Breast Tumor Prognostic Characteristics and Biennial vs Annual Mammography, Age, and Menopausal Status

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IMPORTANCE Screening mammography intervals remain under debate in the United States.

OBJECTIVE To compare the proportion of breast cancers with less vs more favorable prognostic characteristics in women screening annually vs biennially by age, menopausal status, and postmenopausal hormone therapy (HT) use.

DESIGN, SETTING, AND PARTICIPANTS This was a study of a prospective cohort from 1996 to 2012 at Breast Cancer Surveillance Consortium facilities. A total of 15 440 women ages 40 to 85 years with breast cancer diagnosed within 1 year of an annual or within 2 years of a biennial screening mammogram.

EXPOSURES We updated previous analyses by using narrower intervals for defining annual (11-14 months) and biennial (23-26 months) screening.

MAIN OUTCOMES AND MEASURES We defined less favorable prognostic characteristics as tumors that were stage IIB or higher, size greater than 15 mm, positive nodes, and any 1 or more of these characteristics. We used log-binomial regression to model the proportion of breast cancers with less favorable characteristics following a biennial vs annual screen by 10-year age groups and by menopausal status and current postmenopausal HT use.

RESULTS Among 15 440 women with breast cancer, most were 50 years or older (13 182 [85.4%]), white (12 063 [78.1%]), and postmenopausal (9823 [63.6%]). Among 2027 premenopausal women (13.1%), biennial screeners had higher proportion of tumors that were stage IIB or higher (relative risk [RR], 1.28 [95% CI, 1.01-1.63]; P = .04), size greater than 15 mm (RR, 1.21 [95% CI, 1.07-1.37]; P = .002), and with any less favorable prognostic characteristic (RR, 1.11 [95% CI, 1.00-1.22]; P = .047) compared with annual screeners. Among women currently taking postmenopausal HT, biennial screeners tended to have tumors with less favorable prognostic characteristics compared with annual screeners; however, 95% CIs were wide, and differences were not statistically significant (for stage 2B+, RR, 1.14 [95% CI, 0.89-1.47]; P = .29; size >15 mm, RR, 1.13 [95% CI, 0.98-1.31], P = .09; node positive, RR, 1.18 [95% CI, 0.98-1.42], P = .09; any less favorable characteristic, RR, 1.12 [95% CI, 1.00-1.25], P = .053). The proportions of tumors with less favorable prognostic characteristics were not significantly larger for biennial vs annual screeners among postmenopausal women not taking HT (eg, any characteristic: RR, 1.03 [95% CI, 0.95-1.12]; P = .45), postmenopausal HT users after subdividing by type of hormone use (eg, any characteristic: estrogen + progestogen users, RR, 1.16 [95% CI, 0.91-1.47]; P = .22; estrogen-only users, RR, 1.14 [95% CI, 0.94-1.37]; P = .18), or any 10-year age group (eg, any characteristic: ages 40-49 years, RR, 1.04 [95% CI, 0.94-1.14]; P = .48; ages 50-59 years, RR, 1.03 [95% CI, 0.94-1.12]; P = .58; ages 60-69 years, RR, 1.07 [95% CI, 0.97-1.19]; P = .18; ages 70-85 years, RR, 1.05 [95% CI, 0.94-1.18]; P = .35).

CONCLUSIONS AND RELEVANCE Premenopausal women diagnosed as having breast cancer following biennial vs annual screening mammography are more likely to have tumors with less favorable prognostic characteristics. Postmenopausal women not using HT who are diagnosed as having breast cancer following a biennial or annual screen have similar proportions of tumors with less favorable prognostic characteristics.
The frequency at which women should receive screening mammography remains controversial in the United States. In 2009, the US Preventive Services Task Force (USPSTF) updated their breast cancer screening guidelines to recommend routine biennial mammography for women ages 50 to 74 years, based on modeling evidence suggesting that the harms of more frequent screening outweigh the small estimated added benefit of annual screening.\(^2\)\(^\text{,}\)\(^3\) In contrast, some organizations, such as the American Cancer Society\(^3\)\(^\text{,}\) and other groups,\(^4\)\(^\text{,}\)\(^5\)\(^\text{,}\)\(^6\) have for decades recommended annual screening starting at age 40 years. However, during this time, mammography accuracy has improved,\(^7\)\(^\text{,}\)\(^8\) new breast cancer treatments have been developed, and interest in tailoring screening recommendations to individual risk to maximize the balance of benefits vs harms has increased.\(^9\)\(^\text{,}\)\(^10\)\(^\text{,}\)\(^11\)\(^\text{,}\)\(^12\)\(^\text{,}\)\(^13\)

