True and missed interval cancer in organized mammographic screening - a retrospective review study of diagnostic and prior screening mammograms

Abstract

Rationale and Objectives: To explore radiological aspects of interval breast cancer in a population based screening program.

Materials and Methods: We performed a consensus-based informed review of mammograms from diagnosis and prior screening from women diagnosed with interval cancer 2004-2016 in BreastScreen Norway. Cases were classified as true (no findings on prior screening mammograms), occult (no findings at screening or diagnosis), minimal signs (minor/non-specific findings) and missed (obvious findings). We analyzed mammographic findings, density, time since prior screening, and histopathological characteristics between the classification groups.

Results: The study included 1010 interval cancer cases. Mean age at diagnosis was 61 years (SD= 6), mean time between screening and diagnosis 14 months (SD=7). A total of 48% (479/1010) were classified as true or occult, 28% (285/1010) as minimal signs and 24% (246/1010) as missed. We observed no differences in mammographic density except from a higher percentage of dense breasts in women with occult cancer. Among cancers classified as missed, about 1/3 were masses and 1/3 asymmetries at prior screening. True interval cancers were diagnosed later in the screening interval than the other classification categories. No differences in histopathological characteristics were observed between true, minimal signs and missed.

Conclusion: In an informed review, 24% of the cases were classified as missed based on visibility and mammographic findings on priors. Three out of four true interval cancers were diagnosed in the second year of the screening interval. We observed no statistical differences in histopathological characteristics between true and missed interval cancers.

Key words: Mass screening, breast neoplasm, digital mammography, mammography, female

Abbreviations

DM – Standard Digital mammography
PACS – Picture archiving and communication system
BI-RADS – Breast Imaging Reporting and Data System
NST – Invasive carcinoma no special type
CI – Confidence interval
SD – Standard deviation
IQR – Interquartile range
DBT – Digital breast tomosynthesis

Introduction

Interval breast cancer is diagnosed between two scheduled screening rounds, after a negative screening episode or after a negative recall assessment (1). The causes of interval cancers are heterogeneous; some cancers grow rapidly and become clinically and/or radiologically detectable in the inter-screening interval as true interval cancer, while others have been misinterpreted or missed by radiologists at screen reading or consensus/arbitration (2, 3). Mammographically occult cancers are not visible on the mammograms even at the time of diagnosis, usually due to tissue overlap or localization outside the target area of the mammogram. Interval cancers with visible findings on prior screening mammograms in hindsight may be classified as minimal signs or missed, depending on the level of suspiciousness of the mammographic findings (1, 2, 4). Houssami explored several review studies to estimate the proportion of cancers with visible findings on prior screening mammograms (2). However, different study design and classification systems hamper comparison of results and in the reported studies the proportion of missed interval cancer ranged from 13-35%.

Rates of interval cancer vary across screening programs (10, 11) and it is estimated that interval cancer accounts for 17-30% of the cancers in biennial screening programs (2). In general, interval cancers have less favorable histopathological tumor characteristics and reduced survival compared with screen-detected cancers (5-9). Further, the majority of the interval cancers is diagnosed in the second half of the screening interval. In addition to the radiologists' performance, factors influencing the rates and proportions of interval cancer within a program include the background breast cancer incidence, the screening interval, the definition of interval breast cancer and completeness of cancer registration (12). Interval cancer is an inevitable part of all screening programs, but it is important to keep the rates as low as possible, not only to reduce mortality, but also to increase trust in the program among women in the target population, and in the society in general. In BreastScreen Norway, the rate of interval cancer has been relatively stable over the past 20 years. In the period from 1996 - 2016, the interval cancer rate was 1.9 per 1000 screened women, comprising 24% of all breast cancers among the participants in the program (13).

To our knowledge, no unanimous results exist regarding mammographic findings of prior screening mammograms for missed and minimal signs interval breast cancer. Further, whether or how mammographic density varies for different classification categories is not fully understood (3, 14-16). In programs without a central cancer registry, registration of interval breast cancer may be inadequate, in particular if the interval cancer is diagnosed in another clinic than the screening took place, or the woman has moved to another district (10). The Cancer Registry of Norway and BreastScreen Norway is unique in terms of completeness and organization of screening data. By law, all hospitals, medical laboratories and doctors report all cancer cases to the registry and linked with screening data, information on interval cancers is almost 100% complete and available (17).

We took advantage of this completeness and performed a fully informed, consensus-based review of diagnostic and prior screening mammograms from women diagnosed with interval cancer in BreastScreen Norway. The overall aim of the study was to explore radiological aspects of the interval cancers. We described the proportions of true, occult, minimal signs and missed interval breast cancer, and analyzed associations between these groups and mammographic findings, time since prior screening, and histopathological characteristics.

Material and Methods

The Data Protection Officer for the Cancer Registry of Norway and the Heads of Department and/or research administration at the local breast centers approved this retrospective study. The Cancer Registry Regulations waived the requirement to obtain written informed consent (17).

Screening logistics in BreastScreen Norway

In BreastScreen Norway, women aged 50–69 are invited biennially to screening with two-view digital mammography (DM) at 27 stationary or mobile units. Screen-reading and recall assessment is performed by breast radiologists at 17 breast centers (the number of breast centers was 16 when the review was performed). The screen-reading includes independent double reading with consensus/arbitration. Two radiologists assign each breast a score of 1-5 (1 = normal/benign; 2 = probably benign; 3 = indeterminate; 4 = probably malignant; 5 = malignant) and all exams scored ≥2 by either radiologist are discussed in a consensus meeting to decide whether to recall the woman (13). The median annual reading volume for radiologists in BreastScreen Norway during the period from 1996 to 2016 was 4492 exams, and 46 % of the radiologists had more than 10 years of screen-reading experience (18). Pathological specimens are examined by pathologists at the local hospitals. All screening data from BreastScreen Norway, including results from histopathological reports, are reported to the Cancer Registry of Norway and stored in a national database.

Materials

We aimed at reviewing 1200 interval cancer cases; 75 cases from each of the 16 breast centers, spending no more than 8 hours for each review session. From the screening database at the Cancer Registry, data on interval cancer cases diagnosed during the period from March 2004 to September 2016 were identified and extracted. We included standard DM performed in the screening round prior to the diagnosis (within 24 months), and diagnostic DM. To take into account that some cases might not have diagnostic images available for review (interval cancer diagnosed at a private clinic or in another hospital), up to 90 cases were identified from each center. However, the aim of 75 reviewed cases was only achieved in 3 centers; the remaining centers were either not able to provide as many as 75 interval cancer cases with diagnostic and prior images available (either due to a small center size, or many diagnostic exams performed outside the center), or the review session reached the time limit of 8 hours (Suppl.1). The final study population included 1010 interval cancer cases. For comparative analyses of interval versus screen-detected cancer, we used information from a parallel review study of 1257 screen-detected cases. This study is described in detail elsewhere (19).

Review procedure

At each breast center, panels of five breast radiologists performed a fully informed consensus-based review of diagnostic and prior screening mammograms of women diagnosed with interval cancer. The review panel consisted of two radiologists employed at the breast center whose images were reviewed, two radiologists who worked at one of the other 15 breast centers, and additionally, T.H. participated in all review sessions. The mammograms were reviewed locally from the picture archiving and communication system (PACS). The classifications were all based on majority decisions.

The review logistics was similar to a prior review of screen-detected cancer and is described in more detail elsewhere (19).

We identified the tumor on the diagnostic images, reviewed the prior screening mammograms and classified the case according to findings as follows: True (no visible findings on priors), occult (mammographically occult at diagnosis), minimal signs (minor or non-specific findings, recall assessment not mandatory or even not possible within the screening program) or missed (obvious visible abnormal findings on priors)(Figure 1). We classified the mammographic findings on diagnostic and prior screening images according to the American College of Radiology's Breast Imaging – Reporting and Data System (BI-RADS) 5th edition lexicon (20); mass, calcifications, asymmetry, distortion or other findings, with sub-classifications when appropriate (Figure 2). We classified the largest tumor in case of multifocal or bilateral disease, and if calcifications were present alongside another finding (mass, asymmetry or distortion), we classified the malignancy as calcifications only if this was the dominant finding. We measured the diameter of the suspicious mammographic findings using an electronic caliper and classified mammographic density on diagnostic mammograms into BI-RADS 5th edition categories a (entirely fatty), b (scattered areas of fibroglandular density), c (heterogeneously dense) or d (extremely dense).

Histopathological tumor characteristics from the Cancer Registry's database were communicated to the radiologists after complete classification of each case and merged with data from the review. These characteristics included histological type (ductal carcinoma in situ, invasive carcinoma of no special type (NST), invasive lobular carcinoma, other invasive carcinoma), and for invasive cancers histological grade (1-3), histopathological tumor diameter (mm), lymph node status (positive/negative), estrogen receptor and progesterone receptor status (positive/negative).

Statistical analyses

We performed descriptive analyses of age at diagnosis of interval cancer (years), time between diagnosis and the prior screening exam (months), review classification categories, mammographic findings, mammographic density, and histopathological characteristics. Categorical data were presented as frequencies and percentages. Means and standard deviations (SD) were presented for normally distributed continuous variables (age, time since screening), and medians with interquartile ranges (IQR) were presented for non-normally distributed continuous variables (mammographic and histopathological diameter). We used Chi-square tests or Fisher's exact test when appropriate (categorical data), independent sample t-tests (means) and non-parametric tests (medians) to test for differences between review classification categories and mammographic findings or histopathological characteristics. We used the Bonferroni correction to adjust for multiple testing and considered $p<0.001$ statistically significant. We used IBM SPSS Statistics version 25 for all analyses.

Results

We classified 35% (353/1010) of the cases as true interval cancer, 13% (126/1010) as occult, 28% (285/1010) as minimal signs and 24% (246/1010) as missed(Figure 3a-h). Mean age at diagnosis for all women was 61 years (SD=6). No statistically significant difference in age between the review classification categories was identified (Table 1).

Time from screening to diagnosis

Mean time from screening to diagnosis was 16 months (SD=5) for true interval cancers, statistically significantly higher than 13 months (SD=5) for occult, 14 months (SD=9) for minimal signs and 13 months (SD=5) for missed (Table 1). The percentage of cancers diagnosed within the first 12 months after screening ranged from 24% (83/353) for true interval cancers to 52% (66/246) for occult ($p<0.001$), whereas the percentage of cancers diagnosed 19-24 months after screening ranged from 17% (21/126) for occult to 41% (145/353) for true ($p<0.001$) (Figure 4).

