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The Association Between the Pre-Diagnosis Mammography Screening Interval and Advanced Breast Cancer

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Abstract

Background—While screening has been demonstrated to reduce breast cancer mortality, the optimal screening interval is unknown. We designed a study to determine the risk of an advanced breast cancer diagnosis by varying the interval between mammograms.

Methods—We reviewed a single state's mammography records of women diagnosed with breast cancer between 1994 and 2002. The pre-diagnosis screening interval was the number of days between the last two eligible mammograms preceding a cancer diagnosis. The interval was classified as annual (0.75–1.49 years), biennial (1.5–2.49 years) or longer (exceeding 2.49 years). Advanced breast cancer was $\geq$ stage IIB, tumor size $>$ two cm, or $\geq$ one lymph node with cancer.

Results—The probability of an advanced breast cancer diagnosis did not differ between women with an annual pre-diagnosis screening interval and women with a biennial interval (21.1% vs. 23.7%, $p=0.262$). A longer pre-diagnosis screening interval was weakly associated with advanced breast cancer (21.8% for intervals 0.75–2.49 years vs. 26.8% for longer intervals, $p=0.070$). In multivariate analysis, we found an interaction between the pre-diagnosis screening interval and age. Among women 50 years or older, the risk of an advanced breast cancer diagnosis risk was higher for women with a pre-diagnosis screening interval exceeding 2.49 years compared to women with shorter screening intervals (OR 1.99 [1.02–3.90]).

Conclusions—We found no difference in advanced breast cancer rates between women using mammography annually or biennially. Among women 50 years or older, the advanced breast cancer rate increased when the pre-diagnosis screening interval exceeded 2.49 years.

Keywords

breast cancer; cancer screening; delivery of medical care; mammography; resource allocation

Background

Screening mammography reduces breast cancer mortality [1]. However, this effect may depend on the woman's age and the interval between mammograms. National organizations vary in their recommendations for the appropriate interval between screening mammograms for women 40–49 and women 50 and older [2,3].

White *et al.* [4] found women 50 and older who use screening mammography biennially (*i.e.*, 18 to 30 months) were no more likely to be diagnosed with late-stage breast cancer than are women who use screening mammography annually (*i.e.*, nine to 17 months). On the other hand, women 40–49 screened biennially were at increased risk of a late-stage breast cancer at diagnosis compared to women screened annually (OR 1.35, 95% CI 1.01–1.81). These findings suggest biennial mammography is as effective as annual mammography for women 50 and older.

White's analysis was limited to intervals between screening mammograms of nine to 30 months. Longer intervals between mammograms were not studied. In addition, diagnostic mammograms were also excluded. Although diagnostic mammograms are more strongly associated with breast cancer than screening mammograms [5], many women have mammography histories that include screening and diagnostic mammograms that could be considered part of a screening interval (*e.g.*, after a previous screening abnormality or after a breast abnormality detected by a woman or her clinician prior to her scheduled screening mammogram). We designed a study to examine the effect of altering the interval between mammograms performed for any indication and the risk of being diagnosed with advanced breast cancer.

Methods

Data source

We used mammography records from the Vermont Breast Cancer Surveillance System (VBCSS) between January 1, 1994 and December 31, 2002 [6]. The VBCSS records every mammogram performed within Vermont. Vermont women who traveled to New Hampshire for mammography during the study period were also included. The VBCSS collects information from patients, radiologists and hospital pathology departments.

Study population

Our target population was women diagnosed with breast cancer at age 40 or later who underwent at least two mammograms before their diagnosis. We excluded women whose only mammograms occurred after a breast cancer diagnosis since we were interested in the initial pre-diagnosis interval and not the risk of recurrent disease. We also excluded women with only one mammogram during the study period because these women did not have a pre-diagnosis interval. Finally, we excluded women who only had intervals between mammograms less than 273 days (*i.e.*, nine months). We assumed these short interval repeat mammogram "clusters" represent ongoing follow-up instead of screening.

