original reports

Reassessing the Benefits and Harms of Risk-Reducing Medication Considering the Persistent Risk of Breast Cancer Mortality in Estrogen Receptor–Positive Breast Cancer

Jinani Jayasekera, PhD[1]; Amy Zhao, MSc[2]; Clyde Schechter, MD[3]; Kathryn Lowry, MD[4]; Jennifer M. Yeh, PhD[5]; Marc D. Schwartz, PhD[2]; Suzanne O'Neill, PhD[2]; Karen J. Wernli, PhD[6]; Natasha Stout, PhD[7]; Jeanne Mandelblatt, MD[2]; Allison W. Kurian, MD, MSc[8]; and Claudine Isaacs, MD[2]

abstract

PURPOSE Recent studies, including a meta-analysis of 88 trials, have shown higher than expected rates of recurrence and death in hormone receptor–positive breast cancer. These new findings suggest a need to re-evaluate the use of risk-reducing medication to avoid invasive breast cancer and breast cancer death in high-risk women.

METHODS We adapted an established Cancer Intervention and Surveillance Modeling Network model to evaluate the lifetime benefits and harms of risk-reducing medication in women with a ≥ 3% 5-year risk of developing breast cancer according to the Breast Cancer Surveillance Consortium risk calculator. Model input parameters were derived from meta-analyses, clinical trials, and large observational data. We evaluated the effects of 5 years of risk-reducing medication (tamoxifen/aromatase inhibitors) with annual screening mammography ± magnetic resonance imaging (MRI) compared with no screening, MRI, or risk-reducing medication. The modeled outcomes included invasive breast cancer, breast cancer death, side effects, false positives, and overdiagnosis. We conducted subgroup analyses for individual risk factors such as age, family history, and prior biopsy.

RESULTS Risk-reducing tamoxifen with annual screening (± MRI) decreased the risk of invasive breast cancer by 40% and breast cancer death by 57%, compared with no tamoxifen or screening. This is equivalent to an absolute reduction of 95 invasive breast cancers, and 42 breast cancer deaths per 1,000 high-risk women. However, these drugs are associated with side effects. For example, tamoxifen could increase the number of endometrial cancers up to 11 per 1,000 high-risk women. Benefits and harms varied by individual characteristics.

CONCLUSION The addition of risk-reducing medication to screening could further decrease the risk of breast cancer death. Clinical guidelines for high-risk women should consider integrating shared decision making for risk-reducing medication and screening on the basis of individual risk factors.

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INTRODUCTION

Estrogen receptor–positive (ER+) breast cancer is generally considered to have a favorable prognosis. However, recent studies have shown that the annual rates of recurrence and breast cancer death could remain up to 3% for almost three decades after an ER+ breast cancer diagnosis.[1,2] This new information on the long-term burden of ER+ breast cancer warrants a reconsideration of the lifetime benefits and harms of risk-reducing medication for primary prevention of breast cancer.

Several randomized controlled trials have shown that risk-reducing medications such as tamoxifen and aromatase inhibitors (AIs) could decrease the incidence of ER+ breast cancer by 30%-50% in women who are at high risk of developing breast cancer.[3-23] However, in clinical practice, the uptake of risk-reducing medication has remained extremely low.[3] The reasons for underuse are not fully understood, but some studies have posited that insufficient data on the long-term benefits and harms of risk-reducing drugs, lack of biomarkers to measure response to medication, and fear of rare but serious side effects (eg, endometrial cancer and pulmonary embolism) are deterrents—causing women and their clinicians to conclude that the harms of risk-reducing medications outweigh their potential benefits.[24-26] Furthermore, adding to these barriers is the lack of personalized data to help women and their clinicians quantify the net balance of potential benefits and harms of risk-reducing medication

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

We re-evaluated the use of risk-reducing medication to avoid breast cancer deaths in women with a 3% or greater 5-year risk of developing breast cancer. The key objective of the study was to provide the benefits and harms of risk-reducing medication, screening, and supplemental magnetic resonance imaging to facilitate shared decision making about risk-reducing drugs with high-risk women seen in clinical practice.

Knowledge Generated

The addition of risk-reducing medication to annual mammography screening (± magnetic resonance imaging) could further decrease the risk of breast cancer death in high-risk women. However, these drugs are associated with side effects. The benefits and harms of risk-reducing medication could vary on the basis of individual risk factors such as age, prior biopsy, and family history of breast cancer.

Relevance *(K.D. Miller)*

Chemoprevention to reduce the risk of breast cancer is effective but underused. Many physicians and patients underestimate the benefit and overestimate the side effects. This analysis provides important data to guide discussions on the basis of individual risks.*

*Relevance section written by *JCO* Senior Deputy Editor Kathy D. Miller, MD.

in the presence of mammography screening and magnetic resonance imaging (MRI).