Mammographic density

Overall, 49% (494/1010) of the cases were classified as having mammographic density a or b, and 51% (516/1010) density c or d. The distribution of mammographic density categories did not differ statistically between true, minimal signs and missed, ranging 50-53% for a+b and 47-50% for c+d. However, among the occult cases, 38% (31/126) were classified with mammographic density a+b and 69% (88/126) c+d, $p<0.001$ for occult compared with each of the other categories (table 1).

Mammographic findings

The most frequent mammographic finding at diagnosis was a mass for all classification categories, ranging from 53% (186/353) for true to 66% (163/246) for missed ($p<0.001$) (Table 1). The second most frequent mammographic finding was asymmetry, ranging from 13% (31/246) for missed to 26% (90/353) for true ($p<0.001$). The least frequent mammographic finding was calcifications for all classification categories, and no statistically significant differences were observed regarding the proportions of calcifications and distortions among cancers classified as true, minimal signs or missed. Median diameter of mammographic findings at diagnosis in the whole study population was 21 mm (IQR 15-31), no statistical significant differences were observed between classification categories.

The most frequent mammographic finding on prior screening mammograms was asymmetry for both minimal signs (65 %, 186/285) and missed (36%, 88/246; $p<0.001$) (Table 1). A mass was the least frequent finding among minimal signs (5%, 15/285) and the second most frequent finding among missed (32%, 79/246; $p<0.001$). Median diameter of mammographic findings at prior screening was 12 mm (IQR 8-17) for minimal signs and 15 mm (IQR 11-23) for missed ($p<0.001$).

Ninety-seven percent (91/94) of masses at prior screening and 64% (176/274) of asymmetries at prior screening presented as masses at diagnosis. Further, the majority of calcifications at prior screening (59%, 43/59) presented as calcifications also at diagnosis, whereas 60% (54/90) of distortions remained distortions at diagnosis and 36% (32/90) presented as a mass (figure 5).

Among the masses missed at prior screening, 65% (65/78) had irregular shape, and 90% (70/78) had indistinct or spiculated border (Table 2). The most frequent minimal signs asymmetry was one-plane asymmetry (50%, 94/186). The most frequent missed asymmetry was developing asymmetry (51%, 45/88) which is defined as a focal (two-plane) asymmetry that is new, larger or more conspicuous than on the previous examination. At diagnosis, a round/oval mass was more frequent in true (33%, 61/186) than missed (17%, 27/163; $p<0.001$) interval cancer, otherwise no statistical significant differences were observed regarding subclasses of mammographic findings at diagnosis (Table 2).

Histopathological characteristics

No differences in histopathological characteristics were observed between true, minimal sign or missed interval cancer. Ductal carcinoma in situ contributed with 5% (49/1010) of all the cases, and the proportion did not differ between the classification categories (Table 3). The percentage of invasive carcinoma of NST ranged from 52% (66/126) for occult to 81% (284/353) for true interval cancer, p<0.001 for occult compared with true, minimal signs and missed. The percentage of invasive lobular carcinoma ranged from 11% for true (38/353) and missed (27/246) to 18% (22/126) for occult, p=0.001 for true versus occult. The highest proportion of "other invasive carcinomas", which included among others invasive tubular, medullar and mucinous carcinoma, was observed among occult cancers (18%, 22/126) and the lowest among true (5%, 17/353, p<0.001). No statistically significant differences in histopathological tumor diameter were observed between the review classification categories.

The percentage of histological grade 1 tumors was lowest for true interval cancers (8%, 27/328) and highest for occult cancers (25%, 26/105), p<0.001. The smallest median histopathological tumor diameter was observed in occult cancers, 15 mm (IQR 10-23), p<0001 compared with true, minimal signs and missed. No difference in median tumor diameter was observed between the other categories. The percentage of histological grade 3 tumors ranged from 30% (32/105) for occult to 47% (153/328) for true interval cancer, p=0.004. There were no statistical significant differences in lymph node status between classification categories. Estrogen receptor positivity ranged from 73% (243/332) for true to 91% (97/107) for occult cancers (p<0.001), whereas progesterone receptor positivity ranged from 51% (166/326) for true interval cancers to 65% (68/105) for occult (p=0.01, Table 3).

Interval versus screen-detected interval cancer

Comparative analyses of results from the present study and a parallel study of screen-detected breast cancer are presented in the Supplementary material (Suppl. 2). When combining true and occult cancers, no differences in the distribution of true/occult, minimal sign and missed cancers were observed. A higher percentage of BI-RADS c and d mammographic density was observed in interval cancers (51%, 516/1010) compared with screen-detected (34%, 417/1257), p<0.001. The proportion of calcifications were higher in screen-detected than interval cancer, both at diagnosis and prior screening (p<0.001), and the proportion of distortions was higher in interval cancer (p<0.001). Further, a statistically significantly lower proportion of DCIS, a larger tumor diameter, and higher proportions of histological grade 3 invasive cancer, lymph node positive and hormone receptor negative tumors were observed in interval cancer compared with screen-detected.

Discussion

In this fully informed, consensus-based, retrospective review of diagnostic and prior screening mammograms of 1010 interval breast cancer cases in BreastScreen Norway, the radiologists classified 35% of the cases as true interval cancer, 13% as occult, 28% as minimal signs and 24% as missed. Mean time between screening and diagnosis was shortest for occult and longest for true. Sixty-nine percent of the mammograms from women with occult cancer were classified as BI-RADS density c or d, higher than all other classification categories. Among cancers classified as missed, about 1/3 were masses and 1/3 asymmetries at prior screening. Ninety percent of the missed masses

had indistinct or spiculated borders and half of the missed asymmetries were developing asymmetries. We observed a direction of the findings for true interval cancers towards less favorable histopathological characteristics compared with the other classification categories. However, only histological grade 1 and estrogen receptor negative tumors differed statistically; lower in true versus occult interval cancers for both. A smaller median tumor diameter was observed in occult cancers compared with all other categories.

Proportions of true and missed cancer

Our results on classification of interval cancer based on findings on prior screening mammograms are in line with other studies. In four different review studies, all with an informed study design, the percentage of true/occult interval cancer ranged from 38-59 %, and missed interval cancer ranged from 22-35 % (15, 21-23). In a blinded review of interval cancer, 55% were classified as true/occult and 21% as missed (9). The review logistics differ between studies, from blinded to fully informed, and from individual to consensus-based. Little consensus exists on standardization of study design in reviews of interval cancer, thus, comparison between studies is challenging (4). Further, the definition of interval cancer as such as well as the subdivision of the radiological classification groups vary (2). In general, the more information available to reviewers, the higher the proportion of missed cancer cases. This might be due to bias in the review process as the reviewers are aware of where the cancer is located and thus, where to look for even subtle findings on prior mammograms. Further, the closer the review is to a normal screening situation, the lower the proportion classified as missed cancer, associated with the readers' level of expectation to detect interval cancers (24-27). Our fully informed consensus-based study design is thus the design that yields the highest proportion of missed cancer at review.

Mammographic findings on prior screening mammograms - missed and minimal signs

Irregular, spiculated masses are considered more suspicious for cancer than round/oval and circumscribed masses; developing asymmetries are in general more suspicious than one-plane asymmetries, and fine pleomorphic or linear/branching calcifications more indicative of malignancy than amorphous (20). Obviously, in a retrospective review, the allocation of exams into the categories minimal signs or missed is based on the level of suspiciousness of the mammographic findings. The vast majority of missed masses at screening in our study were irregular in shape, with indistinct or spiculated border. Such findings are suspicious of malignancy and usually result in a recall if perceived. Thus, it is likely that a major reason for failure to recall these cases is misperception or reduced vigilance among the screen-readers. However, even suspicious findings are sometimes refrained from recall, especially if stable or slow-growing through consecutive screening rounds (28). Nevertheless, these findings may benefit from recall, even if they are probably not representing the most aggressive cancers. As we only classified one prior screening exam, we have no data on long-term stability of mammographic findings in our study. Almost all masses at prior screening remained masses at diagnosis, and the majority of asymmetries at prior screening turned into masses at diagnosis. This may illustrate a pathway from asymmetry to mass, and is in accordance with our findings for screen-detected breast cancer (19). Further, as for missed screen-detected cancer, the majority of calcifications and distortions remained the same at diagnosis.

We defined minimal signs as minor or non-specific findings in which recall was not considered mandatory or even not possible within the screening program. Hence, the mammographic findings of

these cancers are less suspicious than in the missed cancers; frequent findings in prior screening mammograms were one-plane asymmetries and round/oval circumscribed or obscured masses. Such findings are common in screening mammography and usually represent benign or normal findings. Strategies to improve the radiologists reading skills, including sensitivity and specificity, may change the threshold for which findings that require further assessment to be ruled out. This might be related to the usual and accepted recall rate of the actual screening program, which vary across different countries. In programs with generally low recall rate, the acceptance for not recalling subtle or minor findings would probably be higher than in programs with a higher recall rate. Further, including more sets of prior screening mammograms at screening reading may be a proper strategy to improve sensitivity and specificity as the radiologists may become more aware of subtle changes (19, 29).

Mammographic density and interval cancer

In general, the sensitivity of mammography in detecting breast cancer is lower in dense compared with fatty breasts (30). In line with this, and also in keeping with other studies, we observed a statistically higher mammographic density in women with occult interval cancer compared with all other classification groups (15, 31), and also for interval versus screen-detected cancer. Implementation of supplemental imaging techniques has been proposed as part of stratified screening based on differences in breast cancer risk and mammographic density (32). In studies, digital breast tomosynthesis (DBT) increases the rate of screen-detected cancer (32-37), probably by increasing the conspicuity of lesions and reducing the masking effect of breast tissue. However, an increase was not observed in the highest density category (32). Further, studies have not shown a reduction in interval cancer rates for screening with DBT, and whether DBT may have the potential to reduce interval cancer in dense breasts is not yet demonstrated. Hand-held or automatic breast ultrasound (ABUS) or contrast-enhanced breast MRI is also associated with increased sensitivity for breast cancer in dense breasts (38-40). These techniques may also reduce the occurrence of interval breast cancer, including occult breast cancer outside the anatomical target area for mammography. However, implementation of stratified screening with more resource intensive imaging techniques needs a thorough evaluation of benefits, risks and cost-effectiveness. Further, in our study, only 9% of the interval cancers were actually seen in breasts with BI-RADS d mammographic density.

