Biologic Characteristics of Interval and Screen-Detected Breast Cancers

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Background: Interval breast cancer is defined as a cancer that is detected within 12 months after a negative mammogram. The failure of mammography to detect breast cancer depends on testing procedures, radiologist interpretation, patient characteristics, and tumor properties. Although errors by radiologists explain some interval cancers, another explanation is that the tumor is rapidly growing and was too small to be detected on the last mammogram. To determine whether markers of tumor growth rate are associated with risk of an interval cancer, we conducted a population-based study with the use of data collected statewide by the New Mexico Mammography Project.

Methods: Among women who received a mammographic examination from 1991 throughout 1993, we ascertained records of all patients with breast cancer diagnosed within 12 months of a negative screening mammographic examination (interval cancers) and corresponding tumor samples, when available. We selected an age- and ethnicity-matched comparison group of control patients with screen-detected breast cancers diagnosed during the same period. In tumor samples, p53, bcl-2, and Ki-67 were examined immunologically and the apoptotic index was assessed histologically. We used logistic regression to determine whether interval cancers were associated with selected demographic, radiologic, and biologic characteristics.

Results: It is more likely that mammography did not detect tumors with a high proportion of proliferating cells (>20%) than tumors with a low proportion of proliferating cells (<5%) (odds ratio [OR] = 4.09; 95% confidence interval [CI] = 1.14–14.65). The OR for mammographic failure was 2.96 (95% CI = 1.07–8.20) among cancers that expressed p53 compared with cancers that did not. Interval cancers also had fewer apoptotic cells. Approximately 75% of interval cancers appear to have tumors with 5% proliferating cells or more. Younger women had a higher proportion of rapidly proliferating and aggressive cancers. Conclusion: Rapidly growing and aggressive tumors account for a substantial proportion of mammographic failure to detect breast cancer, especially among younger women, who have a high proportion of aggressive cancers. [J Natl Cancer Inst 2000;92:743–9]

Efforts to reduce breast cancer mortality have focused on early detection and treatment of cancer. Mammographic examination is a mainstay of these efforts. Randomized controlled clinical trials and meta-analyses have consistently demonstrated a reduction of 25%–35% in breast cancer mortality associated with routine screening mammography among women aged 50–74 years and a smaller reduction of 10%–18% among women aged 40–49 years (1–6).

Although the efficacy of mammography is well documented, its use as a modality for mass screening has recognized limitations. Approximately 10%–20% of breast cancers are not routinely detected by mammography (7–9). Women who have interval cancer (i.e., a cancer that is detected within 12 months after a negative mammogram) have tumors at a more advanced stage at diagnosis and have poorer stage-specific survival than women whose cancers were detected by mammography (10–16). The high frequency and poorer outcomes of interval cancer may have a substantial effect on screening-related mortality reduction (14,17,18). Thus, identifying the determinants of interval cancer may contribute to achieving...
the maximum reductions in mortality from mammographic screening.

Studies (7–9,14,18–31) indicate that the failure of mammography to detect breast cancer depends on a complex interplay of testing procedures, radiologist interpretations, patient characteristics, and tumor properties. Most studies (19–32) investigating the performance of mammography have focused on technical factors, such as patient positioning, film quality, and interpretation. Although errors by radiologists explain about 20% of interval cancers, patient factors (such as age and breast density) and tumor properties (such as lobular histology and grade) also explain a portion of the failures (19). Age is a determinant of failure to detect breast cancer by mammography, as indicated by the variation in sensitivity (7,8,23). Mammography has substantially lower sensitivity for women younger than age 50 years (54%–87%) than for older women (83%–98%). Lower sensitivity is also seen for a biennial screening interval and for women with a family history of breast cancer (7,16). Sensitivity is also decreased among women who have higher breast density and use estrogen replacement therapy (8).