We used an established Cancer Intervention and Surveillance Modeling Network (CISNET) model[27-30] to re-evaluate the benefits (avoiding invasive breast cancer and breast cancer death) and harms (side effects) of risk-reducing medication, mammography screening, and MRI in high-risk women. A woman's individual risk for breast cancer may depend on her age, family history of breast cancer, genetic predisposition (eg, *BRCA1/2*), breast density, and prior history of biopsy.[31-33] Recognizing that there are specific guidelines for carriers of pathogenic variants in high-risk genes, in this study, we focused on a larger population of women at increased risk because of age, breast density, prior biopsy, and family history. We considered emerging data[1,2] on the long-term risk of breast cancer death in ER+ breast cancer to estimate the benefits and harms of risk-reducing medication, screening, and MRI on the basis of individual characteristics of high-risk women. The overarching goal of this study was to provide novel personalized data to facilitate shared decision making about risk-reducing medication with high-risk women seen in clinical practice.

METHODS

We adapted an extant CISNET breast cancer model (model G-E) for this study.[27] The study was approved by the Georgetown University Institutional Review Board and was considered as exempt research on the basis of the use of deidentified data.

Model Overview

The development and validation of model G-E has been described in detail elsewhere.[27] In brief, the model simulates life histories for a parallel-universe population that includes breast cancer incidence and survival trends that are specific to ER/human epidermal growth factor receptor 2 (HER2) status, in the absence of risk-reducing medication, screening, MRI, and adjuvant treatment. Life histories are generated for individual women from birth till death or age 100 years to account for her entire potential life history. In this study, a woman's life history also included the trajectory of her individual risk factors such as breast density, family history of breast cancer, and prior history of biopsy conditional on her age, and the joint effects of these risk factors and age on breast cancer incidence. We assumed that 20% of all tumors that would present clinically as ductal carcinoma in situ would never progress to invasive cancer.[27] The effects of screening, MRI, risk-reducing medication, and breast cancer treatment could alter a woman's life history and her health outcomes. Screening (± MRI) could reduce breast cancer death through a stage shift and an age shift resulting from early detection. Risk-reducing medication could reduce ER+ breast cancer incidence, which could lead to a reduction in ER+ breast cancer–related death. If a woman was diagnosed with breast cancer, then we applied the effects of hormonal and adjuvant treatment to reduce her risk of breast cancer death. Simulated women could die of breast cancer or other causes.

Model Inputs

The model input parameters and data sources are summarized in Table 1 and described below.

Breast cancer risk factors and breast cancer incidence. We used the joint distributions of breast density, family history, and prior biopsy by age in Breast Cancer Surveillance Consortium (BCSC) data[34] to simulate the distribution of these risk factors overtime in high-risk women. Breast density

TABLE 1. Input Parameters Used for Model Development

Characteristic	Description	Data Source
Breast cancer risk factors including age, family history of breast cancer, breast density, and prior history of breast biopsy	The joint distribution of family history (one or more first-degree relatives with breast cancer), breast density (BI-RADS), and prior history of breast biopsy (lobular hyperplasia or lobular carcinoma in situ, proliferative changes with atypia, proliferative changes without atypia/nonproliferative lesions or none) by age	BCSC[34]
Natural history of breast cancer incidence in the absence of risk-reducing medication, screening mammography or MRI in women who are at 3% or greater 5-year risk of developing breast cancer on the basis of age, family history, breast density, and prior breast biopsy	Calibrated to observed SEER program rates using an age-period-cohort model; and adjusted using incidence rates of breast cancer in women who are at 3% or greater 5-year risk of developing breast cancer	BCSC[34]; Gangnon et al[36]
Stage distribution	Stage distribution among clinically detected and screen-detected cancers stratified by age at diagnosis (< 50, 50-64, ≥ 65 years), screening round (first, subsequent), screening interval (annual), and density	BCSC[34]
ER/HER2	Probability of ER/HER2 conditional on age and stage	BCSC[34]
Sojourn time	Calibrated parameters: gamma distributions by joint ER/HER2 status and age	Mandelblatt et al[45]
Effects of risk-reducing medication (tamoxifen and aromatase inhibitors)	Reduction in hormone receptor–positive breast cancer incidence because of the use of risk-reducing medication up to 5 years	Nelson et al[3]
Side effects of risk-reducing medication (tamoxifen and aromatase inhibitors)	Absolute rates of venous thromboembolism; deep vein thrombosis, pulmonary embolism, and superficial phlebitis; coronary heart disease; stroke; and endometrial cancer with up to 5 years of risk-reducing drug use compared with a background rate	Nelson et al[3]; NSABP P-1[10,12]
Mammography screening sensitivity/specificity (DBT alone, DBT + MRI)	Age- and density-specific sensitivity and specificity for first and subsequent DBT and DBT + MRI screening examinations	BCSC[34]; Phi et al[37]
Breast cancer treatment use	Assumed receipt of and adherence to guideline specific treatment by age, stage, and hormone receptor status	Mandelblatt et al[45]
Breast cancer treatment effects	Treatment efficacy estimates from meta-analyses of clinical trials	Pan et al[2]; Caswell-Jin et al[39]; Peto et al[40]
Breast cancer survival	Long-term breast cancer survival stratified by ER/HER2 receptor status, age, and AJCC stage	Mandelblatt et al[45]
Nonbreast cancer mortality	Age-specific other-cause mortality rates	Trentham-Dietz et al[41]; Gangnon et al[42]

Abbreviations: AJCC, American Joint Committee on Cancer; BCSC, Breast Cancer Surveillance Consortium; BI-RADS, Breast Imaging Reporting and Data System; DBT, digital breast tomosynthesis; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MRI, magnetic resonance imaging; NSABP, National Surgical Adjuvant Breast and Bowel Project.