Definitions

Mammogram type and intervals—Mammograms were classified as screening or diagnostic in two ways. First, all mammograms identified as diagnostic mammograms by the radiologist at the time the mammogram was performed were considered diagnostic. Second, any screening mammograms performed within 273 days of a screening mammogram were also considered diagnostic mammograms.

We defined two intervals for each woman. First, the woman's pre-diagnosis screening interval was the number of days between the latest two eligible mammograms preceding a breast cancer diagnosis. Eligible mammograms were those mammograms at least nine months apart. We classified intervals as annual (0.75–1.49 years), biennial (1.5–2.49 years) or prolonged (greater than 2.49 years). The pre-diagnosis screening interval could be further described by the type of mammogram (diagnostic or screening) included within the interval. Second, we defined the

diagnostic evaluation interval as the number of days between the last mammogram in the pre-diagnosis screening interval and the date of the subsequent cancer diagnosis.

Other variables—We collected patient-specific and mammogram-specific characteristics. We recorded the woman's age at the first mammogram in the pre-diagnosis screening interval. We also recorded her family history of breast cancer (mother or sister) as documented by any report within the study period. We collapsed the BI-RADS breast density classification [7] into low density ("almost entirely fat" or "scattered fibroglandular densities") and high density ("heterogeneously dense" or "extremely dense"). If a woman's breast density was not available at the time of the pre-diagnosis screening interval's first mammogram, then we used the breast density information from the mammogram most proximate (either before or after) to that mammogram. We excluded women without any breast density information from any regression analyses that included breast density as a covariate.

Outcome—The study's outcome was advanced breast cancer defined as stage IIB or greater. In a series of 1350 cases, Woodward *et al.* [8] observed 10-year overall survivals for patients with Stage IIA, IIB, IIIA and IIIB breast cancer of 75%, 58%, 45% and 42%, respectively. For the 385 women without stage information in our study population, we defined advanced breast cancer as either tumor size greater than 20 mm or at least one lymph node with breast cancer. Schairer *et al.* [9] noted twice the mortality at 10 years for women diagnosed with breast cancer over two centimeters compared with women with breast cancer of two centimeters or less. We combined the women diagnosed with ductal carcinoma in-situ (n=381) and women with early invasive breast cancer (n=1126) into one group because the recommended treatments (*i.e.*, lumpectomy with or without radiation therapy) and favorable prognoses are comparable [10].

Statistical approach

We performed unadjusted comparisons using the Chi-square statistic, and the Mann-Whitney two-sample statistic for variables with continuous distributions. When comparing the comparability of more than two populations, we used a nonparametric test on the equality of medians. We used logistic regression to determine which variables were associated with advanced breast cancer [11]. We conducted bivariate and multivariate analyses controlling for age, family history, breast density and the diagnostic evaluation interval. First, we calculated coefficients for each of the variables in bivariate analysis. Then, we entered all variables with a p-value of 0.2 or less in the bivariate analysis with all possible two-way interaction terms into the initial multivariate model. We performed a backwards step-down variable selection by removing the interaction term with the highest p-value until all remaining interaction terms had p-values less than 0.2. We then sequentially removed variables with p-values greater than 0.2 that were not included in the retained interaction terms.

This research project was approved by the Institutional Review Board at the University of Vermont and the Human Investigation Committee at Wayne State University.

Results

Study population

During the study period, 3820 women with a diagnosis of breast cancer had at least one mammogram recorded in the VBCSS. Figure 1 describes the women removed due to the various exclusion criteria. Our results are based on the remaining 1944 women. Table 1 describes the 1944 women by breast cancer severity. About one quarter of the women studied were under the age of 50 and about one fifth had a family history of breast cancer. Four hundred and sixty-five women (30.9%) diagnosed with early breast cancer did not have breast density information compared to 165 women (37.8%) diagnosed with advanced breast cancer

($p=0.007$). Among the remaining 1314 women with breast density information, nearly one third had high breast density.

