Breast Tumor Characteristics as Predictors of Mammographic Detection: Comparison of Interval- and Screen-Detected Cancers

Peggy L. Porter, Amira Y. El-Bastawissi, Margaret T. Mandelson, Ming Gang Lin, Najma Khalid, Elizabeth A. Watney, Laura Cousens, Donna White, Stephen Taplin, Emily White

Background: **Although mammographic screening is useful for detecting early breast cancer, some tumors are detected in the interval between screening examinations. This study attempted to characterize fully the tumors detected in the two different manners.** ***Methods:*** **Our study utilized a case–control design and involved a cohort of women undergoing mammographic screening within the defined population of a health maintenance organization (the Group Health Cooperative of Puget Sound). Women were classified as having "interval" or "interval-detected" cancers (n = 150) if their diagnosis was made within 24 months after a negative-screening mammogram or one that indicated a benign condition. Cancers were classified as "screen detected" (n = 279) if the diagnosis occurred after a positive assessment by screening mammography. Tumors from women in each group were evaluated for clinical presentation, histology, proliferative characteristics, and expression of hormone receptors, p53 tumor suppressor protein, and c-erbB-2 protein.** ***Results:*** **Interval-detected cancers occurred more in younger women and were of larger tumor size than screen-detected cancers. In unconditional logistic regression models adjusted for age and tumor size, tumors with lobular (odds ratio [OR] = 1.9; 95% confidence interval [CI] = 0.9–4.2) or mucinous (OR = 5.5; 95% CI = 1.5–19.4) histology, high proliferation (by either mitotic count [OR = 2.9; 95% CI = 1.5–5.7] or Ki-67 antigen expression [OR = 2.3; 95% CI = 1.3–4.1]), high histologic grade (OR = 2.1; 95% CI = 1.2–4.0), high nuclear grade (OR = 2.0; 95% CI = 1.0–3.7), or negative estrogen receptor status (OR = 1.8; 95% CI = 1.0–3.1) were more likely to surface in the interval between screening examinations. Tumors with tubular histology (OR = 0.2; 95% CI = 0.0–0.8) or with a high percentage of *in situ* components (50%) (OR = 0.5; 95% CI = 0.2–1.2) were associated with an increased likelihood of screen detection.** ***Conclusions:*** **Our data from a large group of women in a defined population indicate that screening mammography may miss tumors of lobular or mucinous histology and some rapidly proliferating, high-grade tumors. [J Natl Cancer Inst 1999;91: 2020–8]**

The goal of a mammography screening program is to identify breast cancers prior to their dissemination. Although mammography has been shown to be a very useful screening method for the detection of early breast cancer, there remains a group of tumors detected in the interval between screening examinations. There are at least three types of problems that lead to failure of detection by mammography. First, technical or interpretive errors account for somewhere between 10% and 36% of cancers that are missed by mammographic screening *(1–3).* Second, characteristics of the breast or tumor—e.g., increased mammographic breast density, lobular histology, or an absence of microscopic and mammographic calcification *(4–8)*—may lead to the tumor being masked. Third, some subset of cancers not detected by mammography appears to be rapidly growing; they are initially small tumors that grow to a detectable size during the screening interval *(9–11).* As such, interval-detected cancers constitute a heterogeneous group of tumors that must be evaluated with respect to clinical presentation and tumor characteristics to explain the relative contribution of these features to the efficacy of mammographic screening.

Because it is difficult to separate the tumors that are masked from those that arise in the interval between screening because of rapid growth, these two categories of interval-detected cancers are often combined and assumed to be true interval cancers *(12).* Several investigators *(1,12)* have separated these "true" interval-arising cancers from those missed at screening because of technical error—i.e., those that could be identified on the mammogram in retrospect. In reports of series in which such a distinction was made, true interval-arising cancers constituted 65%–75% of the cancers diagnosed in the interval between screening examinations *(1,12–15).* The subset of true interval cancers appears to comprise tumors that are more rapidly growing *(12,13);* in some studies *(1,12,13,16),* associations between interval cancers and measures of tumor aggressiveness, such as nodal metastasis and high histologic grade, have been reported.

The purpose of this study was to identify tumor and patient characteristics associated with increased risk of interval-detected cancer among screened women with breast cancer or, equivalently, characteristics associated with reduced likelihood of screen detection (reduced sensitivity of mammography). We compared the clinical presentation, histology, kinetics, and expression of tumor-related proteins in a study by the use of a case–control design of 150 interval- and 279 screen-detected cancers within the defined population of women participating in a screening program of a large health maintenance organization. Our data represent the largest comprehensive evaluation of the tumor characteristics of breast cancers not detected by mammography in a screened population of women.

METHODS

Selection of Subjects

Subjects were selected from women enrolled in the Group Health Cooperative of Puget Sound (GHC), a health maintenance organization serving

Affiliations of authors: P. L. Porter, Program in Cancer Biology, Division of Human Biology, Fred Hutchinson Cancer Research Center, Seattle, WA, and Department of Pathology, University of Washington, Seattle; A. Y. El-Bastawissi, N. Khalid (Cancer Prevention Research Program, Division of Public Health Sciences), M. G. Lin, E. A. Watney, L. Cousens (Program in Cancer Biology), Division of Human Biology, Fred Hutchinson Cancer Research Center; M. T. Mandelson, Department of Epidemiology, University of Washington, and Center for Health Studies, Group Health Cooperative, Seattle; D. White, Department of Radiology, Group Health Cooperative; S. Taplin, Department of Family Medicine, University of Washington, and Center for Health Studies, Group Health Cooperative, Seattle; E. White, Cancer Prevention Research Program, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, and Department of Epidemiology, University of Washington.

