

Mammography in 40-Year-Old Women: What Difference Does It Make? The Potential Impact of the U.S. Preventative Services Task Force (USPSTF) Mammography Guidelines

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ABSTRACT

Background. This 10-year retrospective chart review evaluates the potential impact the most recent U.S. Preventative Services Task Force (USPSTF) report recommending against annual mammographic screening of women aged 40–49 years.

Methods. The medical record database was systematically searched to discover all women aged 40–49 years treated for breast cancer over a 10-year period. These women were separated into 2 cohorts—mammographically detected cancer (MDC) and nonmammographically detected cancer (NMDC). Statistical analysis of the cohorts was performed for family history (FH), sentinel lymph node (SLN) status, tumor size at presentation, and disease-free and overall survival.

Results. A total of 1581 women were treated for breast cancer; of these, 311 were between the ages of 40 and 49 years with complete diagnostic information, 145 were MDC, and 166 were NMDC. The average tumor diameter of the MDC group was 20.68 mm, which was significantly smaller than that of the NMDC group at 30.38 mm ($P < .0001$). Women with MDC had a significantly lower incidence of SLN positive cancer than the NMDC group, 28 of 113 (24.78%) vs. 85 of 152 (55.92%; $P < .0001$), respectively. The 5-year disease-free survival for both groups was MDC 94% (95% confidence interval [95% CI], 87–97%) and NMDC 71% (95% CI 62–78%). The overall

5-year survival estimates were MDC 97% (95% CI 92–99%) and NMDC 78% (95% CI 69–85%), respectively.

Conclusion. This review demonstrates the significance of mammographic screening for early detection and treatment of breast cancer. Mammographic screening in women aged 40–49 detected smaller tumors with less nodal metastasis, resulting in improved survival, which supports annual mammographic screening in this age group.

Breast cancer is the second-leading cause of cancer-related death in women and is the most common noncutaneous cancer among women.¹ A 40-year-old woman's risk of developing breast cancer in the next 10 years is 1 of 69 (1.44%), and her lifetime risk of developing invasive breast cancer is at least 1 of 8.¹ Fortunately, the mortality rates of breast cancer have been declining since 1990 with larger decreases identified in women younger than 50. This significant decrease in mortality in younger women has been attributed to several factors, including earlier detection of presymptomatic breast cancer through screening mammography.² Randomized clinical trials have previously reported the reduction in mortality from breast cancer as a result of mammographic screening. The most recent meta-analysis of these trials showed a statistically significant reduction in breast cancer mortality for women randomly assigned to mammography screening versus those assigned to controls in the 39–49 (15%) and 50–59 (14%) age groups.³ Despite the similar mortality reductions observed in screening between the 2 age groups, the U.S. Preventative Services Task Force (USPSTF) recently recommended against mammography screening in women aged 40–49, a Grade C recommendation.⁴ This was a change from the Grade B recommendation, annual mammography screening beginning at age 40, which was put forward by the USPSTF in 2002.⁵ The principles behind

this decision were based on the lower incidence and the less severe consequences of the breast cancers observed in women aged 40–49 vs. women aged 50–59.⁴ Because of these differences, the USPSTF argued that the harms of screening in women aged 40–49 years outweighed the benefits of early detection and early intervention.

The objective of this 10-year retrospective study was to evaluate the tumor characteristics and clinical course of women aged 40–49 years diagnosed by mammography screening (MDC) vs. those diagnosed by other means (NMDC).

METHODS

This retrospective study was approved by our institutional review board. The Cancer Registry Database at our large tertiary referral center was systematically searched to identify all women diagnosed with or treated for breast cancer at our institution over a 10-year period (1998–2008). The Cancer Registry Database is entered data collected from the institutions electronic medical record (Powerchart) and follows the Commission on Cancer (CoC) Cancer Programs Standards to ensure quality of cancer registry data compared with the medical record. Women in the Cancer Registry Database were then sorted according to age, with women aged 40–49 years making up the study cohort.

The electronic and medical records of this cohort were reviewed. These women were sorted into mammographically detected breast cancer (MDC) and nonmammographically detected breast cancer (NMDC) groups according to their mammographic screening history. Patients with documentation of screening mammograms in the radiology report with follow-up for suspicious lesions as well as women with clinical note documentation of screening mammography resulting in a cancer diagnosis for which the radiology reports were elsewhere were labeled as MDC. Patients with clinical note documentation of abnormal clinical breast exam (CBE), self-breast exam (SBE), nipple discharge, or breast trauma that were followed up by diagnostic workup were labeled as NMDC. Patients for whom such information was not available were removed from the study (Fig. 1).