was modeled using Breast Imaging Reporting and Data System categories, which included almost entirely fatty, scattered areas of fibroglandular density, heterogeneously dense, or extremely dense.[35] Prior history of biopsy included lobular hyperplasia or lobular carcinoma in situ (LCIS), proliferative changes with atypia, proliferative changes without atypia/nonproliferative lesions or none. Family history included one or more first-degree relatives with breast cancer. Breast density, family history, and prior biopsy were first assigned to a woman at age 35 years, and subsequent changes in these risk factors were applied at age 50 years and then at age 65 years. Then, we dynamically updated each simulated woman's risk of breast cancer incidence on the basis of her changing age, density, family history, and prior biopsy by adjusting an age-period-cohort model.[36] These adjustments considered breast density, family history, prior biopsy, race/ethnicity, age, and interactions between age and other risk factors (Data Supplement, online only). The joint distribution of ER/HER2 status by age and stage (American Joint Committee on Cancer, version 6) were also obtained from BCSC data.

Screening performance. We modeled sensitivity and specificity for digital breast tomosynthesis (DBT) by calibrating the performance characteristics of DBT observed in BCSC data.[34] The sensitivity and specificity for supplemental screening with MRI + DBT were obtained from a meta-analysis of six screening studies.[37] Further details are provided in the Data Supplement.

Effects of risk-reducing medication. We modeled the effects of a 5-year course of tamoxifen and aromatase inhibitor (AI) on the incidence of breast cancer on the basis of a meta-

analysis of trials (Data Supplement).[3-23] We assumed that risk-reducing medication did not have an impact on ER-negative (ER−) disease, and the effects of tamoxifen on ER+ disease did not vary by age.[3]

The side effects attributable to risk-reducing medication were obtained from published data (Data Supplement),[3,10,12,38] which included venous thromboembolism; deep vein thrombosis, pulmonary embolism, and superficial phlebitis; coronary heart disease; stroke; and endometrial cancer. We varied the effects of tamoxifen on endometrial cancer risk by age (< 50; ≥ 50 years) according to the age-specific rates reported in trials.[10,12,38] Potential death due to these side effects were captured in other-cause mortality. We assumed that the side effects only occurred during the 5-year active treatment period on the basis of published data.[8]

Breast cancer treatment and other cause mortality. All women diagnosed with ER+ tumors were assumed to receive 5 years of adjuvant hormonal therapy with a proportion receiving docetaxel and cyclophosphamide.[39] We incorporated the late effects of hormonal therapy in ER+ tumors obtained from a meta-analysis of 88 clinical trials.[2] Women with ER- tumors received anthracycline-based regimens with a taxane.[40] Those with HER2+ tumors received trastuzumab ± pertuzumab in addition to chemotherapy.[39] Treatment effectiveness was based on trial data that assumed women received local therapy.[40] Age-specific other-cause mortality rates were based on published estimates.[41,42] We assumed 100% adherence to isolate the effects of screening and risk-reducing medication.

Population and Subgroups

Risk assessment tools such as the BCSC Breast Cancer Risk Assessment Calculator[43] can be used to estimate a woman's 5-year risk of developing breast cancer. In this study, we analyzed the benefits and harms for women when they first would have a $\geq 3\%$ 5-year risk of developing breast cancer on the basis of the BCSC risk calculator. These women are at high risk of developing breast cancer according to current guidelines.[44]

We also provided results for several subgroups on the basis of the prevalence of individual risk factors in the population (Data Supplement). These subgroups included (1) 35-year-olds with a history of LCIS and family history of breast cancer; (2) 50-year-olds with a history of nonproliferative/proliferative changes without atypia and a family history; and (3) 65-year-olds with a history of nonproliferative/proliferative changes without atypia and no family history of breast cancer.

Strategies

We examined the benefits and harms for 5 strategies, including (1) annual mammography screening (with DBT) alone; (2) 5 years of risk-reducing medication combined with annual screening; (3) annual screening with supplemental MRI; (4) risk-reducing medication combined with annual screening and MRI; and (5) no screening, MRI, or risk-reducing medication. An annual interval was defined as 9-18 months between examinations. We considered tamoxifen for all women in the primary analysis as it is the only risk-reducing medication approved for premenopausal women. We considered the effects of AI in (postmenopausal) women age 50 and 65 years.

Analysis

We simulated 10 million life histories for each strategy described above and summarized the number of invasive (ER+/ER−) breast cancers, breast cancer deaths, side effects of risk-reducing drugs, false positives, and overdiagnosis per 1,000 high-risk women undergoing each strategy. False positives were defined as screens resulting in additional imaging that did not result in a breast cancer diagnosis within 12 months.[45,46] We defined overdiagnoses as breast cancers that would not have been clinically detected in the absence of screening because of lack of progressive potential or preceding death from competing causes other than breast cancer.[46] Therefore, overdiagnosis included screen-detected nonprogressive ductal carcinoma in situ and some ER+ invasive breast cancers that would not have surfaced to clinically detected tumors before the woman's death from other causes. All outcomes (except for side effects) were summarized from the starting age of a given strategy till death or age 100 years.