Correspondence to: Peggy L. Porter, M.D., Fred Hutchinson Cancer Research Center, Cancer Biology, C1-015, 1100 Fairview Ave., N., Seattle, WA 98109 (e-mail: pporter@fhcrc.org).

See "Notes" following "References."

400 000 members in western Washington state. Beginning in 1986, all female members 50 years of age or older and high-risk women aged 40–49 years [those with risk factors including early onset of menarche, nulliparity by age 30 years, family history of breast cancer, or atypical hyperplasia on a previous breast biopsy *(17)*] were invited to participate in a formal Breast Cancer Screening Program (BCSP). Program enrollment begins by completing a BCSP Risk Factor Questionnaire and includes regular reminders to women who are due for screening. Screening occurs through centers where women receive a two-view mammogram and clinical breast examination. Approximately 85% of the women complete the questionnaire and enroll in the program; there was no appreciable change in the rate of participation over the study period. During the study period, women were sent reminders to come in for screening every 1–3 years on the basis of their breast cancer risk factors. Information from the risk factor questionnaire, results, and recommendations of all BCSP examinations and associated pathologic findings are stored in a centralized and linked database *(18,19)*. Physicians also order screening mammograms in the course of usual care or to evaluate a symptomatic woman. These examinations occur through the radiology departments but outside the screening program.

Interval-detected cancer case subjects and comparison subjects whose breast cancer was screen detected (defined as control subjects for the purposes of this study) were drawn from women enrolled in the BCSP who had at least one screening mammogram during the period from January 1, 1988, through December 31, 1993, and who were diagnosed with a first primary invasive breast cancer within 24 months of their last screening mammogram and before their next screening mammogram. Subjects with breast cancer were identified by linking the BCSP database with the Seattle–Puget Sound Surveillance, Epidemiology, and End Results (SEER)[1] cancer registry. Sixty-six percent of the interval-detected cancers were discovered by the patient, and 25% were detected by clinical breast examination. The study was restricted to women who did not have a history of breast cancer prior to their index mammogram and who were enrolled continuously at the GHC for at least 24 months following the index mammogram or who had died of any cause during that 24-month period. Women undergoing a biopsy gave signed consent to use their tissue for research purposes; all study procedures were approved by the human subjects review committee of the GHC.

Classification of Interval- Versus Screen-Detected Cancers

Classification of women's breast cancers into interval-detected (case subjects) versus screen-detected (control subjects) was based on the interpretation of the last BCSP mammogram before the diagnosis of breast cancer (the index mammogram). Evaluations were made after assessment of additional views, if any. For the purposes of this study, we used the BCSP database and information from medical record abstraction of all interval-detected cancer case subjects and screen-detected cancer control subjects diagnosed after 3 months from the index mammogram to reclassify the mammogram according to the Breast Imaging Reporting and Data System (BI-RADS™) of the American College of Radiology *(20)*. Cancers were classified as interval detected (cancer cases) if they occurred after a "negative" (BI-RADS™ code 1) or a "benign" (BI-RADS™ code 2) assessment on the index mammogram. Women who were given a recommendation for a 12-month follow-up (even though their normal follow-up interval was 2 or 3 years) were also considered as "negative" because this is a routine follow-up interval in many settings. We also counted any interpretation as "negative" if abnormalities noted by the radiologist were in the opposite breast from that where the cancer was detected.

Women's cancers were classified as screen detected if they occurred after a "positive" mammogram (BI-RADS™ code 5 = "highly suggestive of malignancy"), if they had a recommendation for surgical evaluation (BI-RADS™ code 4 = "suspicious for malignancy"), or if they had a recommendation for a 6-month follow-up (BI-RADS™ code 3 = "probably benign, short-interval follow-up suggested").

Sample Selection and Sample Size

A total of 578 women with invasive breast cancer met the eligibility requirements. One woman was dropped from the study at her request, and another was excluded because she was symptomatic at the time of the screening visit. Of the remaining 576 subjects, 162 were classified as interval-detected cancer case subjects and 414 were classified as screen-detected control subjects, using the above definitions. To conduct this study, we selected all interval-detected cancers and an approximate 2 to 1 random sample of screen-detected control subjects stratified by year of mammogram. Paraffin-embedded breast tumor tissue samples collected prior to any adjuvant treatment were available for 150 (93%) of the 162 case subjects and for 279 (97%) of the 287 selected control subjects.

Second Mammographic Assessment

We further classified the interval-detected cancers by whether or not they were detected by a second radiologist's review. An expert radiologist (D. White), blinded to the cancer status of each film, read a mixed group of mammograms: all available interval-detected cancers in the study plus mammograms from 50 randomly selected screen-detected cancers and 50 randomly selected age-stratified, cancer-free control subjects. Any additional views or ultrasound images obtained at the original assessment were available, but all marks on the films were removed. Films were interpreted by use of the five-category BI-RADS™ criteria. When a tumor was detected, the location of the lesion was indicated on the form. Of the 150 women with interval-detected cancer, films of eight could not be obtained. Of the 142 women reviewed, 44 (31%) received a positive interpretation (BI-RADS™ code 3, 4, or 5) and the affected breast was correctly identified. Those women with a negative assessment (BI-RADS™ code 1 or 2) (n = 98) from both the initial and second radiologists were termed "true interval cancers."