Screening interval patterns

Nearly two-thirds of the pre-diagnosis screening intervals were annual and about one-quarter of the intervals were biennial. Only one-third of the intervals studied included at least one diagnostic mammogram. The pre-diagnosis screening interval could have one of four patterns depending on the type of mammograms included: screen-to-screen, diagnostic-to-screen, screen-to-diagnostic or diagnostic-to-diagnostic. The median pre-diagnosis screening interval for women with a screen-to-screen pre-diagnosis screening interval was 439 days (IQR, 377–692 days). The median pre-diagnosis screening interval for women whose interval included at least one diagnostic mammogram was 454 days (IQR, 367–727 days). A nonparametric 4-sample test found no significant difference among the median pre-diagnosis screening intervals among the four patterns ($p=0.683$).

Pre-diagnosis screening interval and the diagnosis of breast cancer

We compared the rates of advanced breast cancer diagnosis between women with one-year intervals (*i.e.*, nine months to 18 months) and two-year intervals (*i.e.*, 19 months to 30 months). We found no difference in the rates of advanced breast cancer diagnosis between the two groups (one-year interval 21.1% vs. two-year interval 23.7%, $p=0.262$). With a two-sided α of 0.05 and 80% power, our study's sample size could detect an absolute difference of 7% between the two groups (*e.g.*, 21% vs. 28%). The equivalence between the two types of intervals persisted when dividing the population into three age groups: women 40–49 (28.3% vs. 28.8%, $p=0.925$), women 50–64 (19.2% vs. 22.3%, $p=0.404$) and women 65 and older (19.8% vs. 20.8%, $p=0.780$). Using the same values of α and β , our study's sample size could detect an absolute difference of 15.1% (women 40–49), 11.7% (women 50–64) and 11.4% (women 65 and older) in each of the three subgroups.

We then compared the rates of advanced breast cancer diagnosis between women with intervals less than 2.5 years and women with intervals 2.5 years or longer. Women with pre-diagnosis screening intervals 2.5 years or longer may have higher rates of advanced breast cancer diagnosis than women with pre-diagnosis screening intervals under 2.5 years with a difference approaching statistical significance (less than 2.5 years, 21.8% vs. 2.5 years or longer, 26.8% [$p=0.070$]). For the three age subgroups, the rates were significantly different only for women 50–64 (women 40–49, 28.5% vs. 24.4% [$p=0.453$], women 50–64, 19.8% vs. 30.8% [$p=0.015$] and women 65 and older, 20.1% vs. 25.0% [$p=0.272$]).

We also compared the rates of advanced breast cancer diagnosis by pre-diagnosis screening pattern. There was a significant difference among the four pre-diagnosis screening patterns when including women from all ages (screen-to-screen 17.6%, diagnostic-to-screen 16.3%, screen-to-diagnostic 37.7% and diagnostic-to-diagnostic 42.9% [$p<0.001$]). This difference persisted among the three age groups ($p<0.001$ for all three age groups, data not shown). Comparing patterns ending with the same type of mammogram did not reveal significant differences (screen-to-screen vs. diagnostic-to-screen [$p=0.629$], screen-to-diagnostic vs. diagnostic-to-diagnostic [$p=0.363$]).

Finally, we used logistic regression to determine if the pre-diagnosis screening interval was independently associated with a diagnosis of advanced breast cancer. Due to the similarities in women 50–64 and women 65 and older, these groups were combined in the multivariate analysis. We also aggregated women whose pre-diagnosis screening pattern ended with the same type of mammogram. Table 2 lists the bivariate and multivariate associations between several variables and the odds of being diagnosed with advanced breast cancer. Because they

