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Collaborative Modeling to Compare Different Breast Cancer Screening Strategies

A Decision Analysis for the US Preventive Services Task Force

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IMPORTANCE The effects of breast cancer incidence changes and advances in screening and treatment on outcomes of different screening strategies are not well known.

OBJECTIVE To estimate outcomes of various mammography screening strategies.

DESIGN, SETTING, AND POPULATION Comparison of outcomes using 6 Cancer Intervention and Surveillance Modeling Network (CISNET) models and national data on breast cancer incidence, mammography performance, treatment effects, and other-cause mortality in US women without previous cancer diagnoses.

EXPOSURES Thirty-six screening strategies with varying start ages (40, 45, 50 years) and stop ages (74, 79 years) with digital mammography or digital breast tomosynthesis (DBT) annually, biennially, or a combination of intervals. Strategies were evaluated for all women and for Black women, assuming 100% screening adherence and "real-world" treatment.

MAIN OUTCOMES AND MEASURES Estimated lifetime benefits (breast cancer deaths averted, percent reduction in breast cancer mortality, life-years gained), harms (false-positive recalls, benign biopsies, overdiagnosis), and number of mammograms per 1000 women.

RESULTS Biennial screening with DBT starting at age 40, 45, or 50 years until age 74 years averted a median of 8.2, 7.5, or 6.7 breast cancer deaths per 1000 women screened, respectively, vs no screening. Biennial DBT screening at age 40 to 74 years (vs no screening) was associated with a 30.0% breast cancer mortality reduction, 1376 false-positive recalls, and 14 overdiagnosed cases per 1000 women screened. Digital mammography screening benefits were similar to those for DBT but had more false-positive recalls. Annual screening increased benefits but resulted in more false-positive recalls and overdiagnosed cases. Benefit-to-harm ratios of continuing screening until age 79 years were similar or superior to stopping at age 74. In all strategies, women with higher-than-average breast cancer risk, higher breast density, and lower comorbidity level experienced greater screening benefits than other groups. Annual screening of Black women from age 40 to 49 years with biennial screening thereafter reduced breast cancer mortality disparities while maintaining similar benefit-to-harm trade-offs as for all women.

CONCLUSIONS This modeling analysis suggests that biennial mammography screening starting at age 40 years reduces breast cancer mortality and increases life-years gained per mammogram. More intensive screening for women with greater risk of breast cancer diagnosis or death can maintain similar benefit-to-harm trade-offs and reduce mortality disparities.

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Since 2009, the US Preventive Services Task Force (USPSTF) has recommended biennial mammography screening at ages 50 to 74 years, with clinical recommendations for discussion between patients and their primary care clinicians about individual risks and preferences for starting screening before age 50.[1,2] The USPSTF concluded in 2016 that the evidence was insufficient to assess the benefits and harms of digital breast tomosynthesis (DBT) as a primary screening method. In contrast to digital mammography, which uses a single radiograph projection per view, DBT involves multiple projections that are used to construct image slices, reducing tissue overlap. Screening facilities have been transitioning from digital mammography to DBT because of lower false-positive recall rates and higher cancer detection rates for DBT compared with digital mammography,[3,4] even though data do not show a reduction in rates of advanced cancer diagnosis.[5,6] Other changes since the 2016 recommendation include increasing breast cancer incidence among younger women and advances in treatment.[7] Importantly, Black and African American women (hereafter referred to as Black women) continue to experience higher breast cancer mortality than White women despite similar rates of mammography screening and lower (but steadily increasing) rates of breast cancer incidence.[8] The impact of these new data on the net benefit of screening mammography is unknown.

Population simulation models are a valuable tool for synthesizing evidence from observational and trial data to estimate the impact of different screening strategies. We used well-established Cancer Intervention and Surveillance Modeling Network (CISNET) models to estimate the benefits and harms of breast cancer screening strategies that varied by the ages to start and stop screening, modality, and interval for women overall and for Black women, including the impact of screening strategies on breast cancer mortality disparities for Black women. The results are provided to inform discussions about US breast cancer screening strategies by the USPSTF and other groups.

Key Points

Question What are the benefits and harms of different screening mammography strategies?

Findings Six validated CISNET models found that, compared with no screening, biennial mammography screening with digital breast tomosynthesis from age 40 to 74 yielded a median of 8.2 breast cancer deaths averted per 1000 women screened, equal to a 30% reduction in breast cancer mortality, and 165 life-years gained, 1376 false-positive recalls, 201 benign biopsies, and 14 overdiagnosed cases per 1000 women screened. For each strategy, benefits were larger for Black women than for all women.

Meaning Biennial mammography from ages 40 to 74 years has favorable benefit-to-harm tradeoffs.

Methods

Model Overview

Six CISNET breast cancer models were used to estimate benefits and harms of mammography screening: Dana-Farber Cancer Institute (model D), Erasmus University Medical Center (model E), Georgetown Lombardi Comprehensive Cancer Center-Albert Einstein College of Medicine (model GE), University of Texas MD Anderson Cancer Center (model M), Stanford University (model S), and University of Wisconsin-Madison–Harvard Medical School (model W). These models were included in the 2 previous decision analyses conducted for the USPSTF.[9,10] Since the 2016 analysis, the models have incorporated several updates to inputs including screening performance characteristics for digital mammography and DBT, current breast cancer incidence trends, updated breast cancer stage and hormone receptor distributions, "real-world" treatment assignment and effects for women overall and for Black women. Detailed descriptions of each model are available elsewhere[11-17] and in an online technical report.[18] The University of Wisconsin Health Sciences institutional review board determined that this study was not human subjects research.

Population for Analysis

These analyses modeled a single cohort of US women with no personal history of breast cancer born in 1980 (ie, age 40 years in 2020) excluding women at the highest risk (ie, genetic susceptibility mutations or chest radiation at a young age). The models began with women at birth or age 20 or 25 years (since breast cancer is rare before this age; the initiation age varied by model) and accumulated all outcomes until death. The models evaluated women overall and Black women, and strata according to breast density, elevated risk, or comorbidity level. The term "women" was used while recognizing that not all individuals eligible for mammography screening self-identify as women.[19] Since model results are based on data for sex (ie, female) rather than gender identity, models apply to cisgender women and may not accurately reflect breast cancer risk for transgender men and nonbinary persons. This modeling analysis treated race as a social construct and aimed to provide evidence regarding the trade-offs of mammography screening strategies for self-identified Black women as an approach to reduce the observed disparities in breast cancer mortality.[20]

Model Input Parameters

All 6 models used a common set of data inputs for women overall and 4 models included race-specific inputs for Black women for breast cancer incidence, breast density, digital mammography and DBT performance, treatment assignment and efficacy, and causes of death other than breast cancer (**Table 1**).[18] In addition, model-specific parameters were used to represent preclinical detectable times, lead-time, and age- and estrogen receptor (ER)/human epidermal growth factor receptor 2 (HER2)–specific stage distribution in screen-detected vs non–screen-detected cases on the basis of each model's structure.