Laboratory Measures

Paraffin-embedded primary breast tumor tissue samples were microscopically examined for tumor characteristics and diagnosis and evaluated by immunohistochemistry for expression of selected proteins. For women with bilateral tumors diagnosed synchronously, the laboratory measures from the largest tumor were used in the analyses.

Clinical and Histologic Evaluation

Pathology data were obtained from data collected by the SEER Program and by pathology report abstraction and examination of hematoxylin–eosin-stained slides made from the tissue blocks. Information concerning tumor size, tumor location in the breast, status of surgical margins, distribution (focal versus multifocal), the number of lymph nodes examined, and the number of lymph nodes positive for tumor was abstracted from the pathology report. Tumor size was also obtained from the SEER data to minimize missing values. Data on tumor size, lymph node involvement, and metastasis of tumor were used to generate American Joint Committee on Cancer (AJCC) staging *(21)*. Histologic diagnosis, using the World Health Organization classification of malignant breast tumors, and assignment of a histologic grade, according to the Bloom and Richardson grading scheme for invasive ductal carcinoma *(22)*, were done by one pathologist (P. L. Porter), who was blinded to the case–control status of the material. Individual scores for differentiation, nuclear grade, and mitotic index were assessed from histology slide review along with the presence of lymphatic or vascular invasion, levels of tumor necrosis, stromal and lymphocyte response, and percentage of *in situ* components.

Immunohistochemical Studies

Immunoperoxidase assays for estrogen receptor (ER), progesterone receptor (PR), p53 tumor suppressor gene protein, Ki-67 proliferation-related antigen, c-erbB-2 oncogene protein, apoptosis (programmed cell death) regulatory protein bcl-2, and cell cycle regulatory proteins cyclin E and p27 were performed on sections from a single tumor block from women with interval- and screen-detected breast cancers. All scoring and interpretations of immunohistochemical results were made by the study pathologists (P. L. Porter and M. G. Lin), who had no knowledge of the interval cancer status or other clinical variables. In some instances, tumor tissue was depleted before the completion of all antibody tests, resulting in slightly different numbers of tumors tested for each antibody. Nine of the tissue samples (2%) from study participants were unsuitable for immunohistochemistry either because of an insufficient amount of tumor for analysis or because of loss of overall reactivity in the tumor block, demonstrated by poor immunoreactivity with antibodies to common antigens (e.g., cytokeratins and endothelial cell markers).

Antibodies used for the study have been extensively tested in this and other laboratories. They included monoclonal antiestrogen receptor clone ER1D5 (Immunotech, Westbrook, ME), monoclonal antiprogesterone receptor (clone1A6; Novacastra, Burlingame, CA), anti-Ki-67 clone MIB-1 (Immunotech), anti-p53 clone 1801 (Oncogene Science, Uniondale, NY), rabbit polyclonal anti-c-erbB-2 (Dako, Carpenteria, CA), hamster monoclonal anti-bcl-2 (Hockenbery Laboratory, Fred Hutchinson Cancer Research Center, Seattle, WA) *(23)*, affinity purified polyclonal anticyclin E (Roberts Labora-

tory, Fred Hutchinson Cancer Research Center), and monoclonal anti-p27 clone DCS-72.F6 (Neomarkers Inc., Fremont, CA). Positive control tissue for all antibodies was tested along with the tumor tissue. Normal human tonsil was used as a positive control for p27, Ki-67, and bcl-2; formalin-fixed and paraffin-embedded pellets of rat fibroblast cells that had been engineered to overexpress cyclin E were used as positive controls for cyclin E; normal breast samples served as a control for ER and PR; and previously tested c-erbB-2- and p53-positive tumor samples served as a control for c-erbB-2 and p53. Immunostaining was done by use of previously reported immunoperoxidase procedures and modifications of the standard technique for antigen retrieval when required *(26–28)*.

Antibodies were scored by use of a subjective interpretation of staining intensity and/or the percentage of tumor cells that were positive. Categories of intensity and/or the percentage of positive cells were collapsed into positive/high or negative/low categories according to the assay. For ER and PR, any nuclear staining above negative was considered to be positive. The percentage of Ki-67-positive tumor cells, averaged over four high-power fields, was converted to the lowest quartile (≤5.7%) versus that above (i.e., upper three quartiles). Nuclear staining of more than 10% tumor cells for p53 was considered to be positive. A membranous staining pattern was considered to be positive for c-erbB-2. The negative and low-intensity bcl-2 stains were grouped together as "low," while intermediate or high staining was categorized as "high." Immunostaining for cyclin E and p27 was given a value from 1 (negative) to 7 (highest intensity); low intensity included all values of 1–4, and high intensity included values from 5 to 7 *(29)*.

Statistical Methods

We used unconditional logistic regression to analyze the association of tumor characteristics with risk of interval- versus screen-detected cancers, after adjustment for covariates. We present odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of interval cancer among women diagnosed with breast cancer within 24 months of a screening mammogram. (It should be noted that, by definition, the inverse of each of these ORs is the OR for the sensitivity of mammography, i.e., the odds of screen detection versus detection in the interval after a negative screen among women with breast cancer.) Age at screening and tumor size confounded the associations presented, and these were adjusted for in all models by use of 10-year age groups and five categories of tumor size. For ordered categorical-independent variables, we tested the statistical significance of the presence of a linear trend (P for trend) by treating the factor as a single variable taking on the values $1,2,\ldots n$ equal to the category number; this is the logistic analog of the Mantel–Haenszel trend test. All P values were two-sided and are based on Z scores, except those noted to be based on Fisher's exact test; $P<.05$ was considered to be statistically significant. Effect modification by age was assessed by the statistical significance of an interaction term between age group (<50 years versus ≥50 years) and the tumor characteristic (expressed as a trend variable).