No head-to-head randomized controlled trials (RCTs) have compared annual with biennial screening. Thus, recommended screening intervals have mainly been influenced by interval cancer rates\(^14\)\(^\text{,}\)\(^15\) and inferential evidence on tumor growth rates observed in trials.\(^16\) Based on tumor biology, some have argued that screening intervals should be shorter for younger women, whereas less frequent screening may be sufficient for women 50 years or older.\(^16\)\(^\text{,}\)\(^17\)\(^\text{,}\)\(^18\)\(^\text{,}\)\(^19\) New RCTs comparing screening mammography intervals with mortality end points are impractical; thus, today screening interval guidelines must rely on observational data\(^20\)\(^\text{,}\)\(^21\)\(^\text{,}\)\(^22\)\(^\text{,}\)\(^23\)\(^\text{,}\)\(^24\)\(^\text{,}\)\(^25\) and modeling.\(^26\)\(^\text{,}\)\(^27\)\(^\text{,}\)\(^28\)\(^\text{,}\)\(^29\)\(^\text{,}\)\(^30\)\(^\text{,}\)\(^31\)\(^\text{,}\)\(^32\)

The Breast Cancer Surveillance Consortium (BCSC) has published several large empirical studies comparing the benefits and harms of different screening intervals.\(^20\)\(^\text{,}\)\(^21\)\(^\text{,}\)\(^22\)\(^\text{,}\)\(^23\)\(^\text{,}\)\(^24\)\(^\text{,}\)\(^25\) These observational data suggest no difference in the proportion of advanced-stage invasive cancers with annual compared with biennial screening overall or for women 50 years or older. These analyses classified all women with 2 screening mammograms 9 to 30 months apart as annual screeners (median, 13 months [range, 9-18 months]) vs biennial screeners (median 24 months [range, 19-30 months]). Given the broad ranges used, these prior studies may not address subgroups of women who closely adhere to screening guidelines or evaluate whether screening at intervals more closely approximating 12 vs 24 months influences tumor characteristics in subgroups of women undergoing screening. To more specifically determine if annual vs biennial screening is associated with more favorable prognostic characteristics in younger or older women, we updated our prior analyses using more recent data and narrower definitions for annual (11-14 months) and biennial (23-26 months) screening. We evaluated whether proportions of tumors with less favorable vs more favorable prognostic characteristics differed by annual vs biennial screening in subgroups of women identified by age, menopausal status, and postmenopausal hormone therapy (HT) use.

### Methods

#### Study Setting and Data Sources

We used data from the BCSC (http://breastscreening.cancer.gov).\(^32\) The BCSC registries collect patient and clinical information from community radiation facilities with populations similar to that of the US population.\(^33\) Breast cancer diagnoses and tumor characteristics are obtained by linking with pathology databases; regional Surveillance, Epidemiology, and End Results (SEER) programs; and state tumor registries, with estimated completeness of reporting greater than 94.3%.\(^34\) The BCSC registries and the Statistical Coordinating Center received institutional review board approval for active or passive consenting processes or a waiver of consent to enroll participants, link and pool data, and perform analysis. All procedures were Health Insurance Portability and Accountability Act compliant, and registries and the Coordinating Center received a Federal Certificate of Confidentiality and other protections for the identities of women, physicians, and facilities.

#### Participants and Study Design

Women ages 40 to 85 years were included if diagnosed from 1996 to 2012 with an incident invasive breast cancer or ductal carcinoma in situ (DCIS), either as a screen-detected or interval cancer, and who had had at least 2 screening mammography examinations 11 to 14 or 23 to 26 months apart before diagnosis. The time between the 2 screening examinations was used to classify women as annual (11-14 months) or biennial (23-26 months) screeners.

We aimed to capture 2 mechanisms by which breast cancers with less favorable characteristics might result from a longer vs a shorter screening interval: (1) more tumor growth between 2 screening mammograms, leading to more advanced disease at screen detection, and (2) more time for a tumor to become symptomatic and clinically detected, and therefore more likely to be advanced, after a negative screening mammogram (Figure). Thus, we included both screen-detected and interval breast cancers diagnosed within 1 year of an annual screening mammogram or 2 years of a biennial screening mammogram, as would be done in the analysis of an RCT. Breast cancers following a positive screening mammogram were considered screen detected, and those following a negative screening mammogram were considered interval cancers using standard BCSC definitions for classifying mammography results.\(^35\) Only mammograms that occurred at least 1 year before the end of complete capture of cancers by the BCSC for annual mammograms and at least 2 years for biennial mammograms were included.

#### Measures and Definitions

Screening mammograms were defined using the indication reported by the radiologist or technologist. To minimize misclassification of diagnostic mammography as screening, we excluded...
cluded examinations that were unilateral or were preceded by mammography or breast ultrasonography within 9 months.