Five of the 6 models adapted an age-period-cohort modeling approach to estimate breast cancer incidence in the absence of screening among the overall and Black female population[21,22]; model M used Surveillance, Epidemiology, and End Results (SEER) rates with a linear model based on rates in 1975 and calibrated over time.[12] Incidence was increased for subgroups with elevated risk or with greater breast density. Density was modeled by Breast Imaging Reporting and Data Systems (BI-RADS) categories: almost entirely fatty ("a"), scattered fibroglandular densities ("b"), heterogeneously dense ("c"), and extremely

Table 1. Common CISNET Breast Cancer Model Input Parameters

Input	Description	Updated since 2016	Race-specific	Source[a]
Breast cancer incidence without screening	Age-period-cohort model using SEER breast cancer incidence with a period effect for mammography removed	Yes (recent years added, 1980 instead of 1970 birth cohort)	Yes; incidence varied by race Same data source	Gangnon et al,[21] 2015 Holford et al,[22] 2006
Breast density	Prevalence of breast density (BI-RADS a, b, c, d) by age group (40-44, 45-49, 50-64, 65-74, 75-89 y)	Yes	Yes; density varied by race Same data source	BCSC[18]
Mammography performance[b]	Sensitivity and false-positive recall of initial and subsequent mammography by age (40-44, 45-49, 50-64, ≥65 y), screening interval (annual, biennial), and density (BI-RADS a,b,c,d) for digital mammography and DBT	Yes	Screening sensitivity did not vary by race False-positive recalls did vary by race Same data source	BCSC (Kerlikowske et al,[6] 2022)
Breast cancer stage distribution (AJCC or SEER Summary Stage)	Stage distributions by mode of detection, age group (40-44, 45-49, 50-64, 65-74, 75-89 y), screening round/interval (first, annual, biennial) for screen-detected cancers, and density (BI-RADS a, b, c, d)	Yes	Yes; stage distributions varied by race Same data source	BCSC[18]
ER/HER2 joint distribution	The distribution of ER/HER2 subtypes by age (40-49, 50-74, 75-89 y) and stage at diagnosis	Yes	Yes; subtype distributions varied by race Same data source	BCSC[18]
Survival in the absence of screening and treatment	25-y breast cancer survival by joint ER/HER2 status, age group, AJCC/SEER stage, or tumor size	No	No; base survival did not vary by race	Munoz and Plevritis,[23] 2018 Plevritis et al,[24] 2018
Treatment dissemination	Treatments and rates of use by time period, ER/HER2, stage and age for initial breast cancer diagnosis	Yes	No; treatment assignment did not vary by race	Caswell-Jin et al,[25] 2018 Mandelblatt et al,[26] 2018 Plevritis et al,[24] 2018
Treatment effects	Meta-analyses of clinical trial results by ER/HER2 for initial local therapy; clinical trial reports for efficacy of systemic primary and metastatic therapy, and of newer targeted therapies	Yes	Yes; treatment effectiveness reduced for Black patients based on published NCCN data[27]	Caswell-Jin et al,[25] 2018 Early Breast Cancer Trialists' Collaborative,[28-33] Plevritis et al,[24] 2018 Warner et al,[27] 2015
Other-cause mortality	Age- and cohort-specific mortality rates from non-breast cancer causes by year and level of comorbidity	Yes	Yes; other-cause mortality rates varied by race Same data source	Cho et al,[34] 2013 Gangnon et al,[35] 2018 Lansdorp-Vogelaar et al,[36] 2014
Quality of life	Utility weights for general health and decrements for screening, diagnostic evaluation, and stage-specific treatment	No	No; utility weights did not vary by race	de Haes et al,[37] 1991 Hamner and Kaplan,[38] 2016 Hamner et al,[38] 2006 Stout et al,[39] 2006

Abbreviations: AJCC, American Joint Committee on Cancer; BCSC, Breast Cancer Surveillance Consortium; BI-RADS, Breast Imaging Reporting and Data Systems; CISNET, Cancer Intervention and Surveillance Modeling Network; DBT, digital breast tomosynthesis; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; NCCN, National Comprehensive Cancer Network; SEER, Surveillance, Epidemiology, and End Results.

[a] Additional information regarding model inputs including BCSC data are available in the online Technical Report.[18]

[b] With treatment, screen detection of breast cancer at an earlier stage could lead to improve survival, reduced risk of death, and/or greater chance of cure with a small tumor size, depending on model.

dense ("d").[40] Density category was assigned at age 40 years and remained the same or decreased by 1 level at age 50 years and again at age 65, based on observed age-specific prevalence rates in the Breast Cancer Surveillance Consortium (BCSC).[18] Density was related to breast cancer risk and screening performance but was assumed to not affect molecular subtype or disease natural history (eg, tumor growth rates). Models incorporated screening sensitivity applied to each mammogram a woman received. Age-specific sensitivity values for digital mammography and DBT (hereafter referred to collectively as mammography) overall and by density category were also based on data from the BCSC.[18] Data for the BCSC reflects breast imaging in community practice across the US.[41]

With treatment, screen detection at an earlier stage could lead to improved survival, reduced risk of death, and/or greater chance of cure with a smaller tumor size, depending on model. Treatment was assigned based on age, stage, and molecular subtype. To reflect real-world patterns of breast cancer care, the probability of receiving specific types of systemic treatment was based on data from the National Comprehensive Cancer Network as previously reported and, for newer therapies, expert opinion.[25,26] Efficacy of systemic therapy was based on the most recent published meta-analysis of clinical trials and, for newer therapies, clinical trial reports[28,29]; treatment efficacy (in the setting of optimal stage–based and tumor subtype–based treatment) was assumed to be equal by race.[42] In contrast to efficacy, treatment effectiveness was modeled as lower for Black women due to multiple factors that may arise from systemic racism and lead to worse treatment quality (eg, delayed initiation, suboptimal regimens, dose reductions, and incomplete cycles).[43-46] Based on published data, treatment benefit was therefore reduced by 28% for ER-negative tumors and 56% for ER-positive tumors in models restricted to Black women.[27]

Probability of death from non–breast cancer causes was derived from Centers for Disease Control and Prevention (CDC) Wide-ranging Online Data for Epidemiologic Research (WONDER) and the Human Mortality Database; these values were replaced by comorbidity-specific values in subgroup analyses.[35,36]

Screening Strategies

We compared model results for 36 mammography screening scenarios that varied by modality (digital mammography or DBT performed with concurrent or synthetic digital mammography),[47-52] starting age (40, 45, or 50 years) and stopping age (74 or 79 years), and interval (annual, biennial, or hybrid intervals). The 3 hybrid screening scenarios were (1) annual from ages 40 to 49 then biennial at age 50; (2) annual from ages 45 to 54 then biennial at age 55; and (3) annual from ages 45 to 49 then biennial at age 50. The models assumed 100% adherence to screening.