Analyses were also performed by use of different definitions of interval- versus screen-detected cancers: 1) the definition as described above, 2) the definition as described above except with a 12-month rather than a 24-month interval for follow-up, 3) the definition as described above except that those classified as BI-RADS™ code 3 (probably benign, short-term follow-up) were considered to be interval-detected case subjects rather than screen-detected case subjects, 4) all control subjects and only interval case subjects who had negative mammograms on the expert rereading ("true interval cancers"), and 5) only case and control subjects who presented with carcinoma other than lobular or mucinous.

Results

Table 1 shows the distribution of 150 interval cancers detected within 24 months after a negative mammogram and 279 screen-detected control cancers with respect to AJCC stage, tumor size, and age of subject at screening mammogram. Interval-detected cancers were more likely to occur in women under the age of 50 years and to be detected at a larger size and later stage ($P<.001$ for all three characteristics). Tumor characteristics are by necessity measured at diagnosis rather than at the time of mammogram, which would be ideal. Thus, our findings that interval-detected cancers were larger and detected at a later stage can be interpreted as a result of the later detection of interval cancers rather than a predictor of interval cancer risk. For this reason, all further analyses were adjusted for tumor size at diagnosis as well as for the age of the subject.

Tumor Characteristics of Interval- and Screen-Detected Cancers

The comparison of multiple tumor characteristics related to tumor growth and tumor aggressiveness, adjusted for age at screening mammogram and tumor size, in all interval- and screen-detected cancers is shown in Table 2. As shown, histologic type is a predictor of screen detection: Tubular carcinoma was more likely to be detected by mammography ($P = .002$), whereas mucinous or lobular histology was more likely to be de-

Table 1. Age and stage distribution of 150 interval-detected and 279 screen-detected cancers*

Characteristic	Interval-detected cancers (total, n = 150), No. (%)	Screen-detected cancers (total, n = 279), No. (%)	OR (95% CI)	P
Age at screen, y				
40–49	35 (23.3)	24 (8.6)	1.0 (referent)	<.001†
50–59	40 (26.7)	62 (22.2)	0.4 (0.2–0.9)	
60–69	35 (23.3)	85 (30.5)	0.3 (0.1–0.5)	
70–79	31 (20.7)	88 (31.5)	0.2 (0.1–0.5)	
≥80	9 (6.0)	20 (7.2)	0.3 (0.1–0.8)	
Stage, AJCC‡				
I	73 (50.7)	200 (74.1)	1.0 (referent)	<.001†
IIA	36 (25.0)	37 (13.7)	2.7 (1.6–4.7)	
IIB	10 (6.9)	14 (5.2)	1.7 (0.7–4.0)	
IIIA	22 (15.3)	18 (6.7)	2.8 (1.4–5.6)	
IIIB/IV	3 (2.1)	1 (0.4)	NA	
Unknown	6	9	—	
Tumor size, cm‡				
≤0.5	6 (4.1)	21 (7.8)	1.0 (referent)	<.001†
>0.5–1.0	21 (14.5)	89 (32.8)	0.8 (0.3–2.3)	
>1.0–2.0	72 (49.7)	118 (43.5)	2.0 (0.7–5.3)	
>2.0–5.0	42 (29.0)	38 (14.0)	3.6 (1.3–10.3)	
>5.0	4 (2.8)	5 (1.9)	2.2 (0.4–11.2)	
Unknown	5	8	—	
Regional lymph nodes§				
Negative	108 (72.0)	230 (82.4)	1.0 (referent)	.97‖
Positive	42 (28.0)	49 (17.6)	1.0 (0.6–1.7)	

*OR = odds ratio for risk of interval-detected cancers associated with each factor; CI = confidence interval; NA = not applicable (numbers are too small for precise OR); interval-detected cancers = diagnosed within 24 months after a "negative" or "benign" (BI-RADS™ code 1 or 2) assessment on the index mammogram; screen-detected cancers = diagnosed within 24 months after a "positive," "suspicious for malignancy," or "probably benign, short interval follow-up suggested" mammogram (Breast Imaging Reporting and Data System code 5, 4, or 3, respectively).

†P for trend, two-sided.

‡OR adjusted for age. AJCC = American Joint Committee on Cancer.

§Adjusted for age and tumor size.

‖P for difference between groups, two-sided.

