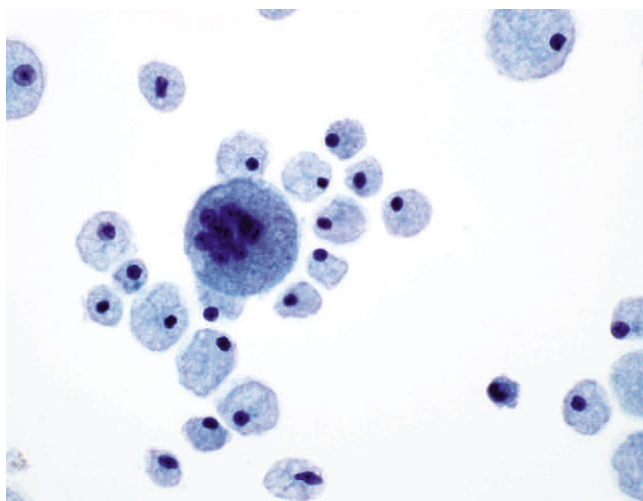
was again noted to impart a relative risk comparable to histologic ADH (RR = 4.9).<sup>7</sup>

While these historic studies support the use of tissue/cellular collection methods as useful for risk assessment, the first well-known collection method of ductal lavage failed clinically. This was most likely due to the general reluctance of patients and physicians to participate in a somewhat invasive and tedious procedure. Thus, attention has fallen back to the original methods of identifying cellular atypia, by collecting NAF using various methods such as manual aspiration, automated collection techniques, fine needle aspiration, ductal lavage and/or ductoscopy. Several of these methods are currently used clinically to aid in risk stratification of patients. Figs. 1 and 2 show examples of normal ductal epithelium and atypical hyperplasia as seen on cytology from collection of NAF.

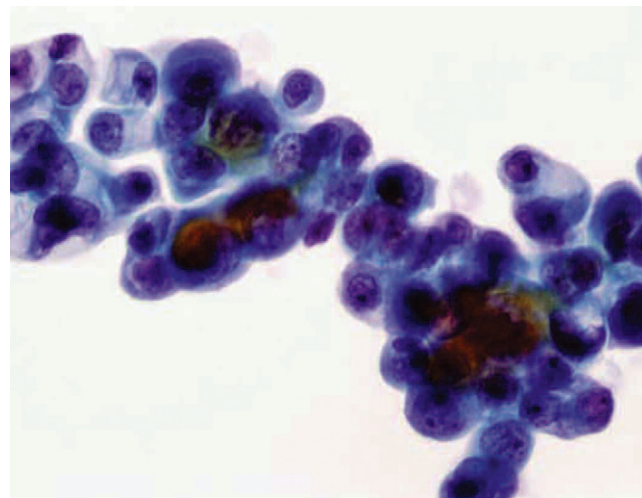
Cellular atypia, independent of how cells are obtained, is probably best suited as a risk stratifier by incorporating this information into one of the mathematical models that utilizes atypical hyperplasia as a data entry point, i.e., the Gail model or Tyrer–Cuzick model. This was not the original intent of cytology researchers who began their work prior to the development of mathematical models, but with the introduction of these models, it seems more appropriate to consider atypia as one piece of the puzzle, rather than a “stand alone” test. Given the comparable risk imparted by cytologic atypia and histologic atypical hyperplasia, it is reasonable to use the mathematical models for quantifying risk, entering a “biopsy that showed atypical hyperplasia” into the calculator or software.<sup>2</sup>

Breast cancer risk modeling was mostly a curiosity in the epidemiologic literature until the Gail model was first utilized in the NSABP P-1 prevention trial,<sup>1</sup> though the original validation came through the 1987 Texas Breast Screening Project, followed by multiple validations using data from the BCDDP (Breast Cancer Detection and Demonstration Project), CASH (Cancer and Steroid Hormone Study), and the Nurses’ Health Study.<sup>2</sup> After the success of the P-1 trial, new emphasis was placed on risk assessment strategies, especially with regard to calculating 5-year absolute risks, which have guided chemoprevention (SERM) risk reduction strategies in the U.S. ever since, including selection of patients for the NSABP P-2 trial, a.k.a. the STAR trial.<sup>8</sup>

Still, risk assessment, as a discipline did not receive widespread adoption into clinical practice. Although risk stratification through mathematical modeling might have profound influence on a woman’s decision to undergo preventive mastectomies (usually



**Fig. 1.** ThinPrep—Pap stain 100×. Normal ductal epithelial cells identified. Multinucleated foam cell seen in center of slide.