The relationship of sensitivity with age, family history of breast cancer, breast density, estrogen use, and screening interval suggests an alternative explanation for the diagnosis of breast cancer after a negative mammographic examination. Women with these characteristics may have more rapidly growing tumors that grow to a detectable size in shorter intervals (7,16,33,34). Rapid growth arises from high cellular proliferation rates, decreased apoptosis, or dysregulation of the cell cycle with associated genetic instability (35–38). Such tumors may not be reliably detected by mammography that is performed at a biennial or longer basis (1,38–40). This may be especially true for younger women, who have a high frequency of interval cancers (16,39). Although rapid tumor growth is a biologically plausible mechanism that could explain some mammographic failures, the relationship of interval cancer, tumor proliferation rates, apoptotic cell death, and dysregulation of the cell cycle has not been extensively examined.

The New Mexico Mammography Project, a member of the National Cancer Institute’s Breast Cancer Surveillance Consortium, offers the opportunity to investigate determinants of interval breast cancer in a community setting (41). We conducted a population-based, case–control study of patients diagnosed with breast cancer within 1 year after a mammogram read as normal (an interval cancer) to assess the hypothesis that interval cancers are, in part, explained by rapid tumor growth.

**Subjects and Methods**

**Patient Population**

Data on the use and outcomes of mammography are collected statewide by the New Mexico Mammography Project. Radiology groups submitted computerized data on all patients for whom they had interpreted mammograms from January 1, 1991, through December 31, 1993. Data were submitted for 119,854 screening mammograms on 102,704 patients (some patients had more than one screening mammogram during this period); 83% of these patients were residents of the Albuquerque (NM) metropolitan area. All radiology groups submitted patient name, date of birth, date of examination, and the type and result of the mammographic examination. Other data items submitted by most groups included ethnicity, specific recommendations for further studies, family history of breast cancer, breast density, estrogen use, and symptoms (e.g., lump, discharge, or breast pain reported by the physician or the patient). The research protocol was approved by the University of New Mexico Human Subjects Research Review Committee.

**Breast Imaging Series Classification**

The mammography screening process may involve more than a single mammographic examination. Additional radiologic work-up may be recommended and performed before a final decision is made. In this analysis, all mammograms from a woman were grouped into a breast-imaging series consisting of an initial mammogram and all additional views and short-term (<3 months) follow-up examinations (8,9). A screening mammogram series was defined as a breast-imaging series beginning with a bilateral mammogram that was not for diagnostic purposes, without symptoms, and occurring at least 9 months after the end of the prior imaging series. Symptoms included lump, discharge, or breast pain reported by the physician or the patient. Screening mammogram series account for 119,854 (77%) of all imaging series in our database from 1991 through 1993.

**Screening Mammogram Series Results**

Screening mammogram series results were classified as positive or negative based on the reading of the interpreting radiologist. No central review was performed. The series result was assigned from the mammogram during this period; 83% of these patients were residents of the Albuquerque (NM) metropolitan area. All radiology groups submitted patient name, date of birth, date of examination, and the type and result of the mammographic examination. Other data items submitted by most groups included ethnicity, specific recommendations for further studies, family history of breast cancer, breast density, estrogen use, and symptoms (e.g., lump, discharge, or breast pain reported by the physician or the patient). The research protocol was approved by the University of New Mexico Human Subjects Research Review Committee.

**Breast Cancers and Interval Cancers Detected by Screening Mammography**

Breast cancers occurring in women who had received a screening mammogram ascertainment by the New Mexico Mammography Project were classified as screen mammography-detected cancers (or screen-detected cancers) or interval cancers. Screen-detected cancers are defined as breast cancers diagnosed within 12 months of a screening mammogram series with a positive result (a true-positive screening mammogram). Interval cancers are defined as breast cancers diagnosed within 12 months of a screening mammogram series with a negative result (a false-negative screening mammogram). The date of diagnosis was determined by the New Mexico Tumor Registry by following the Surveillance, Epidemiology, and End Results (SEER) coding rules. The date of diagnosis was assigned as the date of the mammogram (if read as suspicious or malignant) or the date of the biopsy examination (43). The date of the screening mammogram series was defined as the date of the first mammogram in the breast imaging series. From 1991 through 1993, 94 women with interval cancers and 469 with screen-detected cancers were diagnosed in this population.