Outcomes

Benefits included percent reduction in breast cancer mortality, breast cancer deaths averted, and life-years gained (LYG) over the lifetimes of 1000 women screened compared with no screening. We also examined quality-adjusted life-years (QALYs) gained, which were calculated using age-specific utilities for women in the general population,[38,53] with disutilities applied for undergoing screening, diagnostic evaluation, and breast cancer treatment based on the stage at diagnosis (eTable 1 in the Supplement[37,39]).

Harms accumulated over the lifetime included recalls for additional imaging in women without cancer (hereafter referred to as false-positive recalls), benign results from biopsies recommended for findings on screening mammography (hereafter referred to as benign biopsies), and overdiagnosed cases of ductal carcinoma in situ (DCIS) and invasive breast cancer. Overdiagnosis was defined as the excess breast cancer cases diagnosed in the presence of screening that were not diagnosed in the absence of screening over the lifetime. The harm of overtreatment after overdiagnosis was captured by the treatment-related decrement in utility without a change in life expectancy.

Analysis

Outcomes were tallied from age 40 years (the youngest age to start screening across strategies) to death and expressed per 1000 women. Results were summarized by the median and range across models for each outcome. We also generated efficiency frontiers by plotting the sequence of strategies that represented the largest incremental percent breast cancer mortality reduction (or LYG) per mammogram performed. Screening strategies on this frontier were considered the most efficient (ie, no alternative existed that provided equal or greater benefit with fewer screens or harms). Because a strategy providing outcomes that was very similar to an efficient strategy may be still be considered by decision-makers for other reasons (eg, consistency of starting and stopping ages across screening modalities),[54] we also identified "near-efficient" strategies[55] defined as a strategy within 5% of the value for screening biennially from ages 50 to 74 with DBT. Strategies that had more harms and/or fewer benefits were referred to as "inferior" to (inefficient or dominated by) other strategies.

Analyses were repeated for Black women and for strata according to density category, elevated relative risk of breast cancer, or comorbidity level.

In sensitivity analyses, for comparison with previous modeling in 2009 and 2016, we repeated the analysis assuming all women with cancer received the most effective therapy (vs the real-world patterns used in the primary analyses).

Results

Screening Strategies for the Overall Population

The 6 models produced consistent results for the screening strategies (eTables 2 and 3 in the Supplement). For instance, biennial screening with DBT from ages 40 to 74 years yielded a median 30.0% (range, 24.0%-33.7%) reduction in breast cancer mortality vs no screening, with 1376 (range, 1354-1384) false-positive recalls per 1000 women screened (**Table 2**). Compared with biennial screening with DBT from ages 50 to 74 years, starting at age 40 averted 1.3 (range, 0.9-3.2) additional breast cancer deaths, with 503 (range, 493-506) additional false-positive recalls, 65 (range, 62-66) additional benign biopsies, and 2 (range, 0-4) more overdiagnosed cases per 1000 women screened (**Table 3**).

Annual screening led to greater reductions in mortality than biennial strategies, with a 37.0% median reduction (range, 33.6%-38.9%) (Table 2) with screening annually from ages 40 to 74 years with DBT but resulted in more false-positive recalls, benign biopsies, and overdiagnosed cases.

With biennial screening from ages 40 to 74 years, digital mammography resulted in 1540 false-positive recalls and 210 benign biopsies per 1000 women screened vs 1376 and 201, respectively, with DBT (Table 2). Use of DBT instead of digital mammography further decreased breast cancer mortality by approximately 1 percentage point and averted less than 1 additional breast cancer death per 1000 women and reduced false-positive recalls by approximately 150-300 per 1000 women over their lifetimes among 9 screening strategies stopping at age 74 (eTable 4 in the Supplement).

Stopping screening at age 79 vs 74 years generally resulted in an additional 3- to 5-percentage point mortality reduction, 1 additional breast cancer death averted, 64 to 172 more false-positive recalls per 1000 women, and 2 to 4 additional overdiagnosed cases, depending on strategy (eTable 5 in the Supplement).

Among all possible strategies, 5 DBT screening strategies were identified as efficient or near-efficient for both percent mortality reduction and LYG in at least 5 of 6 models, including one with stopping age 74 years (biennial starting at age 50) and 4 with stopping age 79 (biennial starting at age 40; biennial starting at age 45; annual from ages 40 to 49 with biennial thereafter; and annual starting at age 40) (**Figure 1**; eFigures 1 and 2 and eTable 6 in the Supplement). Efficient strategies ranged from 1.7 to 4.3 more breast cancer deaths averted and 41 to 168 more benign biopsies than screening biennially from ages 50 to 74 years per 1000 women (**Figure 2**). Five similar strategies were identified as efficient when limited to the 18 options with stopping age 74 (biennial starting at age 40, biennial starting at age 45, biennial starting at age 50, annual at ages 40 to 49 with biennial at ages 50 to 74, and annual at ages 40 to 74; eFigure 3 in the Supplement).

Screening Strategies for Black Women

Seven screening strategies were efficient or near-efficient for LYG or breast cancer mortality reduction among Black women (Figure 1; eFigures 4 and 5 and eTable 7 in the Supplement). Three strategies were efficient or near-efficient for both metrics among most models, including biennial from ages 40 to 79 years, biennial from ages 45 to 79, and annual from ages 40 to 79. Expanding biennial screening with DBT from ages 50 to 74 to ages 40 to 74 or 79 averted

Table 2. Median Lifetime Benefits and Harms (and Range Across Models) of Mammography Screening Strategies per 1000 Women Screened Compared With No Screening According to Screening Modality, Interval, Starting Age, and Stopping Age

