DECISION MAKING IN BREAST CANCER PREVENTION

TOMA DE DECISIÓN EN LA PREVENCIÓN DEL CÁNCER DE MAMA

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Resumen

El cáncer de mama es uno de los canceres más comunes y la causa principal de muerte entre las mujeres de las edades de 45 a 60 en la mayoría de los países desarrollados. La eficacia de las opciones preventivas están bien determinadas e incluyen modificaciones en el estilo de vida, quimioprevención y cirugía profiláctica. A pesar de la eficacia de estas opciones, los medios preventivos están infrautilizados, con resultados de morbilidad y mortalidad que podrían evitarse. En el presente trabajo, se exponen las barreras principales del uso efectivo de los medios de prevención del cáncer de mama y se presenta un encuadre para tomar decisiones en la prevención del cáncer de mama centradas en el paciente y basado en datos acerca de su eficacia. Este encuadre se propone para estimular una aproximación a la toma de decisiones compartida en el contexto de la salud global de la mujer. La inclusión de intervenciones efectivas sobre el estilo de vida hace que este encuadre sea relevante para la mayor parte de las mujeres y no sea exclusivo de las que tengan alto riesgo de cáncer de mama.

Palabras clave: Cáncer de mama, evaluación de riesgo, prevención, toma de decisión, intervenciones en el estilo de vida.

Abstract

Breast cancer is one of the most common cancers among women and the leading cause of death in women between the ages of 45-60 in most developed countries. The efficacy of prevention options has been established and includes lifestyle modifications, chemoprevention, and prophylactic surgery. Despite the efficacy of these options, breast cancer prevention remains underused, resulting in avoidable morbidity and mortality. Here, the main barriers to effective use of breast cancer prevention are outlined and a framework to facilitate patient-centered and evidence-based breast cancer prevention decision making is presented. The framework is intended to encourage a shared decision making approach to prevention decisions, within the context of a woman's overall health. The inclusion of effective lifestyle interventions makes this framework relevant to most women, and is not exclusive to women at increased risk of developing breast cancer.

Key words: Breast cancer, risk assessment, prevention, decision making, lifestyle interventions.

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Background

It is estimated that 1.3 million women worldwide will be diagnosed with breast cancer annually and over 450,000 will die from the disease[1]. The aggregate cost of screening and treatment is estimated to be $15-20 billion yearly in the United States alone[2]. Women who live to be 75 years of age have approximately one in eight to one in twelve chance of developing breast cancer, making this a disease that concerns all women[3]. The emotional, financial, and societal burdens of breast cancer are immense and efforts aimed at early detection and prevention are well-founded. Early detection clearly improves prognosis for many women when combined with effective treatments. However, these treatments come at a price of substantial toxicity and fall short of ensuring a cure for many women. Increasingly, it is suggested that breast health practices include risk stratification, targeted screening, and selected consideration of risk-reduction options[4]. Risk-reducing interventions for breast cancer provide an opportunity for progress against this disease and effective use of these strategies is therefore a necessary component of any comprehensive breast cancer control program[5].

Options for breast cancer prevention are typically used in combination with screening and surveillance and include lifestyle modifications, chemoprevention, and prophylactic surgery[6]. While effective, these interventions are not right for all women; some have significant quality of life implications and others have potential for side effects that range from bothersome to life threatening. Prevention decisions present difficult tradeoffs for patients. These decisions are elective and require patients to weigh the risks and benefits for each option. In these decisions, also termed "preference sensitive" decisions, patients' preferences should guide decision making as there is not one medically recommended curse of action. Quality decision making in this environment dictates that patients be informed about their options and have the opportunity to participate in the decision making process. But often the status quo of choosing no intervention in the absence of a risk assessment or discussion is the default course of action for both patients and providers. In contrast, a well informed decision making process in the breast cancer prevention setting should include a risk assessment, followed by careful consideration of prevention options for women at increased risk. This Chapter outlines the current clinical challenges in breast cancer prevention decision making, and concludes with a framework for achieving quality decision making regarding breast cancer prevention in the general population. The framework is intended to encourage a shared decision making approach to prevention decisions, within the context of a woman's overall health and focusing on lifestyle interventions that are appropriate for most women.

Current state of decision making in breast cancer prevention

Although the efficacy of breast cancer prevention options has been demonstrated in multiple clinical trials and their use is clearly appropriate for selected women, they remain underused, resulting in avoidable morbidity and mortality. There are several reasons for this. Often women are not aware of their breast cancer risk or the risk-reducing options available to them[7]. Similarly, physicians find risk assessment and determining patient eligibility challenging in the clinical setting and are reluctant to recommend these medications for women at increased risk[8]. Finally, patients are reluctant to take these medications, citing fear of side effects as the most common deterrent[9]. One study

found that as few as 5% of eligible women accept tamoxifen therapy, while less than 25% of women eligible for prevention trials have elected to enroll[10,11] .

