Annual Screening Mammography Associated With Lower Stage Breast Cancer Compared With Biennial Screening

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OBJECTIVE. The purpose of this study was to compare breast cancer characteristics and treatment regimens among women undergoing annual versus nonannual screening mammography.

MATERIALS AND METHODS. In this retrospective, institutional review board–approved, HIPAA-compliant cohort study, a breast cancer database was queried for patients who received a mammographic or clinical diagnosis of breast cancer during 2016–2017. Annual versus biennial and annual versus nonannual (biennial and triennial) mammography screening cohorts were compared using *t* tests or Wilcoxon rank sum tests for continuous variables and chi-square or Fisher exact tests for categoric variables.

RESULTS. A total of 490 patients were diagnosed with breast cancer during 2016–2017. Among these women, 245 had an assignable screening frequency and were 40–84 years old (mean, 61.8 ± 9.9 [SD] years; median, 62 years). Screening frequency was annual for 200 of these 245 patients (81.6%), biennial for 32 (13.1%), and triennial for 13 (5.3%). Annual screening resulted in fewer late-stage presentations (AJCC stage II, III, or IV in 48 of 200 patients undergoing annual [24.0%] vs 14 of 32 undergoing biennial [43.8%; p = .02] and vs 20 of 45 undergoing nonannual screening [44.4%; p = .006]), fewer interval cancers (21 of 200 for annual [10.5%] vs 12 of 32 for biennial [37.5%; p < .001] and vs 15 of 45 for nonannual [33.3%; p < .001]), and smaller mean tumor diameter (1.4 ± 1.2 cm for annual vs 1.8 ± 1.6 cm for biennial [p = .04] and vs 1.8 ± 1.5 cm nonannual [p = .03]). Lower AJCC stage, fewer interval cancers, and smaller tumor diameter also persisted among postmenopausal women undergoing annual screening. Patients undergoing biennial and nonannual screening showed nonsignificant greater use of axillary lymph node dissection (annual, 24 of 200 [12.0%]; biennial, 6 of 32 [18.8%]; nonannual, 7 of 45 [15.6%]) and chemotherapy (annual, 55 of 200 [27.5%]; biennial, 12 of 32 [37.5%]; nonannual, 16 of 45 [35.6%]).

CONCLUSION. Annual mammographic screening was associated with lower breast cancer stage and fewer interval cancers than biennial or nonannual screening.

Screening mammography is an essential tool for the detection of breast cancer at an early stage and is associated with a reduction in breast cancer morbidity and mortality. Although mammography is widely accepted for breast cancer screening, the recommended screening frequency for women with an average risk for breast cancer remains variable among professional societies and government agencies [1–6].

Specifically, the American College of Radiology and the National Comprehensive Cancer Network (NCCN) recommend annual screening mammography for average-risk women beginning at age 40 years old [1, 4]. The American Cancer Society recommends annual screening mammography between ages 45 and 54 years old and optional annual screening for women between 40 and 44 years old if desired [3]. Per American Cancer Society recommendations, women can transition to biennial screening at age 55 years but also have the opportunity to continue with annual screening if desired [3]. Similarly, the American College of Obstetricians and Gynecologists recommends women be offered annual or bienni-

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al screening mammography at age 40 years and initiate screening no later than age 50 years, with consideration for biennial screening after age 55 years [5]. Meanwhile, the U.S. Preventive Services Task Force recommends biennial screening mammography for average-risk women between ages 50 and 74 years old [6].

In the absence of randomized clinical trials comparing morbidity and mortality of breast cancer as a function of screening frequency, inferences regarding appropriateness of screening mammography frequency are based on modeling or observational studies. Modeling studies have found that shorter screening intervals are associated with greater mortality benefit and greater life-years gained [7–13]. However, such models are influenced and limited by their inputs and assumptions, including background breast cancer incidence, screening mammography effectiveness and compliance rate, and background mortality rate [9]. Differences in these parameters could under- or overestimate the effect of screening mammography on breast cancer outcomes [9]. Additionally, interpretation of model-based studies can be limited by assumptions about the impact of advances in screening mammography and breast cancer treatment [9]. Prior observational studies have found lower tumor stage, fewer interval cancers, and smaller tumor size in breast cancers diagnosed with annual screening compared with biennial screening [14–17]. However, these findings did not persist among postmenopausal women [14, 15].