Strategy, start/stop years	Mammograms	Median lifetime benefits			Median lifetime harms		
		Breast cancer mortality reduction, %	Breast cancer deaths averted	Life-years gained	False-positive recalls	Benign biopsies	Overdiagnosed cases[a]
Digital mammography until age 74 y[b]							
Biennial							
50-74	11 192 (10 999-11 278)	24.3 (18.3-27.5)	6.9 (4.8-8.6)	114.6 (109.8-165.0)	1021 (1003-1027)	148 (146-149)	10 (4-29)
45-74	13 283 (13 078-13 380)	26.4 (20.4-29.3)	7.8 (5.1-9.2)	140.0 (125.0-187.7)	1230 (1212-1238)	173 (170-174)	11 (4-30)
40-74	16 092 (15 863-16 215)	28.4 (22.3-31.7)	8.4 (5.6-10.1)	170.1 (141.2-214.1)	1540 (1520-1551)	210 (207-212)	12 (4-33)
Hybrid							
Annual, 45-49; biennial, 50-74	15 992 (15 807-16 164)	29.3 (22.4-30.5)	8.6 (5.7-9.6)	151.3 (140.8-194.5)	1416 (1400-1430)	189 (187-191)	19 (4-33)
Annual, 45-54; biennial, 55-74	18 006 (17 804-18 197)	29.3 (23.0-30.2)	8.8 (5.8-9.4)	159.3 (148.6-195.5)	1514 (1497-1530)	195 (193-197)	19 (4-33)
Annual, 40-49; biennial, 50-74	20 898 (20 705-21 133)	31.7 (24.4-33.1)	9.3 (6.2-10.7)	178.9 (161.9-234.6)	1896 (1879-1916)	236 (234-239)	21 (4-35)
Annual							
50-74	21 439 (21 010-21 650)	29.4 (24.7-31.7)	9.2 (6.8-9.5)	153.2 (134.0-181.4)	1543 (1513-1557)	192 (188-194)	16 (5-39)
45-74	26 272 (25 776-26 526)	33.4 (29.8-35.4)	10.4 (7.5-11.8)	187.3 (163.6-230.1)	1943 (1907-1960)	233 (229-235)	18 (5-43)
40-74	31 178 (30 649-31 493)	35.2 (31.8-37.6)	11.0 (8.0-13.1)	208.7 (200.7-275.5)	2423 (2385-2446)	281 (276-283)	19 (5-45)
Digital mammography until age 79 y							
Biennial							
50-79	12 456 (12 223-12 560)	26.9 (22.2-30.2)	7.9 (5.6-9.4)	122.7 (118.5-172.8)	1105 (1084-1113)	160 (157-161)	12 (6-34)
45-79	15 176 (14 907-15 297)	31.7 (24.8-33.3)	8.9 (6.3-11.9)	145.6 (137.8-202.5)	1356 (1333-1366)	191 (187-192)	14 (6-37)
40-79	17 354 (17 081-17 494)	32.9 (25.3-34.9)	9.1 (6.4-12.3)	176.8 (149.8-233.9)	1624 (1601-1636)	222 (219-223)	14 (6-37)
Hybrid							
Annual, 45-49; biennial, 50-79	17 242 (17 026-17 443)	31.8 (25.4-33.1)	9.4 (6.4-11.7)	156.7 (149.5-209.4)	1499 (1481-1516)	200 (198-203)	22 (6-37)
Annual, 45-54; biennial, 55-79	19 876 (19 627-20 112)	33.9 (27.5-34.2)	10.0 (6.9-12.4)	168.8 (158.7-217.2)	1639 (1618-1658)	213 (210-215)	24 (6-40)
Annual, 40-49; biennial, 50-79	22 150 (21 921-22 412)	34.9 (27.4-36.2)	10.1 (6.9-13.1)	187.9 (170.5-257.0)	1979 (1960-2002)	248 (245-251)	24 (6-40)
Annual							
50-79	24 563 (24 014-24 831)	33.7 (32.1-35.8)	10.5 (7.9-12.2)	172.7 (145.8-192.7)	1716 (1678-1733)	212 (208-214)	19 (7-46)
45-79	29 389 (28 767-29 702)	38.1 (35.1-39.5)	11.6 (8.9-14.8)	202.9 (172.0-256.1)	2115 (2072-2136)	253 (248-256)	21 (7-50)
40-79	34 289 (33 633-34 667)	41.7 (37.2-42.9)	12.2 (9.4-16.1)	224.3 (211.4-300.6)	2595 (2550-2621)	301 (295-304)	23 (7-52)
Digital breast tomosynthesis until age 74 y[c]							
Biennial							
50-74	11 208 (10 976-11 278)	25.4 (18.8-29.4)	6.7 (5.1-9.2)	120.8 (115.1-175.8)	873 (855-878)	136 (133-137)	12 (4-33)
45-74	13 299 (13 051-13 380)	27.5 (21.7-31.2)	7.5 (5.5-9.8)	141.3 (133.9-200.1)	1080 (1061-1086)	164 (161-165)	13 (4-34)
40-74	16 116 (15 826-16 214)	30.0 (24.0-33.7)	8.2 (6.1-10.6)	165.2 (152.4-221.9)	1376 (1354-1384)	201 (198-203)	14 (4-37)
Hybrid							
Annual, 45-49; biennial, 50-74	16 053 (15 775-16 164)	29.5 (23.9-32.5)	8.0 (6.0-10.2)	153.5 (146.3-207.2)	1242 (1221-1250)	184 (180-185)	19 (4-37)
Annual, 45-54; biennial, 55-74	18 072 (17 772-18 197)	29.9 (24.4-32.1)	8.2 (6.2-10.0)	161.1 (148.2-207.9)	1317 (1296-1326)	193 (189-194)	20 (4-37)
Annual, 40-49; biennial, 50-74	20 979 (20 662-21 133)	32.2 (26.1-34.4)	8.8 (6.6-11.0)	181.2 (163.9-240.1)	1691 (1667-1703)	238 (233-240)	21 (4-39)

(continued)

Table 2. Median Lifetime Benefits and Harms (and Range Across Models) of Mammography Screening Strategies per 1000 Women Screened Compared With No Screening According to Screening Modality, Interval, Starting Age, and Stopping Age (continued)