Additional challenges are found in the communication of breast cancer risk. Studies of women's decisions about breast cancer prevention and screening conclude that women have a tendency to overestimate both their risk of breast cancer and the risks of side effects associated with prevention[12]. However, an inflated estimate of breast cancer risk is not associated with improved screening adherence or quality decision making. For example, it has been shown that women who have undergone prophylactic bilateral mastectomy had significantly exaggerated perception of their risk at the time they made their decisions[13]. In other situations, women often focus on breast cancer risk even though they may be at greater risk for other diseases such as heart disease or lung cancer, risks that can be reduced substantially through lifestyle changes. Conversely, some women are adamantly opposed to risk-reducing interventions due to misconceptions about side effects associated with available interventions, even if breast cancer is their most significant health threat[14].

These compounding factors make clinical discussions about breast cancer prevention between patient and clinician challenging. This setting is one in which effective risk assessment, clinical decision support, and educational tools have the potential to add significant value. Such tools that are designed to educate patients, and support clinicians in this process can encourage patients and providers to make well informed decisions consistent with patient preferences and circumstances.

Components of high quality decision making in breast cancer prevention

The components of a quality decision making process in the breast cancer prevention setting including the following: a complete breast cancer risk assessment in context of overall health, discussion of relevant risk reduction options, and discussion of patient preferences regarding these interventions and possible outcomes involved.

Breast Cancer Risk Assessment

Based on FDA guidelines, over 10 million women in the United States are estimated to be eligible for tamoxifen[15]. However, less than 2% of those eligible for tamoxifen are expected to develop breast cancer[16], highlighting the need for risk stratification and selective use of these interventions from both public health and patient perspectives. Inappropriate underuse and overuse of breast cancer risk-reduction interventions both have negative public health implications. Quality decision making in breast cancer prevention can be realized by identifying appropriate patients for specific risk-reducing interventions based on their individual risk and preferences. To accomplish this, it is necessary to provide women with information concerning both their risk of breast cancer and likely benefit from available interventions. To do this, breast cancer risk must be assessed in context of the woman's overall health. A complete risk assessment should include the following: a breast cancer risk assessment, an overall health assessment, and an assessment of risk of treatment side effects.

There are a number of breast cancer risk assessment models that can facilitate this. For the general population, the NCI based Gail risk assessment model is often used[17]. While this model is well calibrated, it is

not very discriminatory; for a large group of women, the Gail model will successfully predict the expected number of breast cancers but it is not good at predicting which women will develop breast cancer[18]. For this reason, the Gail model is not an ideal risk stratification tool for individual decision making. However, this model is widely known, relatively easy to use in the clinic setting (www.cancer.gov/bcrisktool), and there are not significantly superior models available for the general population. The Women's Health Initiative (WHI) model, and the Breast Cancer Surveillance Consortium (BCSC) model are risk stratification models that build upon the Gail model inputs. These three models require basic data about the patient history, including reproductive history, a partial family history of cancer, biopsy history and results, and breast density[18,19]. Each model has its limitations, but each is more informative than using no model.

Sophisticated mathematical models such as BRCAPRO[20] and Tyrer-Cuzick[21] take into account a full family history, and some include additional risk factors found in the population models. Simpler tools, such as the Claus[22] and Myriad/Frank[23] risk tables are easier to use and can also be used to determine the risk of having a BRCA1 or BRCA2 mutation and/or the future risk of developing breast or ovarian cancer. These family history tools are typically more accurate than those for the general population, but are not always applicable to all populations of women[24].

General Health Risk Assessment

A summary of risk factors are found in Table 1. While these risk factors and risk models are helpful in generating individualized risk estimates for women, these estimates need to be taken in context of the women's overall health. For example, a woman with moderate breast cancer risk who is at risk for diabetes and has a high body mass index is not the best candidate for chemoprevention with tamoxifen. There are a number of tools that can assist either patients or providers in assessing a woman's overall heath. Below is a list of tools available online that can predict some of the most common health threats a woman faces.

