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ARTICLE

Tumor Characteristics Associated With Mammographic Detection of Breast Cancer in the Ontario Breast Screening Program

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Background Few studies have compared the prognostic value of tumor characteristics by type of breast cancer diagnosed in the interval between mammographic screenings with screen-detected breast cancers.

Methods We conducted a case–case study within the cohort of women (n = 431 480) in the Ontario Breast Screening Program who were aged 50 years and older and were screened between January 1, 1994, and December 31, 2002. Interval cancers, defined as breast cancers diagnosed within 24 months after a negative screening mammogram, were designated as true interval cancers (n = 288) or missed interval cancers (n = 87) if they were not identified at the time of screening but were identified in retrospect. Screen-detected breast cancers (n = 450) were selected to match interval cancers. Tumors were evaluated for stage, grade, mitotic index, histology, and expression of hormone receptors and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by conditional logistic regression.

Results Both true and missed interval cancers were of higher stage and grade than matched screen-detected breast cancers. However, true interval cancers had a higher mitotic index (OR = 3.13, 95% CI = 1.81 to 5.42), a higher percentage of nonductal histology (OR = 1.94, 95% CI = 1.05 to 3.59), and were more likely to be both estrogen receptor–negative (OR = 2.09, 95% CI = 1.32 to 3.30) and progesterone receptor–negative (OR = 2.49, 95% CI = 1.68 to 3.70) compared with matched screen-detected tumors.

Conclusions In this study, interval cancers were of higher stage and grade compared with screen-detected cancers. True interval cancers were more likely to have additional adverse prognostic features of estrogen and progesterone receptor negativity and nonductal morphology. The findings suggest a need for more sensitive screening modalities to detect true interval breast cancers and different approaches for early detection of fast-growing tumors.

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There is evidence from several randomized controlled trials that screening mammography is associated with a decreased breast cancer mortality rate (1). Not all breast cancers, however, can be detected by mammography. Interval breast cancers are those detected between screening examinations that follow a normal screening mammogram. They comprise a heterogeneous group of tumors in which recognizable signs of tumor either existed at the time of screening but were not detected for technical or interpretive reasons (missed interval cancers) or were not mammographically detectable at screening (true interval cancers) (2). Missed interval cancers result from oversight on the part of the radiologist or misinterpretation of nonspecific mammographic signs of malignancy (3–5). True interval cancers are those not visible at screening and could have existed at the time of screening but were not detected for several reasons: 1) as a result of their lobular histology, 2) an absence of calcifications, 3) an increased breast density, or 4) these cancers could be incident tumors with a high tumor growth rate (2,6,7). True interval cancers account for 65%–75% of all interval cancers (2,4).

Interval cancers are statistically significantly more likely to be larger (3,8–10) and to have lymph node involvement (3,8,9,11) than screen-detected tumors. Therefore, interval cancers are more likely to be advanced tumors, and are more often diagnosed at stage II or higher (40%–60%), compared with screen-detected tumors (20%–36%) (3,8,11,12). Interval cancers also have a higher histological grade than screen-detected cancers (3,10,13). A higher proportion of interval cancers are estrogen receptor (ER)–negative and have a higher S-phase

fraction (cellular proliferation rate) than screen-detected tumors (8,10,11,13). Therefore, interval breast cancers are more likely than screen-detected cancers to have an unfavorable prognosis (3,10,13,14).

Few studies have examined differences in tumor characteristics by type of interval cancer compared with screen-detected cancers. Two studies compared true interval cancers to screen-detected cancers (15,16). Reports have indicated that true interval cancers were statistically significantly more likely to be larger, of higher grade, and to have more vascular invasion and positive lymph nodes than screen-detected cancers (15,16). In addition, it has been previously reported that expression of biological markers associated with poor prognosis in symptomatic cancer (Ki67, p53, and c-erbB2) have higher expression in true interval cancers (16). Only one recent study has compared a small number of true (n = 34) and missed (n = 13) interval cancers to 115 screen-detected cancers (17). Despite limitations in sample size, missed and true interval cancers were found to be of statistically significantly higher grade and have statistically significantly more positive lymph nodes than screen-detected cancers (17). True interval cancers were also statistically significantly larger (17) than screen-detected cancers.

In previous studies comparing tumor characteristics of true and missed interval cancers, missed interval cancers had a statistically significantly lower histological grade (18,19), smaller size (19,20), and a higher proportion with positive lymph nodes (20), lobular features (18), and ER-positive status (19). Although differences in size, lymph node involvement, and ER status have been shown between true and missed interval cancers, the prognostic value of the distinction between true and missed interval cancers is unclear. Only one study has concluded that missed interval cancers have a less favorable prognosis compared with true interval cancers (20), whereas two studies have found no difference in survival between the two (18,19).

We hypothesized that true and missed interval breast cancers would differ by prognostic features when compared with screen-detected cancers. The purpose of this study was to compare tumor characteristics of true and missed interval cancers with matched screen-detected breast cancers within a population-based screening program to evaluate the effectiveness of screening mammography.