**Fig. 2.** ThinPrep—Pap stain 100×. Atypical ductal epithelial cells in large cohesive grouping showing nuclear crowding and overlap.

guiding patients against this approach, with the exception of BRCA positive patients), no numerical thresholds for preventive surgery have been proposed. After all, if one accepts the convention that preventive surgery is a patient-driven procedure, then an exact mathematical threshold for breast cancer probability is inappropriate, given wide differences in patient perceptions of these numbers derived from mathematical modeling.

So, the discipline of risk assessment seemed to stagnate, adopted primarily by those clinicians interested in the pharmacologic risk reduction of breast cancer. Also underutilized has been the use of mathematical models to identify patients who are candidates for BRCA genetic testing wherein interventions can have profound beneficial outcomes for gene-positive patients. But then, the explosion of interest in risk calculations came in 2007 when the American Cancer Society announced their new guidelines for the utilization of high-risk screening with breast MRI, beginning at age 30 with annual mammograms and annual MRI.<sup>9</sup> Selection of these high-risk patients was to be determined through the use of mathematical models that focused primarily on family history.

With no mortality reduction data to support the American Cancer Society (ACS) in its recommendations, it was felt by the ACS and its advisors that the guidelines should approximate the mathematical modeling that had been used in the six published clinical trials at that time showing vastly superior sensitivity of MRI over mammography. Remarkably, none of these trials had utilized the Gail model, the most convenient, best validated, and simplest mathematical model available. Preferred models emerging from the ACS guidelines through later webcasts and online supplementation featured: BRCAPro, Claus and Tyrer–Cuzick.

This development introduced radiologists to the nebulous world of breast cancer risk assessment and spawned widespread interest in risk assessment, especially that portion of the ACS recommendations for selecting MRI candidates that stated, “lifetime risk of 20–25% or greater, as defined by BRCAPro or other models that are largely dependent on family history.”<sup>9</sup>

A separate indication for annual MRI was a patient who tests BRCA positive or the untested first-degree relative of a BRCA positive patient. This has sparked further confusion, as the *probability* of being BRCA positive is *not* an indication for MRI screening. And, calculating breast cancer risk through the mathematical models is relatively independent from models that calculate BRCA probabilities. There are models unique for breast cancer risk; unique for BRCA probability; and some that cover both probabilities. The point

is that they are different probabilities. A patient can be at high-risk for breast cancer while low risk for being BRCA positive, vice versa, or high-risk for both, low risk for both.

So, today, we have short-term risks being calculated primarily through the Gail model for selecting patients for SERM risk reduction but inadequate for BRCA testing and not ideal for MRI selection, lifetime risks being calculated with selected models for MRI recommendations, and BRCA probability models being utilized for selecting patients for genetic testing, but not for MRI utilization. Furthermore, delivering health care information is sometimes divided between two individuals or two departments, with one person performing “risk assessment” while another performs “genetic counseling/testing.” If a facility does divide these services, then it is incumbent upon the risk assessment specialist to identify candidates for BRCA testing wherein gene-positivity will yield risk levels that trump those levels calculated earlier at the initial risk assessment session.

But the challenge does not end there. Radiologic breast centers are rapidly adopting risk assessment services that are focused on identifying patients for screening breast MRI, specifically the “greater than 20–25%” threshold. However, the very process of quality risk assessment will turn up candidates for SERM risk reduction and discussion of lifestyle changes, as well as candidates for BRCA genetic testing. If the radiologic center is not prepared to deal with these additional issues related to high-risk patients, then referral pathways should be established. To recommend high-risk MRI to a patient and miss the fact that she is a BRCA testing candidate is not clinically productive, and may lead to a very “costly mistake” as an obvious potential source of medical liability.

