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# Mammographic features and histopathological findings of interval breast cancers

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## Abstract

**Background—**Interval cancers are considered a shortcoming in screening mammography due to less favorable prognostic tumor characteristics compared to screening-detected cancers and consequently a lower chance of survival from the disease.

**Purpose—**To describe the mammographic features and prognostic histopathological tumor characteristics of interval breast cancers.

**Material and methods—**A total of 231 interval breast cancer cases diagnosed in prevalently screened women aged 50–69 years old were examined. Thirty-five percent of the cases were retrospectively classified as missed cancers, 23% as minimal sign, and 42% as true negative (including occult cancers) in a definitive classification performed by six experienced breast radiologists. The retrospective classification described the mammographic features of the baseline screening mammograms in missed and minimal sign interval cancers, while histopathological reports were used to describe the tumor characteristics in all the subgroups of interval cancers.

**Results—**Fifty percent of the missed and minimal sign interval cancers combined presented poorly defined mass or asymmetric density and 26% calcifications with or without associated density or mass at baseline screening. Twenty-seven percent of invasive tumors were <15mm for missed and 47% for true interval cancers ($p<0.001$). Lymph node involvements was more common in missed (49%) compared with the true cases (33%, $p<0.05$).

**Conclusion—**Missed interval cancers have less prognostic favorable histopathological tumor characteristics compared with true interval cancers. Improving the radiologists' perception and interpretation by establishing systematical collection of features and implementation of organized reviews may decrease the number of interval cancer in a screening program.

### Keywords

mammography; breast cancer screening; interval cancer; mammographic features; histopathogical findings

The European Guidelines define interval cancer as "a primary breast cancer, which is diagnosed in a woman who had a screening test, with or without further assessment, which was negative

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for malignancy, either before the next invitation to screening or within a time period equal to a screening interval for a woman who has reached the upper age limit for screening" (1). Interval cancers are an expected and intrinsic part of any screening program, and the rate is considered as a quality measure of the radiological performance and an early surrogate measure of the efficacy of the screening program (1). Interval cancers are considered as a shortcoming in screening due to less prognostic favorable tumor characteristics compared to screening-detected cancers (1–3) and consequently less favorable survival from the disease (3,5,6). Studies have shown that a portion of the interval cancers is due to perception as well as interpretation failure (7–10), which is a challenge for the radiologists.

The European Guidelines recommend reviewing the interval cancers as an essential part of routine radiological audit, to enhance radiological learning and subsequently reducing the number of missed cancers (1). The recommended review consists of two parts. The first part is a review of the screening mammograms without the mammograms taken at the time of diagnosis and without knowledge of the histology (blind review). At this point, a provisional classification of the interval cancers is determined and the cancers are usually classified into three subgroups (missed, minimal sign and true). Next, the screening mammograms are classified using the diagnostic mammograms at the time of detection and with the knowledge of histopathological findings in a definitive review. A definitive review usually classifies the mammograms into five subgroups (missed, minimal sign, true, occult and unclassifiable) (1).

In a previous study from the Norwegian Breast Cancer Screening Program (NBCSP), 231 interval cancers were classified both provisionally and definitively (8). The current study is a continuation of that studyand is aimed at describing mammographic features and histopathological findings of the subgroups of interval cancers.

## Material and Methods

The NBCSP is a government organized population based breast cancer screening program administered by the Cancer Registry of Norway. Data collection and quality assurance are integrated parts of the administration of the program. This study was considered as a part of the screening program's evaluation and scientific activities, and is thus covered by the general ethical approval of the program, as a part of the Cancer Registry of Norway (11). During the study period, 159,887 women 50–69 years of age were invited to the first round of the screening program and 127,064 (79.5%) participated. The recall rate was 4.2% (5,370 cases), the cancer detection rate 6.7 per 1,000 screened (856 cases, 169 Ductal Carcinoma In Situ and 687 invasive), and the interval cancer rate 19 per 10,000 screened (247 cases, 17 Ductal Carcinoma In Situ and 230 invasive) (8,12). The program is further described elsewhere (2).