Women completed a questionnaire at each mammography examination to collect information on race and ethnicity, history of first-degree relatives (mother, sister, or daughter) with breast cancer, menopausal status, current postmenopausal HT use, and history of hysterectomy. If self-reported race/ethnicity was missing, we used information from cancer registries. Women were considered postmenopausal if they reported currently having periods or using oral contraceptives.36 Women were considered to have missing menopausal status if they were younger than 55 years and reported having had a hysterectomy without bilateral oophorectomy and were not using HT, or if menopausal status could not be determined based on available information. Postmenopausal women were classified by HT use. Women using HT with nonmissing hysterectomy information (53%) were included in subanalysis by HT type. Women with a uterus using HT were classified as using estrogen plus progestogen; women without a uterus using HT were classified as using estrogen only, based on clinical practice, as previously described.22,37

Four outcomes measured less favorable prognostic characteristics: American Joint Committee on Cancer (AJCC) 38 stage IIB or higher; tumor size greater than 15 mm; positive nodes; and a measure of any 1 or more of these characteristics. For 262 women missing AJCC stage (3% of invasive cancers), stage IIB or higher was imputed based on tumor size or extension, nodal status, metastasis, or SEER summary stage, as previously described.22 In sensitivity analyses to evaluate our choices for stage and size thresholds, we classified tumors as stage IIA or higher and size greater than 20 mm.

Statistical Analysis
We described the participant population by screening interval. We estimated the proportion of women with invasive cancer vs DCIS. Among women with invasive cancer, we estimated the distribution of tumor characteristics (stage, size, lymph node status) at diagnosis by screening interval, and separately by age group and by menopausal status and HT use. Among women with invasive breast cancer, we used log-binomial regression39 to estimate relative risks (RRs) and 95% CIs of less favorable vs more favorable invasive tumor characteristics associated with screening interval by age group and by menopausal status and postmenopausal HT use, adjusting for race/ethnicity, first-degree family history of breast cancer, and BCSC registry. In one case for which the log-binomial model could not be estimated, we used Poisson regression with robust error variances. This approach gave results very similar to those of log-binomial regression in cases that could be estimated using both methods. Based on the observed numbers of women with invasive breast cancer, we had 80% power with a 2-sided α of .05 to detect RRs within age and menopausal status groups of approximately 1.25 to 1.35 for stage IIB or higher, 1.20 to 1.30 for positive nodes, and 1.10 to 1.20 for tumors greater than 15 mm and the measure of any 1 or more characteristics. For analyses subdivided by HT type, we had 80% power to detect an RR of 1.25–1.55. We performed analyses with SAS statistical software (version 9.2; SAS Institute Inc).

Results
Among 15,440 women with breast cancer, most were 50 years or older (13,182 [85.4%], white (12,063 [78.1%]), and postmenopausal (9,823 [63.6%]) (Table 1). Biennial screeners were more likely to be in the youngest (40–49 years) or oldest (70–85 years) age groups and less likely than annual screeners to have a family history of breast cancer. Among annual screeners, 77.8% of cancers were screen detected compared with 72.8% for biennial screeners.

The proportion of DCIS vs invasive cancers and the proportion of invasive tumors associated with less favorable vs more favorable prognostic characteristics decreased with age (Table 2). For example, 21.3% to 24.2% of women ages 40 to 49 years diagnosed as having an invasive cancer after an annual or biennial screen had tumors that were stage IIB or higher, compared with 16.4% or less among women 60 years or older. Within age groups, the proportions of invasive tumors vs DCIS were similar among annual vs biennial screeners. Only small and inconsistent differences were seen in the proportions of invasive tumors with more favorable vs less favorable characteristics for annual vs biennial screeners.

Premenopausal women (2027 [13.1%]) had higher proportions of DCIS vs invasive cancers and invasive tumors with less favorable prognostic characteristics than postmenopausal women (Table 3). For example, 19.8% to 25.7% of premenopausal women diagnosed as having an invasive cancer after an annual or biennial screen had tumors that were stage IIB or higher compared with 13.2% to 15.8% of postmenopausal...
women not using HT and 16.1% to 18.4% of HT users. Within most groups, the proportions of invasive tumors vs DCIS were similar among annual vs biennial screeners; however, postmenopausal women not using HT had a higher proportion of invasive cancers if they were screened biennially compared with annually. Among premenopausal women, women screened biennially vs annually had a higher proportion of stage IIB or higher tumors (25.7% vs 19.8%), tumors greater than 15 mm (65.3% vs 54.6%), and node-positive disease (36.6% vs 31.3%). Differences in these tumor characteristics among postmenopausal women were small and inconsistent, regardless of HT use.