had p-values less than 0.2 in the bivariate analysis, we included a pre-diagnosis screening interval of 2.5 years or longer, age, breast density and pre-diagnosis screening pattern in the multivariate model. In the final multivariate model, breast density was not independently associated with the odds of developing advanced breast cancer, so its odds ratio is not included in Table 2. Among women with breast cancer, the only variables independently associated with the odds of being diagnosed with advanced breast cancer were age, a pre-diagnosis screening interval ending with a diagnostic mammogram and the interaction between a prolonged pre-diagnosis screening interval and age 50 or older. To clarify the interaction between age and the length of the pre-diagnosis screening interval on the odds of developing advanced breast cancer, we compared the advanced breast cancer rates by screening interval and age in Figure 2. There appears to be no difference between one-year intervals and two-year intervals regardless of the age group. For women 50 and older, a pre-diagnosis screening interval of 2.5 years or longer was associated with a higher probability of being diagnosed with advanced breast cancer.

Discussion

Among this cohort of Vermont women with breast cancer, we found no evidence of an increased risk of an advanced breast cancer diagnosis between women using mammography annually or biennially. However, extending the screening interval beyond 2.49 years was associated with nearly a doubling of the odds of an advanced breast cancer diagnosis among women ages 50 and older. This association was independent of the type of mammograms included in the screening interval, family history of breast cancer or breast density. This study indicates that women who undergo mammography at least every 2.49 years will retain mammography's benefit of detecting breast cancer at an early stage. In our study population, extending the screening interval 2.5 years or longer appeared potentially hazardous for women 50 years or older.

Our findings are consistent with other researchers. Vacek *et al.* [12] found a decrease in tumor size, reduced lymph node metastasis and less advanced breast cancer as mammography use increased among Vermont women. Our study confirms these findings but focuses particular attention on the last screening interval before the cancer diagnosis, the interval most likely to be associated with stage of disease at diagnosis. White *et al.* [4] found no difference in rates of advanced breast cancer between women 50–69 undergoing annual screening mammography and women undergoing biennial screening mammography. This group did not examine longer screening intervals or diagnostic mammograms that may be components of a screening interval. Our findings extend previous observations and are consistent with current recommendations that advise screening every one to two years [13].

Our findings are subject to several limitations. This study is a secondary analysis of a retrospective cohort from one state with few minority citizens. Some variables associated with advanced breast cancer (*e.g.*, estrogen receptor status [14], race [15], menopausal status [16]) were not included in our study. Our primary outcome, stage at diagnosis, is an imperfect indicator of other outcomes including mortality. Furthermore, our ability to detect a small, but real difference in the effect of annual versus biennial screening is limited by our sample size. To detect a 5% absolute difference in rates of advanced breast cancer diagnosis with a two-sided α of 0.05 and 80% power, we would need a study of 2400 women (if the two groups were of equal size). To be even more confident that no difference existed between the two groups, we could increase the power to 95%, but that would increase the study's sample size to 3920 women. If we limited the study to women ages 40–49 and looked for an absolute difference in advanced breast cancer rates of 5%, we would need 2726 women for 80% power or 4458 women for 95% power. Our findings are preliminary and should be confirmed with additional studies.

Breast cancer is a heterogeneous disorder and its characteristics appear to differ between younger and older women. Our observation of a higher risk of being diagnosed with advanced disease among women under the age of 50 is consistent with the belief that these women may be susceptible to more aggressive breast cancers. The increase in advanced breast cancer rates among younger women led the American Cancer Society to change its recommendations from biennial to annual mammography for women 40–49 in 1997 [17]. White *et al.* [4] found advanced breast cancer rates of 28% and 21% among women 40–49 who used biennial and annual screening mammography, respectively. It is unknown if an even shorter screening interval might be more effective among younger women. We did not examine intervals less than nine months. More women in this age range will need to be studied to determine the optimal mammography interval for this group.

The reason for a prolonged pre-diagnosis screening interval was not elucidated in this study. We cannot distinguish the role of provider recommendation, patient preference and issues of access as determinants of the pre-diagnosis screening interval. Nor can we define the contributing roles of mammography, self-breast exam or clinical breast exam in the diagnosis of breast cancer. As a retrospective analysis, our characterization of mammograms as screening or diagnostic may be subject to misclassification. We believe such misclassification would not introduce systematic bias into our analysis.