Currently, there are few quality standards in place for those centers claiming risk assessment expertise. The National Accreditation Program for Breast Centers (NAPBC) has taken a first step in the review of these services. However, advanced skill in risk assessment has not really been defined. Most assume that the mathematical models are “automatic,” such that little skill is required. However, there are many caveats with each of the models, strengths and weaknesses to be understood, plus the complexities noted above, such that a thorough working knowledge does not come easy. Human error enters as well, as one can easily enter an incorrect number into the simple Gail model that prompts an inappropriate risk level to emerge. Expertise comes through anticipating a mathematical outcome, such that an outlier is readily seen as a data entry problem, rather than mindlessly transmitting the error to the patient and prompting an inappropriate intervention.

One developing strategy that bears consideration, especially for radiology groups interested in identifying high-risk patients for MRI, is the HughesriskApps™ software that imports data from patient registration demographics and personal health history, then performs risk assessment using multiple models, and generates reports to the patient and referring physician. In addition, candidates for SERM risk reduction as well as candidates for BRCA

testing are identified. The downside of this approach is that, at the time of this writing, the Tyrer–Cuzick model has not yet been incorporated into the software, and Tyrer–Cuzick is one of the “favored” models by the American Cancer Society for breast MRI. Tyrer–Cuzick has the advantage of incorporating tissue risks as well as reproductive/endocrine risks, thus generating higher calculations than the Claus model, which is based entirely on family history.

The purpose of restricting the use of technologies such as breast MRI to those women at higher risk for breast cancer is to generate a corresponding higher yield of cancers to allow for practicalities, most notably cost-effectiveness. When it comes to an individual patient at average risk for breast cancer, there is no reason to believe MRI won't demonstrate double the sensitivity as mammography, just as seen in high-risk patients. As such, individuals who have taken charge of their own health care should not be denied the opportunity of breast MRI screening. However, when it comes to deciding public health policy, the use of breast MRI for general population screening is more difficult to justify.

Many believe that cost-effectiveness of MRI screening would seem to be limited to BRCA positive patients, but one study to date has provided a more accurate method of assessing whether this is true by using the cost per quality-adjusted life-year (QALY) gained with “MRI and mammography” compared to “mammography alone,” based on a continuum of yields.<sup>10</sup> In this model, cost per QALY gained with MRI for women with a BRCA mutation was a very good \$25,277, then a 3% yield in very high-risk patients still had an acceptable \$45,566 cost per QALY gained, while even a 2% yield was arguably cost-effective in the range of \$70,000 per QALY gained (understanding that \$50,000 per QALY has often been tagged as an arbitrary cut-off). In contrast, screening the general population with MRI would generate a cost per QALY gained of over \$300,000.

This is a major reason why risk stratification has become so important today, and the reason why refinements in risk assessment should be welcomed. If one can identify a risk level that converts to a 2–3% yield level with screening breast MRI, then not only will more cancers be discovered earlier by using both mammography and breast MRI, but also it will be done through a cost-effective approach. Other clinical indications for using MRI in conjunction with mammography that may prove cost-effective are listed in Table 2.

While the majority (55–70%) of breast cancer patients present with no known risk factor other than advancing age, it becomes clear that if we were able to identify women at “elevated risk”, especially younger women who have been disenfranchised by current screening recommendations, early clinical evaluation/monitoring, and preventive measures could result in earlier detection, thereby preserving the opportunity for optimal treatment options. The challenge is obvious, and persists – how do we best identify women within the general population with elevated risk who do not have a family history of cancer, and who are too