We calculated the RRs of less favorable tumor characteristics for women with invasive breast cancer following a biennial vs annual screen, adjusting for race/ethnicity, family history of breast cancer, and BCSC registry (Table 4). Within age groups, RR estimates were close to 1 with no significant differences between biennial vs annual screeners. However, among premenopausal women, compared with annual screeners, biennial screeners were at increased risk of stage IIB or higher tumors (RR, 1.28 [95% CI, 1.01-1.63]; \( P = .04 \)), tumors greater than 15 mm (RR, 1.21 [95% CI, 1.07-1.37]; \( P = .002 \)), and tumors with any less favorable prognostic characteristic (RR, 1.11 [95% CI, 1.00-1.22]; \( P = .047 \)). Among postmenopausal women not using HT at the time of the mammogram, RR estimates were close to 1 with no significant differences between biennial vs annual screeners except for a modest increased risk of tumors greater than 15 mm (RR, 1.11 [95% CI, 1.00-1.22]; \( P = .045 \)). Among postmenopausal women using HT at the time of the mammogram, RR estimates for biennial vs annual screeners were consistently higher than 1, with nonsignificant increases in risk of tumors greater than 15 mm (RR, 1.13 [95% CI, 0.98-1.31]; \( P = .09 \)), positive lymph nodes (RR, 1.18 [95% CI, 0.98-1.42]; \( P = .09 \)), and tumors with less favorable prognosis (RR, 1.12 [95% CI, 1.00-1.25]; \( P = .05 \)). Subdividing HT users with known hysterectomy status by the likely type of HT used did not change most results, which remained statistically nonsignificant except for increased risk of tumors greater than 15 mm among biennial vs annual screeners using estrogen plus progestogen (RR, 1.38 [95% CI, 1.04-1.82]; \( P = .02 \)). Sensitivity analyses that classified tumors as IIA or higher or size greater than 20 mm did not substantially change results (data not shown).

**Discussion**

Premenopausal women diagnosed as having invasive breast cancer following a biennial screening mammogram were more likely to have tumors with less favorable prognostic characteristics than women diagnosed following an annual screening mammogram. In contrast, postmenopausal women diagnosed as having invasive breast cancer after biennial vs annual screening showed no statistically significant differences in the likelihood of less favorable prognostic characteristics, with the exception of small but non–statistically significant differences among women currently taking postmenopausal HT. We found no statistically significant differences in breast tumor prognostic characteristics for biennial vs annual screeners within 10-year age groups.

Our findings suggest that menopausal status may be more important than age when considering breast cancer screening intervals, which is biologically plausible. Tumors exposed to estrogen may grow faster, decreasing the detectable preclinical phase and resulting in a higher proportion of interval cancers with poorer tumor characteristics.\(^\text{14,15,16}^\) In addition, breast den-

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**Table 1. Population Characteristics by Screening Interval for Women With Breast Cancer Who Underwent Screening Mammography, 1996 to 2011**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women per Screening Interval, %&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Annual</td>
</tr>
<tr>
<td>Total No. of women</td>
<td>12 070</td>
</tr>
<tr>
<td>Screening interval, median, mo</td>
<td>13</td>
</tr>
<tr>
<td>Age range, y</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>13.6</td>
</tr>
<tr>
<td>50-59</td>
<td>29.7</td>
</tr>
<tr>
<td>60-69</td>
<td>29.4</td>
</tr>
<tr>
<td>70-85</td>
<td>27.3</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>78.4</td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>4.5</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4.5</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>4.9</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>0.4</td>
</tr>
<tr>
<td>Other or mixed race</td>
<td>1.1</td>
</tr>
<tr>
<td>Unknown</td>
<td>6.3</td>
</tr>
<tr>
<td>Menopausal status</td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>12.6</td>
</tr>
<tr>
<td>Postmenopausal without hormone therapy use</td>
<td>42.5</td>
</tr>
<tr>
<td>Postmenopausal with hormone therapy use</td>
<td>21.8</td>
</tr>
<tr>
<td>Surgical menopausal or unknown</td>
<td>23.1</td>
</tr>
<tr>
<td>Type of postmenopausal hormone therapy use at screen&lt;sup&gt;b&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Estrogen + progestogen</td>
<td>46.3</td>
</tr>
<tr>
<td>Estrogen only</td>
<td>53.7</td>
</tr>
<tr>
<td>First-degree family history of breast cancer</td>
<td></td>
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<tr>
<td>Yes</td>
<td>23.3</td>
</tr>
<tr>
<td>No</td>
<td>67.4</td>
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<tr>
<td>Unknown</td>
<td>9.3</td>
</tr>
<tr>
<td>Type of detection&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Screen detected (true-positive screen)</td>
<td>77.8</td>
</tr>
<tr>
<td>Interval detected (false-negative screen)</td>
<td>22.2</td>
</tr>
</tbody>
</table>

<sup>a</sup> Annual cancers diagnosed within 12 months of screening examination performed 11 to 14 months after prior mammogram; biennial cancers diagnosed within 24 months of screening examination performed 23 to 26 months after prior mammogram.