CONTEXT AND CAVEATS

Prior knowledge

Whereas differences in tumor characteristics between screen-detected cancers and interval cancers have been previously described, few studies have compared true and missed interval cancers in terms of prognostic tumor characteristics.

Study design

Tumor characteristics of true and missed interval cancers were compared with matched screen-detected breast cancers within a cohort of women aged 50 years or older in the Ontario Breast Screening Program.

Contribution

True and missed interval cancers were of higher stage and grade compared with matched screen-detected cancers. In addition, true interval cancers were more likely to be characterized as aggressive and fast growing.

Implication

Novel, more sensitive screening methods are needed to detect aggressive, fast-growing true interval breast cancers at earlier stages.

Limitations

Data from diagnostic mammograms and additional tumor characteristics associated with poor prognosis (ie, HER2/neu status) were not analyzed. Because the study population included women of 50 years or more who were predominantly white, the relationship between age or race and true or missed interval cancers was not evaluated.

From the Editors

Methods

Study Population. The study was nested within the cohort of 431 480 women screened through the Ontario Breast Screening Program (OBSP) between January 1, 1994, and December 31, 2002. The OBSP offers eligible women biennial screening consisting of two-view mammography (standard craniocaudal and mediolateral oblique views) and clinical breast examination by a nurse examiner. Women are not eligible if they have had a history of breast cancer, augmentation mammoplasty, or if they currently have symptoms of breast disease including a breast lump, changes to the skin over the breast, or a change in the size or shape of the breast. Although most women participating in the OBSP are screened every 2 years, women considered at high risk for breast cancer are examined annually. A complete description of the details of the operation of the OBSP has been previously published (21).

Selection of Interval and Screen-Detected Breast Cancers

Interval cancers were diagnosed before the next recommended screening visit after a negative mammographic examination. To insure quality of the OBSP data, screening mammograms before diagnosis of all women with interval cancers are routinely reviewed and classified in a blinded fashion by OBSP radiologists as being either missed at screening but seen on retrospective review (missed interval cancers) or without visible tumor signs at screening as confirmed by retrospective review (true interval cancers). Of the 616 eligible interval cancers, 146 were classified as missed intervals, 462 were classified as true intervals, and eight remained unclassified by the end of the study. Screen-detected cancers were diagnosed after a positive mammographic examination. We matched two screen-detected cancers for each missed interval cancer and one screen-detected cancer for each true interval cancer by: 1) region of screening center, 2) within 5 years of age, and 3) within 5 years of last screening mammogram. Of the 3862 eligible screen-detected cancers, 798 were selected as potential matches. The study was approved by the Health Sciences Research Ethics Board at the University of Toronto.

Tumor Characteristics

For invasive breast cancer (found at screening or after screening), pathological confirmation was obtained from regional staff during recall of women for their recommended screen or through record linkage with the Ontario Cancer Registry. Information on tumor characteristics was obtained from the OBSP cancer report that is routinely coded from pathology reports by specially trained Health Record Technicians and overseen by a reference pathologist (F. P. O'Malley). A detailed coding manual allows for standardization of data collection for all women screened as part of the OBSP. Tumor size was defined as the largest diameter of the invasive carcinoma. Among patients who had an axillary dissection, lymph node status was defined as positive if the cancer had invaded the lymph nodes. The number of nodes that contain malignant cells was also recorded. The TNM classification scheme (22) was used for staging of breast cancer and is based on pathological findings. The TNM system is an expression of the anatomical extent of disease and is based on three components: the extent of the primary tumor (T), the absence or presence and extent of regional lymph node metastasis (N), and the absence or presence of distant metastasis (M).

Tumors were graded histopathologically by the Elston modification of the Bloom and Richardson grading system that evaluates architectural differentiation or tubule formation, nuclear pleomorphism, and mitotic rate (23). Scores for mitotic index were assessed on the basis of the number of mitoses per 10 high-power fields and were classified as low (score 1) medium (score 2) and high (score 3) (23).

In Ontario, since 2000, immunohistochemical assays have been used to determine ER and progesterone receptor (PR) status. Before the year 2000, biochemical assays were also used to determine ER and PR status. Hormone receptor status was previously defined as positive if the biochemical findings indicated a concentration of estrogen- and progesterone-binding protein of 10 fmol/mg or greater (24), or if the immunohistochemical assays were at least 1% positive for nuclear staining with antibodies specific for estrogen and progesterone (24). Assays were interpreted by pathologists who recorded this result directly onto a pathology report. Tumor morphology was then coded using the *International Classification of Diseases for Oncology* (*ICD-O*) codes (84013, 85003, 85013, 85033, 85223, 85303, 85413 and 85723 coded as infiltrating duct; 85203 coded as infiltrating lobular; 80013, 80103, 80323, 80503, 82013, 82113, 84803, 85103, 85713, 89803, 90203, and 95903 coded as other) (25). If ductal carcinoma in situ was also present, the grade was coded as low, intermediate, or high.