Table 1. **Risk factors for the development of breast cancer**

Strong Risk Factors
Carrying the BRCA1 or BRCA2 gene mutation
Significant family history of breast and or ovarian cancer
Atypical ductal hyperplasia(ADH)/Atypia
Lobular carcinoma in situ (LCIS)
Age
Moderate Risk Factors
Dense breast tissue
Early exposure to radiation
Use of hormone replacement therapy
High alcohol consumption
High body mass index after menopause
Weak influence
Low age at first menstruation
High age at first pregnancy

Tools for general health assessments:

– Overall health: Your Disease Risk (www.yourdiseaserisk.wustl.edu)
  o This website assesses an individual's risk of developing five of the most common diseases (cancer, diabetes, heart disease, stroke) and provides suggestions for preventing them.
– Heart disease: Framingham Calculator (www.framinghamheartstudy.org/risk/hrdcoronary.html)
  o This is a risk assessment tool for estimating a 10-year risk of developing coronary heart disease outcomes (myocardial infarction and coronary death). This tool is designed to estimate risk in adults aged 20 and older who do not have heart disease or diabetes.
– Diabetes: Diabetes PHD (www.diabetes.org/living-with-diabetes/complications/diabetes-phd)
  o Diabetes PHD (Personal Health Decisions) assesses the risk of diabetes, heart attack, stroke, kidney failure, and foot and eye complications. It also determines the impact on these risks of a variety of health care interventions (losing weight, stopping smoking, and taking certain medications).
– Fractures: The FRAX® tool (www.shef.ac.uk/FRAX)
  o This tool was developed by WHO to assess fracture risk of patients.

Medical Interventions to Reduce Breast Cancer Risk

The options for breast cancer risk reduction range from invasive prophylactic surgeries to lifestyle interventions that are appropriate for all women. Prophylactic surgery (mastectomy and oophorectomy) and ovarian suppression options are very effective risk reduction techniques, but usually reserved for women with the highest levels of risk (often women with BRCA mutations) and those who are relatively risk averse[25]. Patient preferences in these cases commonly dictate the course of action women choose.

For the general population of women who are at moderate to high risk, there are effective medications to reduce the risk of developing breast cancer[26]. These include tamoxifen, raloxifene, and tibolone. Each has been shown to be effective, and each has accompanying side effects, both those that are mild and typically disappear after treatment, and those that are rare but can be life threatening. Because the benefit from risk reduction must be balanced by the risk of serious side effects, these medications are generally considered for women whose risk of breast cancer is moderately elevated over that of the average woman.

Tamoxifen has been shown to reduce the risk of breast cancer by 30-50% over 5-10 years for women with an elevated risk (greater than a 1.67% five year risk as estimated by the Gail model). However, potential side effects can be serious and include endometrial cancer, stroke, and pulmonary embolism[27]. Certain patient characteristics, including age, increase the likelihood of tamoxifen side effects. Assessing the presence of these characteristics can improve estimates of the risk of these side effects and therefore improve the predicted net benefits of tamoxifen. Recent data indicate risk reduction may persist as long as 10 years, providing a positive net therapeutic advantage to appropriately selected women[27,28].

Raloxifene has also been approved for breast cancer risk reduction in postmenopausal women and exhibits a therapeutic effect similar to tamoxifen,

though reduces breast cancer risk by only 38%, while conferring fewer side effects. Raloxifene has been shown to confer 45% less risk of uterine cancer and 25% less risk of thromboembolic events than tamoxifen[29].

Globally, *tibolone* is approved to treat menopausal symptoms and prevent osteoporosis but has yet to be formally approved in the United States. Recently, surprising results have emerged from a placebo-controlled study designed to demonstrate the efficacy of tibolone in reducing vertebral fractures in women with osteoporosis[19]. Tibolone was reported to reduce invasive breast cancer risk by 68%. However the study was prematurely halted due to a doubling of the risk of stroke. This risk was most substantial within the first year and in women more than 70 years of age.

Lifestyle Interventions to Reduce Breast Cancer Risk

Increasingly, research identifies lifestyle factors that contribute to breast cancer incidence. Consequently, modification of these factors through lifestyle interventions can potentially decrease the risk of developing breast cancer in individual women. Research on these risk factors is growing, as is their prominence as effective options for women to consider when making decisions about breast cancer prevention and risk management. The various lifestyle interventions thought to reduce the risk of developing breast cancer in the general population are described below and in Table 2.

Limit Alcohol Consumption

One of the most well documented modifiable risk factors for breast cancer development is alcohol consumption. Numerous prospective studies have demonstrated a linear relationship between alcohol intake and breast cancer risk, suggesting an approximate 10% increase in relative risk for each 10-gram daily increment of alcohol consumption (approximately 0.75 to 1 alcoholic drinks)[30,31].