Table 2. Clinical and tumor characteristics of interval-detected and screen-detected cancers

Characteristic	Interval-detected cancers (total, n = 150), No. (%)	Screen-detected cancers (total, n = 279), No. (%)	OR (95% CI)*	*P*
Histologic type				
Ductal (not otherwise specified)	116 (77.3)	226 (81.3)	1.0 (referent)	
Tubular	2 (1.3)	27 (9.7)	0.2 (0.0–0.8)	.002†
Mucinous	9 (6.0)	4 (1.4)	5.5 (1.5–19.4)	.015†
Medullary	2 (1.3)	2 (0.7)	1.5 (0.2–11.6)	.608†
Lobular	17 (11.3)	18 (6.5)	1.9 (0.9–4.2)	.093‡
Other‖	4 (2.7)	1 (0.4)	3.1 (0.3–35.5)	Not done
Histologic grade¶,#				
Low	39 (29.6)	111 (42.7)	1.0 (referent)	.020§
Intermediate	45 (34.1)	105 (40.4)	1.2 (0.7–2.1)	
High	48 (36.4)	44 (16.9)	2.1 (1.2–4.0)	
Nuclear grade#				
Low	25 (16.8)	75 (27.0)	1.0 (referent)	.035§
Intermediate	72 (48.3)	144 (51.8)	1.4 (0.8–2.4)	
High	52 (34.9)	59 (21.2)	2.0 (1.0–3.7)	
Mitotic count¶,#				
Low	59 (44.7)	176 (67.7)	1.0 (referent)	.002§
Intermediate	33 (25.0)	57 (21.9)	1.4 (0.8–2.5)	
High	40 (30.3)	27 (10.4)	2.9 (1.5–5.7)	
Ki-67 proliferation index#				
Lowest quartile, ⩽5.75%	22 (14.9)	82 (30.7)	1.0 (referent)	.003‡
Highest 3 quartiles, >5.75%	126 (85.1)	185 (69.3)	2.3 (1.3–4.1)	
Estrogen receptor#				
Positive	110 (74.3)	236 (86.8)	1.0 (referent)	.051‡
Negative	38 (25.7)	36 (13.2)	1.8 (1.0–3.1)	
Progesterone receptor#				
Positive	104 (70.3)	208 (76.8)	1.0 (referent)	.102‡
Negative	44 (29.7)	63 (23.2)	1.5 (0.9–2.5)	
In situ component, %,#				
<25	126 (84.6)	206 (74.6)	1.0 (referent)	.073§
25–50	16 (10.7)	38 (13.8)	0.7 (0.4–1.4)	
>50	7 (4.7)	32 (11.6)	0.5 (0.2–1.2)	
p53#				
Negative	92 (62.2)	176 (65.2)	1.0 (referent)	1.000‡
Positive	56 (37.8)	94 (34.8)	1.0 (0.6–1.6)	
c-erbB-2#				
Negative	119 (81.5)	215 (79.3)	1.0 (referent)	.106‡
Positive	27 (18.5)	56 (20.7)	0.6 (0.4–1.1)	

*Odds ratio for risk of interval-detected cancer associated with each factor, adjusted for age and tumor size.

†Two-sided Fisher's exact test for the tumor histologic types that had cells of 5 or fewer.

‡*P* for difference, two-sided based on Z scores.

§P_{trend}, two-sided based on Z scores.

‖Includes one each of papillary carcinoma, metaplastic carcinoma, Paget's disease, carcinosarcoma, and inflammatory carcinoma.

¶Bloom and Richardson grading system *(22)*; 35 lobular cancers, one Paget's disease, and one inflammatory cancer were not assigned histologic grade or mitotic count.

#Numbers in these categories do not sum to the total either because of missing data or because some pathologic indicators are not applicable for criteria histologic types of breast cancer (*see* ¶).

tected in the interval between screening ($P = .015$ and .093, respectively). Women with tumors of high histologic grade ($P = .020$), high nuclear grade ($P = .035$), and high proliferative rate as measured by both mitotic cell count ($P = .002$) and Ki-67 ($P = .003$) were more likely to have interval-detected than screen-detected cancers. ER- and PR-negative cancers were also more likely to be detected in the screening interval, although the association with PR negativity was not statistically significant in the analysis of all of the interval-detected cancers. Ductal carcinomas composed of a high percentage (>50%) of *in situ* disease were more often detected by mammography screening than in the interval between screening. p53 tumor suppressor protein and c-erbB-2 oncogene product, two markers that in many studies are associated with poor prognosis, were not associated with interval-detected cancers. In addition, there were no differences in the expression of bcl-2 apoptosis-inhibitory protein or cell-cycle regulatory proteins cyclin E and p27, tumor location, distribution of tumor (multifocal versus unifocal), lymphovascular invasion, level of tumor necrosis, or presence of lymphocyte or stromal response (data not shown).

When tumor characteristics were evaluated in women under age 50 years and in women aged 50 years or older, we found that women under age 50 years were almost five times more likely to be diagnosed in the interval between screening than by screening mammography if their tumors exhibited a high proliferative rate as determined by Ki-67 (Table 3)

Table 3. Interval cancer risk associated with tumor characteristics in women under age 50 versus age 50 years and older