Questionnaire and Screening Data

All subjects recruited for this study were sent a letter of invitation, a self-administered questionnaire, a consent form permitting access to their mammograms, and a study consent form. Women participating returned a completed questionnaire and gave written informed consent. Information on menopausal status was obtained by asking questions on date or age of the last menstrual period, reasons for menstrual period stopping, and age and dates of any surgeries to remove ovaries. Women were defined as peri- or post menopausal if their periods had stopped for 1 year or more and/or both ovaries had been removed before their last screening mammogram. Additional questions were asked about height, weight at last mammogram, first-degree relatives with breast and/or ovarian cancer, number of pregnancies and length of each pregnancy, hormone therapy use, and diagnosis of benign breast disease by a surgical breast biopsy.

Information on screening history was obtained from the OBSP screening report that included dates and outcomes for each screening examination. For screen-detected cancers, time to diagnosis is defined as the time between the abnormal screening result and diagnosis. For interval-detected cancers, the time to diagnosis is defined as the time between the previous negative mammographic result and diagnosis. The number of mammograms indicates how many mammograms the women had as participants in the OBSP before diagnosis. A previous screening mammogram was defined as the first screening for women with one OBSP screening before diagnosis, and as the time period (≤18 months or >18 months) between the two screening mammograms before diagnosis for women with more than one OBSP screening.

Mammographic density was assessed independently by radiologists and by a computer-assisted method (the radiologist-determined densities are reported herein). The percent mammographic density of the cranial-caudal view of the mammogram from the breast contralateral to the cancer was calculated from the screening mammogram before diagnosis by three radiologists, in a blinded fashion, who each read one-third of all study mammograms. The radiologists classified mammographic density on a six-category scale (0%, >0% to <10%, 10% to <25%, 25% to <50%, 50% to <75%, and ≥75%) by visual estimation of the proportion of the breast area occupied by radiological dense tissue (26). The inter rater agreement of mammographic breast density was strong (intraclass correlation coefficient = 0.86).

Statistical Analysis

The association between tumor characteristics and the mode of detection was estimated for each interval cancer group compared with their set of matched screen-detected cancers and the set of pooled screen-detected cancers by the use of unconditional logistic regression, adjusting for matching variables, and conditional logistic regression. Results did not statistically significantly differ and the true and missed interval cancers had similar distributions for the matching variables. To increase study power and efficiency, final analyses are presented for each group compared with the pooled set of matched screen-detected cancers calculated by conditional logistic regression (27). Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated separately for true and missed interval cancers. We tested for potential confounding by: time since previous OBSP screening mammogram (first screen, ≤18 months ago, or >18 months ago), benign breast disease (yes or no), body mass index (kg/m^2; continuous), family history of breast and/or ovarian cancer (none, moderate [first-degree relative with breast cancer aged 50 years or older; first-degree relative with ovarian cancer at any age], strong [two or more first-degree relatives with breast cancer and/or ovarian cancer at any age; first-degree relative with breast cancer age <50]), parity (parous if one or more pregnancies lasting longer than 6 months or nulliparous),

menopausal status (premenopausal, perimenopausal, or postmenopausal), use of hormone therapy (never, current estrogen, current estrogen and progesterone, or former use; where applicable), and mammographic density (radiologist-determined density reading [categorical; where applicable]). All models were adjusted for age and tumor size, although only age-adjusted odds ratios are reported for stage and lymph node involvement. Tests for trend were conducted by testing the statistical significance of the ordinal term in the logistic model. A P value less than .05 was considered statistically significant for all tests.

Results

We conducted a case–case comparison to identify features of breast tumors that are more likely to be associated with the detection of interval cancers compared with screen-detected cancers. Among the 431 480 women screened through the OBSP between January 1, 1994, and December 31, 2002, there were 7148 women with breast cancer, and 4478 (62.6%) had an invasive breast cancer diagnosis, were alive at the start of the study, and had consented to be contacted for research studies (Figure 1). All of the 616 (13.8%) women with interval breast cancers (462 [75.0%] true interval breast cancers, 146 [23.7%] missed interval breast cancers, and eight [1.3%] unclassified interval breast cancers) were selected for the study. Screen-detected cancers (n = 798 women) were used in the study if the region of the screening center, age (within 5 years), and year (within 5 years) of the last screen matched the interval breast cancers. Of the 1414 women eligible and selected for this study, 1150 were contacted and 825 were interviewed and provided consent (overall response rate = 72%; number of missed interval cancers = 87 cancers [75.7%], number of true interval cancers = 288 [77.2%], and number of screen-detected cancers = 450 [67.9%]). The analytic sample included 450 screen-detected cancers, 288 true interval cancers, and 87 missed interval cancers.