**Subject Selection**

We selected all patients with interval breast cancer diagnosed within 1 year of a screening examination performed from 1991 through 1993 (n = 94). A comparison group of control patients with screen-detected cancers was selected with frequency matching on age (<50 years old or ≥50 years old), ethnicity (Hispanic or non-Hispanic), and year of screening mammography (n = 87). Breast tumor samples were not available from two institutions in the New Mexico Mammography Project ascertainment area (22 women with interval cancer and 14 with screen-detected cancer). Tumor tissue was not available for an additional 18 women with breast cancer because the blocks were missing or had been entirely used for clinical purposes. Of the available specimens, we obtained specimens from 64 patients with interval cancer and from 63 control patients with screen-detected cancer. Demographic and clinical characteristics of subjects with and without tissue specimens were not statistically significantly different, except that those without specimens had more missing information for family history of...
breast cancer, estrogen replacement therapy, and breast density.

**Laboratory Methods**

Archival paraffin-embedded breast tumor tissue specimens were identified, retrieved, and reviewed by the study pathologist (N. Joste), and immunohistochemical assays of freshly cut tissue sections were conducted under her supervision. All pathology and laboratory tests were done with the operator blinded to the group from which the specimen came. We assayed p53, bcl-2, and Ki-67 expression with immunohistochemical assays. In brief, this procedure is an immunoperoxidase method that uses an avidin–biotinylated/horseradish peroxidase complex (Vectorstain Elite ABC; Vector Laboratories, Inc., Burlingame, CA). The primary anti-bcl-2 monoclonal antibody (MAb; Dako Corp., Carpenteria, CA) was a murine anti-human MAb, subclass immunoglobulin G1 (IgG1), specific for a cytoplasmic epitope of bcl-2. We used anti-p53 MABs DO-1 and 1801 (Oncogene Science, Inc., Manhasset, NY), which are IgG1 and IgG2A mouse MABs, respectively, that recognize an epitope at the amino-terminal end of the p53 protein. DO-1 is a p53-specific MAB that may be superior to the Pab 1801 MAB for detecting p53 in formalin-fixed breast tumors. Of 10 in-frame deletions or missense mutations in p53 from paraffin sections, DO-1 detected 90% and PAB 1801 detected 70% (44). Anti-Ki-67 MAB M1M1 (Novac- tra; Vector Laboratories, Inc.) recognizes Ki-67 in paraffin sections. All slides were developed in 3,3′-diaminobenzidine tetrahydrochloride (Sigma Chemical Co., St. Louis, MO) and counterstained with hematoxylin and ammonia water. Immunostaining of p53 and bcl-2 was evaluated by scoring tumors according to the proportion of cells with stained nuclei as follows: 0 = none, 1 = less than 0.05, 2 = 0.05–0.39, and 3 = 0.40 or greater. Sections with less than 0.05 of the nuclei stained were considered to be negative. Ki-67 was scored as the percentage of cells stained by the Ki-67 MABs.

We determined the apoptotic index by counting the total number of apoptotic cells per square millimeter of neoplastic epithelium in five consecutive high-power microscopic fields (magnification = x40; field diameter = 490 μm), which represents 5 mm² of tumor. The apoptotic index is the average number of apoptotic cells per square millimeter of tumor. We categorized the average number of apoptotic cells into groups of zero to one, two through five, and six or more apoptotic cells per square millimeter of tumor. The diagnoses of the 64 interval cancers were substantially delayed, occurring, on average, 180.3 days (median = 175 days) after a false-negative mammogram.

**RESULTS**

The time between mammogram and cancer diagnosis was markedly longer for interval breast cancer than for screen-detected breast cancer. Among the 63 women with screen-detected cancer, histologic diagnosis of breast cancer occurred, on average, 26.7 days (median = 18 days) after the screening mammogram. The diagnoses of the 64 interval cancers were substantially delayed, occurring, on average, 180.3 days (median = 175 days) after a false-negative mammogram.