The incremental benefits for screening, MRI, or risk-reducing medication strategies (ie, strategies 1-4) were calculated in comparison with the strategy with no risk-reducing medication or screening or MRI (strategy 5). We estimated the absolute and relative (ie, %) reductions in invasive (ER+/ER−) breast cancers and breast cancer deaths. Harms of 5 years of risk-reducing medication were calculated as the difference between the number of adverse events and the background rate in untreated women.[3] Harms of screening included the number of false positives and overdiagnoses per 1,000 women screened with DBT ± MRI. The benefits and harms in terms of ER+ tumors were calculated separately.

Sensitivity Analysis

In our primary analysis we assumed that risk-reducing drugs decreased the underlying risk of invasive breast cancer beyond the discontinuation of medication according to follow-up data provided by IBIS-I[7-9] and Marsden trials.[13,14] However, the effect of risk-reducing medication could potentially decline over time. Therefore, in a sensitivity analysis, we decreased the impact of risk-reducing medication by 10% every 5 years up to 15 years following initiation by applying a step function that diminished the drug effects on the underlying risk of breast cancer. The 10% reduction was selected to capture the variation of drug efficacy seen in trials.[47]

Exploratory Analysis: 2 Years of Tamoxifen

In practice, women may opt for a shorter duration (eg, 1-2 years) of tamoxifen. However, currently there are no data on

the effects of a shorter regimen of risk-reducing drugs. Therefore, we modeled the benefits and harms of 2 years of risk-reducing tamoxifen using data from the Stockholm trial,[48] which shows the effects of 2 years of adjuvant tamoxifen on contralateral breast cancer in postmenopausal early-stage breast cancer (Data Supplement).

Validation

Independent validation of results was performed to confirm model accuracy.[49] The oncologist coinvestigators (A.W.K. and C.I.) reviewed the face validity of the model structure, inputs, and results. To assess the external validity of the model, we simulated a modern trial (Marsden trial[14]) and then we compared simulated trial outcomes with the actual trial results.

RESULTS

Overall, 5 years of risk-reducing tamoxifen and screening (± MRI) helped avoid 40% of invasive (ER+/ER−) breast cancers, and 57%-58% of breast cancer deaths in high-risk women compared with no screening or risk-reducing tamoxifen (Table 2). This is equivalent to an absolute reduction of 95-96 invasive breast cancer cases, and 42-43 breast cancer deaths per 1,000 high-risk women. In absolute terms, 5 years of risk-reducing tamoxifen alone was attributable to avoiding 58-59 invasive breast cancers and 13 breast cancer deaths per 1,000 women. Tamoxifen primarily reduced ER+ tumors and related deaths (Data Supplement). Over a 5-year period, tamoxifen resulted in 11 endometrial cancers per 1,000 women. The majority (98%) of women in the overall high-risk population were ≥ 50 years (Data Supplement). As a result, the endometrial cancer events in the overall population reflect the risk in older women. The addition of MRI resulted in more false positives compared with screening alone.

Subgroup Analysis

The benefits and harms varied by age, prior biopsy, and family history (Table 3). More than 95% of 35-year-old high-risk women had LCIS on a prior biopsy (Data Supplement). Tamoxifen with screening (± MRI) could avoid 191-195 invasive breast cancers and 98-100 breast cancer deaths per 1,000 thirty-five-year-old women with a history of LCIS and a family history of breast cancer (Table 3). A reduction in 100-102 invasive breast cancers and 19-20 breast cancer deaths per 1,000 women were attributable to risk-reducing tamoxifen alone. The benefits were primarily seen in ER+ disease (Data Supplement). However, tamoxifen was associated with five venous thromboembolisms and five endometrial cancers per 1,000 women.

The majority of 50-year-old high-risk women had a history of proliferative changes without atypia (68%; Data Supplement), and a family history (75%; Data Supplement). These women could avoid 126-128 invasive breast cancers and 59-60 breast cancer deaths per 1,000 women with tamoxifen and screening (± MRI) (Table 3). However, their endometrial cancers went up to 11 events per 1,000 women. Most high-risk women ≥ 65 years had a history of proliferative changes without atypia (79%), and no family history (55%; Data Supplement). Tamoxifen and screening could avoid up to 60 invasive breast cancers and 25 breast cancer deaths per 1,000 women. However, tamoxifen also increased the number of thromboembolisms and endometrial cancers (Table 3).

The addition of MRI increased false positives in all three subgroups. For example, in 65-year-old women, the number of false positives nearly tripled with MRI.

AIs Versus Tamoxifen in 50- and 65-Year-Old Women

AIs resulted in higher benefits and lower harms compared with tamoxifen in 50- and 65-year-old women (Table 4; Data Supplement for ER+). The absolute reduction attributable to AIs alone in 50- and 65-year-olds were 133-134 and 84 invasive breast cancers, and 54-55 and 14 breast cancer deaths per 1,000 women, respectively.

Sensitivity Analysis

Screening and the diminishing effects of risk-reducing medication over time resulted in a lower absolute reduction of 92 invasive breast cancers and 41 breast cancer deaths (Data Supplement). In 50- and 65-year-olds, the absolute reduction attributable to AIs alone reduced to 91 and 22 invasive breast cancers, and 18 and five breast cancer deaths per 1,000 women, respectively (Data Supplement).