**Table 2**  
Clinical indications for MRI in women with potentially elevated risk of developing breast cancer.

All newly diagnosed patients with breast cancer; to define the extent of disease multifocality, and/or presence of contra lateral abnormalities and to assist with planning of surgical treatment.
Yearly follow-up for breast cancer patients (i.e., following breast conservation & radiation therapy).
Cancer screening in patients at high-risk for developing breast cancer, especially those with suspected or proven mutations of BRCA1/2.
Further evaluation of suspicious clinical findings or imaging results which remain indeterminate after mammographic and ultrasound evaluation.
Breast cancer screening in women with breast implants as adjunct to mammography.
Monitor response to neoadjuvant hormonal and/or chemotherapy.
Evaluation of silicone gel implant integrity (supported by recent FDA recommendations).
To determine possible primary site in patients with axillary nodal disease and unknown primary disease.
Adjunct to mammography and ultrasound in women with clinically difficult exam and dense breasts on these examinations (women under age 40).
Pre-operative assessment in patients with mammographic abnormalities or dense breast tissue (ie pre-op breast reduction, or revision reconstruction).

young to be eligible for screening mammography? If we can identify them, what then is the most efficient, effective and cost-effective mechanism for clinical intervention?

As it stands today, over 100,000 breast cancer patients diagnosed each year are considered to be at high-risk, either through family history, a prior biopsy with atypical ductal hyperplasia (ADH), or a variety of other risk factors. Unfortunately for most of these women, they present at the time of diagnosis—after cancer has already developed and may have had a chance to become systemic. Given the limitations of mathematical models, and clinical history, perhaps new tools such as those that examine cytologic atypia will provide an efficient, effective manner in which to aid in risk assessment and thus stratify patients for cost-effective interventions and preventive programs.

### Screening

Our current approach to breast cancer screening is primarily focused on the implementation and utilization of widespread, high-quality mammography programs. Numerous studies have shown that appropriate screening beginning at age 40 and continuing on an annual basis is an effective way of identifying the majority of breast cancers. In fact, studies have also clearly shown that annual screening significantly decreases the mortality rate from breast cancer, and that cancers are found at an earlier stage.

While it is true that some may argue these programs are costly and may lead to interventional procedures in order to confirm a diagnosis, the overall benefits of screening mammography are well known and are the accepted standard. We have learned from other countries, where screening is done differently (i.e., beginning at age 50 and done every two years), that many cancers are not detected during the interim year, and thus, the cancers are found at a later stage and the mortality rates from breast cancer are consequently much higher. This would result in a less cost-effective screening program.

In light of the recent recommendations of the US Preventive Services Task Force, the suggested change to the British model brings with it the risk of increasing the mortality rates from breast cancer, and detecting disease in women at a later stage. The Task Force clearly states that the cost-benefit ratio is not sufficient in order to continue the current guidelines, however, this conclusion is short-sighted in that it ignores the enormous cost of treating late stage disease versus early stage disease.

The arguments supporting screening every two years versus annually are erroneous, since we have no way of accurately pre-selecting the asymptomatic women (other than those at known “high” risk) who will develop breast cancer. For example, if we were able to say “all women with red hair will need annual screening because they are the ones that will get cancer,” perhaps arguments against annual mammography might be a consideration. However, since we are not able to predict with even minimal certainty, those women who will develop breast cancer, it is irresponsible and imprudent to change the existing mammography guidelines which were established based upon proven scientific evidence that favors the current standards.

In addition to screening mammography, patient teaching of breast self examination (BSE) has recently been scrutinized and discouraged by the USPSTF. Opponents are quick to state that there are no studies that prove BSE decreases mortality, and they argue that organized programs that teach self-exams do not improve detection rates over “natural” self-exams, but instead generate anxiety, increased numbers of benign biopsies, etc. While mammography remains the gold standard and has been proven to reduce mortality, breast self examination is by far the quickest, easiest and MOST cost-effective method available for the detection

of breast cancer. True this only applies to palpable lesions, but for those women who are too young for mammography and/or who have no family history and would therefore not be identified as “elevated risk” patients, BSE may often be the first line of defense in uncovering an abnormal process occurring in the breast.

### Cost-effectiveness of screening mammography

The need to restrain out-of-control government health care expenditures, financial strains on private health care insurers, and steeply rising personal health care costs have all made cost the real underlying issue behind recent screening mammography controversies. Attempts to determine the best trade-off between saving lives and saving dollars represent the real root of this debate, even though the ostensible issues are the amount of benefit from early detection and the frequency of false-positive biopsies.

