Supplemental Online Content

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eMethods

Absolute difference in screening outcome

The absolute difference (AD) in each screening outcome is defined as the absolute difference in their rate per 1000 exams by modality, R_{DBT} for digital breast tomosynthesis (DBT) and R_{DM} for digital mammography, respectively. Under a log-binomial regression,

$$\log(\text{outcome rate} \mid \text{modality}) = \alpha + \beta I(\text{modality=DBT}),$$

the absolute difference can be expressed as following:

$$AD = R_{DBT} - R_{DM} = e^{\alpha+\beta} - e^{\alpha}.$$

Using SAS PROC GENMOD with an independent working correlation, we obtained $\hat{\alpha}$ and $\hat{\beta}$, the estimates of α and β, and their estimated variance-covariance matrix. We then estimated AD by $\widehat{AD} = e^{\hat{\alpha}+\hat{\beta}} - e^{\hat{\alpha}}$. Denote the true value of α and β as α_0 and β_0. The variance of $\widehat{AD}$ was approximated using delta method as shown below:

$$\text{var}\left(\widehat{AD}\right) \approx \text{var}\left[\left(e^{\alpha_0+\beta_0} - e^{\alpha_0}\right)(\hat{\alpha} - \alpha_0) + e^{\alpha_0+\beta_0}\left(\hat{\beta} - \beta_0\right)\right]$$

$$= \left(e^{\alpha_0+\beta_0} - e^{\alpha_0}\right)^2 \text{var}(\hat{\alpha}) + \left(e^{\alpha_0+\beta_0}\right)^2 \text{var}\left(\hat{\beta}\right) + 2e^{\alpha_0+\beta_0}(e^{\alpha_0+\beta_0} - e^{\alpha_0})\text{cov}(\hat{\alpha}, \hat{\beta})$$

$$= \left[e^{\alpha_0+\beta_0} - e^{\alpha_0} \quad e^{\alpha_0+\beta_0}\right] \text{var}\begin{pmatrix}\hat{\alpha}\\ \hat{\beta}\end{pmatrix} \begin{bmatrix}e^{\alpha_0+\beta_0} - e^{\alpha_0}\\ e^{\alpha_0+\beta_0}\end{bmatrix}.$$

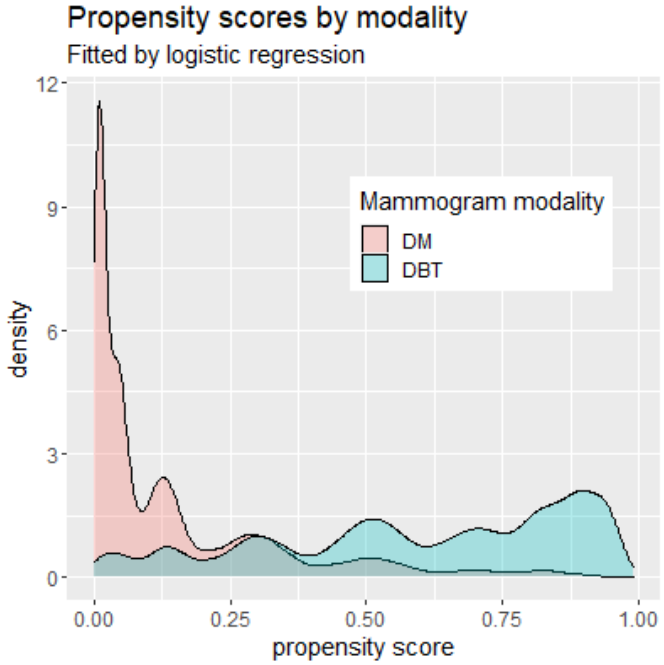
We estimated the variance of $\widehat{AD}$ by

$$s^2 = \left[e^{\hat{\alpha}+\hat{\beta}} - e^{\hat{\alpha}} \quad e^{\hat{\alpha}+\hat{\beta}}\right] \widehat{\text{var}}\begin{pmatrix}\hat{\alpha}\\ \hat{\beta}\end{pmatrix} \begin{bmatrix}e^{\hat{\alpha}+\hat{\beta}} - e^{\hat{\alpha}}\\ e^{\hat{\alpha}+\hat{\beta}}\end{bmatrix}.$$

The 95% confidence interval of $\widehat{AD}$ was obtained by $\widehat{AD} \pm 1.96 \times s$.