Characteristic	Risk of interval-detected cancers among women aged <50 years,* OR (95% CI)†	Risk of interval cancers among women aged ⩾50 years,‡ OR (95% CI)†	P_{trend} for interaction§
Ki-67 proliferation index			
Lowest quartile, ⩽5.75%	1.0 (referent)	1.0 (referent)	.51
Highest 3 quartiles, >5.75%	4.7 (1.0–21.2)	2.2 (1.2–4.0)	
P for difference‖	.046	.013	
Histologic grade			
Low	1.0 (referent)	1.0 (referent)	.95
Intermediate	1.8 (0.4–8.2)	1.2 (0.7–2.2)	
High	3.2 (0.7–15.3)	2.1 (1.1–4.3)	
P_{trend}‖	.14	.039	
Nuclear grade			
Low	1.0 (referent)	1.0 (referent)	.66
Intermediate	3.3 (0.5–23.0)	1.3 (0.7–2.5)	
High	4.1 (0.5–32.0)	2.0 (1.0–4.1)	
P_{trend}‖	.25	.040	
Estrogen receptor			
Positive	1.0 (referent)	1.0 (referent)	.81
Negative	2.4 (0.6–9.2)	1.7 (0.9–3.1)	
P for difference‖	.21	.12	
Progesterone receptor			
Positive	1.0 (referent)	1.0 (referent)	.20
Negative	3.3 (0.8–14.1)	1.3 (0.8–2.2)	
P for difference‖	.12	.33	
In situ component, %			
<25	1.0 (referent)	1.0 (referent)	.15
25–50	0.4 (0.1–2.7)	0.8 (0.4–1.6)	
>50	0.1 (0.0–1.4)	0.7 (0.3–2.0)	
P_{trend}‖	.065	.40	
Cyclin E			
Negative/low positive	1.0 (referent)	1.0 (referent)	.30
Medium/high positive	3.6 (0.8–15.9)	1.2 (0.6–2.5)	
P for difference‖	.089	.67	
Lymphatic/vascular invasion			
No	1.0 (referent)	1.0 (referent)	.05
Yes	4.8 (0.9–25.6)	0.6 (0.3–1.4)	
P for difference‖	.063	.27	
Stromal response			
None	1.0 (referent)	1.0 (referent)	.13
Low	0.8 (0.0–13.9)	1.0 (0.4–2.1)	
Intermediate	0.4 (0.0–5.6)	1.0 (0.4–2.1)	
High	0.2 (0.0–2.5)	0.8 (0.3–1.8)	
P_{trend}‖	.096	.56	

*n = 24 screen-detected control subjects and 35 interval-detected case subjects.

†OR = odds ratio; CI = confidence interval. All ORs and CIs are adjusted for age and tumor size.

‡n = 255 screen-detected control subjects and 115 interval-detected case subjects.

§Significance of an interaction term between age group (<50 years versus ⩾50 years) and the tumor characteristic (expressed as a trend variable). All *P* values are two-sided and based on Z scores.

‖All *P* values are two-sided and based on Z scores.

(OR = 4.7; 95% CI = 1.0–21.2). This compared with only a twofold increased risk for women aged 50 years or older (OR = 2.2; 95% CI = 1.2–4.0). ORs for the association between interval cancer detection and other tumor characteristics (e.g., high histologic grade, high nuclear grade, lack of steroid hormone receptors, high cyclin E, and presence of lymphatic/vascular invasion) were also higher in women under 50 years than in women 50 years or older. Although these results may reflect real differences in the relationship of certain tumor characteristics with interval cancer detection between younger and older women, a statistical test of the interaction between age groups showed a nearly significant difference only with respect to the presence of lymphatic/vascular invasion ($P = .052$).

Comparison of Tumor Characteristics by Use of Alternate Definitions of Case and Control

To interpret more precisely the association of tumor characteristics with screening mammographic or interval detection, we applied alternate definitions for "case" and "control" or excluded tumors from some analyses. As shown in Table 4, this included 1) the exclusion of case subjects originally designated as interval-detected cancers that were given a positive interpretation (BI-RADS™ code 3, 4, or 5) on second assessment of the index mammogram (probable false negatives), 2) the exclusion of tumors with the histologic diagnoses that were associated with failure of mammographic detection—i.e., mucinous and lobular types, and 3) the exclusion of both false negatives and mammographically indistinct subtypes (considered the most representative of tumors that truly develop in the interval between screening or "true interval" cancers). Overall, restriction of the analysis to true interval cancers resulted in increased ORs for the association of high histologic grade (OR = 2.1 [95% CI = 1.2–4.0] for all subjects and OR = 3.0 [95% CI = 1.4–6.2] after exclusion of positive rereads and mucinous and lobular histology) and increased proliferation measured by mitotic count (OR = 2.9 [95% CI = 1.5–5.7] for all subjects and OR = 4.4 [95% CI = 2.1–9.6] after exclusion of positive rereads and mucinous and lobular histology) with interval-detected cancers. A high Ki-67 proliferation index also appeared to be more predictive of interval-surfacing cancers than of true interval cancers but not when just the false negatives were excluded. Tumor stage and size appeared to be less predictive of interval cancers when the analysis was restricted to the true interval cancers.

When data were analyzed by including BI-RADS™ code 3 (probably benign, short interval follow-up suggested) in the case group rather than in the control group, there were no statistically significant changes related to the tumor characteristics associated with screen detection (data not shown). To evaluate how tumor characteristics associated with interval cancer detection might differ as a result of variable definitions of time to diagnosis after screening, we also analyzed the characteristics by use of a 12-month rather than a 24-month interval for case definition. Sixty-eight of the interval cancers (45%) were detected within 12 months of the index screening mammogram, and 119 (79%) were detected within 18 months. We found no apparent differences in the characteristics of the tumors associated with interval detection

Table 4. Relationship of clinicopathologic characteristics to interval cancer using multiple definitions for "interval" cancer