Strategy, start/stop years	Mammograms	Median lifetime benefits			Median lifetime harms		
		Breast cancer mortality reduction, %	Breast cancer deaths averted	Life-years gained	False-positive recalls	Benign biopsies	Overdiagnosed cases[a]
Annual							
50-74	21 500 (20 963-21 650)	30.6 (24.7-32.8)	8.6 (7.0-10.1)	155.6 (137.1-191.7)	1277 (1246-1285)	186 (182-187)	18 (5-42)
45-74	26 349 (25 716-26 526)	34.1 (31.4-36.5)	9.7 (7.9-11.8)	193.3 (165.7-230.1)	1647 (1610-1657)	234 (229-235)	20 (5-46)
40-74	31 273 (30 572-31 492)	37.0 (33.6-38.9)	10.3 (8.5-13.1)	216.6 (190.1-274.9)	2096 (2055-2110)	288 (283-290)	21 (5-48)
Digital breast tomosynthesis until age 79 y							
Biennial							
50-79	12 488 (12 193-12 560)	28.0 (23.6-32.2)	7.6 (6.0-10.1)	129.3 (119.6-184.1)	937 (916-943)	144 (141-145)	14 (6-38)
45-79	15 218 (14 871-15 297)	32.1 (26.5-35.5)	8.6 (6.7-12.1)	153.4 (147.7-213.1)	1176 (1153-1183)	176 (173-177)	16 (6-41)
40-79	17 397 (17 037-17 494)	33.3 (27.2-36.5)	8.9 (6.9-12.5)	173.9 (161.7-237.8)	1440 (1415-1449)	210 (206-211)	17 (6-42)
Hybrid							
Annual, 45-49; biennial, 50-79	17 325 (16 987-17 443)	32.5 (27.2-35.3)	8.9 (6.9-11.9)	160.5 (152.8-215.4)	1306 (1282-1315)	192 (188-193)	22 (6-42)
Annual, 45-54; biennial, 55-79	19 980 (19 585-20 112)	34.1 (29.2-36.4)	9.2 (7.4-12.6)	172.7 (161.0-220.8)	1413 (1387-1423)	205 (202-207)	24 (6-44)
Annual, 40-49; biennial, 50-79	22 255 (21 870-22 412)	35.3 (29.4-37.2)	9.5 (7.4-13.3)	188.7 (173.4-260.1)	1755 (1728-1768)	247 (242-248)	24 (6-44)
Annual							
50-79	24 687 (23 953-24 831)	34.5 (32.6-36.9)	9.8 (8.0-12.2)	173.2 (148.2-203.6)	1405 (1367-1417)	202 (197-204)	22 (7-50)
45-79	29 517 (28 692-29 701)	39.1 (37.1-40.8)	10.9 (9.0-14.8)	207.1 (176.1-255.8)	1774 (1730-1789)	250 (244-252)	24 (7-54)
40-79	34 441 (33 538-34 666)	41.7 (39.2-43.0)	11.5 (9.9-16.1)	229.7 (200.4-300.7)	2224 (2175-2240)	304 (298-307)	25 (7-56)

[a] Overdiagnosed cases are in situ and invasive breast cancer cases that would not have been clinically detected in the absence of screening. Overdiagnosis is calculated by subtracting the number of cases detected in the screening scenario from the number of cases detected in the no-screening scenario. Model S (Stanford University) is excluded because it does not include ductal carcinoma in situ.

[b] Digital mammography strategies show results for models D (Dana-Farber Cancer Institute), E (Erasmus Medical Center), GE (Georgetown Lombardi Comprehensive Cancer Center-Albert Einstein College of Medicine), M (University of Texas MD Anderson Cancer Center), and W (University of Wisconsin-Madison and Harvard Pilgrim Health Care Institute).

[c] Digital breast tomosynthesis strategies show results for models D, E, GE, M, S, and W.

a median of 1.8 and 3.0 additional breast cancer deaths across models, respectively (Figure 2).

Trade-offs between benefits and harms of different screening strategies for Black women followed similar patterns as for all women combined (eTables 8-10 in the Supplement). All strategies resulted in more breast cancer deaths averted and LYG for Black women compared with the same strategies for women overall. However, this gain in averted breast cancer deaths was insufficient to reduce breast cancer mortality disparities for Black women compared with women overall. Specifically, if Black women were screened with the same strategy as for women overall, breast cancer mortality for Black women would remain more than 40% greater than for women overall (**Table 4**). Alternatively, if Black women were screened annually from ages 40 to 49 years with biennial screening from ages 50 to 79 and the overall population was screened biennially from ages 40 to 74, the ratio of breast cancer mortality rate for Black women vs women overall would be reduced from 1.44 (28.8/20.0) to 1.34 (26.8/20.0; a disparity reduction of 23%). Notably, Black women screened annually at ages 40 to 49 and biennially at ages 50 to 79 would experience fewer false-positives and mammograms per breast cancer death averted with greater life-years gained than women overall screened biennially at ages 40 to 74 (eTable 10 in Supplement).

Density, Elevated Risk, and Comorbidity Subgroups

Only 3 strategies were efficient in most models for women with dense breasts (BI-RADS category c and d), including biennial screening from ages 50 to 74 years, biennial screening from ages 40 to 79, and annual screening at ages 40 to 79 (eTable 11 in the Supplement). Across all strategies efficient in at least 1 density category, breast cancer deaths averted using DBT for women with almost entirely fatty breasts ranged from 4.9 for biennial screening at ages 50 to 74 to 7.6 with annual screening at ages 40 to 79 and increased among women with extremely dense breasts from 8.3 to 14.6 (eTable 12 in the Supplement).

Models showed greater benefits and fewer harms as breast cancer risk increased to 150% and 200% of average risk, with the same 3 screening strategies efficient for both elevated risk levels as for dense breasts (eTable 13 in the Supplement). Incremental benefits of screening after age 74 years were reduced in the presence of severe comorbidities (eTable 14 in the Supplement).

Table 3. Lifetime Additional Benefits and Harms of Screening Mammography Starting at Age 40 Years Instead of 50 Until Age 74 per 1000 Women From 6 Models

Benefits and harms by modality	Difference in biennial screening starting at 40 vs 50 until 74 years by model[a]						
	D	E	GE	M	S	W	Median (range)
Mammograms							
DM	4936	4900	4924	4869	NA	4864	4900 (4864-4936)
DBT	4936	4895	4924	4870	4920	4850	4907 (4850-4936)
Breast cancer mortality reduction, %							
DM	4.1	4.1	8.6	6.5	NA	3.1	4.1 (3.1-8.6)
DBT	4.4	4.3	8.6	6.4	4.9	3.6	4.6 (3.6-8.6)
Breast cancer deaths averted							
DM	1.3	1.2	3.2	1.5	NA	0.8	1.3 (0.8-3.2)
DBT	1.4	1.3	3.2	1.5	1.2	0.9	1.3 (0.9-3.2)
Life-years gained							
DM	43.1	35.3	102.7	53.3	NA	31.4	43 (31.4-102.7)
DBT	46.1	36.5	102.9	52.3	27.0	36.3	41 (27.0-102.9)
False-positive recalls							
DM	523	520	521	514	NA	517	520 (514-523)
DBT	506	502	504	493	505	499	503 (493-506)
Benign biopsies							
DM	63	62	62	60	NA	62	62 (60-63)
DBT	66	65	66	62	66	65	65 (62-66)
Overdiagnosed cases (DCIS and invasive)							
DM	1	2	0	3	NA	4	2 (0-4)
DBT	1	2	0	3	NA	4	2 (0-4)

Abbreviations: DBT, digital breast tomosynthesis; DCIS, ductal carcinoma in situ; DM, digital mammography; NA, not available.

[a] D indicates Dana-Farber Cancer Institute; E, Erasmus Medical Center; GE, Georgetown Lombardi Comprehensive Cancer Center-Albert Einstein College of Medicine; M, University of Texas MD Anderson Cancer Center; S, Stanford University; W, University of Wisconsin-Madison and Harvard Pilgrim Health Care Institute.

Sensitivity Analysis

When all breast cancer cases received the most effective treatment for their cancer subtype and screening stopped at age 74 years, the percent reduction in breast cancer mortality increased as compared with the primary analysis, in which cases received treatment based on real-world treatment patterns (eTable 15 in the Supplement).