<sup>b</sup> Restricted to 1767 women with known hysterectomy status: women with uterus assumed to use estrogen plus progestogen; without uterus assumed to use estrogen only.

<sup>c</sup> Screen-detected breast cancer diagnosed after a positive screening mammography result and interval breast cancer detected after a negative screening mammography result and before the next screening examination.
Breast Tumor Characteristics and Biennial vs Annual Mammography

Table 2. Distribution of Tumor Characteristics by Age and Screening Interval

<table>
<thead>
<tr>
<th>Tumor Characteristic</th>
<th>Screening Interval* by Age Range, Years, %</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-85</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Annual</td>
<td>Biennial</td>
<td>Annual</td>
<td>Biennial</td>
<td>Annual</td>
</tr>
<tr>
<td>Breast cancers, No. (n = 15 440)</td>
<td>1645</td>
<td>613</td>
<td>3579</td>
<td>923</td>
<td>3549</td>
</tr>
<tr>
<td>DCIS (n = 3140)</td>
<td>26.3</td>
<td>27.4</td>
<td>24.4</td>
<td>22.0</td>
<td>20.7</td>
</tr>
<tr>
<td>Invasive (n = 12 100)</td>
<td>73.7</td>
<td>72.6</td>
<td>75.6</td>
<td>78.0</td>
<td>79.3</td>
</tr>
<tr>
<td>AJCC stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive cancers, No.</td>
<td>1137</td>
<td>416</td>
<td>2460</td>
<td>665</td>
<td>2542</td>
</tr>
<tr>
<td>Stage I</td>
<td>54.9</td>
<td>51.0</td>
<td>57.2</td>
<td>56.4</td>
<td>62.3</td>
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<tr>
<td>Stage IIA</td>
<td>23.6</td>
<td>24.3</td>
<td>22.7</td>
<td>24.4</td>
<td>21.0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>12.3</td>
<td>13.2</td>
<td>10.9</td>
<td>9.6</td>
<td>8.9</td>
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<tr>
<td>Stage III or IV</td>
<td>9.2</td>
<td>11.5</td>
<td>9.2</td>
<td>9.6</td>
<td>7.8</td>
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<tr>
<td>AJCC stage IIB or higherb</td>
<td>1155</td>
<td>425</td>
<td>2532</td>
<td>680</td>
<td>2616</td>
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<tr>
<td>Invasive cancers, No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21.3</td>
<td>24.2</td>
<td>19.7</td>
<td>19.0</td>
<td>16.4</td>
</tr>
<tr>
<td>No</td>
<td>78.7</td>
<td>75.8</td>
<td>80.3</td>
<td>81.0</td>
<td>83.6</td>
</tr>
<tr>
<td>Tumor size, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Invasive cancers, No.</td>
<td>1171</td>
<td>426</td>
<td>2597</td>
<td>690</td>
<td>2673</td>
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<tr>
<td>&lt;10</td>
<td>23.7</td>
<td>20.2</td>
<td>27.8</td>
<td>23.9</td>
<td>30.6</td>
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<tr>
<td>10 to &lt;15</td>
<td>22.6</td>
<td>17.1</td>
<td>22.9</td>
<td>24.2</td>
<td>24.3</td>
</tr>
<tr>
<td>15 to 20</td>
<td>23.0</td>
<td>28.6</td>
<td>21.0</td>
<td>24.1</td>
<td>20.4</td>
</tr>
<tr>
<td>&gt;20</td>
<td>30.7</td>
<td>34.0</td>
<td>28.2</td>
<td>27.8</td>
<td>24.8</td>
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<tr>
<td>Lymph node, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Invasive cancers, No.</td>
<td>1189</td>
<td>435</td>
<td>2621</td>
<td>692</td>
<td>2725</td>
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<tr>
<td>Positive</td>
<td>32.5</td>
<td>35.9</td>
<td>28.9</td>
<td>30.5</td>
<td>24.3</td>
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<tr>
<td>Negative</td>
<td>67.5</td>
<td>64.1</td>
<td>71.1</td>
<td>69.5</td>
<td>75.7</td>
</tr>
<tr>
<td>≥1 Less favorable characteristicc</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Invasive cancers, No.</td>
<td>1171</td>
<td>425</td>
<td>2545</td>
<td>685</td>
<td>2627</td>
</tr>
<tr>
<td>Any</td>
<td>59.1</td>
<td>63.1</td>
<td>54.0</td>
<td>53.7</td>
<td>48.6</td>
</tr>
<tr>
<td>None</td>
<td>40.9</td>
<td>36.9</td>
<td>46.0</td>
<td>46.3</td>
<td>51.4</td>
</tr>
</tbody>
</table>

Abbreviations: AJCC, American Joint Committee on Cancer; DCIS, ductal carcinoma in situ.