Exploratory Analysis: 2 Years of Tamoxifen

Annual screening with 2 years of tamoxifen could potentially avoid 61 invasive breast cancer cases and 35 breast cancer deaths per 1,000 women (Data Supplement).

Validation

The model closely replicated the estimates observed in the original Marsden trial[14] (Data Supplement).

DISCUSSION

Recent studies with long-term follow-up data have shown higher-than-expected rates of recurrence and death in ER+ breast cancer.[1,2] In light of this new understanding of the long-term burden of ER+ disease, it is more important than previously recognized for clinicians to introduce medical risk reduction when counseling women at high risk of developing breast cancer. Our results show that the addition of risk-reducing medication to annual screening could further reduce the risk of breast cancer death in high-risk women. The benefits and harms of risk-reducing medication and screening may vary on the basis of individual risk factors such as age, family history of breast cancer, and prior history of biopsy. For instance, consistent with trial data,[10,12,38] our results showed that risk-reducing tamoxifen was associated with an increase in endometrial cancers in older women (≥ 50 years). Therefore, AIs may be more suitable for postmenopausal older women.

TABLE 2. Benefits and Harms of Risk-Reducing Medication (Tamoxifen), Screening Mammography, and Supplemental Screening With Magnetic Resonance Imaging in Women With a 3% or Greater 5-Year Risk of Developing Breast Cancer

	Benefits						Harms						
							No. of Adverse Events Per 1,000 High-Risk Women[f]						
Strategy	No. of Invasive Breast Cancers[a] Per 1,000 High-Risk Women	Absolute No. of Invasive Breast Cancers[a] Avoided Per 1,000 High-Risk Women[b]	Percentage of Invasive Breast Cancers[a] Avoided[c]	No. of Breast Cancer Deaths Per 1,000 High-Risk Women	Absolute No. of Breast Cancer Deaths Avoided Per 1,000 High-Risk Women[d]	Percentage of Breast Cancer Deaths Avoided[e]	VTE	DVT; PE; SP	Coronary Heart Disease	Stroke	Endometrial Cancer	False-Positive Results Per 1,000 High-Risk Women[g]	Overdiagnoses Per 1,000 High-Risk Women[h]
Annual S	201	36	15	45	29	39	—	—	—	—	—	1,002	15
Annual S + R	142	95	40	32	42	57	5	2; 3; 2	< 1	2	11	1,054	11
Annual S + MRI	199	38	16	44	30	40	—	—	—	—	—	1,823	15
Annual S + MRI + R	141	96	40	31	43	58	5	2; 3; 2	< 1	2	11	1,918	10
No S or MRI or R	237	—	—	74	—	—						—	—

NOTE. High-risk women are women with a ≥ 3% 5-year risk of developing breast cancer according to the BCSC risk calculator.

Abbreviations: BCSC, Breast Cancer Surveillance Consortium; DVT, deep vein thrombosis; MRI, magnetic resonance imaging; PE, pulmonary embolism; R, 5 years of risk-reducing medication; S, annual screening mammography with digital breast tomosynthesis till age 74 years; SP, superficial phlebitis; VTE, venous thromboembolism.

[a]Includes both estrogen receptor–positive and estrogen receptor–negative breast cancer.

[b]The difference between the number of invasive breast cancer cases per 1,000 high-risk women who underwent a given strategy and the number of cases per 1,000 high-risk women who did not undergo screening or MRI or risk-reducing medication. For example, the absolute difference in invasive breast cancers avoided between S + R and no S, R, or MRI was calculated as (237 − 142) = 95 invasive breast cancers avoided per 1,000 high-risk women.

[c]([Difference between the number of invasive breast cancer cases among women who underwent a given strategy and women who did not undergo screening or MRI or risk-reducing medication]/the number of invasive breast cancer cases among women who did not undergo screening, MRI, or risk-reducing medication) × 100. For example, the % of invasive breast cancers avoided with S + R compared with no S, R, or MRI was calculated as ([237 − 142]/237) × 100.

[d]The difference between the number of breast cancer deaths per 1,000 high-risk women who underwent a given strategy and the number of breast cancer deaths per 1,000 high-risk women who did not undergo screening or MRI or risk-reducing medication. For example, the absolute difference in breast cancer deaths or MRI was calculated as (74 − 32) = 42 breast cancer deaths avoided per 1,000 high-risk women.

[e]([Difference between the number of breast cancer deaths in women who underwent a given screening strategy and women who did not undergo screening or risk-reducing medication]/the number of breast cancer deaths in women who did not undergo screening, MRI, or risk-reducing medication) × 100. For example, the number of breast cancer deaths avoided with S + R compared with no S, R, or MRI was calculated as ([74 − 32]/74) × 100.

[f]The difference between the number of adverse events over 5 years per 1,000 high-risk women treated with risk-reducing medication and the background rate of that event over 5 years per 1,000 high-risk women who did not receive risk-reducing medication. Background rates for venous thromboembolism was 5; DVT was 4; pulmonary embolism was 1; superficial phlebitis was 8; coronary heart disease was 12; stroke was 3; and endometrial cancer was 4 per 1,000 high-risk women over 5 years.