Screening interval

Two thirds of the interval cancers were diagnosed in the second half of the screening interval, which is in keeping with other studies (9, 23). A shortening of the screening interval could thus reduce the number of interval cancers. This could particularly have an effect on the occurrence of true interval cancer, as this group has the highest frequency of cancers diagnosed >12 months after screening. BreastScreen Norway and most other European breast cancer screening programs, screen women biennially, whereas in the United Kingdom (UK) screening is triennial, and in the United States (US) usually annual. In UK the interval cancer rate <24 months after screening is comparable with the rates in BreastScreen Norway, but because of additional interval cancers during the third year of the screening interval the total interval cancer rate is higher (41). Studies comparing interval cancer rates in the US and Norway (42, 43) have demonstrated higher rates of interval cancer in the US compared with Norway, despite annual screening in the US. This is possibly due to additional differences in screening regimes between the US and European countries, among other single-reading, different

screening logistics, lower reading volume and early recalls. Even if reducing the screening interval to 1 year has the potential to reduce the interval cancer rate, this could decrease the cost-effectiveness of the screening program and potentially increase possible risks as false positives. The European Commission Initiative on Breast Cancer (ECIBC) have agreed on a strong recommendation against annual screening (44). This is in contrast to the American College of Radiology and the Society of Breast Imaging, which recommend annual mammography, while the American Cancer Society and the American Society of Surgical Oncologists recommend annual mammography to age 55, then biennial. The United States Preventive Services Task Force recommends biennial screening (45).

Histopathological findings

Histopathological characteristics of tumors classified as true and missed vary between studies (2). In some studies missed interval cancers have a larger tumor diameter and are more often lymph node positive (9, 21, 23) though more frequently low-graded than true interval cancers, whereas others observe less favorable histopathological characteristics among true, in particular higher proportions of high histologic grade and hormone receptor negative disease (15, 31, 46). We did not find any histopathological differences between true and missed interval cancer, whereas true interval cancer more frequently were of histologic grade 3 and hormone receptor negative than occult. Some retrospective reviews combine true and occult cancers into one category, based on the lack of mammographic findings at prior screening. However, due to the differences observed in histopathological characteristics as well as in the time interval between screening and diagnosis, it seems reasonable to separate true and occult interval cancers as two different categories at review.

Interval versus screen-detected breast cancer

When combining true and occult cancer into one category, as none of these show detectable findings on prior screening mammograms, no differences in the distribution of categories were observed between interval and screen-detected cancer (19). The distribution of mammographic density, however, differed statistically significantly between interval and screen-detected cancer, and the difference also holds when excluding the occult cancers. These finding is in line with other studies (15, 30). In keeping with the literature, less favorable tumor characteristics were observed in interval cancers compared with screen-detected, the proportion of DCIS was lower in interval versus screen-detected cancers whereas the proportion of ILC was higher (47, 48). Calcifications were less frequent in interval than screen-detected cancers, both at diagnosis and prior screening, which is probably related to the lower proportion of DCIS. Further, a higher proportion of distortions was observed at diagnosis in interval cancers, which might reflect the higher proportion of ILC. Interestingly, except for calcifications, no differences in the distribution of other mammographic findings were observed at prior screening, indicating that the radiologists may overlook or refrain to recall the same type of lesions in interval and screen-detected cancer.

Possible strategies to reduce interval cancer and missed cancer at screening

As described above, a shortening of the screening interval as well as implementation of supplementary screening techniques may decrease the rates of interval cancer, although such measures may not unanimously increase the overall quality of the screening program. Education, including self-assessment and training schemes, and participation in reviews could be ways to improve the screen-reader's sensitivity to more subtle findings. These strategies may also improve

the radiologists' perception and interpretation, and increase their awareness of possible pitfalls. The experience in mammography screening is also important for the radiologist's sensitivity. A Norwegian study demonstrated optimal performance in screen-reading with an annual reading volume of 4000 -10 000 mammograms and a cumulative volume of at least 20 000 mammograms. However, sensitivity decreased for annual volumes >10 000 mammograms and cumulative volumes >100 000, which may indicate that too high workloads could cause fatigue and reduced attention among the screen-readers (18). Double reading is shown to increase cancer detection (49), and probably also reduce the occurrence of interval cancer; in a study from BreastScreen Norway, 24% of the screen-detected cancers were detected by only one reader (50). Optimization of image quality is also of outmost importance to reduce all types of interval breast cancer. In addition to the technical image parameters, optimal positioning is crucial; some interval cancers may be classified as occult due to suboptimal positioning leaving the tumor incorrectly outside the field of view. Finally, during the past years, artificial intelligence (AI) based on deep convolutional neural networks shows promising results in breast diagnostics and screening (51-53) and if AI in the future demonstrates the ability to detect abnormalities in images not perceived by radiologists, or not even detectable by the human eye, it may be possible to lower the interval cancer rate.

Strength and limitations

The large study sample represents strength in our study. Further, all images were digital, and the study is therefore relevant for the standard screening technique today, in contrast to most prior review studies using screen-film mammography. However, as only DM screening mammograms were included, the external generalizability to screening with DBT was limited. The fully informed consensus-based review design is the design resulting in the highest proportion cancers classified as missed, and least resembling a normal screening situation. This may limit the external generalizability of the results. We chose this design for practical and educational purposes. Further, the study included radiologists from all breast centers and except one (T.H.), all reviewers participated in only two of the 16 reviews. Different pathologists at all centers performed histopathological analyses, and differences between centers may have occurred. Finally, histopathological tumor diameter was missing in 77 cases. This is probably due to neo-adjuvant treatment of the cancers, often resulting in a non-measurable tumor burden at surgery, and illustrated by a higher median mammographic diameter for cases with missing tumor diameter compared with no missing tumor diameter (35 versus 21 mm).

Conclusion

In an informed, retrospective review of interval cancers, ¼ of the cancers were classified as missed at screening, with a potential of earlier diagnosis. Even if retrospective reviews do not reflect a normal screening setting and hindsight findings are not always signs of screening failure, we consider reviews important in the continuous work to assure and improve the quality of the radiologists and the screening programs. Both organized high volume review studies as well as individual reviews of cancer cases personally screened by the screen-reader are valuable in that respect.

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Figure legends

Figure 1: Review procedure

Figure 2: Classification of mammographic findings on diagnostic mammograms and prior screening mammograms, BI-RADS 5th edition.

Figure 3a-b: True interval cancer: Left medio-lateral oblique (MLO) views of a 64 year-old woman presenting with a palpable lump and an indistinct round mass in the upper outer quadrant of the left breast (arrow) at diagnosis (a), diagnosed with a 16 mm invasive carcinoma of no special type (NST). No mammographic findings at prior screening (b).

Figure 3c-d: Missed interval cancer: Right craniocaudal (CC) views of a 64 year-old woman presenting with a palpable lump and an obscured round mass in the medial aspect of the right breast (arrow) at diagnosis (c), diagnosed with a 25 mm invasive carcinoma of NST. A focal asymmetry (arrow) is visible at the cancer site on prior screening mammograms (d).

Figure 3e-f: Minimal signs interval cancer: Left MLO views of an 69 year-old woman presenting with a palpable lump and an irregular spiculated mass in the upper outer quadrant of the left breast (arrow) at diagnosis (e), diagnosed with a 20 mm invasive carcinoma of NST. An asymmetry (arrow) is visible at the cancer site on prior screening mammograms (f).

Figure 3g-h: Occult interval cancer: Right MLO views of a 53 year-old woman presenting with a palpable lump in the upper outer quadrant of the right breast and diagnosed with a multifocal invasive carcinoma. No visible mammographic findings at neither diagnosis (g) nor prior screening (h).

Figure 4: Time since screening by review category.

Figure 5: Number of patients with mammographic findings at diagnosis by findings at prior screening.

Table legends:

Table 1. Age at diagnosis (mean and standard deviation, SD), time since screening (mean and SD), distribution of mammographic density at diagnosis, and mammographic findings on diagnostic and prior screening mammograms for 1010 interval breast cancers, by review classification categories (true, occult, minimal signs and missed). Unless otherwise specified, data are number of patients with percentages in parentheses. BI-RADS: Breast Imaging-Reporting and Data System. SD: standard deviation. IQR: inter-quartile range.

Table 2. Subclassification of mammographic findings on prior screening and diagnostic mammograms. Data are number of patients with percentages in parentheses.

Table 3. Histopathological characteristics by review classification categories. Tumor diameter, histological grade, lymph node status and hormonal receptor status for invasive cancers only. Unless otherwise is specified, data are number of patients and percentages. IQR: interquartile range; NST: no special type.

Supplementary 1. Number and percentages of interval cancer cases reviewed, by breast center.

Supplementary 2. Review category, mammographic density, mammographic findings at diagnosis and prior screening, and histopathological characteristics for screen-detected breast cancer and interval breast cancer after a radiological review. SDC: Screen-detected breast cancer. IC: Interval breast cancer. BI-RADS: Breast Imaging Reporting and Data System. IQR: Interquartile range. Unless else is specified, data are number of patients with percentages in parentheses.

Table 1. Age at diagnosis (mean and standard deviation, SD), time since screening (mean and SD), distribution of mammographic density at diagnosis, and mammographic findings on diagnostic and prior screening mammograms for 1010 interval breast cancers, by review classification categories (true, occult, minimal signs and missed). Unless otherwise specified, data are number of patients with percentages in parentheses.

Variable	All	True	Occult	Minimal signs	Missed
	1010 (100)	353 (35)	126 (13)	285 (28)	246 (24)
Age, mean (SD) years	61 (6)	61 (6)	60 (6)	61 (6)	62 (5)
Time since screening, mean (SD) months	14 (7)	16 (5)	13 (5)[a]	14 (9)[a]	13 (6)[a]
Mammographic density					
BI-RADS a	76 (8)	20 (6)	7 (6)	26 (9)	23 (9)
BI-RADS b	418 (41)	160 (45)[b]	31 (25)	118 (41)	109 (44)[b]
BI-RADS c	420 (42)	142 (40)	56 (44)	122 (43)	100 (41)
BI-RADS d	96 (9)	31 (9)[b]	32 (25)	19 (7)[b]	14 (6)[b]
Diagnostic mammograms					
Mass	507 (57)	186 (53)[c]	.	158 (55)	163 (66)
Calcifications	64 (7)	20 (6)	.	20 (7)	24 (10)
Asymmetry	179 (20)	90 (26)[c]	.	58 (20)	31 (13)
Distortion	130 (15)	53 (15)	.	49 (17)	28 (11)
Other findings	4 (1)	4 (1)	.		
Mammographic diameter, median (IQR) mm	21 (15, 31)	21 (15, 32)	.	21 (15, 30)	23 (15, 32)
Data not available	31	21	.	8	2
Prior screening mammograms			.		
Mass	94 (18)	.	.	15 (5)[c]	79 (32)
Calcifications	73 (14)	.	.	34 (12)	39 (16)
Asymmetry	274 (52)	.	.	186 (65)[c]	88 (36)
Distortion	90 (17)	.	.	50 (18)	40 (16)
Mammographic diameter, median (IQR) mm	14 (9, 20)	.	.	12 (8, 17)[c]	15 (11, 23)
Data not available	118	.	.	104	14

BI-RADS: Breast Imaging-Reporting and Data System. SD: standard deviation. IQR: inter-quartile range.