Selected characteristics of the asymptomatic women who underwent screening and were diagnosed with breast cancer are shown in Table 1. Because we used a frequency-matched sampling design, the distributions of age and ethnicity are not statistically significantly different for women with interval and screen-detected cancers. Women with interval cancers were more likely to have radiographically dense breasts (56.7% versus 40.7% for women with screen-detected cancer); however, this difference was not statistically significant. Women with interval cancers were statistically significantly more likely to have had a recent prior screening mammogram within the past 15 months than women with screen-detected cancers (35.9% versus 15.9%, respectively).

Interval cancers generally had a higher histologic grade than screen-detected cancers (Table 1). Although more interval cancers were diagnosed at a regional stage and the tumors were slightly larger, the distributions of stage and tumor size at diagnosis did not differ substantially between groups with interval and screen-detected cancers. The distribution of tumor histologic types did not differ between the groups.

The proportion of interval cancers with dysregulation of the cell cycle and potential genetic instability, as measured by p53 expression, was higher than that of screen-detected cancers (Table 2). p53 expression was detected in 35.9% of interval cancers compared with 15.9% of screen-detected cancers. Proliferation rates of interval tumors were higher than those of screen-detected cancers (mean % of cycling cells = 14.5% versus 9.9%, respectively). In addition, 26.6% of interval cancers had more than 20% cycling cells compared with 13.1% in screen-detected cancers.

Younger women had a higher proportion of rapidly proliferating and aggressive cancers. Of the 37 women younger than 50 years of age, 32% had greater than 20% of cells expressing Ki-67 compared with 15% of the 90 women aged more than 50 years. p53 expression was higher in the younger age group (43%) than in the older age group (19%). The apoptotic index and bcl-2 expression did not differ between the two age groups.

The tumor markers for interval and screen-detected cancers showed the expected correlations (Table 3). However, the magnitude of the correlations indicates that problems from multicolinearity were unlikely in multivariable logistic models. Although comparisons of correlations between interval and screen-detected tumors were limited by sample sizes, the patterns of correlations among the markers were the same in both types of tumors. Interval and screen-detected tumors with a high apoptotic index had high cell proliferation, greater p53 expression, and lower bcl-2 expression, indicating that rapidly growing and potentially genetically unstable tumors also had substantial apoptotic activity.

In multiple logistic regression analyses, we found that the risk for an interval
cancer was substantially increased for rapidly growing tumors (Table 4). It was more likely that a mammographic exami-
nation did not detect tumors with a high proportion of proliferating cells (>20%) than tumors with a low proportion of pro-
liferating cells (<5%) (odds ratio [OR] = 4.09; 95% confidence interval [CI] = 1.14–14.65). The OR for interval cancers 
was 2.96 (95% CI = 1.07–8.20) in tumors that expressed p53 compared with those that did not.

**DISCUSSION**

The relatively high proportion of interval breast cancers among women who undergo screening is an important clinical and public health issue. We found strong support for our hypothesis that rapidly growing and aggressive cancers explain a substantial portion of mammographic failures. Tumor proliferation rate and p53
expression were independent determinants of interval breast cancers. Breast cancers with a high proportion of proliferating cells or with p53 expression were more likely to be interval cancers than tumors with a low proportion of proliferating cells or no p53 expression. A low apoptotic index was also associated with interval cancers, but the estimates had wide CIs and thus were not statistically significant. Consistent with the data on cell proliferation, p53, and apoptosis, interval cancers had a higher histologic grade than screen-detected cancers. Because the study was population based, risk estimates are generalizable to the ethnically diverse population of women who participate in breast cancer screening. On the basis of these estimates, approximately 75% of interval cancers appear to be rapidly growing tumors with 5% proliferating cells or more. The population attributable risk is also large for aggressive and potentially unstable tumors that express p53 (24%).