* Annual includes cancers diagnosed within 12 months of screening examination performed 11 to 14 months after prior mammogram. Biennial includes cancers diagnosed within 24 months of screening examination performed 23 to 26 months after prior mammogram.

b AJCC stage IIB or higher was imputed based on tumor size or extension, nodal status, metastasis, or Surveillance, Epidemiology, and End Results summary stage, when available, for women missing AJCC stage.

c Stage IIB or higher, tumor size greater than 15 mm, or positive node status.

sity decreases after menopause, making it easier to diagnose breast cancers when they are smaller.8,40,41 In our sample of premenopausal women with breast cancer, 70% were ages 40 to 49 years, and 30% were ages 50 to 54 years. In a study of all women in the BCSC, only 10% of women ages 40 to 49 years were postmenopausal, and 25% of women ages 50 to 54 years were premenopausal.36 Thus, if screening guidelines were based on menopausal status rather than age, some women ages 40 to 54 years might be recommended for more frequent screening and others, less frequent screening.

Our study refines prior BCSC studies20-25 that used wider screening intervals to classify women as annual or biennial screeners. Similar to our study, these prior studies found no difference in the proportion of invasive cancers with less favorable prognostic characteristics with biennial vs annual screening for women 50 years or older.20-22 In contrast to our study, White et al20 found that women ages 40 to 49 years were less likely to have late- vs early-stage invasive cancer if screened annually compared with biennially; however, an updated analysis with more recent data that included digital mammography found no difference by screening interval in the proportions of late-stage disease for women ages 40 to 49 years, consistent with our findings.21 Kerlikowske et al22 found a significantly higher proportion of less favorable tumors with biennial vs annual screening in women ages 40 to 49 years but only among women with extremely dense breasts; however, 95% CIs were wide within density groups. Buist et al18 showed the higher interval cancer rates in women ages 40 to 49 years compared with those of older women observed in RCTs were still evident in modern (film-screen–based) service screening, which they attributed to younger women having faster-growing tumors and greater mammographic breast density.

In other prior BCSC analyses, O’Meara and colleagues25 compared intervals within racial and ethnic groups. Biennial vs annual screening was not associated with overall increased risk of less favorable tumor characteristics among...
women who were white, black, or Hispanic and ages 40 to 49 years, or among Asian women ages 50 to 74 years; however, Hispanic women ages 50 to 74 years who were screened biennially vs annually had an increased risk of late-stage disease and larger tumors, and Asian women ages 40 to 49 years who were screened biennially were at high risk of a node-positive diagnosis. Dittus et al23 observed that premenopausal obese women undergoing biennial screening had a non–statistically significantly increased risk of diagnosis with a tumor greater than 20 mm relative to annual screeners. In contrast, across all body mass index categories, postmenopausal women undergoing biennial screening vs annual screening did not present with more advanced stage or larger tumor sizes. Braithwaite et al24 examined tumor characteristics among women ages 66 to 89 years and found no statistically significant difference in adverse tumor characteristics by screening interval within age-by-comorbidity subgroups. Kerlikowske et al22 found that women ages 50 to 74 years undergoing biennial screening mammography had a risk of advanced-stage disease similar to that of women undergoing annual mammography within subgroups defined by HT use and breast density.

These findings add to the body of evidence that is providing greater confidence in the potential for advising women and their clinicians about screening frequency based on personal risk factors. When considering recommendations regarding screening intervals, the potential benefit of diagnosing cancers at an earlier stage must be weighed against the increased potential for harms associated with more frequent screening, such as false-positive recalls and biopsies, which are 1.5 to 2 times higher in annual vs biennial screeners.2,21-25,29,30 Future studies should focus on strategies to reduce these harms.

### Table 3. Distribution of Tumor Characteristics by Annual (A) or Biennial (B) Screening Interval, Menopausal Status, and Postmenopausal HT Use