Evaluation of propensity model

We first visually examined the density of propensity scores for DBT vs. digital mammography examinations (eFigure 1). The density curves of propensity scores in DBT and digital mammography exams overlapped across a wide range, suggesting a common support of propensity scores in the two treatment groups. We also examined the standardized mean differences of covariates in the propensity model between the two treatment groups before and after weighting with the inverse probability (Table 1). Using a maximum of 25% standardized mean difference,[3] the distributions of these covariates were balanced between DBT and digital mammography exams after weighting.



eFigure 1. Propensity scores for digital mammography and digital breast tomosynthesis examinations.

Multiple imputation of tumor characteristics for calculation of advanced cancer as defined by Tomosynthesis Mammographic Imaging Screening Trial (TMIST)

We used multiple imputation by chained equation (MICE)[1] to impute missing values in components needed for deriving TMIST outcome, including 4.4% missing for primary tumor size, 2.2% for lymph nodes status, 3.7% for tumor grade, 7.8% for human epidermal growth factor receptor 2 (HER2), 2.0% for estrogen receptor (ER) and 2.1% for progesterone receptor (PR). These variables were multiply imputed simultaneously by SAS PROC MI using fully conditional specification (FCS). A detailed description of variables used in the multiple imputation are shown in eTable 2. We computed the rate of TMIST outcomes for DBT and digital mammography exams and the absolute risk differences between DBT vs. digital mammography using each imputed dataset. Estimates and 95% confidence intervals were combined and derived using Rubin's rule.[2]

eTable 1: Summary of variables used to impute tumor characteristics used to calculate TMIST

Description	Type	Variable levels	FCS	Total N = 5,735	
				N Missing	% Missing
Age at mammogram	Continuous	N/A	N/A	0	0
Exam year	Continuous	N/A	N/A	0	0
BCSC Registry	Nominal	5	N/A	0	0
Mammogram modality	Binary	2	N/A	0	0
BI-RADS initial assessment	Binary	2	N/A	0	0
BI-RADS final assessment	Binary	2	N/A	0	0
Most severe benign biopsy result	Ordinal	6	N/A	0	0
Race/ethnicity	Nominal	5 + missing value category	N/A	0	0
BI-RADS breast density category	Ordinal	4 + missing value category	N/A	0	0
First-degree family history of breast cancer	Binary	2 + missing value category	N/A	0	0
Time since previous screening mammogram	Ordinal	4 + missing value category	N/A	0	0
Estrogen receptor status	Binary	2	logistic	108	1.88
Progesterone receptor status	Binary	2	logistic	162	2.82
Positive lymph nodes	Binary	2	logistic	168	2.93
AJCC anatomic stage, 8th edition	Ordinal	9	logistic	193	3.7
Tumor grade	Ordinal	3	logistic	232	4.05
Natural log of tumor size	Continuous	N/A	regression	244	4.25
HER2 receptor status	Binary	2	logistic	452	7.88

Abbreviations: FCS, type of fully conditionally specified statement used in SAS PROC MI; American Joint Committee on Cancer (AJCC); Breast Imaging, Reporting, and Data System (BI-RADS); Tomosynthesis Mammographic Imaging Screening Trial (TMIST)

eReferences

1. White IR, Royston P. Imputing missing covariate values for the Cox model. Stat Med 2009;28:1982–98.
2. Little, R. & Rubin, D. Statistical Analysis with Missing Data (John Wiley, New York, 2002).

eTable 2. Outcomes from screening with digital breast tomosynthesis vs. digital mammography