The average age at last screening exam was 60.2 years among the screen-detected cancers and 60.3 years among the interval cancers as accounted for by the matched sampling design. The distribution of characteristics such as body mass index, family history, parity, and menopause at the time of last screening mammogram was generally similar between the screen-detected and interval groups (Table 1). Mammographic density of 75% or greater was more frequent among women who were diagnosed with an interval cancer (number of missed = 2 [2.5%]; number of true = 20 [7.2%]) compared with those who were diagnosed at screening (n = 8 [1.9%]) as previously reported (28). Current hormone therapy use was more common among women diagnosed with an interval cancer (number of missed interval cancers = 44 [51.8%]; number of true interval cancers = 134 [47.9%]) compared with women diagnosed at screening (n = 143 [32.8%]) as previously reported (28). Previous diagnosis of benign breast disease was more common among women with interval cancers (number of missed interval cancers = 23 [26.7%]; number of true interval cancers = 58 [20.3%]) than among women with screen-detected cancers (n = 65 [14.7%]). None of the variables tested confounded the associations reported in Table 2.

Women diagnosed with an interval cancer had a statistically significantly longer mean waiting time to breast cancer diagnosis compared with women diagnosed with a screen-detected cancer (mean waiting time to diagnosis for missed interval cancers vs true interval cancers vs screen-detected cancers, mean = 393 vs 442 vs 40 days; $P < .001$) (Table 2). Compared with matched screen-detected cancers, interval cancers were larger, of more advanced stage, more poorly differentiated, more likely to have lymph node involvement, and had a higher proliferative rate. These differences were seen for both true interval cancers and missed interval cancers, although the increased risk of nodal involvement was more pronounced for missed interval cancers and the high mitotic index was more pronounced for true interval cancers compared with screen-detected cancers.

True interval cancers were larger (OR = 3.73, 95% CI = 2.31 to 6.03 for tumors >2 cm vs <1 cm; $P_{trend} < .001$), of more advanced stage (OR = 4.39, 95% CI = 1.02 to 18.87 for stage III or IV vs stage I; $P = .047$), more poorly differentiated (OR = 3.48, 95% CI = 2.16 to 5.61 for histological grade 3 vs 1; $P < .001$), and had a high proliferative rate (by mitotic index, OR = 3.13, 95% CI = 1.81 to 5.42 for a high vs low rate of proliferation; $P < .001$) compared with matched screen-detected tumors. True interval cancers were also more likely to be both ER- (OR = 2.09, 95% CI = 1.32 to 3.30; $P = .002$) and PR-negative (OR = 2.49, 95% CI = 1.68 to 3.70; $P < .001$) and had a higher percentage of other morphologies such as tubular, mucinous, and medullary carcinomas (OR = 1.94, 95% CI = 1.05 to 3.59; $P = .003$) compared with matched screen-detected tumors. Missed interval cancers were larger (OR = 11.26, 95% CI = 4.40 to 28.81 for >2 cm vs <1 cm; $P_{trend} < .001$), had more nodal involvement (OR = 1.98, 95% CI = 1.16 to 3.39 for ≥1 positive lymph node vs none; $P_{trend} = .05$ for increasing number of positive lymph nodes), and were more poorly differentiated (OR = 3.17, 95% CI = 1.47 to 6.84 for histological grade 3 vs 1; $P = .002$) than matched screen-detected tumors.

Discussion

We found that interval cancers were larger in diameter, of higher stage and grade, and were more likely to have a greater number of positive nodes compared with screen-detected cancers, a finding that is consistent with results from several previous studies (3,10,13,14). Again, compared with screen-detected cancers, true interval cancers were more likely to have additional adverse prognostic features (ER and PR negative and not being of ductal morphology). We may conclude from these comparisons that true interval cancers are rapidly proliferating and that they became palpable in the interval between mammographic screens but were too small to have been detected on the previous screen. An alternate interpretation is that true interval tumors with less favorable clinicopathologic features are less easily radiographically detectable, and/or that the tumors that go undetected then face a delay in diagnosis, which leads to less favorable features.

Interval cancers constituted 616 or 14% of the cancers diagnosed in this screened population; among the women who participated in the study, 288 or 77% of these were true interval cancers, detected clinically in the 1–2 year interval between screening examinations, reflecting an overall 11% rate of true interval-arising cancers. This is similar to the 17% rate of true interval cancers reported in a similarly large screening setting (10).