Discussion

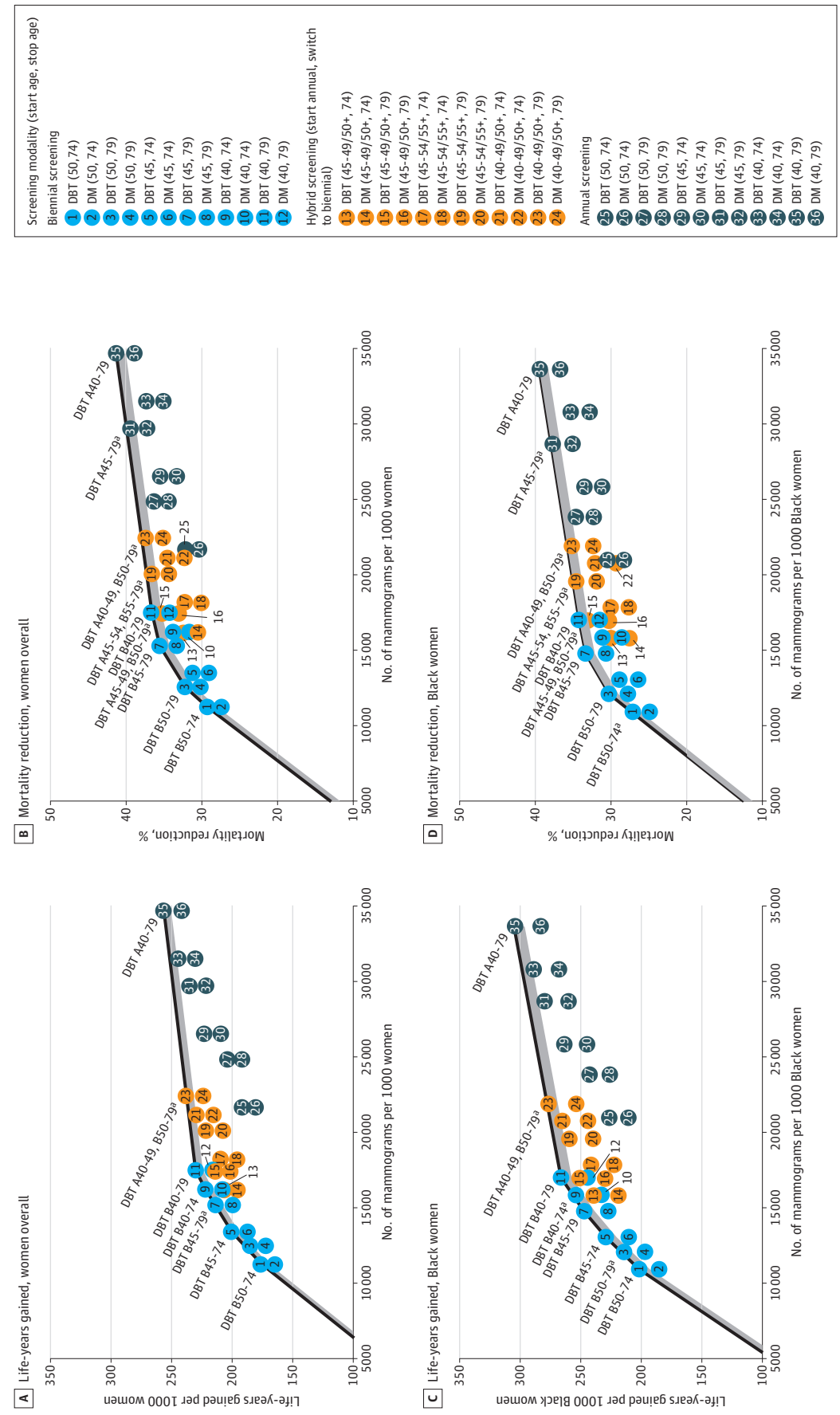
This study used 6 well-established models to estimate the potential benefits and harms of different breast cancer screening strategies in the US. The models demonstrated that screening initiation at age 40 years had superior benefit-to-harm tradeoffs compared with no screening and other screening strategies. Benefits of DBT were comparable with those of digital mammography but resulted in fewer false-positive recalls and similar benign biopsies. Annual screening would lead to greater reductions in breast cancer mortality than biennial strategies but correspondingly more false-positive recalls and overdiagnosed cases. Since breast cancer death rates are higher for Black women, all screening strategies generated greater survival and mortality benefits for Black women than for women overall. However, to reduce racial disparities in breast cancer mortality in the absence of improved equity in the treatment setting, an increase in screening intensity such as annual screening of Black women from ages 40 to 49 would also be needed. Benefits for women with elevated risk or higher breast density were higher than for women overall, but the rankings of strategies were similar to those for women overall. In addition, several strategies with a stopping age of 79 were efficient. For women aged 75 to 79, comorbidities may be an important factor in decisions about when to cease breast cancer screening.

Compared with our 2016 analysis,[10] the predicted benefit-to-harm ratios with biennial strategies starting at age 40 or 45 years have modestly improved. Due to recent increases in breast cancer incidence among women aged 40-49 (154.1 to 160.5 per 100 000 from 1999 to 2018), life-years gained were notably higher for screening strategies that started at age 40 or 45.[7,56] Past analyses assumed optimal treatment selection; starting screening earlier partially compensated for less-than-optimal real-world treatment uptake in the current analysis. Also, with the growing evidence for lower false-positive recall rates with DBT than with digital mammography,[3,4] fewer harms were associated with earlier ages of screening initiation than occurred in prior analyses.

Prospective studies that include multiple rounds of breast cancer screening are needed to determine whether, compared with digital mammography, DBT results in a shift toward detecting breast cancer at earlier stages with a concomitant decrease in advanced stage. Initial studies suggest that DBT leads to increased detection of stage I invasive breast cancer as compared with digital mammography, although a reduction in advanced stage has not yet been demonstrated.[6,57-59] Screening benefit related to reductions in breast cancer deaths depends on the advantage of beginning treatment in earlier vs more advanced stages.