Given heterogeneous guidelines pertaining to screening frequency, limitations of model-based studies for the evaluation of screening mammography outcomes, and differences in observational studies of premenopausal versus postmenopausal women, the purpose of this study was to evaluate differences in breast cancer stage as a function of screening interval in a clinical cohort of premenopausal and postmenopausal women with breast cancer, using breast cancer stage as a surrogate for mortality. We were specifically interested in determining outcome differences among women who had undergone annual versus biennial mammography screening, with a focus on a postmenopausal subgroup. Outcomes among patients who had undergone triennial screening were also evaluated.

Materials and Methods

This retrospective cohort study was institutional review board–approved and HIPAA compliant. Informed consent was waved. The study was performed at a National Cancer Institute–designated cancer center and NCCN member institution.

Patients

Between January 1, 2016, and December 31, 2017, a total of 54,744 screening and 20,581 diagnostic mammography examinations were performed at the University of Michigan. An internal, prospectively maintained breast cancer database was queried for patients diagnosed with breast cancer during this time period. Women age 40–84 years old with mammographically detectable or clinically palpable interval primary breast cancer who had previously undergone annual, biennial, or triennial screening mammography at the time of diagnosis were included. Patients were excluded if they were younger than 40 or older than 84 years old, did not undergo screening at a frequency defined within study intervals, were male, had mammographically occult breast cancer detected by nonmammographic imaging, or had a nonprimary breast cancer. Patients for whom surgery was delayed or not performed and those lost to follow-up were also excluded (Fig. 1).

Screening intervals were prospectively defined to maximize the ability to detect differences between intervals. Annual screening was defined as every 9–15 months, biennial screen-

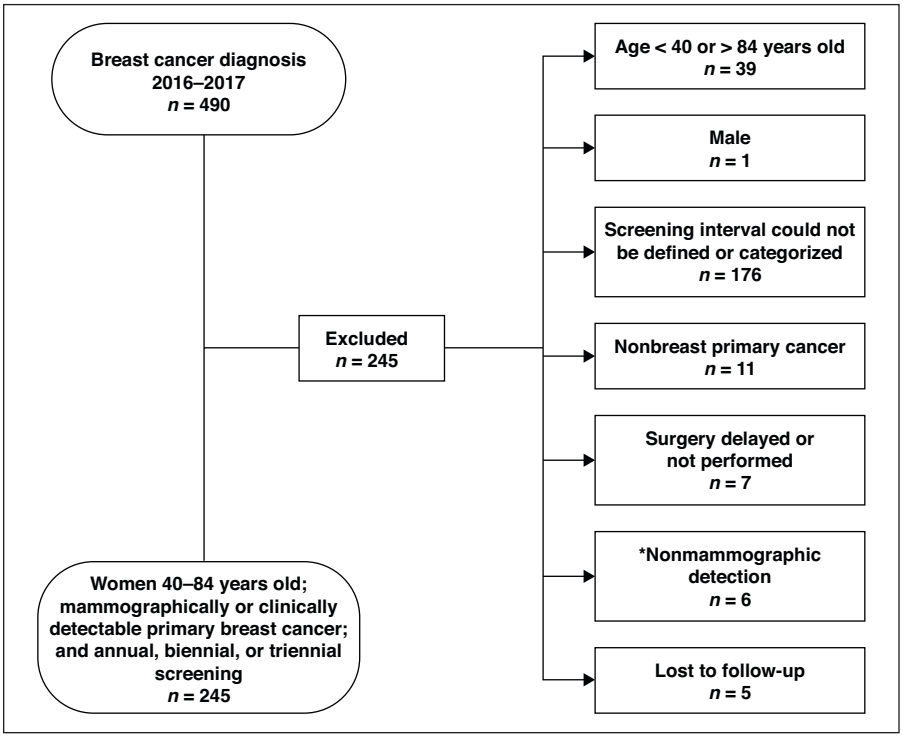

Fig. 1—Flowchart illustrates final study population. Asterisk denotes breast cancer was mammographically occult and detected by ultrasound in two patients undergoing biennial screening and in one patient undergoing triennial screening and was detected by MRI only in three other patients.