[a] $p<0.001$ compared with true

[b] $p<0.001$ compared with occult

[c] $p<0.001$ compared with missed

Table 2. Subclassification of mammographic findings on prior screening and diagnostic mammograms. Data are number of patients with percentages in parentheses.

	Prior screening mammograms		Diagnostic mammograms		
	Minimal signs (n=285)	Missed (n=246)	True (n=353)	Minimal signs (n=285)	Missed (n=246)
Mass					
Shape					
Round/oval	11 (92)[a]	27 (35)	61 (33)[a]	36 (23)	27 (17)
Irregular	1 (8)	51 (65)	125 (67)	122 (77)	136 (83)
Data not available	3	1			
Border					
Circumscribed/obscured/microlobulated	6 (55)	8 (10)	22 (12)	12 (8)	14 (9)
Indistinct/spiculated	5 (45)	70 (90)	164 (88)	146 (92)	149 (91)
Data not available	4	1			
Calcifications					
Typically benign	8 (24)	1 (3)	.	.	.
Suspicious	26 (76)	38 (97)	.	.	.
Morhology suspicious calcfications					
Amorphous/Coarse heterogenous	10 (38)	5 (14)	3 (15)	.	3 (13)
Fine plemorphic/linear/branching	16 (62)	32 (86)	17 (85)	20 (100)	21 (87)
Data not available		1			
Distribution suspicious calcifications					
Diffuse/regional	6 (23)	14 (37)	6 (30)	13 (65)	8 (33)
Grouped	16 (62)	15 (39)	9 (45)	5 (25)	10 (42)
Linear/segmental	4 (15)	9 (24)	5 (25)	2 (10)	6 (25)
Asymmetry					
Asymmetry	94 (50)[a]	19 (22)	24 (27)	17 (29)	5 (16)
Focal/global asymmetry	35 (19)	24 (27)	17 (19)	16 (28)	15 (48)
Developing asymmetry	57 (31)	45 (51)	49 (54)	25 (43)	11 (36)

[a] $p<0.001$ compared with missed

Table 3. Histopathological characteristics by review classification categories. Tumor diameter, histological grade, lymph node status and hormonal receptor status are given for invasive cancers only. Unless otherwise is specified, data are number of patients and percentages in parentheses.

	Total	True	Occult	Minimal signs	Missed
Histopathological tumor type					
Ductal carcinoma in situ	49 (5)	14 (4)	11 (9)	13 (5)	11 (5)
Invasive carcinoma of NST	754 (75)	284 (81)[a]	66 (52)	214 (75)[a]	190 (77)[a]
Invasive lobular carcinoma	129 (13)	38 (11)	28 (22)	36 (13)	27 (11)
Other invasive carcinoma	78 (8)	17 (5)[a]	21 (17)	22 (8)	18 (7)
Tumor diameter, median (IQR) mm	19 (13, 25)	19 (14, 26)[a]	15 (10, 23)	20 (14, 25)[a]	20 (13, 26)[a]
Data not available	75	28	16	19	12
Histological grade					
Grade 1	128 (14)	27 (8)[a]	26 (25)	44 (16)	31 (14)
Grade 2	437 (47)	148 (45)	47 (45)	126 (47)	116 (51)
Grade 3	364 (39)	153 (47)	32 (30)	98 (37)	81 (36)
Data not available	32	11	10	4	7
Lymph node status					
Positive	384 (41)	149 (46)	33 (31)	105 (40)	97 (42)
Data not available	34	12	8	8	6
Hormonal receptor status					
Estrogen receptor positive	745 (79)	243 (73)[a]	97 (91)	217 (81)	188 (81)
Data not available	21	6	8	4	3
Progesterone receptor positive	542 (58)	166 (51)	68 (65)	166 (62)	142 (62)
Data not available	33	12	10	6	5

IQR: interquartile range; NST: no special type.

[a] $p<0.001$ compared with occult

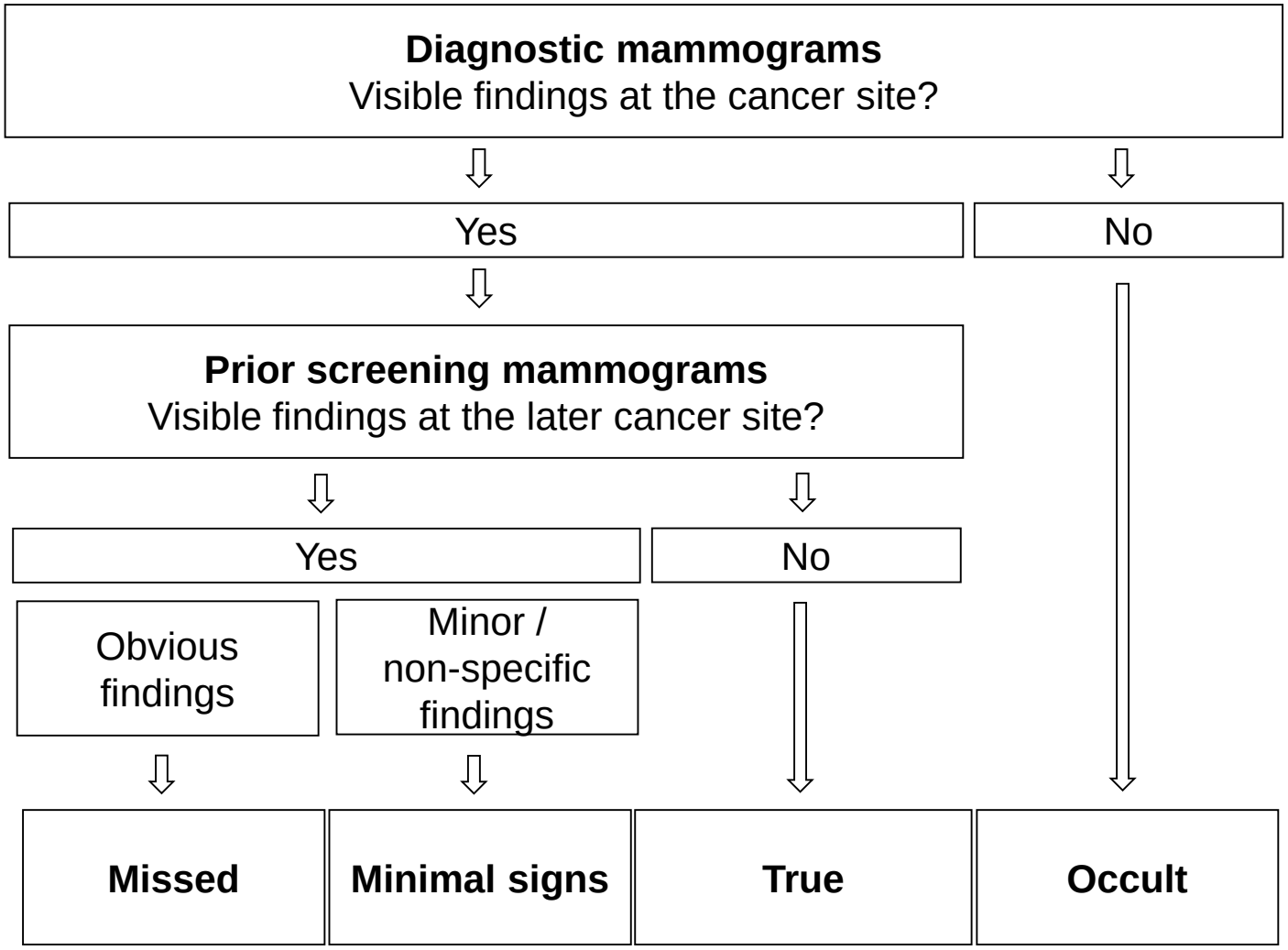
Supplementary 1. Number and percentages of interval cancer cases reviewed, by breast center.