This analysis extended findings published in 2021 for a model (GE) that evaluated strategies for reducing breast cancer mortality disparities and improving health equity between Black and White women.[60] Our models are intended to generate findings for individuals who self-identify as Black, defining race as a social construct where the sociopolitical environment influences biological processes

Figure 1. Lifetime Number of Screening Mammograms, Life-Years Gained, and Breast Cancer Mortality Reduction per 1000 Women Screened From Model D (Dana-Farber Cancer Institute) According to Screening Strategy for Women Overall and for Black Women

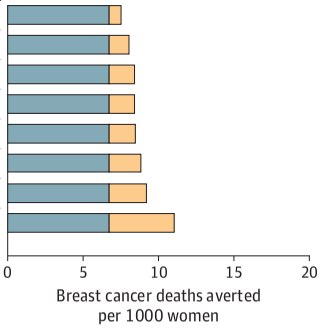


The line represents the estimated efficiency frontier for model D; labels above line indicate efficient and near-efficient strategies. Efficiency frontier graphs for all models are shown in the Supplement. Grey shading, in which near-efficient strategies are located, shows area within 5% of the value for screening biennially during ages 50 to 74 years with digital breast tomosynthesis (DBT). For panels A and C, near-efficient strategies included those within 2.20 days of life gained per woman of the efficient frontier for all women and 3.22 days of life per Black woman. For B and D, near-efficient strategies included those within 5% of the efficiency frontier on a relative scale—on an absolute scale, equivalent to 1.27 percentage points for women overall and 1.21 points for Black women. Strategies vary by age at starting and stopping screening, interval between mammograms, and screening modality. [a]Indicates annual; and B, biennial. [a]Near-efficient.

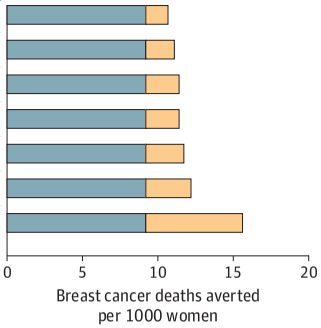
Figure 2. Breast Cancer Deaths Averted and Benign Biopsies per 1000 Women Screened With Various Digital Breast Tomosynthesis Mammography Screening Strategies

A Breast cancer deaths averted

Comparison strategy (screening ages, y)	All women: Deaths averted with biennial screening at ages 50-74 y	All women: Additional deaths averted with comparison strategy
Biennial (50-79)	6.7	0.8
Biennial (40-74)	6.7	1.3
Annual (40-49), biennial (50-74)	6.7	1.7
Annual (50-74)	6.7	1.7
Biennial (45-79)[a]	6.7	1.7
Biennial (40-79)[a]	6.7	2.1
Annual (40-49), biennial (50-79)[a]	6.7	2.5
Annual (40-79)[a]	6.7	4.3

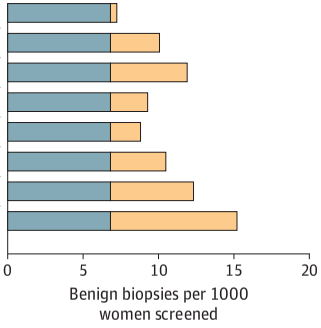


Comparison strategy (screening ages, y)	Black women: Deaths averted with biennial screening at ages 50-74 y	Black women: Additional deaths averted with comparison strategy
Biennial (50-79)	9.2	1.4
Biennial (40-74)	9.2	1.8
Annual (40-49), biennial (50-74)	9.2	2.2
Annual (50-74)	9.2	2.2
Biennial (45-79)[a]	9.2	2.5
Biennial (40-79)[a]	9.2	3.0
Annual (40-79)[a]	9.2	6.4

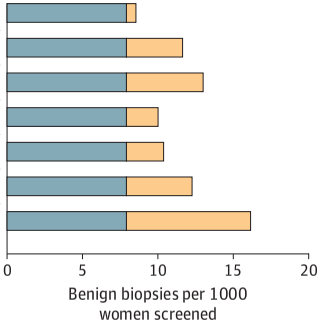


B Benign biopsies

Comparison strategy (screening ages, y)	All women: Benign biopsies with biennial screening at ages 50-74 y	All women: Additional benign biopsies with comparison strategy
Biennial (50-79)	136	8
Biennial (40-74)	136	65
Annual (40-49), biennial (50-74)	136	102
Annual (50-74)	136	50
Biennial (45-79)[a]	136	41
Biennial (40-79)[a]	136	74
Annual (40-49), biennial (50-79)[a]	136	111
Annual (40-79)[a]	136	168



Comparison strategy (screening ages, y)	Black women: Benign biopsies with biennial screening at ages 50-74 y	Black women: Additional benign biopsies with comparison strategy
Biennial (50-79)	158	12
Biennial (40-74)	158	74
Annual (40-49), biennial (50-74)	158	102
Annual (50-74)	158	41
Biennial (45-79)[a]	158	49
Biennial (40-79)[a]	158	87
Annual (40-79)[a]	158	164



All strategies use digital breast tomosynthesis. Results shown as medians across 6 models of women overall (D [Dana-Farber Cancer Institute], E [Erasmus Medical Center], GE [Georgetown Lombardi Comprehensive Cancer Center-Albert Einstein College of Medicine], M [University of Texas MD Anderson Cancer Center], S [Stanford University], and W [University of Wisconsin-Madison and Harvard Pilgrim Health Care Institute]) and across 4 models of Black women (D, GE, M, and W). Differences in medians calculated by subtracting values in Table 2, Table 3, and eTables 8 and 9 in the Supplement may not be equivalent to the median of the differences across models, as shown in this figure.

[a]Efficient or near-efficient in most models.

Table 4. Ratios of Breast Cancer Deaths and Life-Years for Black Women vs Women Overall by Screening Strategy

Screening strategy (interval, start-stop ages in years)	All women[a]	Screening strategy (interval, start-stop ages in years), Black women								
		No screening	Biennial (50-74)[b]	Biennial (40-74)[b]	Annual (40-49), biennial (50-74)[b]	Biennial (45-79)	Biennial (40-79)	Annual (40-49), biennial (50-79)[b]	Annual (40-74)[b]	Annual (40-79)
Breast cancer deaths per 1000 women										
Breast cancer deaths, No.		39.3	30.0	28.8	28.3	27.5	27.3	26.8	26.0	23.7
No screening	28.3	1.39	1.06	1.02	1.00	0.97	0.97	0.95	0.92	0.84
Biennial (50-74)	21.1	1.86	1.42	1.36	1.34	1.30	1.29	1.27	1.23	1.12
Biennial (40-74)[c]	20.0	1.97	1.50	1.44	1.42	1.38	1.37	1.34	1.30	1.19
Annual (40-49); biennial (50-74)[c]	19.6	2.01	1.53	1.47	1.44	1.41	1.39	1.37	1.33	1.21
Biennial (45-79)	19.4	2.03	1.55	1.48	1.46	1.42	1.41	1.39	1.34	1.23
Biennial (40-79)	19.1	2.05	1.57	1.50	1.48	1.44	1.43	1.40	1.36	1.24
Annual (40-49); biennial (50-79)	18.7	2.10	1.60	1.53	1.51	1.47	1.46	1.43	1.39	1.27
Annual (40-74)[c]	18.2	2.16	1.65	1.58	1.55	1.51	1.50	1.47	1.43	1.30
Annual (40-79)	16.9	2.33	1.78	1.71	1.68	1.63	1.62	1.59	1.54	1.41
Life-years per 40-year-old woman										
		No screening	Biennial (50-74)[b]	Biennial (45-79)	Biennial (40-74)[b]	Biennial (40-79)	Annual (40-49), biennial (50-74)[b]	Annual (40-49), biennial (50-79)[b]	Annual (40-74)[b]	Annual (40-79)
Life-years, No.		41.783	41.994	42.058	42.063	42.080	42.080	42.097	42.116	42.139
No screening	43.670	0.957	0.962	0.963	0.963	0.964	0.964	0.964	0.964	0.965
Biennial (50-74)	43.789	0.954	0.959	0.960	0.961	0.961	0.961	0.961	0.962	0.962
Biennial (45-79)	43.850	0.953	0.958	0.959	0.959	0.960	0.960	0.960	0.960	0.961
Biennial (40-74)[c]	43.866	0.953	0.957	0.959	0.959	0.959	0.959	0.960	0.960	0.961
Biennial (40-79)	43.879	0.952	0.957	0.959	0.959	0.959	0.959	0.959	0.960	0.960
Annual (40-49), biennial (50-74)[c]	43.882	0.952	0.957	0.958	0.959	0.959	0.959	0.959	0.960	0.960
Annual (40-49), biennial (50-79)	43.897	0.952	0.957	0.958	0.958	0.959	0.959	0.959	0.959	0.960
Annual (40-74)[c]	43.907	0.952	0.956	0.958	0.958	0.958	0.958	0.959	0.959	0.960
Annual (40-79)	43.927	0.951	0.956	0.957	0.958	0.958	0.958	0.958	0.959	0.959

