# A simulation modeling study to support personalized breast cancer prevention and early detection in high-risk women

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## Introduction

- Majority of women who develop breast cancer in the US are diagnosed with estrogen receptor positive (ER+) tumors.[1]
- A landmark clinical trial in 1998 demonstrated that risk-reducing medication can prevent up to 50% of ER+ breast cancer among high-risk women.[2]
- There are no other prevention interventions with this magnitude of effect on avoiding breast cancer.
- Despite this, use of risk reducing medication in clinical practice has been low.[3,4]
- Current clinical guidelines for women with a 3% or greater 5-year risk of developing breast cancer (known as "high risk") include a five-year course of risk-reducing medication such as tamoxifen and aromatase inhibitors.[5]
- In addition, these women may undergo annual screening starting at age 30 and supplemental screening with magnetic resonance imaging [MRI].
- Each of these choices has a different profile of benefits and harms that may depend on individual risk factors such as age, breast density, family history and prior biopsy.

## Purpose

- The overarching goal of this study was to evaluate the impact of early detection with screening and primary prevention with risk-reducing medication to provide personalized data that will help identify women who are more likely to benefit from various interventions or combinations of interventions with the least harms.

## Methods and Materials

- We adapted the Cancer Intervention and Surveillance Modeling Network (CISNET) microsimulation model G-E of breast cancer natural history to evaluate the harms and benefits of annual mammography and risk reducing medication among high-risk women (i.e., with a 5-year risk >= 3%).
- Model G-E is a discrete event microsimulation model that follows millions of women from birth to death and captures the variability in distributions of events.
- Each simulated woman is assigned a cohort-specific life expectancy which is used to select a date of breast cancer death or other cause death.
- For this study, we dynamically updated the risk of developing breast cancer for each simulated woman based on her family history, breast density, age and history of biopsy.
- We used large observational and clinical trial data to derive input parameters for cohort-specific birth rates, incidence and stage without screening, other cause mortality by age, screening performance (sensitivity/specificity), survival by age, stage, and subtype without treatment, treatment efficacy, and other cause mortality.
- Model outcomes for each strategy included, the benefits of risk-reducing drugs (avoiding breast cancer) and screening with Digital breast tomosynthesis (DBT) (breast cancer stage, breast cancer-specific survival), and harms of screening (false positives, overdiagnosis). We also conducted sensitivity analysis to estimate the effects of uncertainty in model inputs or assumptions on results.

## Results

Table 1. Benefits and Harms of Risk Reducing Medication and Breast Cancer Screening Strategies for Women at High-risk of Developing Breast Cancer