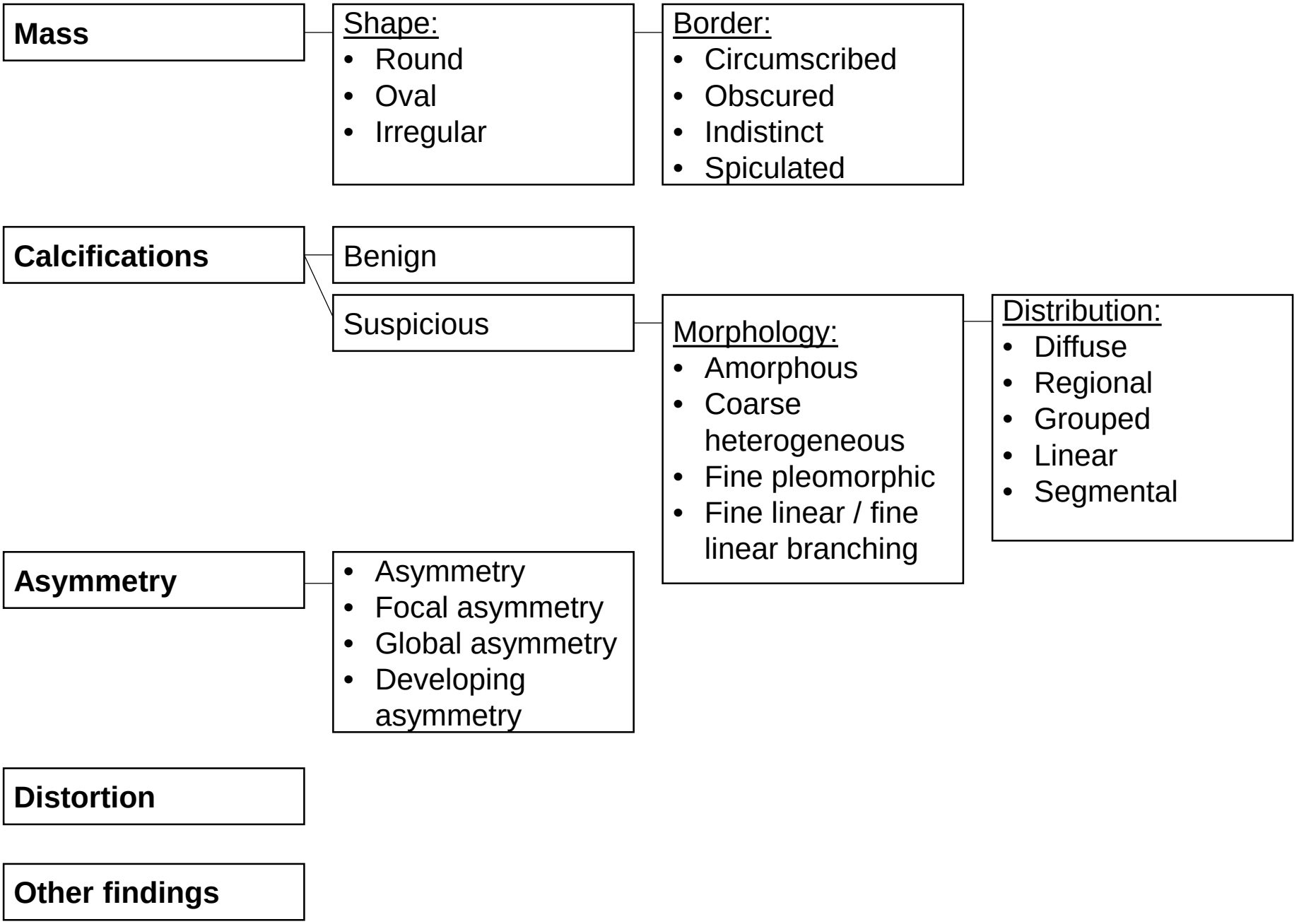
Breast Center	n (%)
Rogaland	75 (7.4)
Hordaland	72 (7.1)
Oslo	57 (5.6)
Telemark	66 (6.5)
Agder	69 (6.8)
Troms og Finnmark	75 (7.4)
Østfold	66 (6.5)
Nordland	73 (7.2)
Trøndelag	70 (6.9)
Oppland	62 (6.1)
Møre og Romsdal	60 (5.9)
Sogn og Fjordane	54 (5.3)
Vestfold	30 (3.0)
Hedmark	40 (4.0)
Akershus Øst	66 (6.5)
Vestre Viken	75 (7.4)
Total	1010 (100)

Supplementary 2. Review category, mammographic density, mammographic findings at diagnosis and prior screening, and histopathological characteristics for screen-detected breast cancer and interval breast cancer after a radiological review. SDC: Screen-detected breast cancer. IC: Interval breast cancer. BI-RADS: Breast Imaging Reporting and Data System. IQR: Interquartile range. Unless else is specified, data are number of patients with percentages in parentheses.

	SDC (n=1257)	IC (n=1010)
Review category		
True/occult	569 (46)	479 (48)
Minimal signs	392 (32)	285 (28)
Missed	266 (22)	246 (24)
Mammographic density		
BI-RADS a	180 (15)	76 (8)[a]
BI-RADS b	630 (51)	418 (41)[a]
BI-RADS c	353 (29)	420 (42)[a]
BI-RADS d	64 (5)	96 (9)[a]
Diagnostic mammograms		
Mass	777 (63)	507 (57)[a]
Calcifications	242 (20)	64 (7)[a]
Asymmetry	106 (9)	179 (20)[a]
Distortion	97 (8)	130 (15)[a]
Other findings	3 (0.2)	4 (1)[a]
Mammographic diameter, median (IQR) mm	14 (10, 21)	21 (15, 31)[a]
Prior screening mammograms		
Mass	134 (20)	94 (18)
Calcifications	142 (22)	73 (14)[a]
Asymmetry	302 (46)	274 (52)
Distortion	78 (12)	90 (17)
Other findings	2 (0.3)	
Mammographic diameter, median (IQR) mm	9 (6, 14)	14 (9, 20)[a]
Histopathological tumor type		
Ductal carcinoma in situ	180 (15)	49 (5)[a]
Invasive carcinoma of NST	882 (72)	754 (75)
Invasive lobular carcinoma	94 (8)	129 (13)[a]
Other invasive carcinoma	71 (6)	78 (8)
Tumor diameter invasive cancer, median (IQR) mm	13 (9, 19)	19 (13, 25)
Histological grade invasive cancer		
Grade 1	289 (28)	128 (14)[a]
Grade 2	520 (50)	437 (47)
Grade 3	222 (22)	364 (39)[a]
Lymph node negative invasive cancer	799 (80)	543 (59)[a]
Estrogen receptor positive invasive cancer	921 (91)	745 (79)[a]
Progesterone receptor positive invasive cancer	730 (72)	542 (58)[a]

[a] $p<0.001$ compared with screen-detected breast cancer.


Diagnostic mammograms
Visible findings at the cancer site?
Yes
No
Prior screening mammograms
Visible findings at the later cancer site?
Yes
No
Obvious findings
Minor / non-specific findings
Missed
Minimal signs
True
Occult