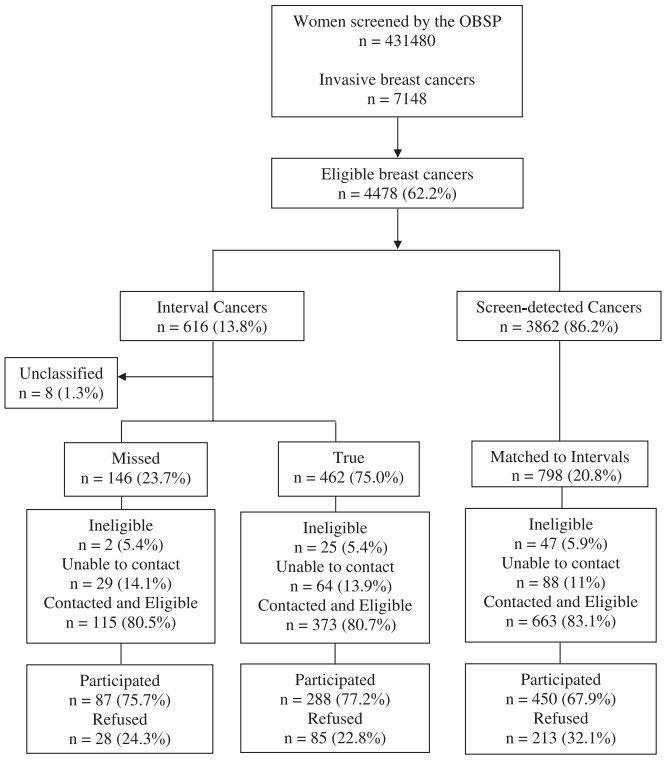

Figure 1. Flow chart describing initial dataset and exclusions leading to final cohort. OBSP = Ontario Breast Screening Program (January 1, 1994, to December 31, 2002).

True interval cancers were more likely to be larger (>2 cm vs <1 cm diameter) than screen-detected cancers, consistent with studies that considered interval cancers overall (3,8,9,16) and true interval cancers specifically (15–17). The larger tumor size could be due to several reasons. First, we have previously shown that extensive mammographic density—which may mask the tumor from detection—is strongly positively associated with the risk of interval-surfacing breast cancer in our study population (28). Thus, when the tumors do become apparent (mean = 441 days after the negative screen), the lead time associated with screen detection has been lost, and the cancers are more advanced in their natural history and therefore larger. Second is that true interval cancers are rapidly growing tumors, as reflected by our finding of a higher mitotic count. The association was even more pronounced for missed interval cancers, which were even more likely to be large sized (>2 cm vs <1 cm diameter). Our finding that missed interval cancers are larger than screen-detected cancers agrees with one previous study (15) and contrasts with another (17); however, a small sample size may have led to instability in the latter study (17). Although the tumor was not masked from detection (it was identified in retrospect), it may have been obscured, resulting in an interpretive radiologists' error that led to a delay in diagnosis (mean = 393 days) (if these cancers were in fact clinically evident at screening, the loss of lead time to diagnosis would then be greater in the missed compared with the true interval cancers, perhaps accounting for the higher odds of a large tumor size at diagnosis among the latter group).

Tumors that are missed by mammography may be more likely to metastasize to the regional lymph nodes and beyond, decreasing long-term survival. Lymph node involvement is likely related to the invasiveness of the primary lesion in addition to the size of the tumor at diagnosis, thus lymph node involvement may be associated with the longer time to diagnosis of interval cancers. Indeed, lymph node involvement has also been found to be associated with interval cancers (3,8–11,15), although the presence and increasing number of lymph nodes involved was only statistically significantly associated with the missed interval cancers in our study. There was, however, a non-statistically significant trend toward an increased number of positive lymph nodes among the true interval cancers, compared with the screen-detected cancers. Both subgroups—the missed and true interval cancers—experienced a similar delay in diagnosis, but the missed interval cancers may have had a longer lead time to diagnosis. Other findings stratified by missed and true interval cancers are inconsistent with one study noting that both subgroups were statistically significantly more likely to have positive lymph nodes status compared with screen-detected cancers (17), and a second—restricted to true interval cancers—finding no difference (16).

Stage at diagnosis represents a summary of several of the aforementioned characteristics: the extent of the primary tumor, the absence or presence and extent of regional lymph node metastasis, and the absence or presence of distant metastasis. Two studies have compared stage at diagnosis between interval cancers and screen-detected cancers: Similar to our findings, one reported both missed and true interval cancers to be of statistically significantly higher stage (17), whereas the other noted no difference (19). We found that both the histological grade and the mitotic index—characteristics associated with aggressive clinical behavior—were associated with interval-detected cancers (particularly among the true interval cancers). Almost 30% of the true interval–detected cancers had a high mitotic index compared with 11% of the screen-detected cancers. Faster-growing tumors generally have a shorter asymptomatic phase than slower-growing tumors, and a high proliferative rate is a well-documented feature of interval-detected cancers (2,8,14). Although there are large variations in individual breast tumor doubling times (29), the rates are thought to decelerate with increasing tumor size. Our model was adjusted for tumor size, indicating that mitotic index is an independent predictor of interval cancer risk. Our finding of a higher histological grade among interval cancers compared with screen-detected cancers lends further strength to this hypothesis and concurs with most (3,10,13,15,16) but not all (17) other findings (although the latter study had few grade 3 cancers). It is difficult to interpret the results showing non-statistically significantly higher mitotic index and a higher histological grade among the missed interval cancers than true interval cancers, although two other studies have also reported high grade in both true and missed interval cancers (15,16).