[a] Calculations use the median values for breast cancer deaths from 4 models (D [Dana-Farber Cancer Institute], GE [Georgetown Lombardi Comprehensive Cancer Center-Albert Einstein College of Medicine], M [University of Texas MD Anderson Cancer Center], and W [University of Wisconsin-Madison and Harvard Pilgrim Health Care Institute]). Strategies limited to efficient and near-efficient strategies for both percent breast cancer mortality reduction and life-years gained vs no screening in most models for all women, listed in eTable 6 in the Supplement, along with selected other strategies.

[b] Strategy not efficient nor near-efficient for at least 3 of 4 models for both percent breast cancer mortality reduction and life-years gained vs no screening for Black women as shown in eTable 7 in the Supplement.

[c] Strategy not efficient nor near-efficient for at least 5 of 6 models for both percent breast cancer mortality reduction and life-years gained vs no screening for women overall as shown in eTable 6 in the Supplement.

over the life course.[61-63] The current study showed that Black women gained more life-years per mammogram than women overall for each screening strategy. This was due in part to Black women having higher breast cancer mortality, especially among younger women, and gaining less benefit from intended therapy due to worse quality of care. If Black women obtained annual mammography from age 40 to 49 years with biennial screening afterward, mortality disparities were projected to decline while also achieving similar benefit-to-harm tradeoffs as biennial screening starting at age 40 for women overall. These results are similar to those recently published by others using US mortality data that more intensive screening could potentially reduce the Black/White disparity in breast cancer mortality.[64] If health care systems, policymakers, clinicians, and scientists work to fully eliminate disparities experienced by Black women, the balance of benefits and harms for screening could eventually change to the extent that more intensive screening strategies for Black women are no longer needed to increase equity. However, as described by Chapman et al,[60] until treatment disparities are substantially decreased or eliminated, screening Black women more intensively represents an immediate possible solution for improving equity. Optimal implementation of any strategy will also require improved equity in DBT access and timely diagnostic workup.[65]

Our analysis considered breast cancer screening strategies using mammography, which has poorer performance in women with dense breasts compared with nondense breasts. Our models estimated that for any given mammography screening strategy, women with dense breasts had more deaths averted and greater life-years gained per mammogram than those with nondense breasts, but false-positive recall rates were higher. Evidence on the impact of supplemental screening with breast magnetic resonance imaging (MRI) or ultrasound for women with dense breasts is limited.[66,67] With federal regulations expanding breast density notification in September 2024 and the

absence of consistent clinical guidelines for supplemental screening,[68] this is a critical area for future research and policymaking.

After accounting for recent trends in life expectancy (prior to the COVID-19 pandemic) and improvements in breast cancer therapies, strategies with screening until age 79 years were identified as efficient. This is consistent with a recent simulation study but contrasts with an emulated trial based on Medicare data showing that breast cancer mortality was not significantly reduced among women screened through age 79.[69,70] Current breast cancer screening trials in progress, including TMIST and WISDOM, are not recruiting women older than 74, and trials testing screening in older women are unlikely to be conducted. Evidence from other types of studies is needed to better understand outcomes of screening for older women.

Relative rankings of strategies were similar across the models. However, the models differ in meaningful ways in structure and assumptions. For example, some models incorporated a benefit from screening due to within-stage shift in detection and subsequent treatment (models E, S, and W) while others required a stage shift (models D and GE) or assigned greater benefit for screen-detected than clinically detected cases within each stage at detection (model M). Among the 5 models that included DCIS as well as invasive breast cancer, 3 models found that the overall number of overdiagnosed cases exceeded the number of breast cancer deaths averted for all screening strategies considered. Underlying incidence in the absence of screening and the proportion of tumors that were nonprogressive are unknown and unobservable; therefore, the different results across models with their respective assumptions about breast cancer natural history provide a range of possible estimates.

Limitations

This research has many important strengths, including the collaboration of 6 independent modeling teams with consistent results and use of the most current data on incidence, screening performance, and modern, real-world therapy. Several caveats should also be considered in interpreting our results. First, the models portray the entire lifetime of women in the 1980 birth cohort and assume that future trends continued along the same trajectories as observed now. Second, we compared results for Black women with the overall female population, which leads to an underestimate of the impact of racism. This was a necessary simplification because these models did not produce estimates for other minoritized groups, non-Black women, or White women. In future research, models will be developed to examine results by racial and ethnic groups as well as interventions to improve health equity. Finally, some analyses were based on findings from fewer than 6 models for pragmatic reasons. In particular, some models were well-poised to examine analyses of racial disparities,[60] breast density,[71] or comorbidities[36] due to programming completed in previous projects.

Conclusions

Overall, this analysis suggests that biennial screening starting at ages 40 or 45 years with digital mammography or DBT and continuing through age 74 or 79 provides gains in life-years and breast cancer mortality reduction per mammogram—and averts more deaths from breast cancer among Black women—than waiting to start screening at age 50. More intensive screening for populations of women with greater risk of breast cancer diagnosis or death can maintain similar benefit-to-harm trade-offs and reduce breast cancer mortality disparities. In the presence of recent changes in breast cancer incidence and improvements in screening technology and breast cancer therapy, mammography screening remains an important strategy to reduce breast cancer burden.

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