### Study population

This study is based on screening and diagnostic mammograms, in addition to histopathological reports from 231 interval breast cancers diagnosed in women aged 50–69 years old when participating in the first round of screening in the NBCSP, from November 1995 to March 1998 (8,12). The breast clinics report all cancer cases diagnosed in women in the target group of the screening program (including cancers diagnosed at the age of 70–71 years) to the screening database at the Cancer Registry. In addition, regular cross-checks with the Cancer registry database are performed to ensure complete capture of the interval cancers. A law has mandated the report of all cancer cases to the Cancer Registry of Norway since 1952, and the Cancer Registry is thus considered almost complete (13).

### Image interpretation

The screening program performs independent double reading with consensus. The same five-point rating scale used in the screening examination was used in the retrospective interpretation performed in this study. A score of one was considered negative and five as a high probability of cancer (1- normal; 2 - probably benign; 3 - intermediate; 4 - probably malign or; 5 - malign). All cases having a score of two or higher by one or both radiologists were discussed at consensus where the final decision was made as to whether a woman should be recalled for further assessment. Additional imaging, needle biopsy and eventual treatment took place at centralized breast clinics and associated hospitals. The program does not recommend short-term follow up.

### Interval cancer

All women diagnosed with breast cancer after a negative screening mammogram or a normal or benign finding at assessment (including negative radiological work-up and/or a needle biopsy with benign outcome) within the two year screening interval was defined as an interval cancer. The diagnosis of an interval cancer could be based on symptoms, clinical findings by a physician, or as a result of a cancer detected at opportunistic screening performed outside the organized program in the period between two screening sessions in the NBCSP. All interval cancers were thus diagnosed after a diagnostic mammogram, but some of the diagnostic mammograms might have been performed subsequent to a screening examination performed at a private clinic.

### Subgroups

A retrospective definitive classification of the interval cancers was performed by six experienced breast radiologists in a consensus meeting (8). At the review, both screening and diagnostic mammograms were available, in addition to histopathological and surgical reports. A cancer was defined as missed if all the radiologists agreed that the tumor was visible at the screening mammogram and that the woman should have been recalled (n = 80). The minimal sign lesions were also visible in retrospect, but the mammographic features were subtle and non-specific and a recall for further assessment was not that obvious (n = 53). True (n = 82) and occult cases (n = 16) were not visible at the screening mammogram. Cases without an available diagnostic mammogram were considered unclassifiable (n=16).

Since the purpose of this study was to retrospectively analyze the mammographic features of the screening mammograms we grouped the occult cancers (n = 16) with the true interval cancers (n = 82) for a total of 98 cases and excluded the group of unclassifiable cases (n=16). Thirty-five percent (80/231) of the interval cancers were classified as missed, 23% (53/231) as minimal sign, and 42% (98/231) as true (including occult) interval breast cancer. The study is thus based on three groups of interval cancers (missed, minimal sign, and true including the occult cases) based on a definitive classification.

### Mammographic features

Mammographic features for missed and minimal sign cancers found at baseline screening mammograms were categorized according to a modified BI-RADS classification (14) in the consensus review. The features were described as mass (circumscribed and spiculated), distortion, poorly defined mass or asymmetric density, in addition to calcifications with and without associated densityand mass. Due to the small numbers, calcifications associated with mass, densityor distortion were combined.

### Histopathological findings

Histopatological finding were provided for missed, minimal sign and true (including occult) interval cancers. The cancer type and tumor characteristics were mainly based on histology of surgical specimens, but in three cases the characteristics are given from the core biopsy.

### Statistics

Differences in proportions of subgroups were tested using Chi-square tests. A p-value less or equal to 0.05 was regarded as statistically significant. The analyses were conducted using SPSS (Version 12.0.1 for Windows, SPSS Inc, Chicago, Illinois), R Statistical Computing (Version 2.0.1).

## Results

The women diagnosed with interval cancer were on average 58 years old at screening, varying from 59 years for the missed cases, 56 years for the minimal sign cases and 58 years for the true interval cancer cases.