A limited number of studies (37–40,50) have examined the relationship of interval breast cancers, cell proliferation, and genetic instability. In a study of 50 patients with interval cancers and 161 patients with screen-detected cancers among participants in a randomized trial of mammographic screening in two Swedish counties, interval cancers had increased mean S-phase levels compared with screen-detected cancers. Aneuploid tumors were more often found among interval cancers (72%) than among screen-detected cancers (55%) (37). In a large population-based study in Finland, Klemi et al. (36) reported that, after adjustment for the primary tumor size, interval cancers had larger S-phase fractions than screen-detected cancers. This study also showed that invasive interval cancers were more frequent among women aged 40–49 years if screening was done at 1-year (27%) or 3-year (39%) intervals than among older women screened at 2-year intervals (18%). Brekelmans et al. (38) studied the radiologic and histopathologic characteristics of 104 interval cancers diagnosed within the Utrecht program for the early detection of breast cancer. In a mammographic review, 77 interval cancers were identified. Thirty-four of these cancers (44%) had an elevated mitotic rate greater than three mitoses per HPF. Compared with screen-detected cancers, interval cancers had a shorter doubling time, more aneuploidy, and a higher S-phase fraction (50).

Although it is not entirely consistent, the balance of the existing evidence indicates that women with interval cancers have poorer outcomes (10–16,22). Delays in diagnosis and treatment subsequent to false-negative examinations may account for a portion of the poorer outcomes; however, the poorer outcomes for interval cancers may also be associated with their biologic differences and more rapid tumor growth. Indices of rapid growth are associated with aggressiveness of breast cancers and with poorer prognosis (44,51–54). The same tumor characteristics also appear to be determinants of mammographic failure, supporting the hypothesis that interval cancers are more aggressive and patients with interval cancer have poorer survival (34,37,38).

Our study has a number of important strengths and some potential limitations that need to be considered when interpreting the results. The case–control study was nested in a population-based cohort of women who participated in mammographic screening programs conducted by all institutions in the region offering mammography. Our case ascertainment was likely to be nearly complete because the New Mexico Tumor Registry ascertains more than 98% of the patients with breast cancer diagnosed in New Mexico and the yearly migration out of the state is low, especially among women in the age groups undergoing mammography (55,56). Because we obtained tissue for 70% of interval and selected screen-detected cancers, our results are likely to be representative of breast cancers in the community. It is possible that the incomplete ascertaining of tissue led to a selection bias; however, we believe it is unlikely. Of the 54 missing specimens, 36 were from two institutions that refused to provide samples. Bias would arise if cancers from these institutions had different distributions of p53 or Ki-67 or other factors related to interval cancer. We see no reason

Table 3. Spearman rank correlations (P values) of Ki-67, p53, bcl-2, and apoptotic index (AI)* among 127 interval and screen-detected cancers, the New Mexico Mammography Project, 1991 through 1993

<table>
<thead>
<tr>
<th></th>
<th>Ki-67</th>
<th>p53</th>
<th>bcl-2</th>
<th>AI</th>
</tr>
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<tr>
<td><strong>Screen-detected and interval cancers</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ki-67</td>
<td>1.00</td>
<td>0.16</td>
<td>0.12</td>
<td>0.34</td>
</tr>
<tr>
<td>p53</td>
<td>1.00</td>
<td>0.12</td>
<td>0.21</td>
<td>0.23</td>
</tr>
<tr>
<td>bcl-2</td>
<td>1.00</td>
<td>-0.13</td>
<td>-0.23</td>
<td>-0.08</td>
</tr>
<tr>
<td>AI</td>
<td>1.00</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

| **Screen-detected (n = 63)** |
| Ki-67    | 1.00  | 0.25  | 0.10  | 0.39  |
| p53      | 1.00  | -0.13 | -0.26 | -0.10 |
| bcl-2    | 1.00  | 0.00  | 0.00  | 0.00  |
| AI       | 1.00  | 0.00  | 0.00  | 0.00  |

| **Interval (n = 64)** |
| Ki-67    | 1.00  | 0.04  | 0.15  | 0.30  |
| p53      | 1.00  | -0.14 | 0.17  | 0.17  |
| bcl-2    | 1.00  | 0.00  | -0.38 | -0.38 |
| AI       | 1.00  | 0.00  | 0.00  | 0.00  |

*AI = number of apoptotic cells per mm² of tumor tissue.