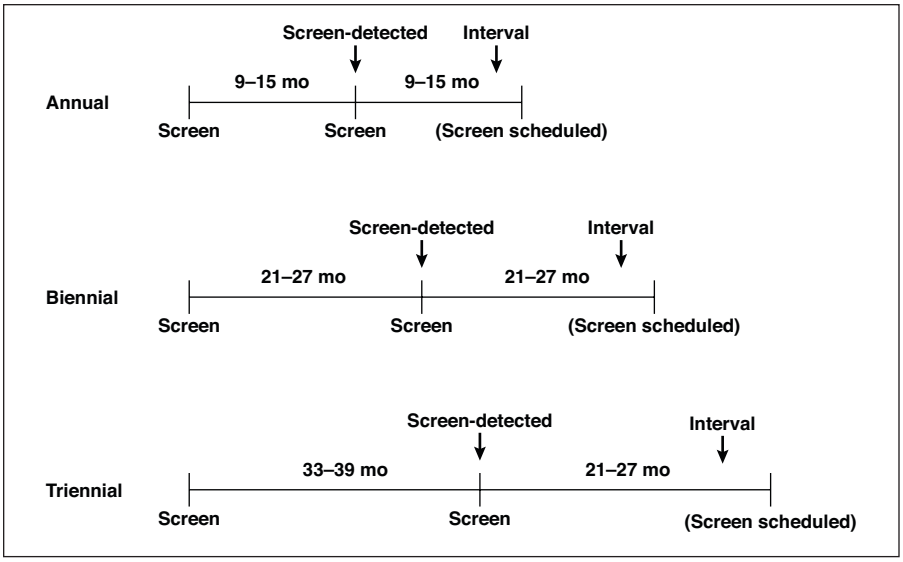

Fig. 2—Schematic shows classification of breast cancer as screen-detected or interval cancer for each screening frequency.

ing as every 21–27 months, and triennial screening as every 33–39 months (Fig. 2), similar to Miglioretti et al. [14]. Nonannual screening was defined as biennial and triennial. At least two screening mammography examinations before cancer diagnosis were required to establish each patient's screening interval. Interval cancer was defined as cancer diagnosed before a patient's next screening mammography examination as determined by the patient's screening frequency: annual, biennial, or triennial (Fig. 2). Patients with lobular carcinoma in situ and those transferred to our institution for management of newly diagnosed breast cancer were excluded. Electronic medical records were reviewed for patient demographics including age, menopausal status, hormone replacement therapy, high-risk status, family history, and race. Race was included because of a reported association between race and the risk of being diagnosed with more aggressive (triple negative) breast cancer [18]. When menopausal status was unknown, women age 55 years old or older were presumed to be postmenopausal.

During the 2016–2017 inclusion interval, digital mammography was interpreted on a routine clinical basis by 14 fellowship-trained Mammography Quality Standards Act–qualified breast imaging radiologists. Digital breast tomosynthesis was not used for routine screening. The same interpretation criteria were used for all screening and diagnostic cases; there was no institutional policy regarding mammography interpretation based on screening interval or breast density. Following a negative screening examination, patient letters were sent that referenced NCCN guidelines and acknowledged variability among professional societies regarding the recommended screening interval.

Cancer Characteristics and Treatment

We evaluated cancer characteristics including AJCC cancer stage [19], screen or clinical detection, tumor diameter at pathologic evaluation (or at diagnosis by imaging in patients who underwent neoadjuvant chemotherapy), axillary lymph node involvement, and histopathology. AJCC stage II or higher was considered late stage for this investigation. Treatment regimens were recorded, including extent of axillary lymph node surgery, use of chemotherapy or hormone therapy, and type of surgery (lumpectomy vs mastectomy). During the study period, a validated prognostic assay (Oncotype DX, Genomic Health) was used to guide treatment pertaining to chemotherapy and hormonal therapy at our institution [20–23].