The screening mammograms showed a poorly defined mass or asymmetric density in half of the missed as well as the minimal sign cancers (Table 1). Distortion was seen in 16% (13/80) and 19% (10/53), respectively in missed and minimal sign cancers at the screening mammogram (p = 0.876). Calcifications with associated density or mass was present in 20% (16/80) of the missed cases and in 9% (5/53) of the minimal sign (p = 0.164), while calcifications alone was seen in 6% (5/80) of the missed and 15% (8/53) of the cancers showing minimal sign at the screening mammogram (p = 0.167). Eight of the 34 (24%) missed and minimal sign interval cancers showing calcifications at the screening mammogram were Ductal Carcinoma *In Situ* (DCIS) (not in table).

Histopathological type did not differ significantly between the subgroups (p > 0.05 for all, Table 2). However, invasive lobular cancer was twice as common in missed (20%, 16/80) compared to true (including occult) interval cancers (9%, 9/98), approaching borderline statistical significance (p = 0.064).

Average histopathological tumor size of the invasive cases was 23 mm in missed and 18 mm in true (including occult) interval cancers (p = 0.017, Table 2). The proportion of invasive cancers less than 15 mm was 27% (20/73) for missed and 47% (41/87) for true interval cancers (p = 0.017). There was a higher proportion of cancers with positive lymph node among the missed, 49% (34/70) and minimal sign, 53% (24/45) compared to the true interval cancers, 33% (27/83) (p = 0.064 and p = 0.035 for missed and minimal sign, retrospectively). Grading and estrogen and progesterone receptor status did not differ between the three groups (p > 0.05 for all).

Invasive lobular cancer had a larger mean tumor size (25mm) compared to the invasive ductal carcinomas (20mm) (p = 0.027, data not in table). Lymph node involvement was more common in invasive lobular cancers, 47% (15/32), compared to invasive ductal cancers, 43% (68/157), but the finding did not reach a statistically significantly level (p = 0.861).

## Discussion

About half of the missed and minimal sign interval cancers were represented as a poorly defined mass or asymmetric density. The missed and minimal sign interval cancers had less prognostic favorable tumor characteristics compared with true (including occult) interval cancer.

Interval cancer has several definitions (1,15–17), and the classification of subgroups can be performed in several ways (1,7,8,10). The inconsistency makes comparison of rates, proportions and tumor characteristics between studies difficult (15,16). In our analysis we chose to use subgroups derived from the definitive classification, which was based on availability of both the screening and diagnostic mammograms and considered the most valid method of classifying interval cancers (1). A total of 35% of the interval cancers in this study were classified as missed (8), a proportion well within the range of several studies (7,10) but higher than the upper limit proposed in the European Guidelines (20%) (1). A definitive classification makes it possible to retrospectively identify minimal signs, which may not have been identified on the provisional review. In addition, the definitive classification allows one to confirm that missed and minimal signs identified on the provisional review correlate exactly with the location of the interval cancer. Subtle minimal sign lesions could otherwise have been classified as true negative.

Poorly defined mass or asymmetric density contributed to half of the missed and minimal sign interval cancers in this study. However, the finding of a mass is not unusual on the screening mammograms (18,19). Broeders showed that 53%–64% of the interval cancers were classified as density without microcalcifications (20), while Vitak et al reported 28% of the interval cancers to present as a circumscribed mass and 17% to be a non-specific density (3), and Bird found about 30% of the cancers missed at screening to be mass (21). A mass is usually not a problem of visual perception, but more a problem of interpretation. A benign mass occasionally presents with a poorly defined contour, due to overlapping normal breast tissue.

Asymmetric densities and architectural distortion may represent perception and interpretation challenges. These findings should be an indication for a biopsy, except for cases with previous surgical treatment (19). Distortion was the most significant feature in 16% of the missed and minimal sign interval cancer in this study, which is somewhat higher than reported by Vitak (3,22).