<table>
<thead>
<tr>
<th>Tumor Characteristic</th>
<th>Menopausal Status</th>
<th>Postmenopausal Without HT Use</th>
<th>With HT Use</th>
<th>Type of HT Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Premenopausal A</td>
<td>B</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Breast cancers, % (n = 11 850)</td>
<td>1525</td>
<td>502</td>
<td>5130</td>
<td>1353</td>
</tr>
<tr>
<td>DCIS, % (n = 2469)</td>
<td>24.1</td>
<td>27.7</td>
<td>21.6</td>
<td>16.9</td>
</tr>
<tr>
<td>Invasive, % (n = 9381)</td>
<td>75.9</td>
<td>72.3</td>
<td>78.4</td>
<td>83.1</td>
</tr>
<tr>
<td>AJCC stage, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive cancers, No.</td>
<td>1074</td>
<td>339</td>
<td>3605</td>
<td>1027</td>
</tr>
<tr>
<td>Stage I</td>
<td>54.2</td>
<td>46.9</td>
<td>64.4</td>
<td>63.5</td>
</tr>
<tr>
<td>Stage II A</td>
<td>25.8</td>
<td>26.8</td>
<td>19.5</td>
<td>22.9</td>
</tr>
<tr>
<td>Stage II B</td>
<td>10.5</td>
<td>13.6</td>
<td>9.0</td>
<td>6.8</td>
</tr>
<tr>
<td>Stage III or IV</td>
<td>9.5</td>
<td>12.7</td>
<td>7.1</td>
<td>6.8</td>
</tr>
<tr>
<td>AJCC stage II B or higher, %c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive cancers, No.</td>
<td>1095</td>
<td>346</td>
<td>3720</td>
<td>1071</td>
</tr>
<tr>
<td>Yes</td>
<td>19.8</td>
<td>25.7</td>
<td>15.8</td>
<td>13.2</td>
</tr>
<tr>
<td>No</td>
<td>80.2</td>
<td>74.3</td>
<td>84.2</td>
<td>86.8</td>
</tr>
<tr>
<td>Tumor size, mm, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive cancers, No.</td>
<td>1123</td>
<td>349</td>
<td>3841</td>
<td>1073</td>
</tr>
<tr>
<td>&lt;10</td>
<td>22.4</td>
<td>21.2</td>
<td>33.2</td>
<td>29.1</td>
</tr>
<tr>
<td>10 to &lt;15</td>
<td>23.1</td>
<td>13.5</td>
<td>23.6</td>
<td>25.0</td>
</tr>
<tr>
<td>15 to 20</td>
<td>24.1</td>
<td>26.9</td>
<td>18.6</td>
<td>22.6</td>
</tr>
<tr>
<td>&gt;20</td>
<td>30.5</td>
<td>38.4</td>
<td>24.6</td>
<td>23.4</td>
</tr>
<tr>
<td>Lymph node, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive cancers, No.</td>
<td>1130</td>
<td>355</td>
<td>3882</td>
<td>1088</td>
</tr>
<tr>
<td>Positive</td>
<td>31.3</td>
<td>36.6</td>
<td>21.3</td>
<td>20.7</td>
</tr>
<tr>
<td>Negative</td>
<td>68.7</td>
<td>63.4</td>
<td>78.7</td>
<td>79.3</td>
</tr>
<tr>
<td>Composite measure of any less favorable characteristic, %d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive cancers, No.</td>
<td>1105</td>
<td>349</td>
<td>3735</td>
<td>1062</td>
</tr>
<tr>
<td>Any</td>
<td>59.7</td>
<td>65.6</td>
<td>46.5</td>
<td>46.5</td>
</tr>
<tr>
<td>None</td>
<td>40.3</td>
<td>34.4</td>
<td>53.5</td>
<td>53.5</td>
</tr>
</tbody>
</table>

Abbreviations: AJCC, American Joint Committee on Cancer; DCIS, ductal carcinoma in situ; HT, hormone therapy.

* Analysis restricted to women with known hysterectomy status. Women with a uterus were assumed to be using estrogen plus progesterone. Women without a uterus were assumed to be using estrogen only.

* Annual includes cancers diagnosed within 12 months of screening examination performed 11 to 14 months after prior mammogram; biennial includes cancers diagnosed within 24 months of screening examination performed 23 to 26 months after prior mammogram.

* AJCC stage II B or higher was imputed based on tumor size or extension, nodal status, metastasis, or Surveillance, Epidemiology, and End Results summary stage, when available, for women missing AJCC stage.

* Stage II B or higher, tumor size greater than 15 mm, or positive node.
Table 4. Less Favorable Invasive Cancer Characteristics for Biennial vs Annual Screeners*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tumor Prognostic Characteristic, RR (95% CI)</th>
<th>Lymph Node Positive vs Negative</th>
<th>Less vs More Favorable Prognostic Characteristics*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stage IIB, III, or IV vs I or IIA</td>
<td>Tumor Size &gt;15 vs ≤15 mm</td>
<td></td>
</tr>
<tr>
<td>Age range, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>1.17 (0.93–1.46)</td>
<td>1.10 (0.98–1.25)</td>
<td>1.09 (0.92–1.29)</td>
</tr>
<tr>
<td>50–59</td>
<td>0.98 (0.80–1.21)</td>
<td>1.09 (0.97–1.21)</td>
<td>1.05 (0.90–1.22)</td>
</tr>
<tr>
<td>60–69</td>
<td>0.99 (0.79–1.24)</td>
<td>1.13 (1.00–1.27)</td>
<td>0.93 (0.78–1.12)</td>
</tr>
<tr>
<td>70–85</td>
<td>0.98 (0.76–1.27)</td>
<td>1.13 (0.99–1.29)</td>
<td>0.91 (0.74–1.12)</td>
</tr>
</tbody>
</table>