Refrain from Using Hormone Replacement Therapy

Another important modifiable risk factor is postmenopausal hormone replacement therapy (HRT). The Women's Health Initiative (WHI) randomized trial have found that estrogen plus progestin use causes a 24% increase in relative risk of developing breast cancer, while estrogen use alone does not increase risk[32]. A follow up study of WHI found that in addition to an increased risk of developing cancer, women who received estrogen plus progestin HRT experienced more deaths attributable to breast cancer as well as more deaths from all causes when compared to women who received no HRT[33,34]. Interestingly, the only reason to give progestin in combination with estrogen is to prevent endometrial cancer. This cancer however is much less common than breast cancer and associated with significantly less mortality. Therefore, if HRT is going to be used, estrogen alone is a much more reasonable option.

Maintain a Healthy Weight

Higher body mass index and weight gain after menopause are associated with higher risk of breast cancer. This risk is estimated to be as high as a two-fold risk[35]. However, an inverse relationship between body mass index and breast cancer risk is found in premenopausal woman.

Engage in Physical Activity

Numerous epidemiologic studies have shown a reduction in the risk of

Table 2. **Modifiable risk factors**

Risk Factor	Relative Risk	References
Alcohol: Strong dose response affect, consistent across many observational studies		
· For each 10-gram increment in alcohol consumption	1.10	30, 31
Hormone Replacement Therapy: Strong randomized controlled trial evidence		
· Combination therapy (estrogen and progestin)	1.24	32,33
· Estrogen alone	No additional risk	34
Obesity: Strong, consistent evidence across many observational studies	1.2 – 2	35
Physical activity: Strong evidence		
· Moderate to vigorous recreational activities	0.74	36
· Outdoor activities	0.81	36
· Heavy physical work	0.6	36
Smoking: Fair evidence	1.25	37

developing breast cancer in women who are physically active. Together, these studies suggest a risk reduction on the order of 30-40% and has been shown for various activities including moderate to vigorous recreational activities, outdoor activities, and heavy physical work[36].

Refrain from Smoking

No discourse on cancer is complete without mentioning smoking. However, the data related to smoking and breast cancer are conflicting; some suggest as much as a 25% relative increase in risk associated with a personal history of smoking, others suggest only certain subtypes of breast cancer may be affected, other studies show

no affect at all[37]. Regardless, smoking should be avoided at all costs as a general health improvement due to the numerous detrimental health effects of smoking.

In summary, these lifestyle interventions are likely to benefit breast cancer risk, but are also beneficial to a woman's overall health. Table 3 shows the top ten causes of death that a woman faces[38,39]. Six of these top ten health threats are also thought to benefit from lifestyle interventions that benefit breast cancer risk. These healthy lifestyle interventions should be encouraged for all women, and particularly for women who are at moderate to high risk for breast cancer but are reluctant to take chemoprevention.

Table 3. **Top ten health threats for women**[38,39].
The following top ten health threats are impacted by the lifestyle interventions indicated below.

Health Threat	Physical Activity	Weight Control	Smoking Cessation	Moderate alcohol consumption
1. Heart disease	✓	✓	✓	✓
2. Cancer	✓	✓	✓	✓
3. Stroke	✓	✓	✓	✓
4. COPD			✓	
5. Alzheimer's	✓	✓	✓	✓
6. Injuries				
7. Diabetes	✓	✓		
8. Influenza				
9. Kidney disease	✓	✓		
10. Sepsis				

Proposed Decision Framework for Breast Cancer Risk Reduction

Decisions about breast cancer prevention begin with understanding what a woman's breast cancer risk level is, and then determining whether this risk is sufficient to alter standard screening recommendations or initiate a preventive intervention. Because this prevention decision is not urgent, women are able to take the time to become fully informed and thoughtfully consider the options she faces. To facilitate, we have developed a framework for integrating breast cancer prevention decisions within the context of a woman's general health. The framework is designed to provide structure for consultations regarding breast cancer prevention and to assist practitioners when having these discussions with patients. The framework integrates breast cancer risk assessment, an overall health assessment, and elicitation of patient preferences to appropriately frame this decision.