Mass
Shape:
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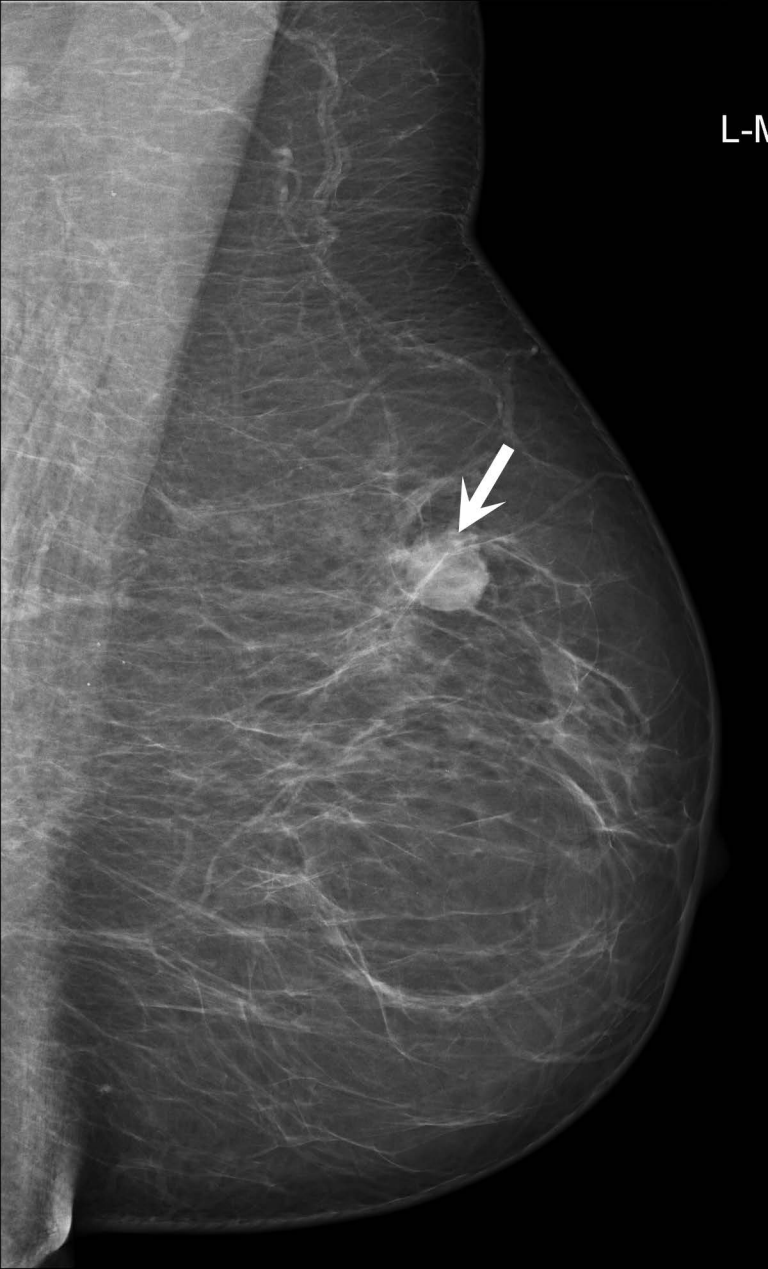
• Oval
• Irregular
Border:
• Circumscribed
• Obscured
• Indistinct
• Spiculated
Calcifications
Benign
Suspicious
Morphology:
• Amorphous
• Coarse heterogeneous
• Fine pleomorphic
• Fine linear / fine linear branching
Distribution:
• Diffuse
• Regional
• Grouped
• Linear
• Segmental
Asymmetry