	Digital breast tomosynthesis N=374002	**Digital mammography** N=1003900	
Screening outcomes	**Rate per 1,000 exams (95% CI)**[a]	**Rate per 1,000 exams (95% CI)**[a]	**Difference (95% CI)**[a]
Screening benefit			
Stage I screen-detected invasive cancer	3.45 (3.06, 3.90)	2.99 (2.78, 3.23)	0.46 (-0.01, 0.93)
Screening failures			
Interval invasive cancer	0.57 (0.50, 0.65)	0.61 (0.54, 0.68)	-0.04 (-0.14, 0.06)
Stage II or higher invasive cancer[b]	0.36 (0.29, 0.44)	0.45 (0.38, 0.53)	-0.09 (-0.18, -0.01)
TMIST advanced cancer[c]	1.80 (1.19, 2.70)	1.89 (1.66, 2.18)	-0.09 (-0.80, 0.62)
Screening false-alarms			
False-positive recall	66.2 (62.0, 70.7)	83.4 (75.5, 92.2)	-17.2 (-25.2, -9.2)
False-positive short interval follow-up	11.2 (8.9, 14.1)	17.9 (14.1, 22.7)	-6.7 (-11.2, -2.2)
False-positive biopsy recommendation	10.9 (10.1, 11.7)	11.7 (9.8, 14.0)	-0.84 (-2.6, 0.87)
Screening consequences			
Screen-detected DCIS[d]	1.24 (1.07, 1.44)	1.24 (1.03, 1.48)	0.00 (-0.27, 0.27)

[a]Based on log-binomial model fit via generalized estimating equations with inverse probability weighting
[b]American Joint Committee on Cancer (AJCC) 8th edition, prognostic stage II or higher
[c]Tomosynthesis Mammographic Imaging Screening Trial (TMIST) defined as 1) tumor ≥20 mm, or 2) tumor >10mm and either HER2-positive or triple-negative, or 3) cancer that spread from the breast to at least one nearby lymph node or 4) cancer that spread from the breast to a distant organ
[d]Ductal carcinoma in situ

eTable 3. Rate of screening benefits and failures by breast density for digital breast tomosynthesis vs digital mammography (DM)[a]

	SCREENING BENEFIT			SCREENING FAILURES								
	Stage I Screen-detected invasive cancer			Interval invasive cancer			Prognostic Stage II or higher invasive cancer[b]			TMIST advanced breast cancer definition[c]		
	per 1,000 exams		Difference	per 1,000 exams		Difference	per 1,000 exams		Difference	per 1,000 exams		Difference
Breast density (DBT N /DM N)	(95% CI)			(95% CI)			(95% CI)			(95% CI)		
	DBT	DM	DBT vs. DM	DBT	DM	DBT vs. DM	DBT	DM	DBT vs. DM	DBT	DM	DBT vs. DM
Almost entirely fatty (39059/101842)	2.39 (2.10,2.73)	2.09 (1.71,2.55)	0.30 (-0.22,0.82)	0.12 (0.04,0.40)	0.24 (0.13,0.43)	-0.12 (-0.31,0.07)	0.07 (0.02,0.29)	0.21 (0.13,0.33)	-0.14 (-0.28,0.00)	1.14 (0.08,1.57)	0.98 (0.70,1.31)	0.16 (-0.25,0.57)
Scattered fibroglandular densities (173534/428513)	3.74 (3.54,3.94)	3.30 (2.98,3.65)	0.44 (0.07,0.81)	0.31 (0.20,0.48)	0.39 (0.33,0.47)	-0.08 (-0.24,0.07)	0.46 (0.26,0.80)	0.41 (0.33,0.50)	0.05 (-0.21,0.31)	1.54 (1.11,2.15)	1.75 (1.50,2.05)	-0.20 (-0.76,0.34)
Heterogeneously dense (127740/357811)	3.54 (2.70,4.64)	2.80 (2.41,3.26)	0.74 (-0.22,1.71)	0.99 (0.80,1.22)	0.87 (0.76,1.01)	0.11 (-0.11,0.34)	0.33 (0.14,0.74)	0.51 (0.40,0.65)	-0.19 (-0.46,0.09)	2.21 (1.26,3.88)	2.23 (1.86,2.68)	-0.02 (-1.21,1.16)
Extremely dense (24361/70519)	2.73 (2.37,3.14)	2.37 (1.94,2.90)	0.36 (-0.17,0.89)	0.87 (0.59,1.27)	1.21 (0.93,1.58)	-0.34 (-0.76, 0.07)	0.42 (0.34,0.51)	0.59 (0.42,0.83)	-0.17 (-0.39,0.04)	2.34 (1.94,2.83)	1.87 (1.52,2.31)	0.47 (-0.05,0.99)