Menopausal status

|                                |                                             |                                 |                                                  |
| Premenopausal                  | 1.28 (1.01–1.63)                           | 1.21 (1.07–1.37)                | 1.15 (0.96–1.38)                                 |
| Postmenopausal, without HT use | 0.95 (0.79–1.15)                           | 1.11 (1.00–1.22)                | 0.89 (0.77–1.04)                                 |
| Postmenopausal, with HT use    | 1.14 (0.89–1.47)                           | 1.13 (0.98–1.31)                | 1.18 (0.98–1.42)                                 |
| Estrogen plus progestogen used  | 1.01 (0.94–1.08)*                          | 1.38 (1.04–1.82)               | 0.95 (0.64–1.41)                                 |
| Estrogen only used              | 1.19 (0.78–1.83)                           | 1.19 (0.95–1.50)                | 1.26 (0.90–1.77)                                 |

Abbreviations: HT, postmenopausal hormone therapy; RR, relative risk. Bold font indicates value that is significantly different from 1.

* Adjusted for race/ethnicity, first-degree family history of breast cancer, and Breast Cancer Surveillance Consortium registry using log-binomial regression unless otherwise specified.

Analysis restricted to women with known hysterectomy status: with uterus assumed to be estrogen plus progestogen; without uterus assumed to be estrogen only.

Relative risk estimated by Poisson regression with robust error variance and adjusted for race/ethnicity, first-degree family history of breast cancer, and Breast Cancer Surveillance registry.

We also need studies that will improve our understanding of tumor growth rates and aggressiveness among premenopausal and postmenopausal women, the duration of the transition from shorter to longer sojourn times, and the degree to which risk factors may change the association among menopausal status, screening interval, and tumor characteristics observed herein.

Our study has several limitations. First, the potential for confounding is always a concern in observational studies. For example, women who know they have breast cancer risk factors might undergo more frequent screening than women without these factors. We adjusted for family history, race, and ethnicity in our analyses to minimize bias but did not adjust for other risk factors, such as benign breast disease or reproductive factors. Second, some of our comparisons might be significant by chance alone, so the magnitude and consistency of differences and 95% CIs should be considered. Another limitation is that we maximized sample sizes within subgroups by including data back to 1996, which included film-screen mammograms. Overall, the sensitivities of digital and film-screen mammography are similar, but sensitivity may be higher for digital mammography in some subgroups, especially women with dense breasts and premenopausal women.8,42,43

We did not collect HT type, relying instead on a surrogate based on hysterectomy status, which was available for only 53% of HT users. Results within HT-type subgroups were inconsistent and had wide 95% CIs, limiting our ability to make inferences in this group. Finally, we did not measure breast cancer mortality. Thus, we do not know if the observed increases in the proportions of less favorable tumors with biennial vs annual screening would result in differences in breast cancer mortality.

Conclusions

Premenopausal women diagnosed as having breast cancer following a biennial mammogram are more likely to have tumors with less favorable prognostic characteristics than women with breast cancers diagnosed after annual screening. Postmenopausal women not using HT who are diagnosed as having breast cancer following a biennial or annual screen have similar proportions of tumors with less favorable prognostic characteristics. Results are less clear for women using postmenopausal HT. Our findings of a lower proportion of less favorable tumors with more frequent screening in premenopausal women, and no statistically significant difference in the proportion of less favorable tumors in postmenopausal women by screening interval, add to evidence about the potential benefits and harms of screening that policymakers can use to set guidelines about screening intervals and women can use when making personal screening decisions with their clinicians.
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Author Contributions: Ms Zhu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Miglioretti, Kerlikowske, Sprague, Buist, Smith. Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Miglioretti, Kerlikowske, Smith. Critical revision of the manuscript for important intellectual content: Zhu, Kerlikowske, Sprague, Omega, Buist, Henderson, Smith. Statistical analysis: Miglioretti, Zhu. Obtained funding: Miglioretti, Kerlikowske, Sprague, Omega, Buist, Henderson, Smith. Study supervision: Miglioretti.

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Role of the Funder/Sponsor: The American Cancer Society Inc requested the study to inform their screening guidelines but had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit to the American Society for Clinical Oncology for publication. The National Cancer Institute had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit to the American Society for Clinical Oncology for publication.

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Additional Information: The procedures for requesting BCSC data for research purposes are provided at http://breastscreening.cancer.gov/

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REFERENCES