• Asymmetry
• Focal asymmetry
• Global asymmetry
• Developing asymmetry
Distortion
Other findings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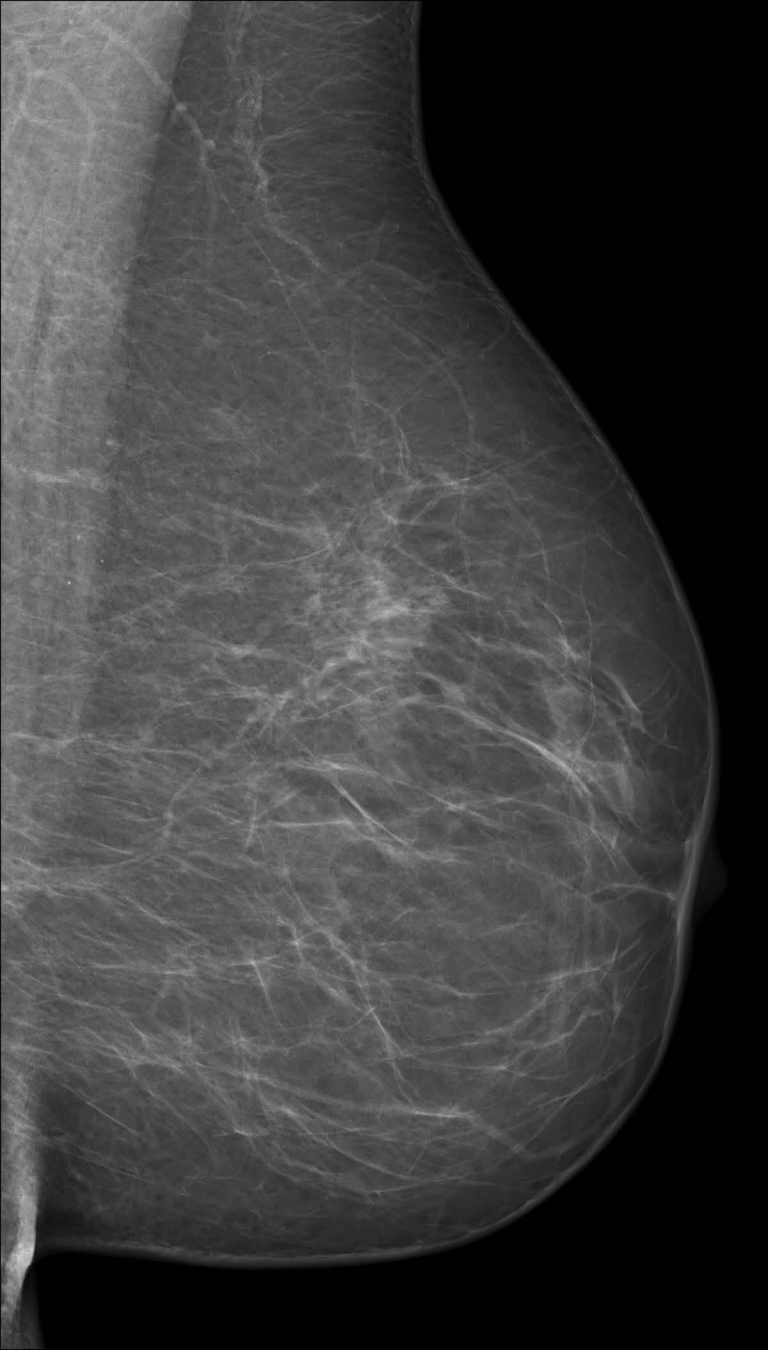
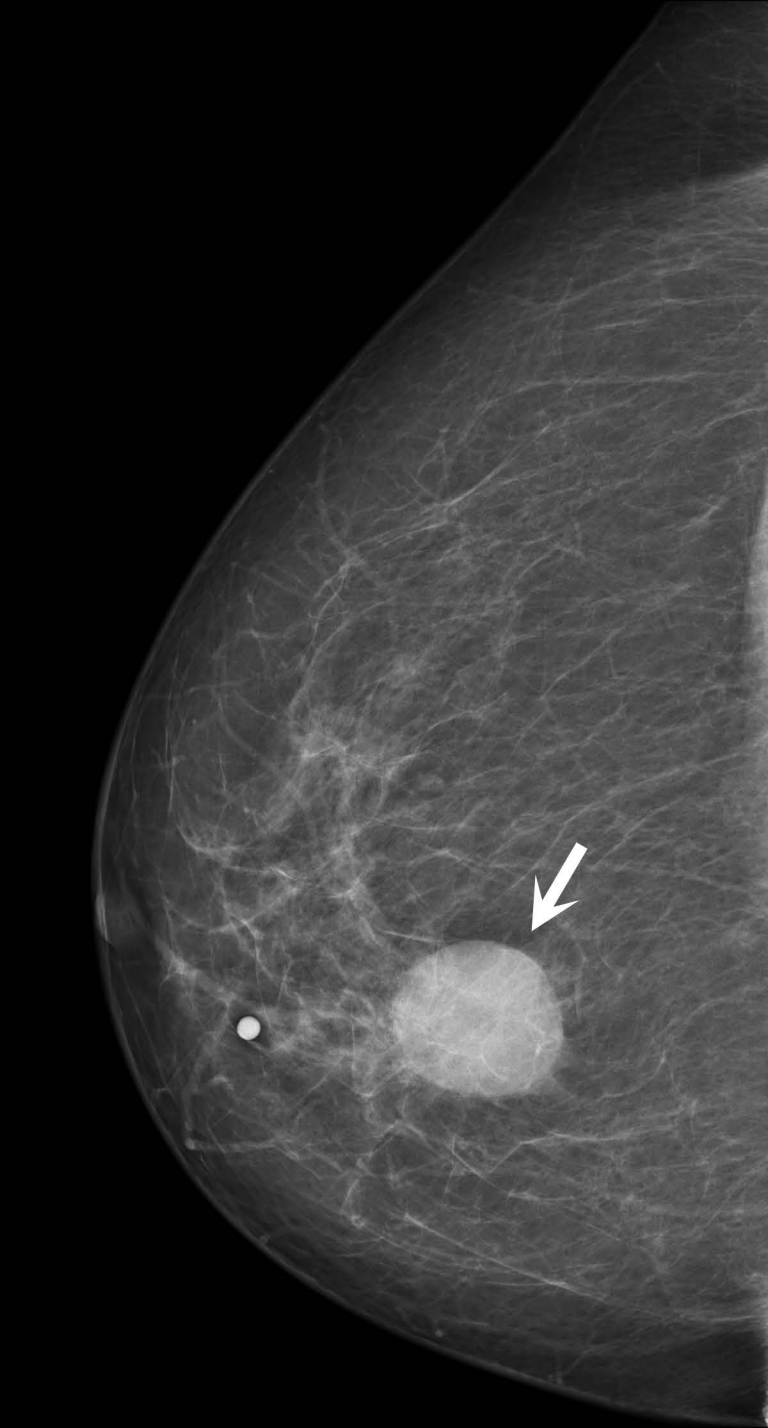
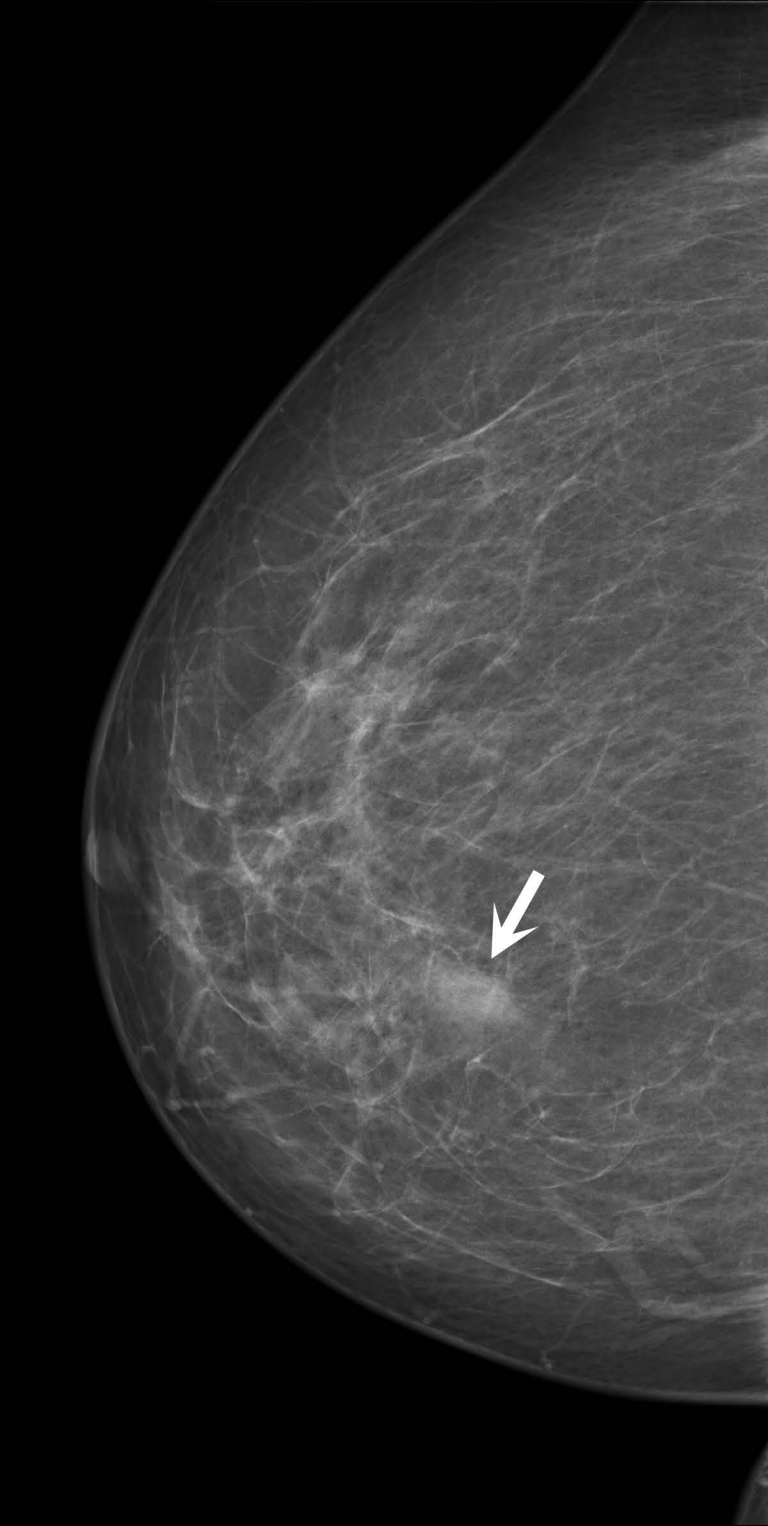
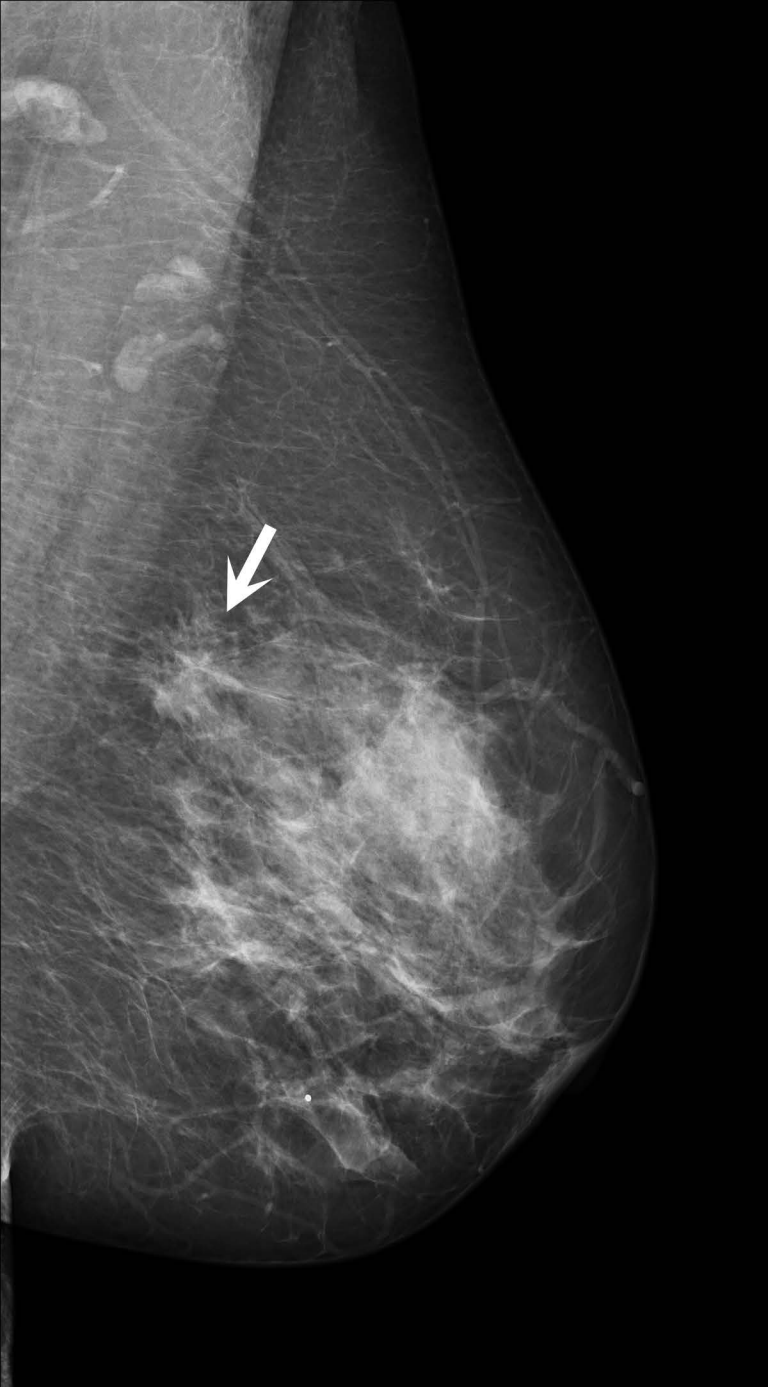
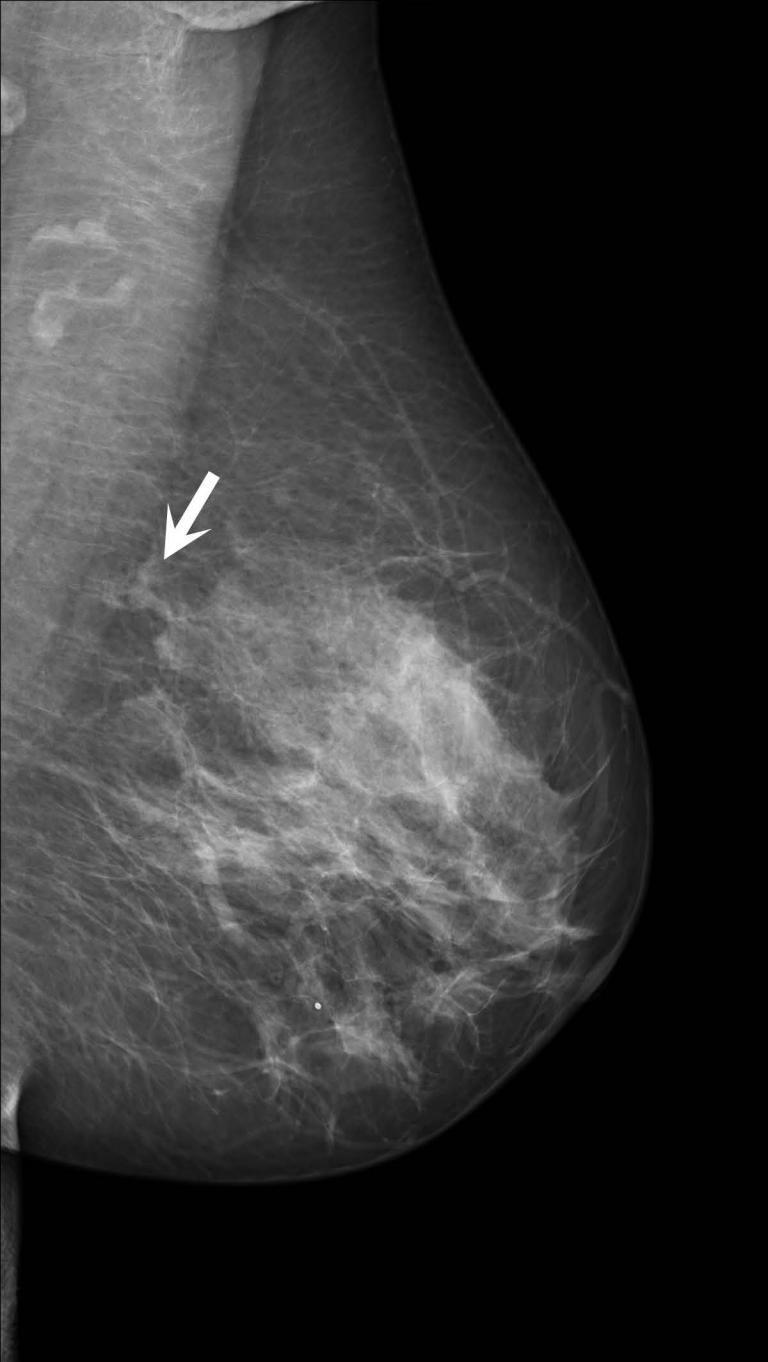
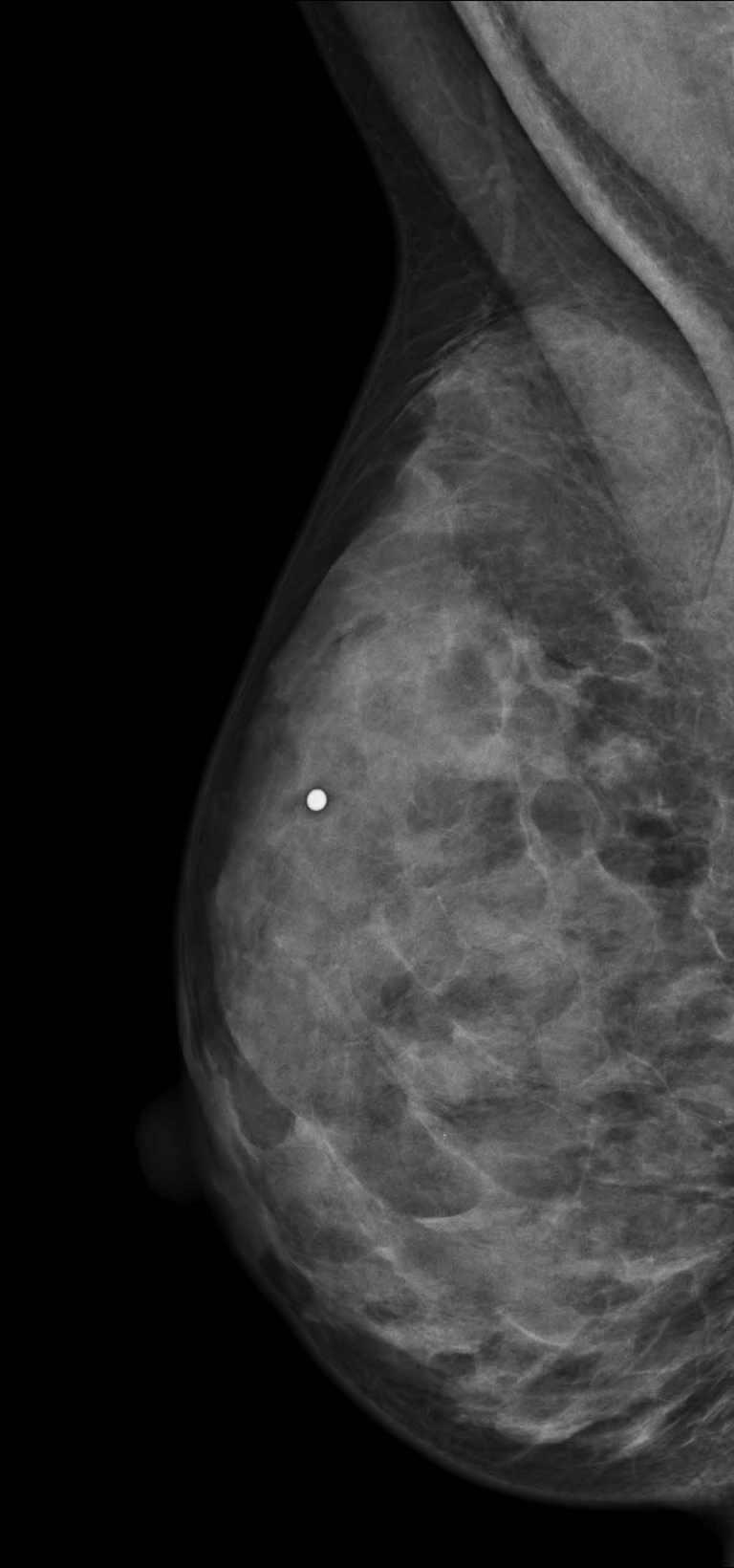