[a]Based on log-binomial model fit via generalized estimating equations with inverse probability weighting
[b]American Joint Committee on Cancer (AJCC) 8th ed. prognostic pathologic stage II or higher
[c]Tomosynthesis Mammographic Imaging Screening Trial (TMIST) defined as 1) tumor ≥20 mm, or 2) tumor >10mm and either HER2-positive or triple-negative, or 3) cancer that spread from the breast to at least one nearby lymph node or 4) cancer that spread from the breast to a distant organ

eTable 4. Rate of screening false-alarms by breast density for digital breast tomosynthesis vs. digital mammography (DM)[a]

Breast Density (DBT N /DM N)	SCREENING FALSE-ALARMS								
	False-positive recall			False-positive short-interval follow-up recommendation			False-positive biopsy recommendation		
	per 1,000 exams (95% CI)		Difference (95% CI)	per 1,000 exams (95% CI)		Difference (95% CI)	per 1,000 exams (95% CI)		Difference (95% CI)
	DBT	DM	DBT vs. DM	DBT	DM	DBT vs. DM	DBT	DM	DBT vs. DM
Almost entirely fatty (39059/101842)	36.2 (33.6,38.0)	46.1 (38.7,54.0)	-9.9 (-17.1,-2.6)	6.5 (4.7,9.1)	10.4 (8.3,13.0)	-3.9 (-6.9,-0.84)	5.9 (5.3,6.6)	8.0 (6.4,10.1)	-2.1 (-3.9,-0.34)
Scattered fibroglandular densities (173534/428513)	56.8 (50.4,64.0)	79.6 (71.6,88.0)	-22.8 (-31.0,-14.6)	9.8 (6.7,14.5)	17.8 (14.1,22.0)	-8.0 (-13.1,-2.9)	8.4 (7.5,9.4)	10.7 (9.0,12.5)	-2.2 (-4.0,-0.82)
Heterogeneously dense (127740/357811)	83.0 (75.3,91.0)	96.9 (83.7,112)	-13.9 (-29.1, 1.3)	13.4 (10.4,16.0)	20.8 (16.4,26.0)	-7.4 (-12.5,-2.4)	14.2 (12.8,15.0)	12.7 (10.2,15.0)	1.5 (-1.3,4.2)
Extremely dense (24361/70519)	89.2 (83.1,95)	86.6 (78.5,95)	2.6 (-7.9,13)	16.5 (14.5,18.0)	16.5 (12.8,21.0)	0.05 (-4.0,4.1)	16.7 (14.6,19.0)	14.6 (12.3,17.0)	2.1 (-5.5,5.6)

[a]Based on log-binomial model fit via generalized estimating equations with inverse probability weighting

eTable 5. Rate of screening benefits and failures by breast density for digital mammography (DM) and digital breast tomosynthesis[a]