Data was collected from the electronic and paper records of the remaining MDC and NMDC patients. The date of cancer diagnosis used in the study was that on the first available positive pathology report. The date last seen was that on the last electronic or paper clinic note that conveyed the patient's cancer status: alive with no evidence of disease (NED), alive with disease (AWD), died of disease (DOD), died of other causes (DOC). NED patients were those who had no radiographic or physical evidence of cancer, even though they may have been receiving chemotherapy, radiation therapy, or hormonal therapy.

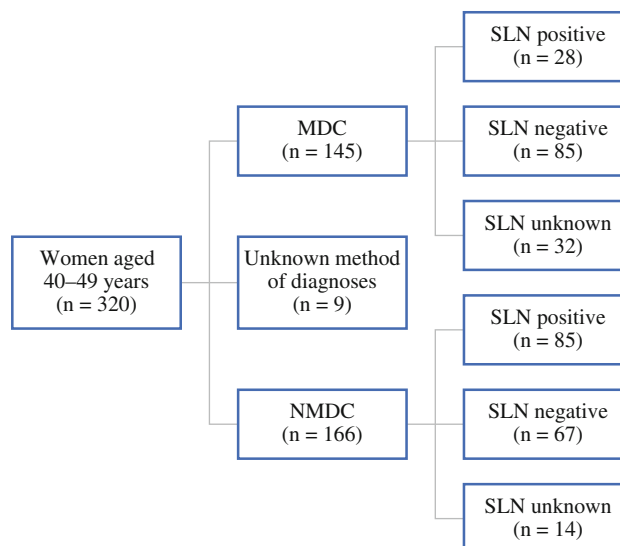


FIG. 1 Method of diagnosis

Therefore, AWD patients were those with radiographic or physical evidence of cancer. DOD patients were those who had documentation showing that their death was a result of complications derived from their breast cancer. DOC patients were defined as those with clinical notes suggesting their cancer was not their cause of their death.

When assessable, additional parameters were recorded, including FH (first-degree relative with breast cancer), BRCA1 or BRCA2 genetic testing, sentinel lymph node (SLN) status, date of recurrence, and tumor size. SLN status was determined by pathology report. The largest tumor diameter size documented on the diagnostic pathology report was used to describe the primary tumor size. Reference to positive pathology or radiographic reports in clinic notes when the actual pathology report was not available were used in dating and determining recurrence.

To compare outcomes for breast cancer patients diagnosed via mammography vs. other diagnostic methods, statistical analyses of the 2 cohorts, MDC and NMDC, were performed for FH, SLN status, tumor size at presentation, and disease-free and overall survival. The survival analysis of the MDC and NMDC groups were compared using the Kaplan–Meier estimate of survival and the Cox proportional hazards models. The latter model was able to include multiple predictors of survival whether discrete or continuous. The Wilcoxon rank sum test was used to compare groups relative to tumor size. The chi-square test was used to compare groups relative to categorical variables. These methods were used to examine the effects that the parameters (method of diagnosis, FH, SLN status, and tumor size) individually and collectively had on the outcome of survival.

RESULTS

There were 1581 women diagnosed with breast cancer over the 10-year period: 320 aged 40–49 years, 466 aged 50–59 years, 403 aged 60–69 years, 275 aged 70–79 years, and 117 aged 80–89 years. Of the 320 women aged 40–49 years, 311 women had documented information regarding the method of their breast cancer diagnosis: 145 (46.62%) were MDC and 166 (53.38%) were NMDC. The mean, median, and range for follow-up time for MDC in years were 5.02, 4.37, and 0.04–12.49, respectively. The mean, median, and range for follow-up time for NMDC in years were 4.53, 3.88, and 0.00–12.33, respectively.

All patients in the study were evaluated for tumor size, sentinel node status, recurrence, cancer-specific and overall survival, and family history (Table 1). Mean tumor size was 26.43 mm with a median of 21.00 mm and a range from 2.00 to 137.00 mm. There were 152 (57.36%) with a negative sentinel node biopsy, and 113 (42.64%) had a positive sentinel node. Only 57 women (20.21%) had a positive FH, while 225 (79.79%) had a negative FH. During the follow-up period there were 47 patients (15.26%) with documented evidence of recurrence. At last follow-up 249 women (80.06%) remained NED, 23 (7.40%) were AWD, 36 (11.58%) were DOD, and 3 (0.96%) were DOC.