When helping a woman make an informed decision about the appropriate breast cancer screening interval, risks and benefits should be weighed. This study only explores one risk of using mammography less frequently (*i.e.*, the risk of advanced breast cancer diagnosis). Possible benefits of less frequent mammography are fewer false-positive mammograms, less radiation exposure, reduced costs, less subsequent diagnostic testing and less associated anxiety. Some women will value the reassurance of a negative mammogram more highly than the possible risks of false-positive test results. The policy decision concerning screening intervals will be better informed by a formal cost-effectiveness analysis of annual, biennial or other interval mammography.

Our research supports several conclusions. First, among women 50 and older, extending the screening interval beyond 2.49 years appears to be associated with an increased risk of being diagnosed with advanced breast cancer. Second, breast cancer screening intervals are not limited to “screening” mammograms. Other events, including diagnostic mammograms, are important components of breast cancer screening and must be included in any policy consideration of the optimal screening interval. Finally, our approach using empiric data to examine the impact of varying screening intervals to detect advanced breast cancer may be informative when assessing other screening services that are performed periodically.

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Figure 1.
Women excluded from the analysis

Figure 2.

Relationship between pre-diagnosis screening interval, age and percent of women diagnosed with advanced breast cancer (with 95% confidence intervals)

Table 1

Baseline characteristics

Characteristic at time of the first mammogram of the pre- diagnosis screening interval	Total, n (%)	Ductal carcinoma in-situ or early invasive cancer, n (%)	Advanced cancer, n (%)
Number of women	1944 (100.0)	1507 (100.0)	437 (100.0)
Age			
40–49 years	447 (23.0)	323 (21.4)	124 (28.4)
50–64 years	799 (41.1)	631 (41.9)	168 (38.4)
65 years and older	698 (35.9)	553 (36.7)	145 (33.2)
Women with a female first-degree relative with breast cancer	386 (19.9)	294 (19.5)	92 (21.1)
Women with high breast density (heterogeneously dense or extremely dense) among women with breast density information available (n=1314)	621 (31.9)	482 (32.0)	139 (31.8)
Pre-diagnosis screening pattern			
Screen-to-screen	1281 (65.9)	1055 (70.0)	226 (51.7)
Diagnostic-to-screen	203 (10.4)	170 (11.3)	33 (7.6)
Screen-to-diagnostic	369 (19.0)	230 (15.3)	139 (31.8)
Diagnostic-to-diagnostic	91 (4.7)	52 (3.5)	39 (8.9)
Pre-diagnosis screening interval			
0.75–1.49 years	1236 (63.6)	975 (64.7)	261 (59.7)
1.5–2.49 years	439 (22.6)	335 (22.2)	104 (23.8)
2.5 years or longer	269 (13.8)	197 (13.1)	72 (16.5)
Diagnostic evaluation interval, median (IQR)	27 days (14–73 days)	29 days (15–76 days)	19 days (9–63 days)

Table 2

Relationship of patient and pre-diagnosis screening interval characteristics to the odds of being diagnosed with advanced breast cancer

Characteristic	Unadjusted		Adjusted	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age 50 and older	0.69 (0.54–0.88)	0.002	0.67 (0.51–0.87)	0.003
Family history	1.10 (0.85–1.43)	0.476	--	--
High breast density	1.21 (0.93–1.59)	0.154	--	--
Pre-diagnosis screening interval over 2.5 years	1.31 (0.98–1.76)	0.070	0.73 (0.42–1.30)	0.288
Pre-diagnosis screening interval ending with a diagnostic mammogram	2.99 (2.37–3.76)	<0.001	2.92 (2.31–3.68)	<0.001
Diagnostic evaluation interval over 90 days	1.02 (0.79–1.31)	0.901	--	--
Pre-diagnosis screening interval over 2.5 years X age 50 and older	--	--	1.99 (1.02–3.90)	0.044