Breast density/BCSC 5-year risk[d] (DBT N /DM N)	SCREENING BENEFIT			SCREENING FAILURES								
	Stage I Screen-detected invasive cancer			Interval invasive cancer			Prognostic Stage II or higher invasive cancer[b]			TMIST advanced breast cancer definition[c]		
	per 1,000 exams		Difference	per 1,000 exams		Difference	per 1,000 exams		Difference	per 1,000 exams		Difference
	(95% CI)			(95% CI)			(95% CI)			(95% CI)		
Almost entirely fatty	DBT	DM	DBT vs. DM	DBT	DM	DBT vs. DM	DBT	DM	DBT vs. DM	DBT	DM	DBT vs. DM
0-<1.67% (33692/88143)	1.66 (1.25, 2.19)	1.84 (1.48, 2.30)	-0.19 (-0.77,0.40)	0.08 (0.02,0.30)	0.23 (0.12,0.46)	-0.15 (-0.31,0.01)	0.08 (0.02,0.33)	0.22 (0.14,0.36)	-0.14 (-0.30,0.01)	0.44 (0.11,1.70)	0.98 (0.72,1.34)	-0.54 (-1.18, 0.09)
≥1.67% (2710/5427)	2.65 (1.03,6.83)	3.87 (2.07, 7.25)	-1.22 (-4.60,2.16)	0.95 (0.27,3.37)	0.42 (0.14,1.29)	0.53 (-0.78,1.85)	NA	NA	NA	1.78 (0.51,6.25)	0.95 (0.39,2.32)	0.82 (-1.53, 3.19)
Scattered fibroglandular densities												
0-<1.67% (117322/306387)	2.78 (2.49, 3.09)	2.69 (2.43, 2.97)	0.09 (-0.30,0.48)	0.24 (0.12,0.46)	0.28 (0.23, 0.34)	-0.04 (-0.21,0.13)	0.35 (0.23, 0.51)	0.33 (0.25,0.45)	0.02 (-0.13,0.16)	0.98 (0.66,1.45)	1.41 (1.18,1.67)	-0.42 (-0.86, 0.01)
≥1.67% (45985/91383)	6.96 (6.15, 7.88)	4.72 (4.07, 5.48)	2.24 (1.17,3.32)	0.56 (0.41,0.78)	0.69 (0.51, 0.92)	-0.12 (-0.40,0.15)	0.70 (0.28,1.73)	0.54 (0.39,0.75)	0.16 (-0.51,0.83)	3.28 (2.26,4.76)	2.56 (2.08,3.15)	0.72 (-0.52, 1.96)
Heterogeneously dense												
0-<1.67% (56810/185489)	1.54 (0.97, 2.43)	1.73 (1.46, 2.05)	-0.19 (-0.94,0.55)	1.12 (0.69,1.82)	0.70 (0.58, 0.85)	0.42 (-0.17,1.01)	0.27 (0.10,0.74)	0.39 (0.29,0.54)	-0.12 (-0.39,0.15)	1.39 (0.78,2.49)	1.50 (1.25,1.81)	-0.10 (-0.90, 0.69)
≥1.67% (66180/156785)	5.50 (4.50, 6.72)	3.78 (3.11, 4.60)	1.72 (0.56,2.87)	0.86 (0.55,1.35)	1.03 (0.85, 1.24)	-0.17 (-0.62,0.28)	0.41 (0.21,0.81)	0.61 (0.49,0.77)	-0.20 (-0.50,0.10)	3.29 (1.90,5.67)	2.88 (2.38,3.47)	0.41 (-1.27, 2.09)
Extremely dense												
0-<1.67% (10611/37796)	1.99 (1.43, 2.77)	1.69 (1.25, 2.29)	0.30 (-0.48,1.08)	0.93 (0.74,1.17)	1.07 (0.78, 1.46)	-0.13 (-0.49,0.22)	0.54 (0.30.68)	0.42 (0.29,0.62)	0.12 (-0.09,0.32)	2.55 (1.94,3.36)	1.66 (1.30,2.11)	0.90 (0.14, 1.7)
≥1.67% (13291/31300)	3.28 (2.41, 4.45)	2.98 (2.29, 3.87)	0.30 (-0.87,1.47)	0.81 (0.37,1.76)	1.39 (1.01, 1.92)	-0.59 (-1.27,0.09)	0.27 (0.14,0.52)	0.80 (0.49,1.31)	-0.53 (-0.97,-0.10)	1.70 (0.98,2.95)	2.12 (1.55,2.91)	-0.42 (-1.43, 0.58)

[a]Based on log-binomial model fit via generalized estimating equations with inverse probability weighting
[b]American Joint Committee on Cancer (AJCC) 8th ed. prognostic pathologic stage II or higher
[c]Tomosynthesis Mammographic Imaging Screening Trial (TMIST) defined as 1) tumor ≥20 mm, or 2) tumor >10mm and either HER2-positive or triple-negative, or 3) cancer that spread from the breast to at least one nearby lymph node or 4) cancer that spread from the breast to a distant organ
[d]Breast Cancer Surveillance Consortium (BCSC) 5-year risk calculated using age, race, first degree family history of breast cancer, history of breast biopsy, BI-RADS density

eTable 6. Rate of screening harms by breast density and BCSC 5-year risk for digital breast tomosynthesis vs. digital mammography (DM)[a]