Negative ER status is also an adverse prognostic feature that has been reported to be overrepresented in interval-detected tumors (8,10,13,17,30) relative to screen-detected cancers. Estrogen has an important role in growth regulation and differentiation of normal breast and in the proliferation of early-stage breast cancer (31,32). Paradoxically, some breast tumors lose ER expression (33); almost 30% of the true interval cancers in the current study were ER-negative compared with only 15% of the

Table 1. Characteristics of the study population (N = 825)

Characteristic*	Screen-detected cancers (n = 450) No. (%)	Missed interval cancers (n = 87) No. (%)	True interval cancers (n = 288) No. (%)	*P*†
Age, y				.83
50–59	236 (52.4)	41 (47.1)	154 (53.5)	
60–69	157 (34.9)	32 (36.8)	99 (34.4)	
≥70	57 (12.7)	14 (16.1)	35 (12.2)	
Prior screening mammogram				.04
First screen	181 (40.2)	35 (40.2)	89 (30.1)	
≤18 mo	37 (8.2)	11 (12.6)	38 (13.2)	
>18 mo	232 (51.6)	41 (47.1)	161 (55.9)	
No. of mammograms				.003
1	181 (40.2)	35 (40.2)	89 (30.9)	
2–3	179 (39.8)	32 (36.8)	154 (53.5)	
≥4	90 (20.0)	20 (23.0)	45 (15.6)	
Benign breast disease				.01
No	376 (85.3)	63 (73.3)	227 (79.7)	
Yes	65 (14.7)	23 (26.7)	58 (20.3)	
Body mass index, kg/m^2				.39
<25	163 (37.8)	41 (48.2)	121 (43.2)	
25–29.9	174 (40.4)	26 (30.6)	110 (39.3)	
30–34.9	60 (13.9)	12 (14.1)	34 (12.1)	
≥35	34 (7.9)	6 (7.1)	15 (5.4)	
Family history				.11
None	365 (81.1)	68 (78.2)	217 (75.9)	
Moderate	46 (12.4)	14 (16.1)	49 (17.1)	
Strong	29 (6.4)	5 (5.8)	20 (7.0)	
Parity				.62
Nulliparous	59 (13.1)	13 (14.9)	45 (15.6)	
Parous	391 (86.9)	74 (85.1)	243 (84.4)	
Menopause				.69
Premenopausal	41 (9.2)	6 (7.0)	22 (7.8)	
Peri- or postmenopausal	403 (90.8)	80 (93.0)	261 (92.2)	
Hormone therapy				<.001
Never	238 (54.6)	35 (41.2)	115 (41.1)	
Current estrogen alone	72 (16.5)	17 (20.0)	68 (24.3)	
Current combination	71 (16.3)	27 (31.8)	66 (23.6)	
Former	55 (12.6)	6 (7.0)	31 (11.0)	
Mammographic Density, %				<.001
<10	78 (18.2)	9 (11.1)	24 (8.7)	
10 to <25	98 (22.8)	11 (13.6)	49 (17.7)	
25 to 50	149 (34.7)	31 (38.3)	78 (28.1)	
50 to <75	96 (22.4)	28 (34.5)	106 (38.3)	
≥75	8 (1.9)	2 (2.5)	20 (7.2)	

* The following cutoffs were used for analysis: time since previous program screening mammogram (first screen, ≤18 months ago, or >18 months ago); benign breast disease (yes or no); body mass index (continuous); family history of breast and/or ovarian cancer (none, moderate [first-degree relative with breast cancer aged 50 years or older; first-degree relative with ovarian cancer at any age], strong [two or more first-degree relatives with breast cancer and/or ovarian cancer at any age; first-degree relative with breast cancer less than 50 years of age]); parity (parous if one or more pregnancies lasting longer than 6 months or nulliparous); menopausal status (premenopausal, perimenopausal, or postmenopausal); use of hormone therapy (never, current estrogen, current estrogen and progesterone, or former use; where applicable); and mammographic density (radiologist-determined density reading [categorical; where applicable]).

† All *P* values were calculated by a two-sided Pearson χ^2 test.

screen-detected breast cancers. Breast cancers lacking ER expression are unlikely to benefit from endocrine therapy and are associated with a lower grade of histological differentiation (34), higher proliferative rate, and a lower overall survival rate (34). Although both hormone therapy and chemotherapy are more effective for women with ER-positive tumors (35), if screening mammography is also more effective in this subgroup, as our data suggest, this too could be contributing to the greater decline in breast mortality that has been seen since the early 1990s among women with ER-positive compared with those with ER-negative tumors (34). It is also possible, however, that screening detects a disproportionate number of ER-positive tumors due to length bias (36), which refers to the tendency of the screening test to detect slower-growing tumors that have a longer asymptomatic stage, and are less likely to have lost ER gene expression. A greater loss of ERs and PRs was not seen among the missed interval cancers compared with the screen-detected cancers, as is also noted by others who found that the lowest estrogen and progesterone expression was seen in true

Table 2. Characteristics of interval-detected breast cancers relative to screen-detected breast cancers*