| Strategy | Screening/Risk Reducing Medication Outcomes Per 1000 Women Screened (vs. No Screening/No Risk Reducing Medication) | | | | | | | | | | | Benefit to Harm Ratio | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Benefits | | | | Harms | | | | | | | | |
| | | | | | | | Side Effects of Risk Reducing Medication for Five-years: Number of events per 1000 women screened | | | | | | |
| | LYG per 1000 | Change in Invasive Breast Cancers Detected | Change in Stage IV Breast Cancers Detected | Breast Cancer Deaths Averted | False Positives | Overdiagnoses | Venous Thromboembolism | Deep Vein Thrombosis, Pulmonary Embolism, and Superficial Phlebitis | Coronary Heart Disease | Stroke | Endometrial cancer | LYG per 1000 mammograms | LYG per Overdiagnosis |
| **Annual S (35,89)** | 1606 | -57 | -23 | -77 | 3696 | 31 | - | - | - | - | - | 41 | 53 |
| **Annual S + C (35,89)** | 1829 | -123 | -23 | -87 | 3881 | 24 | 10 | 6 | 12 | 5 | 8 | 44 | 76 |
| **Annual S (40,89)** | 1569 | -64 | -22 | -76 | 3112 | 30 | - | - | - | - | - | 45 | 52 |
| **Annual S (35,74)** | 1549 | -110 | -17 | -69 | 3255 | 18 | - | - | - | - | - | 46 | 86 |
| **Annual S + C (40,89)** | 1758 | -129 | -23 | -86 | 3279 | 23 | 14 | 9 | 17 | 7 | 12 | 48 | 76 |
| **Annual S (45,89)** | 1489 | -76 | -21 | -74 | 2548 | 29 | - | - | - | - | - | 50 | 52 |
| **Annual S + C (35,74)** | 1790 | -163 | -19 | -82 | 3378 | 14 | 10 | 6 | 12 | 5 | 8 | 51 | 128 |
| **Annual S + C (45,89)** | 1656 | -138 | -22 | -83 | 2692 | 22 | 23 | 14 | 28 | 11 | 20 | 52 | 75 |
| **Annual S (40,74)** | 1516 | -118 | -17 | -69 | 2673 | 17 | - | - | - | - | - | 53 | 89 |
| **Annual S + C (40,74)** | 1716 | -168 | -19 | -81 | 2778 | 13 | 14 | 9 | 17 | 7 | 12 | 58 | 132 |
| **Annual S (45,74)** | 1435 | -130 | -16 | -66 | 2107 | 16 | - | - | - | - | - | 60 | 90 |
| **Annual S + C (45,74)** | 1617 | -177 | -18 | -78 | 2194 | 12 | 23 | 14 | 28 | 11 | 20 | 65 | 135 |
| **Biennial S (35,89)** | 1497 | -60 | -21 | -72 | 1886 | 28 | - | - | - | - | - | 74 | 54 |
| **Biennial S + C (35,89)** | 1753 | -125 | -22 | -84 | 1979 | 22 | 10 | 6 | 12 | 5 | 8 | 82 | 81 |
| **Biennial S (40,89)** | 1464 | -68 | -20 | -70 | 1578 | 26 | - | - | - | - | - | 83 | 56 |
| **Biennial S (35,74)** | 1441 | -117 | -15 | -65 | 1651 | 10 | - | - | - | - | - | 85 | 144 |
| **Biennial S + C (40,89)** | 1685 | -132 | -21 | -82 | 1659 | 21 | 14 | 9 | 17 | 7 | 12 | 90 | 82 |
| **Biennial S (45,89)** | 1413 | -77 | -19 | -69 | 1309 | 26 | - | - | - | - | - | 92 | 55 |
| **Biennial S (40,74)** | 1421 | -118 | -16 | -64 | 1372 | 16 | - | - | - | - | - | 96 | 89 |
| **Biennial S + C (35,74)** | 1715 | -168 | -18 | -79 | 1711 | 13 | 10 | 6 | 12 | 5 | 8 | 98 | 132 |
| **Biennial S + C (45,89)** | 1606 | -139 | -21 | -80 | 1383 | 20 | 23 | 14 | 28 | 11 | 20 | 99 | 80 |
| **Biennial S + C (40,74)** | 1653 | -169 | -18 | -78 | 1426 | 13 | 14 | 9 | 17 | 7 | 12 | 108 | 130 |
| **Biennial S (45,74)** | 1361 | -134 | -14 | -62 | 1075 | 14 | - | - | - | - | - | 113 | 96 |
| **Biennial S + C (45,74)** | 1564 | -181 | -17 | -75 | 1117 | 11 | 23 | 14 | 28 | 11 | 20 | 125 | 140 |

## Discussion

- Any screening strategy with risk-reducing medication provide relatively higher reductions in invasive breast cancers detected compared to screening alone.
- Biennial screening with DBT, starting screening at age 45 and stopping at age 74, with risk reducing medication had the lowest side-effects per 100,000 women screened, highest life-years gained per 1000 mammograms and life-years gained per overdiagnosis.
- Annual screening starting at 35 and stopping at 89 years had the lowest benefit to harm ratio; and adding risk reducing medication to this strategy produced the highest number of events associated with side effects per 100,000 women screened.

## Conclusions

Simulation modeling is useful in assessing the relative benefits and harms of screening and risk reducing medication in high-risk women.

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