Calcifications with or without density were found in every fourth missed or minimal sign interval cancer. Various types of calcifications have different probabilities of malignancy (23–25). Studies of radiological features of interval cancer are showing large variations in the percentage of mammograms showing calcifications (3,19–21). Calcifications were seen in 13% of the missed interval cancers in women aged 40–74 years old in a study by Vitak et al (3,22) while a recent study by Porter et al showed tumor related calcifications in 35% of the missed cases in women aged 50–64 years (4). In screening-detected cancers, 24–34% is reported to show calcifications (19,26). A possible distinction between screening-detected and interval breast cancer in respect to calcifications is thus difficult to identify without a detailed description of the types of calcifications. Breast cancer with calcifications is usually considered easyto detect on a mammogram, although the interpretation can be difficult (19,23). One way to avoid missing cancers with calcifications is to recall all cases with calcifications, which is not acceptable in daily practice. To be more accurate in the selection of mammograms with calcifications for recalls, the characteristics of the calcifications should be carefully analyzed (19,26). Digital mammography and Computer Aided Detection (CAD) have made perception of calcifications easier (27,28) but CAD does not help with the interpretation of calcifications. Neither digital mammography nor CAD was used in this study.

The European Guidelines do not have recommendations for classifying mammograms by mammographic features or recommended levels for sensitivity and specificity as part of the performance indicators (1). This omission hampers valid comparison and does not emphasize the importance of quality assurance of the radiological performance. The Breast Image Reporting and Data System (BI-RADS) for classification of radiological features (14) is used in the United States and some European countries (29). Although several challenges in the use

of BI-RADS are reported (30), the use of standardized terminology and criteria for classification of mammographic features would improve the ability to compare results and learn from different screening programs. In addition, systematic analysis of the mammographic findings according to the BI-RADS results is an indication of whether a woman should be recalled or not (14). The European Guidelines and the NBCSP have recommendations and desirable levels for recalls, but no advice for which findings should be recalled.

Less prognostic favorable histopathological tumor characteristics according to tumor size and lymph node involvements were found in missed compared to true interval cancers in this study but no differences were seen according to grading or receptor status. Substantial benefit for the individual and program can be achieved by reducing the number of missed interval cancers. The missed and minimal sign cancers were more likelyto be invasive lobular cancers than the true interval cancers. Invasive lobular cancers are known to spread diffusely, have short mean sojourn time (2.3 years) and are less likely to be detected at mammography(19). In addition we found a larger mean tumor size and a higher proportion of lymph node involvements in the lobular cancers compared with invasive ductal carcinomas.

True interval cancers may be considered faster growing and with less prognostic favorable tumor characteristics compared with missed interval cancers since it is not visible on the screening mammograms. However, missed interval cancers could be expected to have even less favorable tumor characteristics since the tumors were detectable at the previous screening and have had time between the screening mammogram and diagnosis to progress. Previous studies have shown contradictory results in respect to tumor characteristics in subgroups of interval cancer (3,4,6,31,32). Our study found that true interval cancers were smaller than the missed and minimal sign cancers. A limitation of this study is that it includes a rather small number of interval cancers. A larger study including interval cancers diagnosed from both prevalent and subsequent screening mammograms would improve the impact of the findings.

Histopathological characteristics are of particular interest because of their relationship to survival and mortality from the disease. Although the outcomes of various studies diverge they tend to show no differences in survival by subgroups of interval cancer (3,31,32).

The group of minimal sign interval cancers represents a challenge in screening mammography, represented by the issue of visual perception versus interpretation. The European Guidelines suggest dividing the minimal signs into actionable and not actionable (4). Such a classification is expected to raise the percentage of minimal sign interval cancer at the sacrifice of true interval cancers (33). Use of CAD is thus relevant if the problem is one of visual perception, assuming marks on several lesions that perhaps would be overlooked or categorized as minimal sign not actionable. However, the sensitivity of CAD is reported to be high, but a high sensitivity is usually at the cost of the specificity(34). This study does not divide minimal sign interval cancers into actionable and not actionable. A study that can discriminate between visual perception and interpretation would help educating radiologists to improve their specific deficits.

In conclusion, this study found that half of the missed and minimal sign interval breast cancers were presented as poorly defined mass and twenty-five percent showed calcifications on the screening mammograms. The invasive missed interval cancers tended to have less prognostic favorable tumor characteristics according to tumor size and lymph node involvements, compared to true and occult interval cancers. Reviews and classifications of the interval cancers should perhaps have priority and be considered as an important and necessary tool for continuing education for screening radiologists. Standardization of mammographic features as found in the BI-RADS is attractive, and collecting more details on types of calcification may help the radiologist better understand what findings are most likely to become a missed or

minimal sign interval cancer. A protocol for reviewing and analyzing interval cancers is necessary to improve the quality of the radiological skills in the NBCSP.