The 2 cohorts MDC and NMDC were evaluated for tumor characteristics and overall outcomes. The average tumor diameter of the MDC group was 20.68 mm, which was significantly smaller than that of the NMDC group 30.38 mm ($P < .0001$). Women with MDC had a significantly lower incidence of sentinel node positive cancer than the NMDC group, 28 of 113 (24.78%) vs. 85 of 152 (55.92%), respectively, ($P < .0001$). There were 7 recurrences observed in the MDC, which was less than the 40 recurrences observed in the NMDC. A significantly better overall 5-year survival (Fig. 2) and disease-free survival

(Fig. 3) was observed in the MDC when compared with the NMDC. The overall 5-year survival estimates for MDC and NMDC were 97% (95% confidence interval [95% CI], 92–99%) vs. 78% (95% CI 69–85%), respectively. The 5-year disease-free survival for both groups was MDC 94% (95% CI 87–97%) and NMDC 71% (95% CI 62–78%). These estimates were based on a simple univariate model.

Tumor size, SLN status and FH were further evaluated for survival significance. Women with MDC had a significantly lower incidence of a FH of breast cancer than the NMDC group, 19 of 130 (14.62%) and 38 of 152 (25%), respectively ($P = .0304$) (Table 1). While FH did not significantly impact survival, SLN involvement (log-rank test, $P < .0001$) (Fig. 4), and tumor size (Wald test, $P = .0003$) were found to have an adverse effect on survival. Even when the 38 NMDC group patients were removed from the study, there was still a significant difference in survival based on MDC vs. NMDC, $P < .0001$. When multivariate analysis was performed using a Cox model starting with variables of detection method, tumor size and SLN status and using a backward elimination procedure, MDC and SLN remained significant ($P = .0414$ and $P = .0002$, respectively), while tumor size was no longer significant ($P = .1005$). Univariate analysis for the women who developed recurrence during the follow-up identified significant differences for the MDC group ($P < .0001$) (Fig. 3). Additionally negative SLN biopsies ($P < .0001$) and smaller tumor size ($P = .0067$) were also significantly associated with a lower recurrence rate. Multivariate analysis of these significant univariate variables MDC, SLN, and tumor size were again analyzed jointly to determine effect on recurrence using a Cox proportional hazards model with a backward elimination procedure. Again MDC remained significant ($P = .0221$) as did SLN ($P < .0001$), while tumor size was not significant ($P = .4291$).

TABLE 1 Comparison of MDC and NMDC characteristics

	MDC	NMDC	<i>P</i> value
Patients, <i>n</i> (%)	145 (47%)	166 (53%)	
Tumor size in mm, (range)	20.68 (2.00–90.00)	30.38 (2.50–137.00)	<.0001
SLN positive, <i>n</i> (%)	28 (24.78%)	85 (55.92%)	<.0001
FH positive, <i>n</i> (%)	19 (14.62%)	38 (25%)	.0304
Recurrence, <i>n</i> (%)	7 (4.86%)	40 (23.39%)	
5-year DFS (95% CI)	94 (87–97)	71 (62–78)	
5-year OS (95% CI)	97 (92–99)	78 (69–85)	
<i>FH</i> family history, <i>DFS</i> disease-free survival, <i>OS</i> overall survival, <i>NED</i> no evidence of disease, <i>AWD</i> alive with disease, <i>DOD</i> died of disease, <i>DOC</i> died of other cause			
NED, <i>n</i> (%)	130 (89.66%)	119 (71.69%)	
AWD, <i>n</i> (%)	10 (6.9%)	13 (7.83%)	
DOD, <i>n</i> (%)	5 (3.45%)	31 (18.67%)	
DOC, <i>n</i> (%)	0 (0%)	3 (1.81%)	