Screening interventions can be assessed in terms of cost-effectiveness. The cost per year of life expectancy gained through screening, the most commonly used measure of cost-effectiveness, is calculated by dividing the total screening program costs by the years of life expectancy gained for all women who benefit from screening. The years of life expectancy for an individual woman with screen-detected breast cancer is equal to her lifespan (measured or estimated), which is lengthened as a result of early detection, minus the lifespan of an otherwise comparable breast cancer patient who was not screened.

Assuming a 30% reduction in breast cancer mortality through annual screening, Rosenquist and Lindfors estimated that the cost per year of life expectancy saved was \$26,000, \$16,000, \$15,000, \$20,000, and \$35,000 for women ages 40–49, 50–59, 60–69, 70–79, and 80–85 years of age at detection, respectively.<sup>11</sup> Although population costs per year of life expectancy gained are higher for screening women in their 40’s, the average woman with breast cancer detected by screening during that decade stands to gain more years of life expectancy than her older counterpart with breast cancer detected by screening during a later decade of life.

Many investigators have calculated the cost-effectiveness of screening women in their forties. These estimates have varied because they have used different assumptions for benefits and costs as well as different methods of calculation. Studies, such as one published by Salzmann et al. in 1997, claiming that screening women ages 40–49 is not cost-effective, are no longer valid because their estimates for benefits, particularly those for women aged 40–49 years (16% mortality reduction), were too low.<sup>12</sup> On the basis of results from the Breast Cancer Detection Demonstration Projects (BCDDP), conducted in the United States by the American Cancer Society and the National Cancer Institute in the 1979’s, separate calculations by Moskowitz, Eddy, and Feig all derived estimates for the cost-effectiveness of screening women ages 40–49 years that were similar to or lower than those of Rosenquist and Lindfors.<sup>13–16</sup>

Calculations by Rosenquist and Lindfors assumed a cost of \$84 for a conventional film-screen mammogram in 1994 US dollars. Current 2010 Medicare reimbursement is approximately \$82 US dollars for conventional screening mammography and \$130 for digital screening mammography.<sup>11</sup> Recent service screening studies performed with conventional mammography have found a 40–45% mortality reduction for screened women ages 40–74.<sup>17,18</sup> However even if current costs per year of life expectancy saved are higher than those used by Rosenquist and Lindfors, they still are lower than \$100,000 per year of life threshold deemed to be acceptably cost-effective for other preventive medical procedures and tests.<sup>19</sup>

A subsequent study by Rosenquist and Lindfors estimated that annual screening mammography beginning at age 40 years and continuing until age 79 years would cost \$18,800 per year of life

expectancy saved.<sup>20</sup> The assumption for screening benefit in that study was that annual screening would reduce breast cancer deaths by 36% for cancers detected in women aged 40–49 years and by 45% for cancers detected in women 50–79 years. The cost per year of life gained from annual screening mammography (\$18,800) is higher than that of screening for colorectal cancer (\$3000) and cervical cancer (\$12,000), comparable to osteoporosis screening (\$18,000), but is much lower than that for coronary artery bypass surgery (\$26,000) and the use of seat belts and airbags in automobiles (\$32,000).<sup>21</sup> Several other investigations found that both annual and biennial screenings are cost-effective for all ages studied.<sup>13,14,22,23</sup> Annual screening is proven to be more effective, but may be less cost-effective.

Screening program costs depend on screening protocols. Annual screening finds cancers earlier than biennial screening but costs twice as much.<sup>24</sup> Screening with both craniocaudal (CC) and mediolateral oblique (MLO) views detects more cancers but is more costly than screening using a single MLO view alone.<sup>25</sup> Digital mammography detects more cancers in women below age 50 with dense breasts but is more expensive than conventional mammography.<sup>26,27</sup>

Cost per cancer detected is always lower in older populations since screening detection rates parallel the natural cancer incidence and thus increase with age. Cost per life saved and cost per year of life expectancy gained progressively will decrease from age 40 until age 70 but then increases as a result of the lower normal life expectancy among older women.