Framework for quality decision making in breast cancer prevention:

- Risk assessment in context
  - Breast cancer risk assessment using available risk assessment tools
    - Determine if the patient is at increased risk for breast cancer.
  - Overall health assessment, including current health issues and risk of other diseases
    - If the patient is at increased risk of breast cancer, determine if this risk is a priority when compared to other possible health issues she may be facing.
  - Risk of side effects of relevant risk-reducing interventions

- If the patient is at increased risk for breast cancer and it is a top priority for her, determine if she has more than average risk of intervention side effects (i.e., clotting events, endometrial cancer).
- Discussion of relevant options
  - Lifestyle interventions
    - Reasonable for all women to consider.
  - Chemoprevention
    - Reasonable for women at moderate to high risk without significant health issues or elevated risk of side effects to consider.
  - Surgical interventions
    - Typically reserved for women at very high risk.
- Discussion of patient preferences
  - Patient risk threshold for interventions
    - Determine if the patient level of breast cancer risk meets her threshold for intervention.
  - Patient risk threshold for side effects of relevant interventions
    - Determine if the expected net benefit for the patient (when considering the risk reduction and the additional risk of side effects) meets her threshold for intervention.
  - Patient willingness to engage in lifestyle interventions
    - Determine which lifestyle interventions, if any, are appropriate and determine patient interest in engaging with any particular recommendation. Direct to any relevant support services if available (i.e., smoking cessation courses).

Role for Decision Support Tools in Breast Cancer Prevention

Working through this assessment process and deciding which patients have sufficient risk of breast cancer and potential benefit to warrant risk-reducing interventions is a primary obligation of both primary care clinicians and breast care specialists. In turn, patients must absorb substantial information concerning their breast cancer risk and prevention options to make well-informed preventive treatment decisions. In addition, women's preferences for intervention options vary widely and must be an integral part of decision making. It is therefore critical that clinicians be able to accurately inform patients of their risks and options; and, understand patients' values regarding possible outcomes.

Clinical decision aids are tools that can be helpful in these situations by educating patients and encouraging patient participation in decisions about their medical care. Typically decision aids provide information about available options, help patients clarify their preferences regarding the outcomes associated with each option, and may include support for communicating with their clinician. The use of clinical decision aids has been shown to be beneficial and effective for both patients and clinicians. In systematic reviews, decision aids have improved medical decision-making processes by increasing patient knowledge, decreasing decisional conflict, and encouraging patients to be more actively involved in their decisions when compared to standard care[40]. A recent systematic review of interactive, computer-based education programs and decision aids found that these tools offer a feasible means for patient education and are well-received by patients in most circumstances[41]. Additionally, decision aids that are tailored to individual patients provide only the most relevant information, avoid unnecessary

confusion, and are more effective than general informational brochures. Interactive computerized decision aids display personalized information and can respond to patient feedback, offering advantages over non-computerized decision aids[42]. Decision aids designed specifically for clinicians to use during a patient visit have been shown to improve decision making and treatment adherence[43].

Clinical decision aids have been developed for a broad range of medical decisions. However, very few decision aids have been developed for breast cancer risk reduction. Most decision aids for breast cancer prevention are in the form of DVDs, CD-ROMs and written educational materials. The available decision aids in breast cancer risk reduction are designed for small subgroups of women such as women considering genetic testing or women already known to have a BRCA mutation. When considering population-wide breast cancer risk assessment and risk reduction, effective decision support tools need to be tailored to patients' individual breast cancer risks and other health characteristics, suitable for a the general population by including the body of evidence on effective lifestyle interventions, and they need to actively encourage communication between clinicians and patients about patient assessed risk and preferences.

There are a few decision support tools that fall into this category and are tools that can automate the breast cancer risk assessment process, guide providers about the relative priority of an individual's breast cancer risk, provide individually tailored risk projections, and discuss possible options for risk reduction. Such tools are needed to effectively communicate the necessary information for informed decision making regarding breast cancer risk reduction. Tools available to do this include:

- CancerGene (www4. utsouthwestern.edu/breasthealth/ cagene)
- Hughes riskApps™ (www. hughesriskapps.com)
- Breast Health Decisions (www. breasthealthdecisions.org).

Summary and Conclusions

Breast cancer risk-reduction interventions have the potential to substantially decrease the incidence of the disease, yet remain underused. With millions of women are at some level of increased risk and could benefit, there is a distinct opportunity to improve health outcomes by helping women with decision making. While these interventions hold the potential to substantially decrease the incidence of the disease, treating all patients the same is not the most effective option. Methods to stratify women by their risk of disease and the potential benefit of prevention interventions are necessary to guide appropriate use of prevention. Similarly, patient preferences need to be a main driver of these decisions. There is a clear need for a process that can facilitate the often challenging tasks of risk assessment, risk communication, and preference elicitation in the clinical setting. The framework is intended to encourage an evidence based, patient-centered approach to breast cancer prevention decisions that can guide such processes.

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