Characteristic	All subjects,* OR (95% CI)†	Exclude case subjects with positive reread,‡ OR (95% CI)†	Exclude case and control subjects with mucinous and lobular histology,§ OR (95% CI)†	Exclude positive reread and mucinous and lobular histology,‖ OR (95% CI)†
Age at screen, y				
40–49	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
50–59	0.4 (0.2–0.9)	0.4 (0.2–0.7)	0.4 (0.2–0.9)	0.3 (0.2–0.7)
60–69	0.3 (0.1–0.5)	0.3 (0.1–0.6)	0.3 (0.1–0.5)	0.2 (0.1–0.5)
70–79	0.2 (0.1–0.5)	0.2 (0.1–0.5)	0.2 (0.1–0.4)	0.1 (0.1–0.3)
⩾80	0.3 (0.1–0.8)	0.2 (0.1–0.6)	0.2 (0.1–0.6)	0.1 (0.0–0.5)
Stage, AJCC¶				
I	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
IIA	2.7 (1.6–4.7)	2.0 (1.0–3.8)	2.5 (1.4–4.4)	1.6 (0.8–3.2)
IIB	1.7 (0.7–4.0)	2.4 (1.0–5.9)	1.3 (0.5–3.6)	1.7 (0.6–5.0)
IIIA	2.8 (1.4–5.6)	2.8 (1.3–6.1)	2.2 (1.0–4.7)	1.8 (0.7–4.4)
IIIB/IV	7.4 (0.7–74.8)	7.4 (0.6–87.5)	4.5 (0.4–52.6)	3.3 (0.2–56.4)
Tumor size, cm				
⩽0.5	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
>0.5–1.0	0.8 (0.3–2.3)	0.6 (0.2–2.0)	0.8 (0.3–2.2)	0.6 (0.2–1.9)
>1.0–2.0	2.0 (0.7–5.3)	1.2 (0.4–3.5)	1.7 (0.6–4.6)	1.1 (0.4–3.4)
>2.0–5.0	3.6 (1.3–10.3)	2.4 (0.8–7.4)	2.8 (1.0–8.2)	1.7 (0.5–5.6)
>5.0	2.2 (0.4–11.2)	1.5 (0.2–9.1)	1.7 (0.3–10.2)	1.1 (0.1–8.2)
Regional lymph node				
Negative	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 referent)
1–2 positive	1.2 (0.6–2.3)	1.5 (0.7–3.0)	1.1 (0.5–2.3)	1.4 (0.6–3.2)
⩾3 positive	0.8 (0.4–1.7)	0.8 (0.3–2.0)	0.8 (0.3–1.7)	0.8 (0.3–2.0)
Histologic grade				
Low	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Intermediate	1.2 (0.7–2.1)	1.3 (0.7–2.4)	1.3 (0.7–2.3)	1.3 (0.7–2.5)
High	2.1 (1.2–4.0)	2.4 (1.2–4.9)	2.6 (1.4–5.0)	3.0 (1.4–6.2)
Nuclear grade				
Low	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Intermediate	1.4 (0.8–2.4)	1.3 (0.7–2.6)	2.1 (1.0–4.3)	1.8 (0.8–4.1)
High	2.0 (1.0–3.7)	1.9 (0.9–4.0)	3.7 (1.7–8.1)	3.2 (1.3–7.7)
Mitotic count				
Low	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Intermediate	1.4 (0.8–2.5)	1.7 (0.9–3.2)	1.6 (0.9–3.0)	2.0 (1.0–4.0)
High	2.9 (1.5–5.7)	3.5 (1.7–7.3)	3.5 (1.8–6.9)	4.4 (2.1–9.6)
Ki-67 proliferation index				
Lowest quartile, ⩽5.75%	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Highest 3 quartiles, >5.75%	2.3 (1.3–4.1)	2.0 (1.0–3.8)	2.8 (1.4–5.3)	2.7 (1.3–5.9)
Estrogen receptor				
Positive	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Negative	1.8 (1.0–3.1)	1.8 (1.0–3.5)	2.3 (1.3–4.2)	2.3 (1.2–4.6)
Progesterone receptor				
Positive	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Negative	1.4 (0.9–2.5)	1.3 (0.7–2.5)	1.7 (1.0–3.3)	1.4 (0.8–2.5)
In situ component, %				
<25	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
25–50	0.7 (0.4–1.4)	0.7 (0.3–1.5)	0.7 (0.4–1.4)	0.6 (0.3–1.5)
>50	0.5 (0.2–1.2)	0.4 (0.1–1.3)	0.5 (0.2–1.2)	0.5 (0.2–1.4)
p53				
Negative	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Positive	1.0 (0.6–1.6)	1.2 (0.7–2.0)	1.3 (0.8–2.1)	1.4 (0.8–2.4)
c-erbB-2				
Negative	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Positive	0.6 (0.4–1.1)	0.5 (0.3–1.0)	0.6 (0.3–1.1)	0.6 (0.3–1.1)

*n = 150 interval-detected case subjects and 279 screen-detected control subjects.

†OR = odds ratio; CI confidence interval. All ORs and CIs are adjusted for age and tumor size.

‡n = 98 interval-detected case subjects and 279 screen-detected control subjects.

§n = 124 interval-detected case subjects and 257 screen-detected control subjects.

‖n = 82 interval-detected case subjects and 257 screen-detected control subjects.

¶AJCC = American Joint Committee on Cancer.

when an interval of either 12 or 24 months was used (data not shown).

DISCUSSION

Interval-detected cancers are a diverse group of tumors that can include cancers missed on screening examination and cancers present but mammographically indistinct, as well as cancers that truly arise in the interval between screening. Total interval cancers in this screened population constituted 28% of the invasive cancers identified during the study period. If cancers detectable in retrospective review were excluded, the "true" interval surfacing cancer rate was 17%. Our data are in agreement with those of others who report a 3%–17% rate of true interval cancers for a 1-year *(4,30)* or 2-year *(1)* interval between screening.