Characteristic	Screen-detected cancers (n = 450)	All interval cancers (n = 375)		Missed interval cancers (n = 87)		True interval cancers (n = 288)	
	No. (%)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)	No. (%)	OR (95% CI)
Mean age at last screening examination, y	60.2	60.3	NA	60.9	NA	60.2	NA
Mean time between last OBSP mammogram and diagnosis, d	40.1	430.5	NA	393.2	NA	441.8	NA
Mean tumor size at diagnosis, mm	15	21		22		20	
<10	130 (28.9)	44 (11.9)	1.00 (Referent)	6 (6.9)	1.00 (Referent)	38 (13.5)	1.00 (Referent)
10–15	166 (37.0)	111 (30.2)	2.04 (1.34 to 3.11)	22 (25.3)	3.06 (1.19 to 7.86)	89 (31.7)	1.87 (1.19 to 2.93)
16–20	65 (14.5)	81 (22.0)	3.70 (2.28 to 5.95)	21 (24.1)	7.02 (2.60 to 18.94)	60 (21.3)	3.08 (1.84 to 5.15)
>20	88 (19.6)	132 (35.9)	4.83 (3.09 to 7.57)	38 (43.7)	11.26 (4.40 to 28.81)	94 (33.5)	3.73 (2.31 to 6.03)
P_{trend}†		NA	<.001	NA	<.001	NA	<.001
Lymph nodes‡							
Negative	298 (75.3)	225 (69.0)	1.00 (Referent)	46 (60.5)	1.00 (Referent)	179 (71.6)	1.00 (Referent)
Positive	98 (24.7)	101 (31.0)	1.41 (1.01 to 1.96)	30 (39.5)	1.98 (1.16 to 3.39)	71 (28.4)	1.27 (0.88 to 1.83)
Number of positive lymph nodes‡							
0	298 (75.3)	225 (69.0)	1.00 (Referent)	46 (60.5)	1.00 (Referent)	179 (71.6)	1.00 (Referent)
1–3	78 (19.7)	73 (22.4)	1.31 (0.91 to 1.89)	23 (30.3)	1.98 (1.10 to 3.55)	50 (20.0)	1.17 (0.78 to 1.76)
4–9	15 (3.8)	19 (5.8)	1.67 (0.82 to 3.39)	5 (6.6)	2.01 (0.68 to 5.95)	14 (5.6)	1.46 (0.68 to 3.15)
≥10	5 (1.2)	9 (2.8)	2.55 (0.84 to 7.73)	2 (2.6)	4.34 (0.68 to 27.55)	7 (2.8)	2.27 (0.71 to 7.27)
P_{trend}	NA	NA	.05	NA	.05	NA	.13
Stage at diagnosis§							
I	112 (62.6)	77 (43.0)	1.00 (Referent)	17 (38.6)	1.00 (Referent)	60 (44.4)	1.00 (Referent)
II	64 (35.7)	92 (51.4)	2.16 (1.39 to 3.36)	25 (56.8)	3.19 (1.54 to 6.59)	67 (49.6)	2.04 (1.25 to 3.33)
III or IV	3 (1.7)	10 (5.6)	4.46 (1.12 to 17.70)	2 (4.6)	6.52 (0.93 to 45.69)	8 (6.0)	4.39 (1.02 to 18.87)
Histologic grade							
1	163 (39.8)	74 (22.6)	1.00 (Referent)	17 (21.2)	1.00 (Referent)	57 (23.0)	1.00 (Referent)
2	185 (45.1)	131 (39.9)	1.32 (0.90 to 1.92)	37 (46.3)	1.70 (0.87 to 3.32)	94 (37.9)	1.24 (0.82 to 1.87)
3	62 (15.1)	123 (37.5)	3.42 (2.19 to 5.35)	26 (32.5)	3.17 (1.47 to 6.84)	97 (39.1)	3.48 (2.16 to 5.61)
Mitotic index, No. of mitotic bodies per 10 high power fields							
Low	198 (70.2)	125 (51.2)	1.00 (Referent)	38 (58.5)	1.00 (Referent)	87 (48.6)	1.00 (Referent)
Medium	54 (19.2)	53 (21.7)	1.36 (0.86 to 2.16)	13 (20.0)	1.13 (0.53 to 2.43)	40 (22.3)	1.43 (0.87 to 2.36)
High	30 (10.6)	66 (27.1)	2.89 (1.73 to 4.83)	14 (21.5)	1.96 (0.84 to 4.56)	52 (29.1)	3.13 (1.81 to 5.42)
Estrogen receptor							
Positive	291 (84.6)	210 (74.7)	1.00 (Referent)	55 (85.9)	1.00 (Referent)	155 (71.4)	1.00 (Referent)
Negative	53 (15.4)	71 (25.3)	1.68 (1.09 to 2.59)	9 (14.1)	0.65 (0.27 to 1.55)	62 (28.6)	2.09 (1.32 to 3.30)
Progesterone receptor							
Positive	250 (74.9)	159 (57.8)	1.00 (Referent)	43 (69.4)	1.00 (Referent)	116 (54.5)	1.00 (Referent)
Negative	84 (25.1)	116 (42.2)	2.07 (1.43 to 2.98)	19 (30.6)	1.18 (0.62 to 2.53)	97 (45.5)	2.49 (1.68 to 3.70)
Ductal carcinoma in situ							
Absent	99 (34.5)	92 (36.2)	1.00 (Referent)	22 (36.1)	1.00 (Referent)	70 (36.3)	1.00 (Referent)
Grade I/II (low to intermediate)	127 (44.2)	86 (33.9)	0.87 (0.58 to 1.31)	23 (37.7)	0.91 (0.46 to 1.79)	63 (32.6)	0.82 (0.53 to 1.27)
Grade III (high)	61 (21.3)	76 (29.9)	1.61 (1.01 to 2.55)	16 (26.2)	1.27 (0.57 to 2.82)	60 (31.1)	1.63 (0.99 to 2.67)
Morphology							
Infiltrating duct	389 (86.4)	302 (80.5)	1.00 (Referent)	76 (87.4)	1.00 (Referent)	226 (78.4)	1.00 (Referent)
Infiltrating lobular	31 (6.9)	43 (11.5)	1.34 (0.78 to 2.25)	8 (9.2)	0.80 (0.33 to 1.99)	35 (12.2)	1.57 (0.90 to 2.75)
Other||	30 (6.7)	30 (8.0)	1.60 (0.89 to 2.88)	3 (3.4)	0.62 (0.16 to 2.38)	27 (9.4)	1.94 (1.05 to 3.59)