[g]The total number of screens that resulted in additional imaging that did not result in the diagnosis of breast cancer within 12 months. A single woman could experience several false positives on the basis of the number of screens she received in her lifetime. The false positives are based on the specificity of the screening method. Specificity of screening refers to the correct identification of women who do not have breast cancer as negative.

[h]The total number of women who would not have been clinically detected in the absence of screening because of lack of progressive potential or preceding death from competing causes other than breast cancer per 1,000 high-risk women screened.

TABLE 3. Benefits and Harms of Risk-Reducing Medication (Tamoxifen), Screening Mammography, and Supplemental Screening With Magnetic Resonance Imaging in 35-, 50-, and 65-Year-Old Women on the Basis of History of Breast Biopsy and Family History of Breast Cancer

	Benefits						Harms						
							No. of Adverse Events Per 1,000 High-Risk Women[f]						
Strategy	No. of Invasive Breast Cancers[a] Per 1,000 High-Risk Women	Absolute No. of Invasive Breast Cancers[a] Avoided Per 1,000 High-Risk Women[b]	Percentage of Invasive Breast Cancers[a] Avoided[c]	No. of Breast Cancer Deaths Per 1,000 High-Risk Women	Absolute No. of Breast Cancer Deaths Avoided Per 1,000 High-Risk Women[d]	Percentage of Breast Cancer Deaths Avoided[e]	VTE	DVT; PE; SP	Coronary Heart Disease	Stroke	Endometrial Cancer	False-Positive Results Per 1,000 High-Risk Women[g]	Overdiagnoses Per 1,000 High-Risk Women[h]
35-year-old women with a history of LCIS and a family history[i] of breast cancer													
Annual S	460	89	16	92	78	46	—	—	—	—	—	2,916	23
Annual S + R	358	191	35	72	98	58	5	2; 3; 2	< 1	2	5	3,122	23
Annual S + MRI	454	95	17	89	81	47	—	—	—	—	—	4,988	24
Annual S + MRI + R	354	195	35	70	100	59	5	2; 3; 2	< 1	2	5	5,341	24
No S or MRI or R	549	—	—	170	—	—						—	—
50-year-old women with nonproliferative or proliferative lesion without atypia on a prior biopsy and a family history of breast cancer													
Annual S	310	42	12	63	42	40	—	—	—	—	—	1,631	21
Annual S + R	226	126	36	46	59	56	5	2; 3; 2	< 1	2	11	1,713	18
Annual S + MRI	308	44	13	62	43	41	—	—	—	—	—	2,692	22
Annual S + MRI + R	224	128	36	45	60	57	5	2; 3; 2	< 1	2	11	2,835	18
No S or MRI or R	352	—	—	105	—	—						—	—
65-year-old women[j] with nonproliferative or proliferative lesion without atypia on a prior biopsy and no family history of breast cancer													
Annual S	116	24	17	29	16	35	—	—	—	—	—	440	10
Annual S + R	80	60	43	20	25	55	5	2; 3; 2	< 1	2	11	458	7
Annual S + MRI	115	25	18	29	16	36	—	—	—	—	—	1,136	10
Annual S + MRI + R	80	60	43	20	25	56	5	2; 3; 2	< 1	2	11	1,184	7
No S or MRI or R	140	—	—	45	—	—						—	—

NOTE. High-risk women are women with a ≥ 3% 5-year risk of developing breast cancer according to the BCSC risk calculator.

Abbreviations: BCSC, Breast Cancer Surveillance Consortium; DVT, deep vein thrombosis; LCIS, lobular carcinoma in situ; MRI, magnetic resonance imaging; PE, pulmonary embolism; R, 5 years of risk-reducing medication; S, annual screening mammography with digital breast tomosynthesis till age 74 years; SP, superficial phlebitis; VTE, venous thromboembolism.

[a]Includes both estrogen receptor–positive and estrogen receptor–negative breast cancer.

[b]The difference between the number of invasive breast cancer cases per 1,000 high-risk women who underwent a given strategy and the number of cases per 1,000 high-risk women who did not undergo screening or MRI or risk-reducing medication.

[c]([Difference between the number of invasive breast cancer cases among women who underwent a given strategy and women who did not undergo screening or MRI or risk-reducing medication]/the number of invasive breast cancer cases among women who did not undergo screening, MRI, or risk-reducing medication) × 100.

[d]The difference between the number of breast cancer deaths per 1,000 high-risk women who underwent a given strategy and the number of breast cancer deaths per 1,000 high-risk women who did not undergo screening or MRI or risk-reducing medication.

[e]([Difference between the number of breast cancer deaths in women who underwent a given screening strategy and women who did not undergo screening or risk-reducing medication]/the number of breast cancer deaths in women who did not undergo screening, MRI, or risk-reducing medication) × 100.

[f]The difference between the number of adverse events over 5 years per 1,000 high-risk women treated with risk-reducing medication and the background rate of that event over 5 years per 1,000 high-risk women who did not receive risk-reducing medication. Background rates for venous thromboembolism was 5; DVT was 4; pulmonary embolism was 1; superficial phlebitis was 8; coronary heart disease was 12; stroke was 3; and endometrial cancer was 4 per 1,000 high-risk women over 5 years.