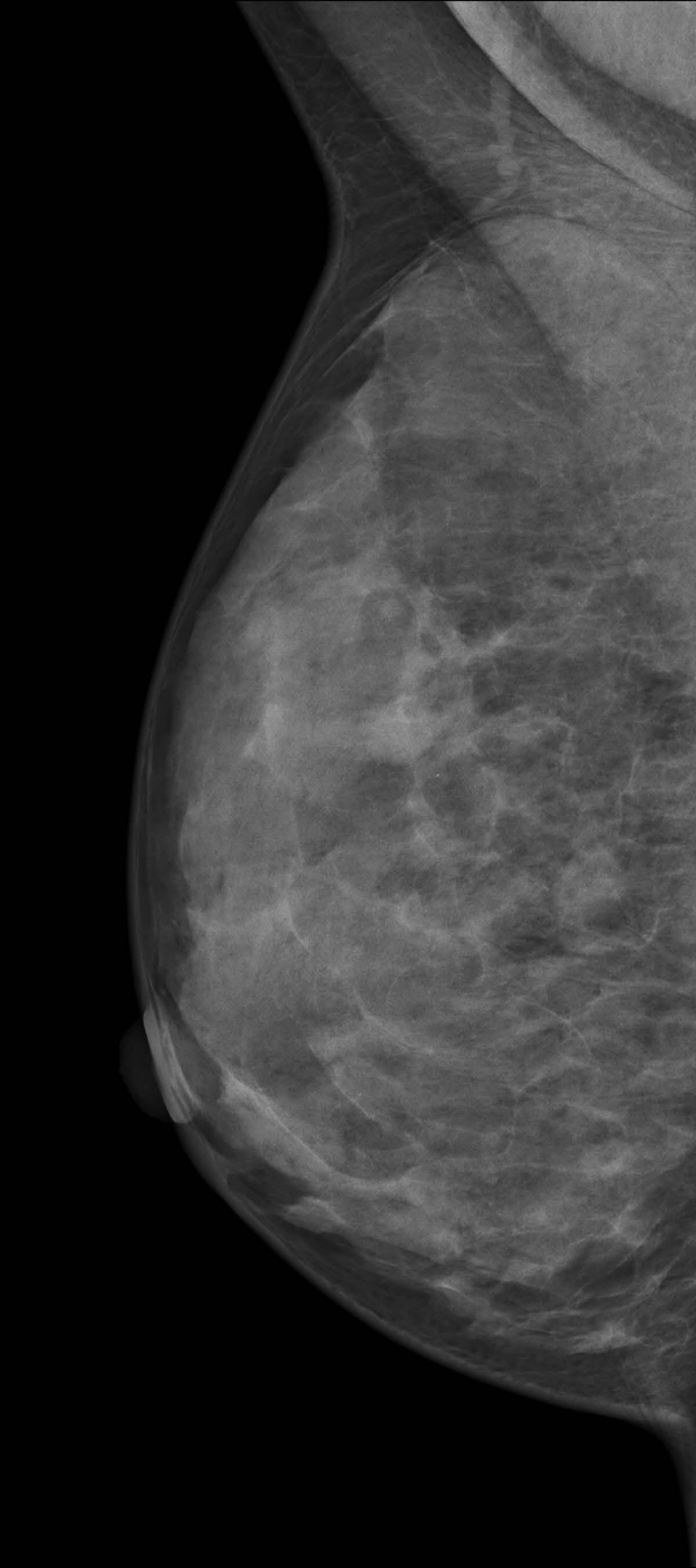


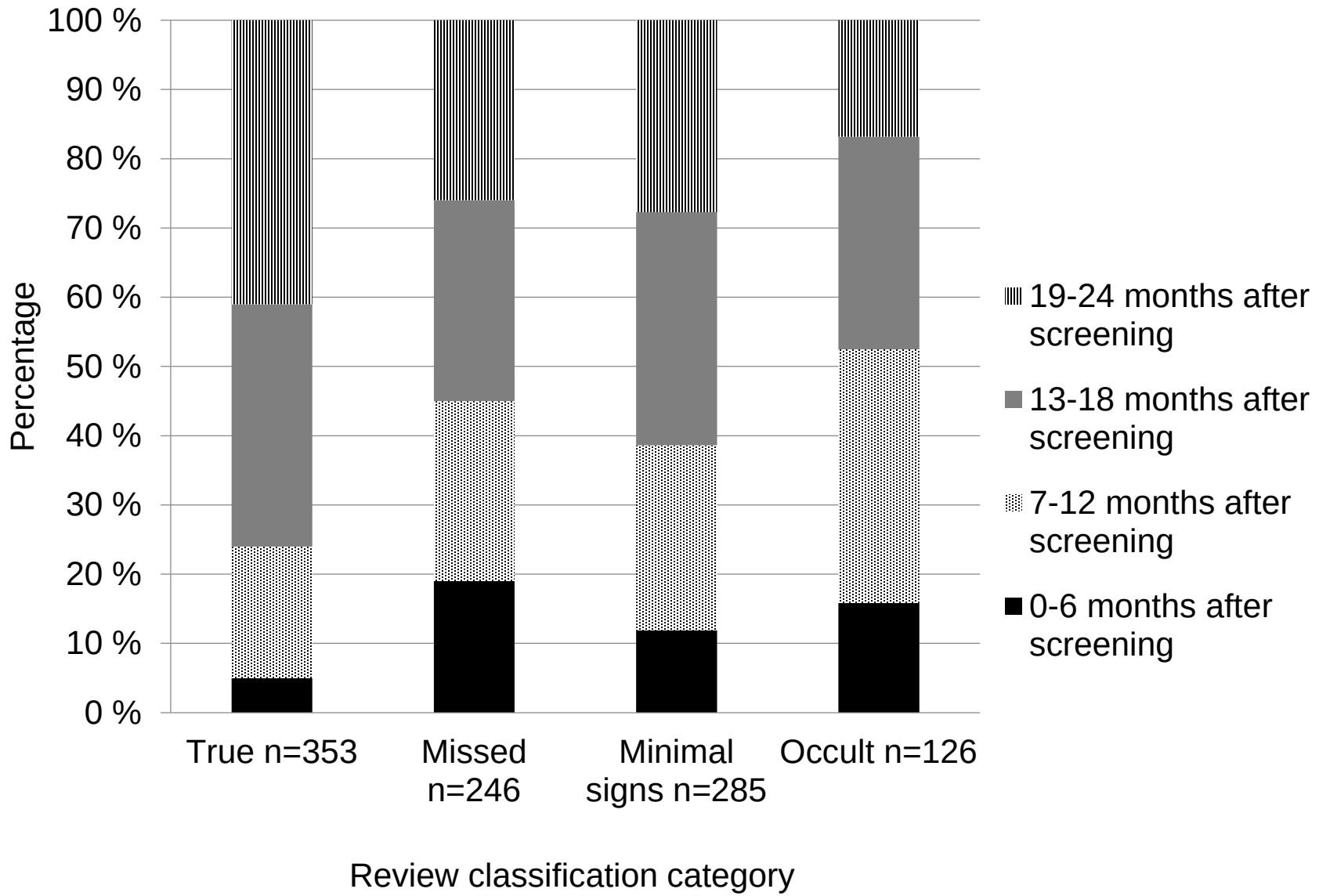


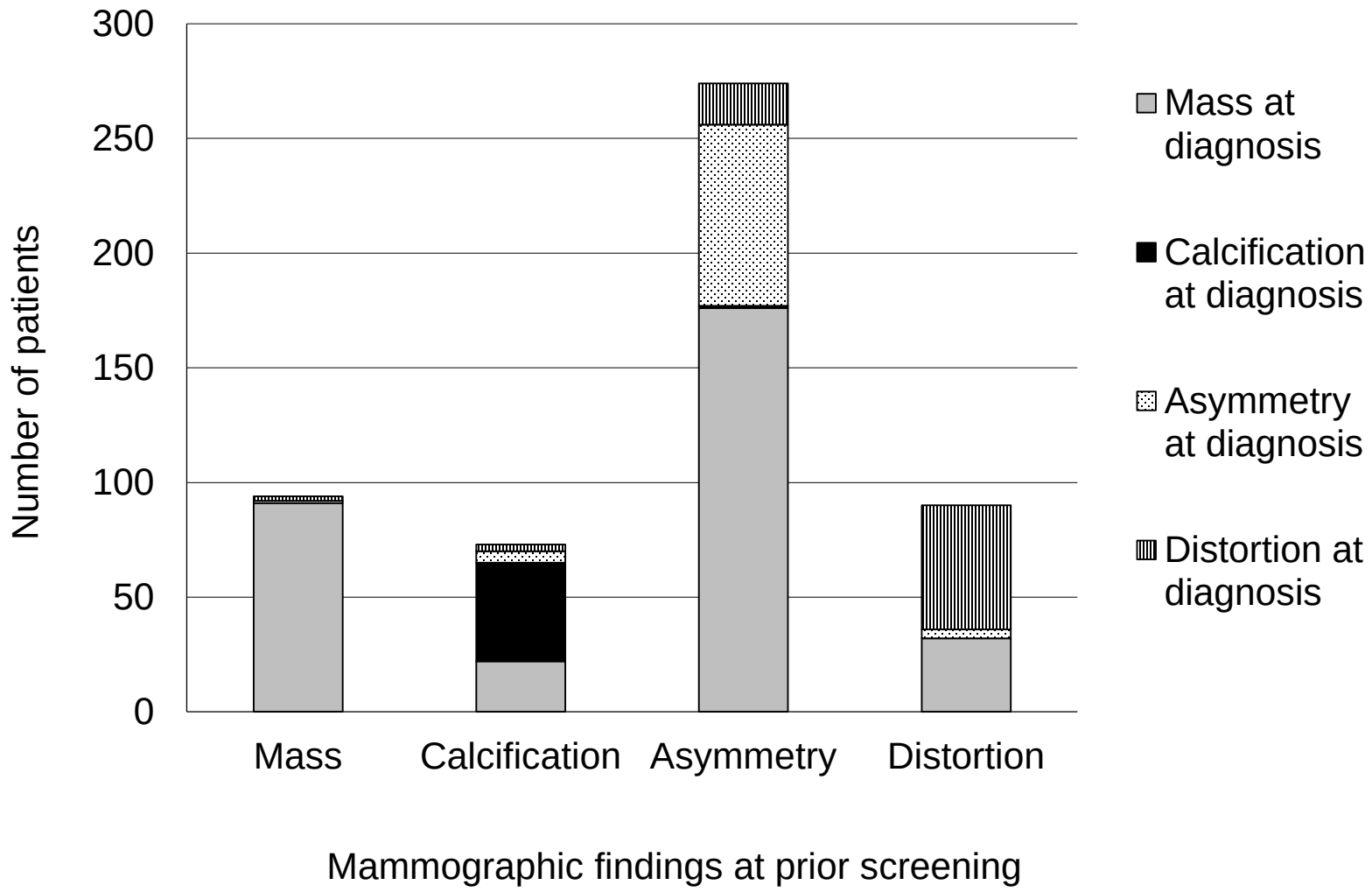









100 %
90 %
80 %
70 %
60 %
50 %
40 %
30 %
20 %
10 %
0 %
Percentage
True n=353
Missed n=246
Minimal signs n=285
Occult n=126
Review classification category
19-24 months after screening
13-18 months after screening
7-12 months after screening
0-6 months after screening


300
250
200
150
100
50
0
Number of patients
Mass
Calcification
Asymmetry
Distortion
Mammographic findings at prior screening
Mass at diagnosis
Calcification at diagnosis
Asymmetry at diagnosis
Distortion at diagnosis