* ORs are adjusted for age at last screening examination (continuous) and tumor size (categorical), except for stage, lymph nodes, and number of positive lymph nodes which were age-adjusted only. CI = confidence interval, NA = not applicable, OBSP = Ontario Breast Screening Program, OR = odds ratio.

† Two-sided tests for trend were conducted by testing the significance of the ordinal term in the logistic model.

‡ Among women who had an axillary dissection.

§ Among women first diagnosed with breast cancer from January 1, 1999, to December 31, 2002.

|| Other morphology includes tubular, mucinous, metaplastic, papillary, medullary and carcinomas not otherwise specified.

interval cancers compared with missed, occult, or unknown interval cancers (18,19). Our findings lend support to the hypothesis that true interval–detected cancers are either particularly biologically aggressive or may indicate a greater likelihood of mammographic masking among ER-negative tumors.

Lobular histology is known to be less easily visualized mammographically (7,37) and has been reported to be overrepresented in interval-detected tumors compared with screen-detected tumors (2,5), although we did not observe a statistically significant difference in our study. We did, however, find that a higher percentage of heterogeneous tumors, including tubular and mucinous carcinomas, were associated with true interval–detected cancers, relative to screen-detected cancers. Histologically, tubular cancers are well-differentiated cellular clusters with an orderly distribution of tubules in a loose fibrous stroma (38). Although they are often easily visualized on mammography, false negatives do frequently occur (38,39). The majority of pure types of mucinous carcinomas present as well-defined masses with circumscribed or lobulated margins on mammogram; the vast majority present as a mammographically evident mass, although few do present as occultation (40). Thus, either one of these histological types may be associated with the masking of tumors; the group of other tumors was, however, too small to explore the findings through further stratification.

Our study has several strengths, including the use of routine follow-up data collected on a population-based group of women who were all part of the same mammography screening program. Identification and classification of interval- and screen-detected breast cancers are identical for all women screened as participants in the OBSP and are tracked consistently by active follow-up of the program or linkage with the Ontario Cancer Registry. This is also the largest study to compare subgroups of interval cancers—distinguishing between true and missed interval cancers—to screen-detected cancers. Technical or interpretive error is one of the problems that may lead to failure of detection by mammography. By separating missed interval cancers from true interval cancers, we were able to interpret more precisely the association of characteristics of the breast tumor and measures of rapid growth in the efficacy of mammographic screening.

There are also some limitations. First, we do not have data from diagnostic mammograms performed at the time of detection for the interval cancers. Such information would allow us to address the hypothesis that tumors that are of high tumor grade and ER negative, for example, might be less easily detectable by mammography. Second, we did not measure other parameters outside of proliferation rate that may help explain the larger size of the true interval–detected breast cancers, such as angiogenic potential, degree of stromal response, and susceptibility to apoptosis (41). Third, because this study included women diagnosed between 1994 and 2002, we had limited information on presence of HER2/neu protein (reported for <10%) and therefore we were unable to assess the risk of triple-negative breast cancers being interval detected. Fourth, the impact of mammographic detection on women younger than age 50 could not be evaluated because only women aged 50 years and older were included. Finally, as the women participating were predominately white (95.07%), we were unable to evaluate any excess risk attributed to other races and/or ethnicities.

In conclusion, we found that both true and missed interval cancers were of higher stage and grade than are screen-detected cancers. However, compared with screen-detected cancers, true interval cancers were more likely to have additional adverse prognostic features, such as being ER- and PR-negative and of other morphology (a heterogeneous group that includes tubular and mucinous carcinoma). The aggressive tumor features we observed for interval cancers are likely partly because of the rapid proliferative rate, the delay in diagnosis, and partly reduced tumor detection on mammograms. This suggests a need for further advancement in imaging technologies to detect certain types of breast carcinomas and different approaches for early detection of fast-growing tumors.

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