

Risk factors for advanced breast cancer diagnosis within two years of a negative mammogram

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Introduction

- Mammography screening is an effective, but imperfect tool for early detection of breast cancer
- 15% of breast cancers are diagnosed after a negative mammogram before the next recommended screening exam
- These interval cancers, or **screening failures**, tend to have poor prognosis
- Women at high risk for screening failures may benefit from supplemental screening techniques (i.e. MRI) to reduce breast cancer mortality
- Study Objective:** Examine risk factors for advanced breast cancer within two years of a negative mammogram

Methods

Study Population

- Negative screening mammograms among women 40-85 years at Massachusetts General Hospital from 2006-2015
- Excluded women with prior breast cancer, breast implants, prior screening mammogram within 90 days, *BRCA1/2* carriers, missing BI-RADS breast density, non-MA residents

Data Elements & Outcome

- Patient risk factors ascertained from patient questionnaires at the time of mammography
- Procedures, results, and patient characteristics extracted from electronic medical records
- Breast cancers diagnosed within 2 years of mammogram ascertained from linkage with MA Cancer Registry & hospital cancer registries through 2017
- Prognosis defined using TMIST definition of advanced cancer, which incorporates size, subtype and lymph node/distant involvement
 - Advanced cancer defined as >2cm, >1cm and triple-negative or HER2+, positive lymph nodes, or metastatic

Statistical Analysis

- Cox proportional hazards regression to assess associations of risk factors with early-stage and advanced cancer within two years of negative mammogram
 - Censored at end of study, date of next mammogram, death, or date of either early-stage or advanced cancer depending on model (Figure 1)
 - Stratified by time since mammogram

Table 1: Characteristics of Cohort by Breast Cancer Diagnosis within 2 Years of Negative Mammogram

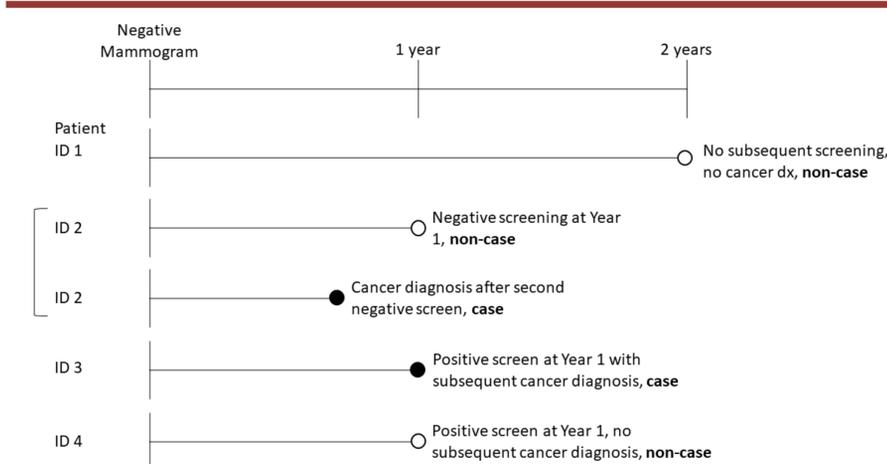
	No Cancer N = 292175 (99.54%)	Early Stage N = 971 (0.33%)	Advanced Cancer N = 374 (0.35%)
Age, Mean (SD)	57.35 (11.06)	60.49 (11.05)	57.65 (10.87)
Breast Density, N (%)			
BI-RADS 1	29089 (10.0%)	70 (7.2%)	8 (2.1%)
BI-RADS 2	134908 (46.2%)	421 (42.4%)	140 (37.4%)
BI-RADS 3	112962 (38.7%)	410 (42.2%)	202 (54.0%)
BI-RADS 4	15216 (5.2%)	70 (7.2%)	24 (6.4%)
Prior Biopsy, N (%)	4630 (1.6%)	34 (3.5%)	16 (4.3%)
BMI, N (%)			
Underweight/Normal (< 25)	123779 (42.4%)	373 (38.4%)	148 (39.6%)
Overweight (25-29)	81332 (27.8%)	294 (30.3%)	115 (30.8%)
Obese (30+)	71180 (24.4%)	238 (24.5%)	91 (24.3%)
Race/ethnicity			
Non-Hispanic White	241632 (82.7%)	861 (88.7%)	331 (88.5%)
Non-Hispanic Black	15778 (5.4%)	42 (4.3%)	10 (2.7%)
Hispanic	13712 (4.7%)	19 (2.0%)	11 (2.9%)
Asian/Pacific Islander	15052 (5.2%)	35 (3.6%)	18 (4.8%)
Other Race	6001 (2.1%)	14 (1.4%)	4 (1.1%)
Family History	40613 (13.9%)	204 (21.0%)	73 (19.5%)

Table 2: Hazard ratios for early stage and advanced cancer within 2 years of negative screening mammogram

	Advanced Cancer						Early Stage Cancer					
	Year 1 (N = 112 cases)			Year 2 (N = 262 cases)			Year 1 (N = 147 cases)			Year 2 (N = 824 cases)		
	HR	95% CI	p									
Age	1.01	0.99-1.03	0.48	1.02	1.00-1.03	0.02	1.02	1.00-1.04	0.10	1.04	1.03-1.04	<0.01
Dense vs. non-dense	4.01	2.52-6.39	<0.01	2.09	1.59-2.75	<0.01	1.98	1.36-2.88	<0.01	1.65	1.41-1.92	<0.01
Ever Biopsy vs. none	3.12	1.37-7.12	0.01	2.83	1.50-5.33	<0.01	3.24	1.58-6.62	<0.01	2.32	1.57-3.43	<0.01
BMI 25-29 vs. <25	1.24	0.78-1.97	0.37	1.53	1.13-2.05	0.01	0.75	0.49-1.15	0.19	1.41	1.19-1.67	<0.01
BMI 30+ vs. <25	1.77	1.06-2.95	0.03	1.45	1.03-2.03	0.03	0.73	0.44-1.20	0.22	1.40	1.16-1.69	<0.01
Family History	1.74	1.10-2.75	0.02	1.48	1.08-2.03	0.01	1.70	1.14-2.54	0.01	1.71	1.44-2.03	<0.01

Models additionally adjusted for digital breast tomosynthesis vs digital mammography, menopause status

Figure 1: Illustration of Person Time and Censoring



Results

Table 1

- The study included 293,520 negative screening exams among 74,736 women.
- A total of 1345 breast cancers were diagnosed within two years of follow-up time (4.6 per 1000 exams), of which 374 (1.3 per 1000) were advanced cancers and 971 (3.3 per 1000) were early stage cancers.
- Women diagnosed with advanced cancers were younger and more likely to be premenopausal than women diagnosed with early stage cancers.
- A greater proportion of women diagnosed with advanced cancers had heterogeneously or extremely dense breasts than women without advanced cancer.

Table 2

- Significant interaction of follow-up time with BMI ($p < 0.001$).
- Breast density, prior breast biopsy, and family history of breast cancer were associated with increased risk of both advanced and early stage cancers.
- Overweight and obese women had 40% higher risk of early stage cancer in year 2.
- Obese women had 77% increased risk of advanced cancer in year 1 and overweight and obese women had greater than 40% increased risk in year 2.

Conclusions

- Higher BMI was significantly associated with advanced breast cancer diagnosis within two years of a negative mammogram.
- These results may have important implications for risk assessment, screening intervals, and use of supplemental screening.

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