Table 4. Odds ratios (ORs) and 95% confidence intervals (CIs) for interval cancers from a multiple logistic regression model*

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast density</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>High</td>
<td>1.95</td>
<td>0.84–4.50</td>
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<tr>
<td>Prior screen, mo</td>
<td></td>
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<tr>
<td>&gt;15</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>≤15</td>
<td>2.83</td>
<td>0.99–8.03</td>
</tr>
<tr>
<td>Apoptotic index†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>2.00</td>
<td>0.62–6.43</td>
</tr>
<tr>
<td>2–5</td>
<td>1.09</td>
<td>0.38–3.12</td>
</tr>
<tr>
<td>≥6</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>bcl-2 expression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>Yes</td>
<td>0.59</td>
<td>0.20–1.74</td>
</tr>
<tr>
<td>p53 expression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>Yes</td>
<td>2.96</td>
<td>1.07–8.20</td>
</tr>
<tr>
<td>Ki-67, %</td>
<td></td>
<td></td>
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<tr>
<td>0–4</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>5–19</td>
<td>2.72</td>
<td>1.04–7.15</td>
</tr>
<tr>
<td>≥20</td>
<td>4.09</td>
<td>1.14–14.65</td>
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*Model also included terms for age at diagnosis, ethnicity, and year of diagnosis.
†Apoptotic index = number of apoptotic cells per mm² of tumor tissue.

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why such an association would exist. The other 18 missing samples could differ from the samples included, but the potential for bias from about 10% of the missing samples is not likely to be large. Supporting this conclusion is the observation that the characteristics of patients for whom no tissue was available did not differ from the patients for whom tissue was available, except in the amount of missing data for family history of breast cancer, estrogen replacement therapy, and breast density. This is probably because of our inability to obtain tissue from two institutions that did not routinely record this information in their mammogram databases. Our relatively small sample size limited the detection of associations of smaller magnitudes and resulted in some strata having few patients. As always, estimates of effect from small strata should be interpreted with caution.

We conducted a standardized pathology review for case and control patients. Immunohistochemical assays were done on freshly cut sections to avoid artifacts (57). We did not conduct a review of mammograms for interval cancers. The usefulness of retrospective reviews is limited because they show a strong dependence on specific methodology (58). The retrospective classification of mammograms with visible lesions as false-negative mammograms is likely to reduce any differences between screen-detected and interval cancers.

Finally, the time-dependent processes that arise from multiple routine screening mammograms are complex. Women have a screening history that varies by age, number of previous mammograms, and timing of previous mammograms. These associated factors are likely to have an impact on the length time bias in a nonlinear manner. Consistent with a length time bias from repeated screenings, we found that a screening mammogram within 15 months of the index screening mammogram was associated with a greater risk of an interval cancer. Logistic regression models do not directly model the complex time-dependent processes of mammographic screening, and the length time bias is not directly considered in this modeling approach. To adjust for the length time bias, we included the time between the index screening mammogram and the previous mammogram in our models.

Our results may have important implications for breast cancer screening programs. Mass mammographic screening for breast cancer has recognized limitations, including lower than optimal sensitivity and specificity. A number of strategies have been advocated or implemented to reduce the number and proportion of interval cancers (59–61). Although reducing the interval between routine screening should reduce the number of interval cancers, it has not been extensively studied (39,40). A subgroup of rapidly growing and aggressive tumors may account for a substantial proportion of interval breast cancers, especially among younger women who have a higher proportion of rapidly growing tumors. If rapid tumor growth is associated with a substantial proportion of failures to detect breast cancer mammographically, then decreasing the interval between mammograms offers one approach that may decrease the number of interval cancers and maximize the reduction in mortality from screening without a concomitant decrease in specificity. Further research is needed to define the benefits and risks associated with reducing interval cancers by reducing the time between screening examinations.

REFERENCES


**NOTES**

1**Editor’s note:** SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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