Statistical Analysis

An a priori power calculation was performed to detect a 0.4-cm difference in mean tumor diameter between screening cohorts of interest using 90% power. Tumor volume was calculated as $4\pi \times \text{radius}^3 / 3$. Continuous variables were compared using *t* tests or Wilcoxon rank sum tests, and categoric variables were compared using chi-square tests or Fisher exact tests. Annual, biennial, and triennial screening groups were compared, as were annual versus nonannual (biennial and triennial) screening cohorts. Statistical analysis was performed among all women and among a subset of postmenopausal women to address considerations for biennial screening beginning at age 55 years old according to the American Cancer Society [3] and the American College of Obstetricians and Gynecologists [5]. SAS software (version 9.4, SAS Institute) and Excel (Microsoft) were used for all analyses. A *p* value less than .05 was considered to denote statistical significance.

Results

Patients

A total of 490 patients were diagnosed with primary breast cancer at our institution during the 2-year span. Of these, 245 were women age 40–84 years old (mean age, 61.8 ± 9.9 [SD] years) who had undergone annual, biennial, or triennial screening at the time of mammographic or clinical detection; six patients with breast cancer detected by nonmammographic imaging (three by ultrasound and three by MRI) were excluded. These 245 women made up the final study population (Fig. 1). Among these patients, 200 (81.2%) underwent annual screening, 32 (13.1%) underwent biennial screening, and 13 (5.3%) underwent triennial screening. The capture rate from breast imaging abnormality to image-guided biopsy was 99%.

No significant differences in baseline demographic characteristics were observed between the three groups with regard to age at

TABLE 1: Patient Characteristics of 245 Women With Breast Carcinoma

Characteristic	All Patients (*n* = 245)	Annual Screening (*n* = 200)	Biennial Screening (*n* = 32)	*p* (Annual vs Biennial)	Triennial Screening (*n* = 13)	Nonannual Screening[a] (*n* = 45)	*p* (Annual vs Nonannual)
Age at diagnosis (y)	61.8 ± 9.9	62.0 ± 9.9	60.2 ± 8.8	.32	61.5 ± 12.9	60.6 ± 10.4	.36
Postmenopausal	191 (78.0)	159 (79.5)	24 (75.0)	.31	8 (61.5)	32 (71.1)	.22
Current HRT	36 (14.7)	33 (16.5)	2 (6.3)	.18	1 (7.7)	3 (6.7)	.09
High-risk mutation	19 (7.8)	15 (7.5)	4 (12.5)	.33	0 (0)	4 (8.9)	.75
Positive family history	72 (29.4)	62 (31.0)	7 (21.9)	.29	3 (23.1)	10 (22.2)	.24
Race[b]							
Asian	13 (5.3)	13 (6.5)	0 (0)	.22	0 (0)	0 (0)	.08
Black	15 (6.1)	12 (6.0)	2 (6.3)	> .99	1 (7.7)	3 (6.7)	.86
Other	4 (1.6)	3 (1.5)	1 (3.1)	.45	0 (0)	1 (2.2)	.73
White	213 (86.9)	172 (86.0)	29 (90.6)	.58	12 (92.3)	41 (91.1)	.36

Note—Values are the mean ± SD or number of patients with column percentages in parentheses unless otherwise indicated. HRT = hormone replacement therapy.
[a]Biennial plus triennial screenings.
[b]Racial categories provided in this table reflect those reported in patient electronic medical records, in which additional specificity regarding the category "Other" was not available.

diagnosis, menopausal status, use of hormone replacement therapy, high-risk mutation, positive family history, or race (Table 1).