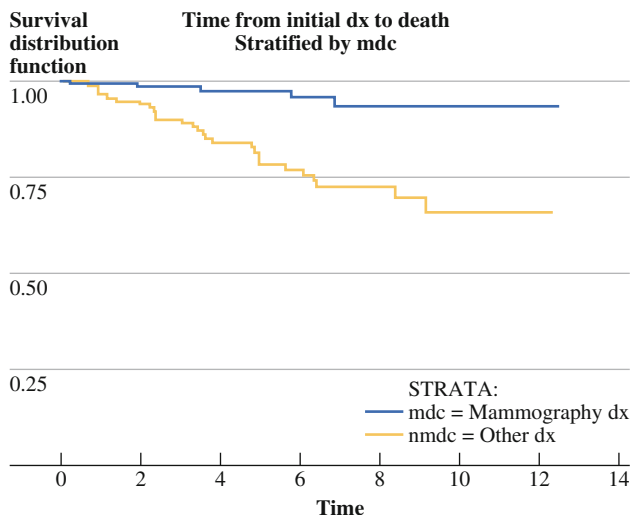


FIG. 2 Kaplan-Meier estimate of survival comparing MDC to NMDC

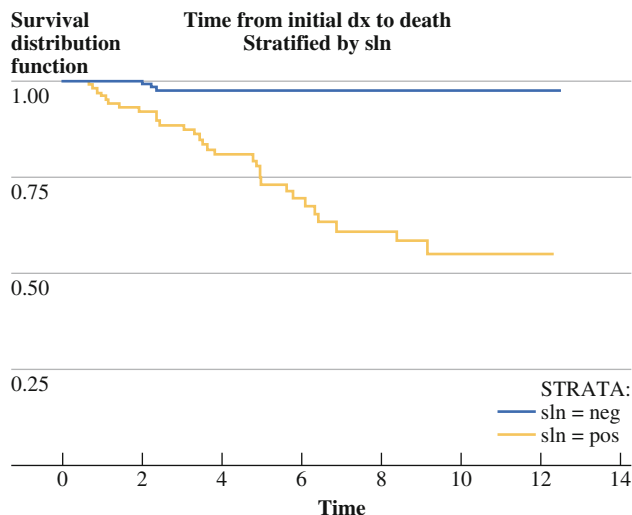


FIG. 4 Kaplan-Meier estimate of survival comparing positive or negative. Stratified by SLN

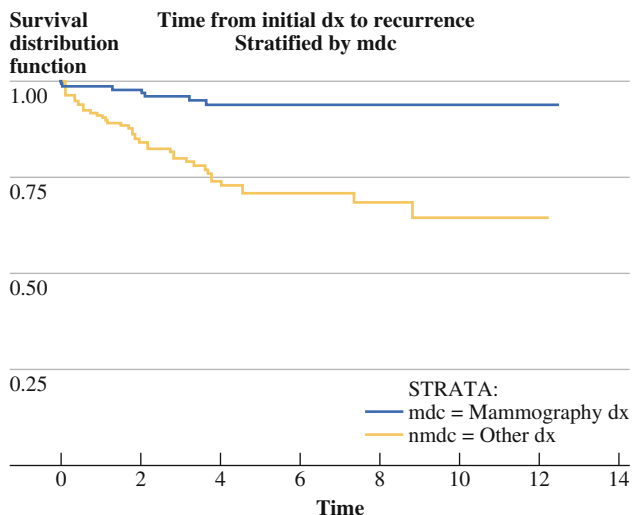


FIG. 3 Kaplan-Meier estimate of recurrence comparing MDC to NMDC

DISCUSSION

Screening for cancer, heart disease, and other illness is important for early detection and treatment of many diseases. Most screening guidelines are annually reviewed, taking into account new supporting evidence that emphasizes the importance of weighing the benefits and harms of screening as well as the importance of patients being involved in the decision to be screened.⁶ As such, mammography-screening guidelines were recently reviewed and updated in 2009 by the USPSTF.⁴ The major change in mammographic screening for breast cancer was to remove women aged 40–49 years from annual mammogram screening. This decision was based on the statistical

principle that the harm associated with screening the average 40–49 year old woman outweighed the benefit of catching a mammography detectable cancer.⁴

Newer studies not only challenge the presumed costs as reasons not to screen women aged 40–49 years presented in the USPSTF recommendation but also present the potential consequences.^{7–9} Hendrick and Helvie, using Cancer Intervention and Surveillance Modeling Network modeling, recently explored the potential harm of the 2009 recommendations.¹⁰ The study found that mortality reduction was greatest, 39.6%, when women aged 40–84 years were screened annually. Following the 2009 USPSTF guidelines, screening women aged 50–74 years biannually resulted in a 23.2% mortality reduction. This significantly lower mortality reduction was suggestive of the benefits of annual screening and screening women aged 40–49 years as well as 74–84 years. Our study supports this observation by identifying a significant overall 5-year survival advantage in the MDC group (97%) compared with the NMDC group (78%). This 19% increase in survival for the MDC group was also reflected in those patients alive with disease, since similar percentages of women AWD were observed between the 2 cohorts: 10 of 145 (6.90%) and 13 of 166 (7.83%) for MDC and NMDC, respectively. A significantly higher percentage of women with MDC were NED 130 of 145 (89.66%) than those with NMDC 119 of 166 (71.69%). This suggests an increased cure rate was probably a reflection of the earlier detected, smaller, nonmetastatic cancers in the MDC group.