The costs of screening mammograms accounted for less than one-third of the total screening program costs, while two-thirds of screening costs resulted from diagnostic imaging work-ups, surgical consultations and biopsies for benign disease in a low cost screening project in Southern California, 1986–1988 reported by Cyrllak.<sup>28</sup> In contrast, a screening program in New Hampshire conducted one decade later found that 68% of that programs' costs were from screening and only 32% were from consequent diagnostic imaging, biopsy, and surgical consultation.<sup>29</sup> This probably reflects a lower screening callback rate, substitution of short-term follow-up for biopsy, a high rate of image guided core biopsies versus surgical biopsies, and fewer surgical consults. Results from the 1996–2000 study of Poplack et al. are similar to contemporary studies by Lidbrink et al. and Elmore et al. in which additional costs of evaluating false-positive results can add up to one-third of the total cost of screening all women.<sup>30,31</sup>

Thus, while it is clear that detection of early cancers requires annual screening mammography which ultimately offers the most effective method of decreasing mortality from breast cancer, the complexities of defining "cost-effectiveness" have confused this issue. True, the ultimate diagnosis of an early cancer may require an intensive diagnostic work-up that results in additional costs, however, the savings in treatment of an early cancer versus a late cancer more than make up for those costs. In addition, it is clear that cost of the conventional annual screening programs are in fact a small portion of the process, and eliminating or changing current screening mammography guidelines would be foolish, imprudent and a disservice to all women of this country and abroad.

## Prevention

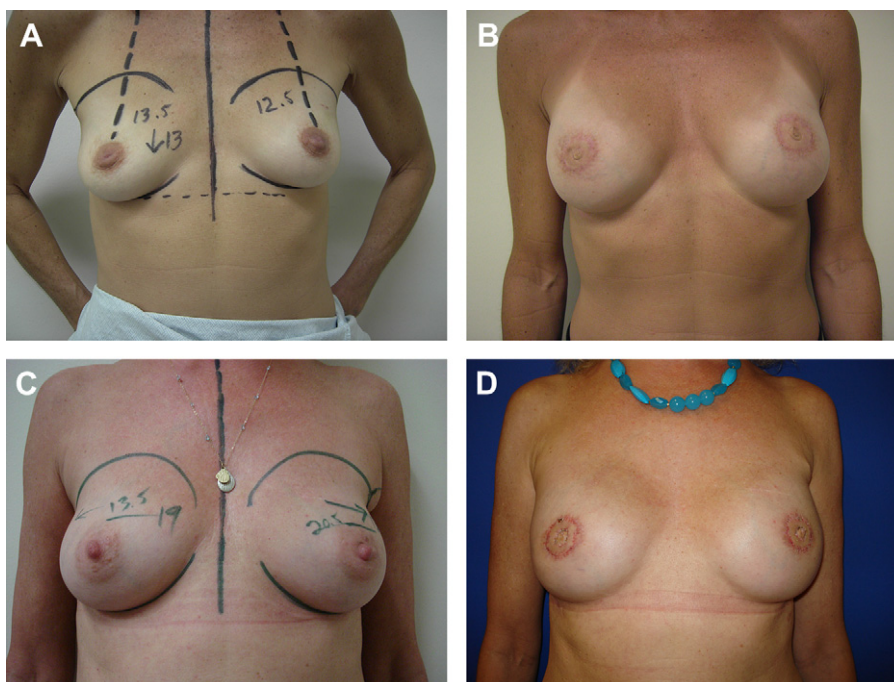
Only recently have we begun to realize the full potential that preventive measures may have on the incidence, diagnosis and treatment of breast cancer. The thought of prevention was a novel concept, and has grown out of efforts related to familial types of breast cancer. These efforts primarily focused on chemoprevention and surgery. However, more recently, the scientific community has

begun to understand the importance of lifestyle issues that may also impact the incidence of many different types of cancer, including breast cancer. The literature is congested with regard to the impact of lifestyle and breast cancer, with anywhere from 10 to 30% of breast cancer cases attributed to lifestyle issues. In fact, many of the general lifestyle attributes that help prevent cardiovascular disease seem to be identical to those that may prevent cancer. For example, we know that smoking, obesity and alcohol consumption are risk factors for cardiovascular disease and cancer as well. Thus, even a simple educational campaign may be very effective in helping to reduce the incidence of cancer years down the line.