Cancer Characteristics

All women—Annual screening mammography was associated with fewer late-stage presentations compared with biennial (48/200 [24.0%] vs 14/32 [43.8%]; $p = .02$) and nonannual screening (20/45 [44.4%]; $p = .006$) (Table 2). Moreover, patients undergoing annual screening were less likely to present with an interval cancer compared with patients undergoing biennial (21/200 [10.5%] vs 12/32 [37.5%]; $p < .001$) or nonannual screening (15/45 [33.3%]; $p < .001$]). Mean tumor diameter was smaller among patients undergoing annual screening compared with biennial (1.4 ± 1.2 cm vs 1.8 ± 1.6 cm; $p = .04$) and nonannual screening (1.8 ± 1.5 cm; $p = .03$), representing an estimated increase in mean tumor volume by a factor of 2.1 with biennial or nonannual screening. Median tumor diameter was nonsignificantly smaller in the setting of annual screening versus biennial (1.1 ± 1.2 cm vs 1.2 ± 1.6 cm; $p = .09$) and nonannual screening (1.2 ± 1.5 cm; $p = .05$).

In total, 181 of 245 patients (73.9%) had invasive cancer. Ductal carcinoma in situ was more common among women screened annually versus biennially, though this finding was not statistically significant (56/200 [28.0%] vs 5/32 [15.6%]; $p = .14$). Cancer characteristics among the 245 patients are summarized in Table 2.

Postmenopausal women—Of the 245 women included, 191 (78.0%) were postmenopausal at the time of cancer diagnosis. Screening frequency in the postmenopausal subgroup was annual for 159 of these 191 patients (83.2%), biennial for 24 (12.6%),

TABLE 2: Cancer Characteristics in 245 Women With Breast Carcinoma

Characteristic	All Patients (*n* = 245)	Annual Screening (*n* = 200)	Biennial Screening (*n* = 32)	*p* (Annual vs Biennial)	Triennial Screening (*n* = 13)	Nonannual Screening[a] (*n* = 45)	*p* (Annual vs Nonannual)
Pathologic diagnosis							
Invasive ductal	166 (67.8)	135 (67.5)	24 (75.0)	.39	7 (53.8)	31 (68.9)	.85
Invasive lobular	15 (6.1)	9 (4.5)	3 (9.4)	.24	3 (23.1)	6 (13.3)	.02
Ductal carcinoma in situ	64 (26.1)	56 (28.0)	5 (15.6)	.14	3 (23.1)	8 (17.8)	.15
Interval cancer	36 (14.7)	21 (10.5)	12 (37.5)	< .001	3 (23.1)	15 (33.3)	< .001
Tumor diameter (cm)							
Mean ± SD	1.4 ± 1.2	1.4 ± 1.2	1.8 ± 1.6	.04	1.7 ± 1.4	1.8 ± 1.5	.03
Median ± SD	1.1 ± 1.2	1.1 ± 1.2	1.2 ± 1.6	.09	1.5 ± 1.4	1.2 ± 1.5	.05
Node positive	45 (18.4)	37 (18.5)	6 (18.8)	.97	2 (15.4)	8 (17.8)	.91
Mean no. of positive nodes (*n* = 45)	3.0 ± 3.7	2.8 ± 3.6	4.3 ± 4.9	.37	4.0 ± 2.8	4.3 ± 4.3	.31
Advanced AJCC stage (II, III, or IV)	68 (27.8)	48 (24.0)	14 (43.8)	.02	6 (46.2)	20 (44.4)	.006

Note—Values are the number of patients with column percentages in parentheses or the mean ± SD unless otherwise indicated.
[a]Biennial plus triennial screenings.

TABLE 3: Cancer Characteristics in 191 Postmenopausal Women With Breast Carcinoma

Characteristic	All Patients (*n* = 191)	Annual Screening (*n* = 159)	Biennial Screening (*n* = 24)	*p* (Annual vs Biennial)	Triennial Screening (*n* = 8)	Nonannual Screening[a] (*n* = 32)	*p* (Annual vs Nonannual)
Interval cancer	28 (14.7)	16 (10.1)	11 (45.8)	< .001	1 (12.5)	12 (37.5)	< .001
Tumor diameter (cm)							
Mean ± SD	1.4 ± 1.2	1.3 ± 1.0	1.8 ± 1.6	.04	1.7 ± 1.6	1.8 ± 1.6	.04
Median ± SD	1.1 ± 1.2	1.1 ± 1.0	1.2 ± 1.6	.27	1.4 ± 1.6	1.2 ± 1.6	.26
Advanced AJCC stage (II, III, or IV)	52 (27.2)	38 (23.9)	11 (45.8)	.02	3 (37.5)	14 (43.8)	.02