[g]The total number of screens that resulted in additional imaging that did not result in the diagnosis of breast cancer within 12 months. A single woman could experience several false positives on the basis of the number of screens she received in her lifetime. The false positives are based on the specificity of the screening method. Specificity of screening refers to the correct identification of women who do not have breast cancer as negative.

[h]The total number of women who would not have been clinically detected in the absence of screening because of lack of progressive potential or preceding death from competing causes other than breast cancer per 1,000 high-risk women screened.

[i]First-degree relative.

[j]Women age 65 years received biennial screening from age 50 to 64 years before switching to annual screening at age 65 years following a ≥ 3% increase in breast cancer risk according to the BCSC risk calculator.

TABLE 4. Benefits and Harms of Risk-Reducing Medication (Aromatase Inhibitors), Screening Mammography, and Supplemental Screening With Magnetic Resonance Imaging in 50- and 65-Year-Old Women on the Basis of History of Breast Biopsy and Family History of Breast Cancer

	Benefits						Harms						
							No. of Adverse Events Per 1,000 High-Risk Women[f]						
Strategy	No. of Invasive Breast Cancers[a] Per 1,000 High-Risk Women	Absolute No. of Invasive Breast Cancers[a] Avoided Per 1,000 High-Risk Women[b]	Percentage of Invasive Breast Cancers[a] Avoided[c]	No. of Breast Cancer Deaths Per 1,000 High-Risk Women	Absolute No. of Breast Cancer Deaths Avoided Per 1,000 High-Risk Women[d]	Percentage of Breast Cancer Deaths Avoided[e]	VTE	DVT; PE; SP	Coronary Heart Disease	Stroke	Endometrial Cancer	False-Positive Results Per 1,000 High-Risk Women[g]	Overdiagnoses Per 1,000 High-Risk Women[h]
50-year-old women with nonproliferative or proliferative lesion without atypia on a prior biopsy and a family history[i] of breast cancer													
Annual S	310	42	12	63	42	40	—	—	—	—	—	1,631	21
Annual S + R	176	176	50	36	69	66	2	NE	NE	< 1	NE	1,757	15
Annual S + MRI	308	44	13	62	43	41	—	—	—	—	—	2,692	22
Annual S + MRI + R	175	177	50	35	70	67	2	NE	NE	< 1	NE	2,912	15
No S or MRI or R	352	—	—	105	—	—						—	—
65-year-old women[j] with nonproliferative or proliferative lesion without atypia on a prior biopsy and no family history of breast cancer													
Annual S	116	24	17	29	16	35	—	—	—	—	—	440	10
Annual S + R	61	79	56	15	30	66	2	NE	NE	< 1	NE	468	6
Annual S + MRI	115	25	18	29	16	36	—	—	—	—	—	1,136	10
Annual S + MRI + R	61	79	56	15	30	66	2	NE	NE	< 1	NE	1,208	6
No S or MRI or R	140	—	—	45	—	—						—	—

NOTE. High-risk women are women with a ≥ 3% 5-year risk of developing breast cancer according to the BCSC risk calculator.

Abbreviations: BCSC, Breast Cancer Surveillance Consortium; DVT, deep vein thrombosis; MRI, magnetic resonance imaging; NE, nonestimable; PE, pulmonary embolism; R, 5 years of risk-reducing medication; S, annual screening mammography with digital breast tomosynthesis till age 74 years; SP, superficial phlebitis; VTE, venous thromboembolism.

[a]Includes both estrogen receptor–positive and estrogen receptor–negative breast cancer.

[b]The difference between the number of invasive breast cancer cases per 1,000 high-risk women who underwent a given strategy and the number of cases per 1,000 high-risk women who did not undergo screening or MRI or risk-reducing medication.

[c]([Difference between the number of invasive breast cancer cases among women who underwent a given strategy and women who did not undergo screening or MRI or risk-reducing medication]/the number of invasive breast cancer cases among women who did not undergo screening, MRI, or risk-reducing medication) × 100.

[d]The difference between the number of breast cancer deaths per 1,000 high-risk women who underwent a given strategy and the number of breast cancer deaths per 1,000 high-risk women who did not undergo screening or MRI or risk-reducing medication.

[e]([Difference between the number of breast cancer deaths in women who underwent a given screening strategy and women who did not undergo screening or risk-reducing medication]/the number of breast cancer deaths in women who did not undergo screening, MRI, or risk-reducing medication) × 100.

[f]The difference between the number of adverse events over 5 years per 1,000 high-risk women treated with risk-reducing medication and the background rate of that event over 5 years per 1,000 high-risk women who did not receive risk-reducing medication. Background rates for venous thromboembolism was 5; DVT was 4; pulmonary embolism was 1; superficial phlebitis was 8; coronary heart disease was 12; stroke was 3; and endometrial cancer was 4 per 1,000 high-risk women over 5 years.

[g]The total number of screens that resulted in additional imaging that did not result in the diagnosis of breast cancer within 12 months. A single woman could experience several false positives on the basis of the number of screens she received in her lifetime. The false positives are based on the specificity of the screening method. Specificity of screening refers to the correct identification of women who do not have breast cancer as negative.

[h]The total number of women who would not have been clinically detected in the absence of screening because of lack of progressive potential or preceding death from competing causes other than breast cancer per 1,000 high-risk women screened.

[i]First-degree relative.