In regards to chemoprevention, both tamoxifen and raloxifene are FDA-approved for breast cancer risk reduction, with tamoxifen utilized more often in pre-menopausal women where risk: benefit ratios are more favorable, given that thromboembolic phenomenon and the uterine cancer risk seems to be limited primarily to post-menopausal use. On the other hand, raloxifene is restricted to post-menopausal use based on its pharmacology, and is preferred by many over tamoxifen in this age group as it appears to be "uterine neutral" for both benign and malignant changes, while the thromboembolic risk is less than tamoxifen, more comparable to other hormonal agents. With raloxifene, we do have the unusual caveat that equivalency to tamoxifen from the P-2 trial is limited to invasive disease only.<sup>8</sup> At this point in time, it is not clear why the reduction in risk for noninvasive cancer with raloxifene was not as strong as tamoxifen. However, since there was no placebo in the P-2 trial, it cannot be stated that there was no effect at all. Studies have shown that agents such as tamoxifen and raloxifene can reduce the risk of breast cancer, particularly in women with a strong family or personal history. Multiple studies document a 49% risk reduction in high-risk patients, and a subset of those with ADH showed a remarkable 86% reduction when these chemo preventive (SERM) agents are used.

Relative risk reduction in the P-1 trial was 49% overall, and as mentioned above, the remarkable 86% risk reduction for women who entered the trial based on a diagnosis of atypical hyperplasia launched research into the active pursuit of atypia.<sup>1</sup> In the P-2 trial where 19,747 patients were randomized to either tamoxifen or raloxifene, the largest cohort of atypical hyperplasia ever studied (22.7% of enrollees) were accrued to the trial, probably due to the dramatic risk reduction seen in this group in the earlier P-1 study.<sup>8</sup> In the subset analysis of the P-2, those women with atypical hyperplasia had equivalent risk reduction for invasive breast cancer with either tamoxifen or raloxifene. Because there was no placebo group in the P-2, we are not privileged to see whether or not the 86% relative risk reduction held up in this larger group of women. Nevertheless, on a theoretical basis, it is intriguing to conceive of antihormonal therapy as being of greater benefit when used for an actual tissue diagnosis that transmits risk to all remaining tissue, than when antihormonal therapy is based on historical risks such as family history.

One of the most interesting developments in the concept of SERM risk reduction is the recent appreciation that the risk-lowering benefit of tamoxifen seems to last long after cessation of therapy. Although the long-term preventive capabilities of tamoxifen were theorized from multiple therapeutic trials where contralateral risk data was monitored, the recent updates from the prevention trials, IBIS-I and the Royal Marsden trial, suggest that true prevention is occurring with tamoxifen, rather than a simple delay in inevitable cancers.<sup>32,33</sup> In the IBIS-I, risk reduction with tamoxifen persisted for at least 10 years, while side effects did not persist after the 5-year treatment period. Notably, this risk reduction was only 26% in years 0–4, but 44% risk reduction beyond 5 years. Similarly, in the Royal Marsden trial, there was negligible risk



**Fig. 3.** A–D Both patients with strong family history and positive genetic testing before and after bilateral prophylactic mastectomy with bilateral breast and nipple reconstruction.