Tumor growth patterns associated with histologic presentation are known to affect the efficacy of mammography; lobular cancer spreads diffusely and is less likely than ductal carcinoma to evoke a stromal response *(5,14,31)*. Similarly, mucinous carcinoma exhibits a minimal stromal response and is composed of radiologically indistinct mucin. On the other hand, tubular cancers are discrete lesions composed of well-differentiated tubules of ductal epithelium surrounded by sometimes very dense collagenous stroma that are more readily visualized on mammography *(12)*. Our finding that a high percentage of *in situ* component in the invasive tumor was associated with screening could conceivably result from multifocal distribution. Alternatively, this finding may suggest a greater likelihood of mammographic detection because of some factor such as calcification in *in situ* tumors, although it most likely reflects the limitations—i.e., low probability—of detecting predominantly *in situ* tumors on clinical examination.

The established profile of aggressive breast tumors includes metastasis to regional lymph nodes, high histologic grade, loss of ERs and PRs, high proliferative rate, overexpression of c-erbB-2 oncogene, and, in some series, expression of p53 tumor suppressor protein *(32,33)*. The tumor characteristic most frequently studied and equated with aggressive tumor behavior in interval-detected cancers is proliferative rate. More than 30% of interval-detected cancers in this study exhibited high mitotic rate versus 10% of screen-detected cancers, and 85% of the interval-detected tumors had a Ki-67 proliferation index in the highest three quartiles compared with 69% of the screen-detected cancers.

Although a high proliferative rate (as measured by flow cytometrically determined S-phase fraction or mitotic rate) has been identified by other investigators as a feature of interval-detected cancers *(12,13,16,31)*, it is difficult to interpret the meaning of a high proliferative rate with respect to the overall aggressive nature of interval tumors, given the lead time to diagnosis, the variable proliferative rate of the tumor, and the measurement of proliferative rate at a single point in time *(34)*. Our findings that additional tumor characteristics commonly associated with aggressive clinical behavior in breast cancer (high histologic grade, high nuclear grade, and loss of steroid receptors) were also associated with interval-detected cancers (especially when the analysis was restricted to those most likely to have truly developed in the screening interval) lend support to the hypothesis that interval cancers are biologically more aggressive than their screen-detected counterparts. The findings of other studies *(13,31)* that abnormal DNA content (aneuploidy) is associated with interval cancers lend further strength to the hypothesis.

One of the major features of aggressive breast cancer—metastasis to regional lymph nodes—is found by others to be associated with interval-surfacing cancers *(13,31)*. In an unadjusted analysis, we also found a statistically significant association between lymph node-positive disease and interval cancer (data not shown). However, when we took into account the longer time to diagnosis of interval cancers by adjusting for tumor size (using tumor size as a surrogate for longer time to diagnosis), interval cancers were no more likely than screen-detected cancers to be lymph node positive. This finding held true using all definitions of case and control subjects and either 12 or 24 months for the definition of interval between screenings and suggests that the association between interval-surfacing tumors and lymph node-positive breast cancers stems primarily from increased time to diagnosis, even when false-negative case subjects are excluded from the analysis. Since tumor size is a function of both time and tumor growth rate, controlling for tumor size controls somewhat for both. Nonetheless, tumor growth rate as measured by the Ki-67 proliferation index and by mitotic count was still statistically significant after controlling for tumor size.

As has been reported in most studies *(13–15,35,36)* of interval-detected cancers, we found that interval cancers were more likely to occur in young women. Overall, women under age 50 years were about three times more likely to have a cancer that was not detected at their most recent screening mammogram than women over age 70 years. Even more striking, when we limited the analysis to those tumors most likely to have truly arisen in the interval, women under age 50 years were 10 times more likely to have interval cancer by this definition.

The increased risk of interval-detected cancers in young women has been attributed to the higher overall growth rate and aggressive nature of tumors occurring in young women; however, few studies *(11,37,38)* have directly compared tumor characteristics of interval- and screen-detected cancers between younger and older women. We found that high proliferation was associated with increased ORs in all age groups but with an especially high likelihood of interval cancer in young women. The association of aggressive features, such as high-grade histology and lack of steroid receptors, with interval cancer risk also appeared stronger in the group of young women. In addition to features associated with interval cancer risk, we found tumor characteristics, including percent *in situ* components and stromal response, which seemed to predict screen detection in young women. It is not clear why these tumor characteristics appeared to be more associated with screen detection in younger women, but it is possible that they are characteristics that enhance the detection of tumors in breasts that exhibit high radiographic density compared with those of lower radiographic density. Evaluation of mammographic density in this group of women is under way, and this may help explain the possible differences between mode of detection and tumor characteristics in young versus older women.

In summary, we have identified and characterized cancers diagnosed in the interval after screening within a defined population of women who are enrolled in a high-quality mammography screening program. The assessment of multiple markers of aggressive tumor behavior in these groups of interval- and screen-detected cancers provided a more com-

prehensive representation of true interval cancers than has previously been reported. We have shown that, even if observer accuracy could become optimal, there remains a subset of the most rapidly growing and highest grade tumors that will arise in the interval after screening. However, by understanding how tumor characteristics influence the sensitivity of mammography, we may be able to better understand why the sensitivity for mammography is lower for certain groups, such as younger women *(39)* and women on hormone replacement therapy *(40)*. Such understanding could help inform the choice of optimal intervals between breast cancer screening examinations and improve screening technologies for specific groups of women.

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NOTES

[1]SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organ-

izations 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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