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**Table 1**

Radiological features determined on the screening mammograms in missed and minimal sign interval cancers diagnosed in women aged 50–69 years old at screening, in the first screening round of the Norwegian Breast Cancer Screening Program

| Radiological features | Missed | | Minimal sign[1] | | All | |
|---|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | No. | (%) |
| Distortion | 13 | (16) | 10 | (19) | 23 | (17) |
| Poorly defined mass or asymmetric density | 40 | (50) | 27 | (51) | 67 | (50) |
| Mass | | | | | | |
| Circumscribed | 2 | (3) | 2 | (4) | 4 | (3) |
| Spiculated | 4 | (5) | 1 | (2) | 5 | (4) |
| Calcifications | | | | | | |
| Calcifications only | 5 | (6) | 8 | (15) | 13 | (10) |
| Density or mass with calcifications | 16 | (20) | 5 | (9) | 21 | (16) |
| Total | 80 | | 53 | | 133 | |

[1] No statistically significant differences between the missed and minimal signinterval cancers

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**Table 2**

Histopathological tumor characteristics stratified by subgroups, in 231 interval cancers diagnosed in women aged 50–69 years, in the first screening round of the Norwegian Breast Cancer Screening Program

| Characteristics | Missed (n=80) | | Minimal sign (n=53) | | True[1] (n=98) | | All (n=231) | |
|---|---|---|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | No. | (%) | No. | (%) |
| Histopathological type | | | | | | | | |
| Ductal Carcinoma In Situ | 4 | (5) | 5 | (9) | 5 | (5) | 14 | (6) |
| Invasive ductal carcinoma | 54 | (68) | 40 | (75) | 76 | (78) | 170 | (74) |
| Invasive lobular carcinoma | 16 | (20) | 7 | (13) | 9 | (9) | 32 | (14) |
| Other invasive | 6 | (7) | 1 | (2) | 8 | (8) | 15 | (6) |
| | Invasive cases (n=76) | | Invasive cases (n=48) | | Invasive cases (n=93) | | Invasive cases (n=217) | |
| Tumor size | | | | | | | | |
| Mean mm | 23 mm[2] | | 22 mm | | 18 mm | | 21 mm | |
| Median mm | 20 mm | | 20 mm | | 16 mm | | 20 mm | |
| <15mm (n, %) | 20 | (27)[2] | 15 | (33) | 41 | (47) | 76 | (37) |
| 15–20mm (n, %) | 19 | (26) | 10 | (22) | 16 | (18) | 45 | (22) |
| >20mm (n, %) | 34 | (47) | 21 | (46) | 30 | (34) | 85 | (41) |
| Missing/not available (n) | 3 | | 2 | | 6 | | 11 | |
| Lymph node involvements | | | | | | | | |
| Yes (n, %) | 34 | (49)[2] | 24 | (53)[2] | 27 | (33) | 85 | (43) |
| Missing/not available (n) | 6 | | 3 | | 10 | | 19 | |
| Grading | | | | | | | | |
| I (n, %) | 13 | (19) | 13 | (28) | 19 | (21) | 45 | (22) |
| II (n, %) | 39 | (57) | 20 | (43) | 47 | (52) | 106 | (51) |
| III (n, %) | 17 | (25) | 14 | (30) | 25 | (27) | 56 | (27) |
| Missing/not available (n) | 7 | | 1 | | 2 | | 10 | |
| Receptor status | | | | | | | | |
| Estrogen positive (n, %) | 42 | (67) | 25 | (64) | 56 | (67) | 123 | (66) |
| Missing/not available (n) | 13 | | 9 | | 10 | | 32 | |

| Characteristics | Missed (n=80) | | Minimal sign (n=53) | | True[1] (n=98) | | All (n=231) | |
|---|---|---|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | No. | (%) | No. | (%) |
| Progesterone positive (n, %) | 31 | (49) | 20 | (56) | 39 | (47) | 90 | (49) |
| Missing/not available (n) | 13 | | 12 | | 10 | | 35 | |

[1] True interval cancers including occult cancers

[2] Significantly different from true interval cancers at $p<0.05$