[j]Women age 65 years received biennial screening from age 50 to 64 years before switching to annual screening at age 65 years following a ≥ 3% increase in breast cancer risk according to the BCSC risk calculator.

Current clinical guidelines for high-risk women provide limited information on the basis of individual risk factors or the benefits of adding risk-reducing medication to screening.[44,50] Our results suggest that shared decision making regarding risk-reducing medication and mammography screening should be integrated into clinical guidelines for high-risk women, considering their individual risk factors. In a future study, these model results could be developed into a web-based decision tool to further facilitate shared decision making about risk-reducing drugs and mammography screening in clinical practice.

Several studies have shown that one of the major barriers to the uptake of risk-reducing medication is the concern among women and their clinicians that the risks of therapy will not outweigh its benefits.[24-26] Some of these concerns could be addressed by data on the long-term impact of risk-reducing medication on breast cancer death; combined effects of risk-reducing medication, screening, and MRI; and variation of harms and benefits of these strategies on the basis of individual risk factors. At present, to our knowledge, there is no single data source that could provide all the information needed to quantify the long-term benefits and harms of risk-reducing medication with screening (± MRI) on the basis of individual characteristics. To the best of our knowledge, currently there are no such planned or ongoing trials. In such situations, the Institute of Medicine has recommended mathematical modeling as a virtual laboratory to synthesize existing knowledge and extrapolate results from trials to provide novel data that could help inform clinical guidelines and practice.[51] This study was conducted using a well-established CISNET mathematical model (model G-E), which has been used to inform breast cancer screening guidelines and practice.[28,29,52-55]

Our model results should be considered within the context of the limitations of the data sources and the assumptions used for model development. There were limited data to model the direct effects of risk-reducing medication on breast density. Although studies have shown that risk-reducing medication could reduce breast density,[56] there are limited data on the long-term impact of tamoxifen/AI on changing breast density.[57] A decrease in breast density because of tamoxifen/AI could increase the sensitivity of screening/MRI, which could lead to an early detection of breast cancer and a further reduction in breast cancer death. Therefore, our results could be considered conservative estimates of the impact of risk-reducing drugs on breast cancer death. We also did not have data to model side effects beyond the treatment period or side effects considering medical history. There were limited data on the effects of a shorter duration of risk-reducing tamoxifen/AI in high-risk women. Future studies should explore the dose-response relationship between risk-reducing medication and breast cancer in high-risk women.

Overall, our results show that risk-reducing medication could help avoid breast cancer deaths in high-risk women. To our knowledge, this is the first study to incorporate the current understanding of the long-term trajectory of ER+ breast cancer and emphasize the substantial value of preventing a breast cancer diagnosis with medical risk reduction. These results will enable physicians to counsel patients more effectively about the benefits of risk-reducing medication, and potentially save lives.

AFFILIATIONS

[1]Population and Community Health Sciences Branch, Intramural Research Program, National Institute on Minority Health and Health Disparities, National Institutes of Health, Bethesda, MD
[2]Department of Oncology, Georgetown University Medical Center and Cancer Prevention and Control Program, Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC
[3]Departments of Family and Social Medicine and Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY
[4]Department of Radiology, University of Washington, Seattle Cancer Care Alliance, Seattle, WA
[5]Department of Pediatrics, Harvard Medical School, Boston Children's Hospital, Boston, MA
[6]Kaiser Permanente Washington Health Research Institute, Seattle, WA
[7]Department of Population Medicine, Harvard Medical School, Harvard Pilgrim Healthcare Institute, Boston, MA
[8]Departments of Medicine and of Epidemiology and Population Health, Stanford University School of Medicine, Stanford, CA

CORRESPONDING AUTHOR

Jinani Jayasekera, PhD, Health Equity and Decision Sciences Research Laboratory, Population and Community Health Sciences Branch, Intramural Research Program, National Institute on Minority Health and Health Disparities, National Institutes of Health, 2 White Flint North, C09, Bethesda, MD 20892; e-mail: jinani.jayasekera@nih.gov.

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A.W.K. and C.I. contributed equally to this work.

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AUTHOR CONTRIBUTIONS

Conception and design: Jinani Jayasekera, Kathryn Lowry, Jeanne Mandelblatt, Allison W. Kurian, Claudine Isaacs
Collection and assembly of data: Jinani Jayasekera, Amy Zhao
Data analysis and interpretation: Jinani Jayasekera, Amy Zhao, Clyde Schechter, Jennifer M. Yeh, Karen J. Wernli, Natasha Stout, Jeanne Mandelblatt, Allison W. Kurian, Claudine Isaacs
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Reassessing the Benefits and Harms of Risk-Reducing Medication Considering the Persistent Risk of Breast Cancer Mortality in Estrogen Receptor–Positive Breast Cancer

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Suzanne O'Neill
Research Funding: Pfizer

Allison W. Kurian
Research Funding: Myriad Genetics (Inst)
Other Relationship: Ambry Genetics, Color Genomics, GeneDx/BioReference, InVitae, Genentech

Claudine Isaacs
Consulting or Advisory Role: Pfizer, Genentech/Roche, Novartis, Puma Biotechnology, Seattle Genetics, Sanofi/Aventis, Eisai, Ion Solutions, bioTheranostics, AstraZeneca/MedImmune, Gilead Sciences
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