Note—Values are the number of patients with column percentages in parentheses unless otherwise indicated.
[a]Biennial plus triennial screenings.

and triennial for eight (4.2%). Annual screening mammography was associated with fewer late-stage presentations compared with biennial screening (38/159 [23.9%] vs 11/24 [45.8%]; $p = .02$) and nonannual screening (14/32 [43.8%]; $p = .02$). Postmenopausal patients undergoing annual screening mammography were also less likely to present with an interval cancer compared with those undergoing biennial screening (16/159 [10.1%] vs 11/24 [45.8%]; $p < .001$) or nonannual screening (12/32 [37.5%]; $p < .001$). Mean tumor diameter was smaller among postmenopausal patients undergoing annual screening compared with patients undergoing biennial (1.3 ± 1.0 cm vs 1.8 ± 1.6 cm; $p = .04$) or nonannual screening (1.8 ± 1.6 cm; $p = .04$), representing an estimated increase in mean tumor volume by a factor of 2.6 with biennial or nonannual screening. Median tumor diameter was nonsignificantly smaller among postmenopausal women in the setting of annual screening versus biennial (1.1 ± 1.0 cm vs 1.2 ± 1.6 cm; $p = .27$) and nonannual screening (1.2 ± 1.6 cm; $p = .26$). Table 3 summarizes the cancer characteristics among postmenopausal women.

Nodal Disease

Forty-five of the 245 women (18.4%) had positive lymph nodes. No significant differences in frequency of axillary lymph node positivity were observed among annual, biennial, and nonannual screening groups. Among the 45 patients with positive lymph nodes, those undergoing annual screening had nonsignificantly fewer positive lymph nodes compared with those undergoing biennial (2.8 ± 3.6 vs 4.3 ± 4.9; $p = .37$) and nonannual screening (4.3 ± 4.3; $p = .31$).

Histopathology

No significant differences in pathologic diagnosis were observed between annual and biennial screening groups; however, patients who underwent nonannual screening were more likely to be diagnosed with invasive lobular carcinoma compared with patients undergoing annual screening ($p = .02$).

Treatment

Women in the annual screening group were more likely not to undergo any axillary nodal surgery compared with those in the biennial or nonannual screening groups, though the differences were not statistically significant (annual, 43/200 [21.5%]; biennial, 5/32 [15.6%]; nonannual, 7/45 [15.6%]) (Table 4). Conversely, compared with patients undergoing annual screening, those undergoing biennial and nonannual screening showed nonsignificantly greater use of axillary lymph node dissection (annual, 24/200 [12.0%]; biennial, 6/32 [18.8%]; nonannual, 7/45 [15.6%]). Re-

TABLE 4: Treatment Regimens in 245 Women With Breast Carcinoma

Treatment	All Patients (*n* = 245)	Annual Screening (*n* = 200)	Biennial Screening (*n* = 32)	*p* (Annual vs Biennial)	Triennial Screening (*n* = 13)	Nonannual Screening[a] (*n* = 45)	*p* (Annual vs Nonannual)
Primary operation							
Lumpectomy	172 (70.2)	137 (68.5)	24 (75.0)	.53	11 (84.6)	35 (77.8)	.21
Mastectomy	73 (29.8)	63 (31.5)	8 (25.0)	.53	2 (15.4)	10 (22.2)	.21
Nodal surgery							
None	50 (20.4)	43 (21.5)	5 (15.6)	.48	2 (15.4)	7 (15.6)	.59
Sentinel node	164 (66.9)	133 (66.5)	21 (65.6)	.48	10 (76.9)	31 (68.9)	.59
ALND	31 (12.7)	24 (12.0)	6 (18.8)	.48	1 (7.7)	7 (15.6)	.59
Adjuvant therapy							
Chemotherapy	71 (29.0)	55 (27.5)	12 (37.5)	.81	4 (30.8)	16 (35.6)	.28
Hormone therapy	156 (63.7)	123 (61.5)	25 (78.1)	.35	8 (61.5)	33 (73.3)	.13