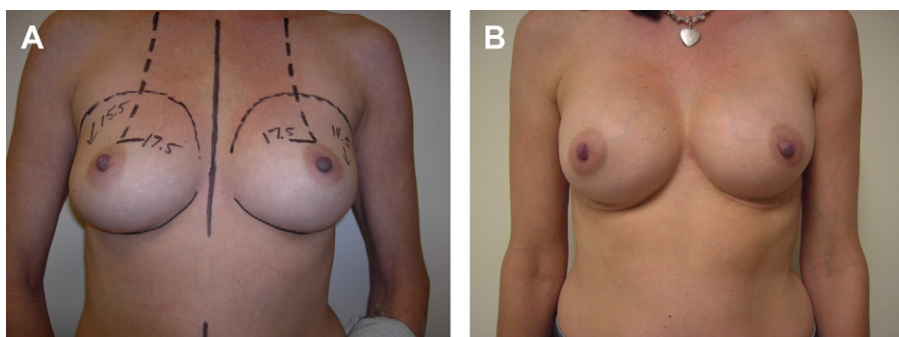
reduction in their initial reports, with the 20-year follow-up revealing a 23% (non-significant) risk reduction of ER + tumors during tamoxifen therapy, but a 52% risk reduction in the post-treatment period, statistical significance reached only after cessation of tamoxifen. Whether or not this same long-lasting effect will be seen with raloxifene is unknown at present, though optimal duration of raloxifene therapy for breast cancer risk reduction is an area of active investigation.

Although these drugs are effective in reducing the risk of breast cancer, they are not without their own implicit risk, and thus the use of chemoprevention is limited to women known to be at “high-risk.” As noted above, raloxifene is restricted to post-menopausal women and tamoxifen is indicated for pre-menopausal patients. Side effects can range from menopausal symptoms, increased number of thromboembolic events, to a significantly increased risk of developing endometrial cancers. But, it is important to note that the absolute increase in risk is small thus the risk: benefit ratio is reasonable, particularly in groups of women stratified by increased risk.

Still, SERM risk reduction is greatly underutilized, partially due to the menopausal symptoms that can accompany these agents in some patients, but also due to a failure to identify appropriate candidates through risk assessment and stratification. In an

exhaustive review of risk reduction efforts in post-menopausal women through lifestyle changes and the use of SERMs, both the use of mathematical models and/or mammographic density were felt to be helpful in selecting patients for interventions.<sup>34</sup> SERM risk reduction required threshold levels of high-risk status, but lifestyle counseling was recommended regardless of risk. The conclusion of this review was that all post-menopausal women should be screened for breast cancer risk. Certainly, the same can be said for younger women, too, given that the American Cancer Society guidelines for aggressive screening in high-risk women with MRI and mammography begin at age 30.

In some patients, surgical intervention is preferred as the ultimate “preventive measure.” With the recent advent of Oncoplastic Surgery, the use of prophylactic mastectomy in women with high-risk is a more reasonable approach than it has been previously. Fig. 3A–D shows two patient examples. Each of these women were young, physically active, and had strong family history with BRCA testing that was positive. After considering all options open and available to them, they chose bilateral mastectomy with immediate reconstruction. Both women have subsequently done very well, and they have returned to leading fully normal lives. Thus, today we have more palatable options



**Fig. 4.** A and B Before and after photos of patient following nipple-areolar sparing prophylactic mastectomy with immediate reconstruction using sub muscular saline implants.

available, and surgery can now be viewed in a more positive light for patients who are more comfortable accepting removal of the breast tissue as an option. In addition, nipple sparing mastectomy can also safely be considered in some patients, and using Oncoplastic Surgery can result in an aesthetically pleasing outcome (Fig. 4A and B).

## Conclusion

Following consideration of the above review, it is clear that the cost-effectiveness surrounding the many clinical areas as they relate to breast cancer are difficult, if not impossible to fully assess. However, within the literature we begin to see an important framework for the future. This includes the importance of risk assessment for stratification of women of various ages, preventive measures including lifestyle, chemoprevention and surgery, as well as the continued support for the essential component of mammographic screening according to present guidelines. It is these measures taken together as a whole that ultimately will save lives with the most effective, efficient and most cost-effective approach to breast cancer throughout the world.

## Conflicts of interest statement

Dr. Lebovic serves as a consultant for Neomatrix, Inc. Dr. Hollingsworth serves as consultant to NeoMatrix, Inc. and serves on the speaker's Bureau for Eli Lilly & Co.

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