	SCREENING FALSE-ALARMS								
	False-positive recall			False-positive short-interval follow-up recommendation			False-positive biopsy recommendation		
Breast density/BCSC 5-year risk[b] (DBT N /DM N)	per 1,000 exams (95% CI)		Difference	per 1,000 exams (95% CI)		Difference	per 1,000 exams (95% CI)		Difference
Almost entirely fatty	DBT	DM	DBT vs. DM	DBT	DM	DBT vs. DM	DBT	DM	DBT vs. DM
0-<1.67% (33692/88143)	35.9 (33.5,38.4)	46.2 (38.6,55.3)	-10.3 (-17.9, -2.7)	6.5 (5.0,8.4)	10.4 (8.2,13.1)	-3.9 (-6.6,-1.1)	6.2 (5.5,6.9)	7.9 (6.3,10.0)	-1.8 (-3.5, -0.10)
≥1.67% (2710/5427)	59.0 (45.8,76.0)	53.3 (46.1,61.6)	5.7 (-10.9, 22.3)	7.6 (2.6,22.1)	11.7 (8.6,16.1)	-4.2 (-13.5,5.1)	5.2 (1.6,16.4)	10.4 (7.4,14.6)	-5.2 (-11.8, 1.4)
Scattered fibroglandular densities									
0-<1.67% (117322/306387)	57.2 (50.3,65.0)	81.8 (73.6,90.8)	-24.6 (-33.4,-15.8)	9.8 (6.6,14.6)	18.2 (14.5,22.8)	-8.4 (-13.6,-3.2)	7.8 (6.9,8.9)	10.3 (8.7,12.1)	-2.4 (-4.2, -0.69)
≥1.67% (45985/91383)	58.9 (53.5,64.8)	77.0 (68.6,86.4)	-18.1 (-25.2,-11.0)	10.4 (7.4,14.5)	17.8 (13.5,23.3)	-7.4 (-12.8,-2.0)	10.8 (7.9,14.8)	12.0 (9.9,14.5)	-1.2 (-4.8, 2.5)
Heterogeneously dense									
0-<1.67% (56810/185489)	96.3 (87.0,107)	107.7 (93.7,124)	-11.4 (-27.9, 5.1)	15.7 (12.9,19.1)	22.8 (17.8,29.3)	-7.1 (-12.9,-1.3)	16.3 (14.0,19.1)	13.3 (10.7,16.5)	3.0 (-0.56, 6.6)
≥1.67% (66180/156785)	68.1 (62.1,74.7)	87.1 (73.9,103)	-19.0 (-33.5,-4.5)	10.7 (7.8,14.5)	18.9 (14.8,24.2)	-8.2 (-13.2,-3.2)	11.8 (9.9,14.0)	12.4 (9.8,15.7)	-0.60 (-3.6, 2.4)
Extremely dense									
0-<1.67% (10611/37796)	96.5 (92.2,101)	97.1 (84.5,112)	-0.63 (-14.5,13.2)	19.2 (16.9, 21.8)	18.8 (14.2, 24.9)	0.34 (-4.8,5.5)	17.7 (16.3,19.2)	15.8 (13.4,18.6)	1.9 (-0.87, 4.7)
≥1.67% (13291/31300)	81.8 (70.6,94.8)	76.0 (69.1,83.6)	5.8 (-8.3,19.9)	13.6 (11.7,15.7)	14.2 (11.0,18.4)	-0.65 (-4.5,3.2)	15.7 (12.2,20.3)	13.6 (11.0,16.9)	2.1 (-2.7, 6.9)

[a]Based on log-binomial model fit via generalized estimating equations with inverse probability weighting
[b]Breast Cancer Surveillance Consortium (BCSC) 5-year risk calculated using age, race, first degree family history of breast cancer, history of breast biopsy, BI-RADS density