Note—Values are the number of patients with column percentages in parentheses unless otherwise indicated. Patients who received adjuvant therapy received chemotherapy, hormone therapy, or both. ALND = axillary lymph node dissection.
[a]Biennial plus triennial screenings.

garding adjuvant therapy, women with breast cancers diagnosed in the setting of annual screening mammography showed nonsignificantly less frequent use of chemotherapy compared with biennial and nonannual screening (annual, 55/200 [27.5%]; biennial, 12/32 [37.5%]; nonannual, 16/45 [35.6%]). Those undergoing annual screening also showed nonsignificantly less frequent use of hormone therapy compared with biennial and nonannual screening (annual, 123/200 [61.5%]; biennial, 25/32 [78.1%]; nonannual, 33/45 [73.3%]). Table 4 shows treatment regimens as a function of screening interval. Rates of lumpectomy versus mastectomy for primary surgical treatment of breast cancer were not associated with screening interval.

Discussion

Mammography is widely used for breast cancer screening. One study estimated that from 1990 to 2018, between 384,000 and 614,000 breast cancer deaths were averted by mammographic screening and advances in treatment [9]. Despite the large number of lives saved because of cancer detection with screening mammography, controversy persists regarding screening frequency for women at average risk for breast cancer [1–6]. In this study, among all women and among postmenopausal women analyzed separately, annual screening was associated with lower AJCC stage, fewer interval cancers, and smaller mean tumor size compared with biennial or nonannual screening.

Breast cancers categorized as a higher AJCC stage include larger cancers with varying degrees of lymph node involvement and metastatic disease and are associated with poorer outcomes and increased mortality [24]. Whereas tumor size is one component of AJCC stage, larger tumor size is also an independent predictor of increased mortality [16, 24–26]. Therefore, although mortality was not a measured outcome of this study, the observed reduction in tumor size associated with annual mammographic screening suggests a probable mortality benefit compared with biennial and nonannual screening in premenopausal and postmenopausal women combined and in postmenopausal women alone.

In addition to more favorable AJCC stage and smaller mean tumor size, annual screening in this study was also associated with fewer interval cancers compared with biennial and nonannual screening. Interval cancers—cancers that present clinically between screening intervals—are associated with worse prognosis and poorer outcomes than screen-detected breast cancers, likely because of more aggressive biology and increased metastatic potential [16, 25–27]. Hofvind et al. [26] found that interval breast cancers had a twofold higher hazard ratio for death compared with screen-detected breast cancers, independent of age, tumor size and characteristics, and lymph node involvement. Of note, invasive lobular carcinoma was more common among women who underwent nonannual screening in our study compared with annual screening; further study is needed to understand the reason for this observed difference.

Our data show that breast cancers diagnosed in the setting of annual screening require less extensive treatment, which is not surprising given the lower AJCC stage, fewer interval cancers, and smaller mean tumor size. Although differences in treatment were not statistically significant, axillary lymph node dissection, which is associated with lymphedema, paresthesia, and decreased upper extremity range of motion [28, 29], was less frequent in patients undergoing annual screening at the time of diagnosis. Chemotherapy and hormone or endocrine therapy also contribute to breast cancer morbidity and were less frequent in the annual screening cohort. Patients receiving chemotherapy may suffer from neuropathy, cardiomyopathy, and myelosuppression [30]. Meanwhile, hormone therapy may induce postmenopausal symptoms while increasing a patient's risk of developing endometrial cancer [30].