It is known that as the median tumor size decreased from 3.5 cm in the 1950 s to 2.0 cm in 2006, breast cancer mortality also decreased. This size reduction has been attributed to the introduction of mammographic

screening.¹¹ In our study, tumors in the MDC group were significantly smaller in size than NMDC group (20.68 vs. 30.38 mm) and as expected tumor size was associated with better prognosis in univariate analysis ($P = .0003$). This data would support the findings of Cady et al., who reported on 2648 women with breast cancer and identified an association between smaller mammographically detected tumors and improved overall survival.¹¹

Stage at diagnosis is a well-known predictor of overall survival with 98.3% survival for localized breast cancer vs. 83.5% in patients with regional lymph node metastasis.¹² More recently, Spencer et al. reported on the Rhode Island Department of health data base identifying an association with smaller tumor size, lower stage at presentation, and less mortality in women who underwent routine mammographic screening.¹³ This was similarly supported in our study as univariate and multivariate analysis of negative SLN was associated with a significant increase in 5-year survival ($P < .0001$). Additionally, those women with MDC had a significantly lower incidence of having a positive SLN than those with NMDC (24.78% vs. 55.92%; $P < .0001$).

Family history is a known risk factor for breast cancer; relative risk (RR) = 2.1–4.0 for first-degree relative with breast cancer.¹² Those women with a first degree relative with breast cancer are encouraged to undergo yearly screening as early as 5 years prior to the age of the relative at the time of diagnosis. Our study identified women with MDC had a significantly lower incidence of a family history of breast cancer than the NMDC group, 19 of 130 (14.62%) and 38 of 152 (25%), respectively ($P = .0304$). There was no association with FH and survival noted in this study.

Univariate analysis of MDC ($P < .0001$), tumor size ($P = .0003$), and SLN status ($P < .0001$) were observed to significantly improve 5-year survival. However, in multivariate analysis of these parameters, MDC and SLN significantly improved 5-year survival $P = .0414$ and $P = .0002$, respectively, while tumor size was no longer significant, $P = .1005$. Thus, patients presenting with a self or clinically palpated breast cancer would trend toward having a larger tumor at diagnosis, which would indicate a worse prognosis than a patient with a smaller mammographically detected cancer. However, as might be expected, stage at presentation was most significant regarding overall survival. Interestingly, even in multivariate analysis the method of detection, MDC vs. NMDC, remained a significant predictor of survival, supporting the role screening mammography has on the declining death rates of breast cancer in the United States.

Despite being smaller, less invasive cancers, there was no significant difference in treatment received when comparing MDC vs. NMDC. There were 98 of 114 (85.96%) of

MDC and 131 of 142 (91.61%) of NMDC who had mastectomy rather than lumpectomy ($P = .15$). The net number of patients with lumpectomy compared with mastectomy was small, $n = 28$. There was not a significant difference in survival based on lumpectomy vs. mastectomy.

In addition to survival analysis, a time-to-recurrence analysis was also done. The same previous variables were analyzed in relation to their impact on recurrence. A significant increase in the incidence of recurrence was observed in NMDC (23.39%) compared with the MDC (4.86%, RR = 4.81) group. When comparing survival curves for the 2 groups, significant differences for MDC ($P < .0001$), SLN ($P < .0001$), and tumor size ($P = .0067$) were found, but FH ($P = .1770$) was again insignificant. A multivariate analysis was performed using these univariate significant parameters, and again tumor size was found to be insignificant ($P = .4291$) while MDC ($P = .0221$) and SLN ($P < .0001$) remained significant.

Because MDC was associated with fewer positive SLN biopsies and less recurrence, a limitation of the study is to know the significance of MDC on survival independent of these parameters. While this was a limitation, the research suggests that these variables do not work independently; mammographically detected cancers were significantly smaller and had fewer positive SLN than NMDC. Thus, the multivariate analysis was more generalizable than the univariate. Because survival time was measured from time of diagnosis, another limitation of the study was lead-time bias; since survival time was not measured from the start of the cancer first forming, there could be an apparent positive effect on survival of earlier diagnosis. For the women who had not died or died but of causes other than breast cancer, only partial information about survival time was collected, namely that these patients will have survived for at least as long as they have been followed to date.

Despite these limitations, this study challenges the recent publications suggesting that better treatment and breast cancer awareness, not mammography screening, were responsible for the declines in breast cancer mortality.¹⁴ The significance of mammographic screening in women aged 40–49 years was evidenced in the significantly higher 5-year overall and DFS when compared with those who did not undergo mammographic screening.

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