The results of this study support the recommendation for annual screening mammography for pre- and postmenopausal patients, consistent with annual screening recommendations by the American College of Radiology and NCCN, which recommend screening initiation at age 40 years old. Our results, including the postmenopausal subgroup analysis, are also consistent with Cancer Intervention and Surveillance Modeling Network (CISNET) models, which suggest a decrease in mortality with annual versus biennial screening. In CISNET models among women age 50–74 years old, a median mortality reduction of 25.8% has been shown with biennial screening compared with a 33.0% mortality reduction with annual screening; this absolute difference of 7.2% equates to a 27.9% greater relative mortality reduction with annual screening compared with biennial screening [7, 8].

In the general screening mammography population, our results show detection of lower breast cancer stage and smaller tumors with annual screening compared with biennial screening, which is similar to results of prior studies [14–16, 31]. Tabar et al. [27] suggested that shorter screening intervals would be particularly beneficial for detecting lower stage breast cancer in women age 40–49 years old, because tumors within this population tend to progress more quickly.

Conversely, in the postmenopausal cohort, our findings of lower AJCC stage and smaller tumor size with annual screening differ from Miglioretti et al. [14], who did not find a difference in stage or tumor size among postmenopausal women undergoing annual versus biennial screening. Our results in the postmenopausal cohort also differ from White et al. [15], who found no increase in late-stage breast cancer in women over 50 years old undergoing biennial screening compared with annual screening. Our finding of more interval cancers among postmenopausal women (and all women) undergoing biennial screening compared with annual screening is similar to Bennett et al. [17], who found increased interval cancers with biennial screening compared with annual screening in women age 50–64 years old.

Although previous studies have shown that reduced mortality is associated with screening mammography [9, 32], potential risks or harms also associated with screening mammography include overdiagnosis, false-positive callbacks, and benign biopsies. Model results show that frequency of screening does not have a large effect on invasive cancer overdiagnosis estimates (3.2/1000 vs 2.8/1000 in patients age 50–74 years old undergoing annual vs biennial screening, respectively) [7]. Type 1 overdiagnosis secondary to death during mammographic lead time is primarily seen in women over 80 years old [33]. Only 0.79% of women age 62 years old, the median age in our study, would be expected to die between 1 and 2 years after diagnosis, showing lead time differences to be minimal [34]. Indolent cancers (type 2 overdiagnosis) would be diagnosed at the same rate with either annual or biennial screening because, by definition, they would

not symptomatically present during the patient's lifetime. As such, screening intervals should not be a substantial contributor to overdiagnosis.

Regarding callbacks and benign biopsies, a small increase in false-positive findings on screening mammograms has been reported with annual screening compared with biennial screening in women 50–74 years old [6]. The benign biopsy rate for 10-year annual screening starting at age 40 years has been reported at 7.0 (0.70%/year) versus 4.8 (0.48%/year) for biennial screening [6]. However, Blanchard et al. [35] showed that the rate of benign biopsies actually decreased after several years in women undergoing annual screening compared with patients who did not undergo screening (0.25% per year with annual screening). Although the risks associated with annual screening persist, we suggest that greater harm is posed by excess late-stage cancer, larger tumors, and more interval cancers with biennial screening and nonannual screening.

This study has limitations, including its retrospective nature and lack of prospective randomization. It was performed at a single institution, though with a high number of patients and capture rate. Moreover, the population included an overwhelmingly high number of White patients. Although demographics were similar across screening cohorts, unknown case selection bias may have occurred, which could have influenced the results. The biennial and nonannual screening cohorts were relatively small because of patient and referring physician preference for annual screening. Notably, referring physician preference for annual screening mammography is not unique to the current study. Radhakrishnan et al. [36] conducted a survey of internal medicine physicians, family medicine physicians, and gynecologists and found the majority recommended annual screening mammography. We used digital mammography in our study but not digital breast tomosynthesis. Our study did not evaluate age at initiation of screening, surgically indicated versus patient-requested mastectomy, overdiagnosis, callback rate, or benign biopsy rate associated with annual versus biennial or nonannual screening.

Conclusion

In conclusion, annual screening mammography was associated with lower breast cancer stage and fewer interval cancers compared with biennial or nonannual screening in premenopausal and postmenopausal women. Screening mammography performed at intervals greater than 1 year may result in increased mortality for women diagnosed with breast cancer.

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