Early performance measures following regular versus irregular screening attendance in the population-based screening program for breast cancer in Norway

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Abstract

Objective: Irregular attendance in breast cancer screening has been associated with higher breast cancer mortality compared to regular attendance. Early performance measures of a screening program following regular versus irregular screening attendance have been less studied. We aimed to investigate early performance measures following regular versus irregular screening attendance.

Methods: We used data about 3,302,396 screening examinations from the Cancer Registry of Norway. Examinations were classified as regular or irregular. Regular was defined as an examination 2 years +/- 6 months after the prior examination, and irregular examination >2 years and 6 months after prior examination. Performance measures included recall, biopsy, screen-detected and interval cancer, positive predictive values, and histopathological tumor characteristics.

Results: Recall rate was 2.4% (72,429/3,070,068) for regular and 3.5% (8217/232,328) for irregular examinations. The biopsy rate was 1.0% (29,197/3,070,068) for regular and 1.7% (3825/232,328) for irregular examinations, while the rate of screen-detected cancers 0.51% (15,664/3,070,068) versus 0.86% (2003/232,328), respectively. The adjusted odds ratio was 1.53 (95% CI: 1.49-1.56) for recall, 1.73 (95% CI: 1.68-1.80) for biopsy, and 1.68 (95% CI: 1.60-1.76) for screen-detected cancer after irregular examinations compared to regular examinations. The proportion of lymph node positive tumors was 20.1% (2553/12,719) for regular and 25.6% (426/1662) for irregular examinations.

Conclusion: Irregular attendance was linked to higher rates of recall, needle biopsies, and cancer detection. Cancers detected after irregular examinations had less favorable histopathological tumor characteristics compared to cancers detected after regular examinations. Women should be encouraged to attend screening when invited to avoid delays in diagnosis.

Introduction

Breast cancer is the most common cancer type and the leading cause of cancer death among women worldwide (1). Organized mammographic screening is shown to reduce mortality from the disease, and thus recommended by international health authorities (2, 3). As breast cancer mortality estimates require at least ten years of follow up after diagnosis, early performance measures are used to ensure that the objective of screening programs can be achieved (2). Early performance

measures may include rates of recall for further assessment, needle biopsy, screen-detected and interval cancer, positive predictive values, and histopathological tumor characteristics.

The overall attendance rate in organized screening programs for breast cancer is about 75% in Europe (4, 5). However, it is well known that some women skip one or more examinations for various reasons (6, 7). Irregular screening attendance has been shown to be associated with higher breast cancer mortality compared to regular attendance (8). A study from the Netherlands reported 17% increased risk of advanced breast cancer after irregular versus regular screening attendance (9), but further knowledge is needed to better understand the effect of the regularity of attendance on early performance measures (10, 11).

Irregular screening attendance is expected to increase the time between disease onset and detection compared to regular attendance, which in turn might lead to delayed diagnosis (5). As far as we are aware, no studies have investigated early performance measures following regular versus irregular screening attendance in a large population screening setting. In a previous study from BreastScreen Norway, it was reported that 52% of the women who had received 10 invitations attended all 10 screening sessions (12). We aimed to fill some of the knowledge gaps related to regular versus irregular attendance in mammographic screening by utilizing data collected as part of BreastScreen Norway in the period from 1996 to 2021. The aim of the study was to compare selected early performance measures for regular versus irregular attendees in BreastScreen Norway.

Methods

This study has a legal basis in accordance with Articles 6 (1) (e) and 9 (2) (j) of the General Data Protection Regulation (GDPR). The data was disclosed with legal basis in the Cancer Registry Regulations section 3-1 and the Personal Health Filing System Act section 19 a to 19 h. (13).

We received pseudonymized data about screening invitations, attendance, and outcome from the Cancer Registry of Norway. The Cancer Registry administers BreastScreen Norway, the nationwide program for breast cancer screening in Norway, which started in 1996. The program invites about 670,000 women to two-view digital mammography biennially (5). During the first 25 years, the average attendance rate was about 75% with a recall rate between 3% and 4%. The rate of screen-detected cancer was between 5 and 6 per 1000 screening examinations and the interval cancer rate 1.8 per 1000. Cancer reporting has been mandatory by law in Norway since 1953 (13). The overall completeness of solid cancers in the Cancer Registry's database was estimated to be 98.8% for the registration period 2001–2005, and 99.3% of the breast cancer cases were histologically proven (14).

Study population

During the period from January 1st, 1996, to December 31st, 2021, 5,938,066 screening invitations to BreastScreen Norway were sent from the Cancer Registry to 1,130,534 women. A total of 4,448,416 examinations were performed following these invitations, resulting in an overall attendance rate of 75%. We excluded information from first time (prevalent) screening examinations, examinations after diagnosis of breast cancer, examinations performed as a part of intervention studies (15-20) and screening examinations outside the definition of regular or irregular (Figure 1). Due to exclusion of prevalent examinations, the final study sample included examinations from 1998 to 2021.

Exposure variable and outcomes

Standard screening interval in BreastScreen Norway is 2 years +/-6 months. Screening intervals may be longer for different reasons. A reminder is sent to women who do not attend their originally scheduled appointment, 4-6 weeks after the missed appointment. The reminder is an open invitation encouraging the recipient to contact their breast center to schedule a new appointment. Women who attend after a reminder have an extended time from their last to the current examination. Furthermore, they normally receive a new invitation 2 years after their attendance date, not from the originally scheduled date. Rural areas in Norway use mobile screening units (buses). The bus might leave the area before non-attending women have scheduled their reminder appointment. The reminder appointment is performed later, when the bus returns, and the screening interval is therefore extended. However, screening intervals longer than 3 years and 6 months are in most cases due to women skipping one or more screening rounds.

Each screening examination was classified as regular or irregular (Figure 1). A regular examination was defined as an examination performed 2 years +/- 6 months (730 +/-182 days) after the prior screening examination. An irregular examination was defined as an examination performed >2 years and 6 months (>911 days) after the prior screening examination. Irregular examinations were further divided into three groups, with short, medium, and long time-intervals between examinations. Short irregular interval was from 2.5 to 3.5 years (912-1276 days), medium from 3.5 to 4.5 years (1277-1641 days), while long was >4.5 years (1642 days or more).

Recall rate was defined as the percentage of screening examinations resulting in recall for further assessment due to abnormal mammographic findings (21). Biopsy rate was defined as the number of needle biopsies at recall, divided by number of screening examinations.

Screen-detected cancer was defined as breast cancer diagnosed after further assessment within 6 months following the screening examination. Breast cancer included ductal carcinoma in situ and invasive cancer. Interval cancer was defined as breast cancer diagnosed within 24 months of a

negative screening result or within 6-24 months of a false positive screening examination. In the analysis of interval cancers, examinations performed during the period from 1998 to 2019 were included, to ensure 2 years' follow-up. Women diagnosed with symptomatic breast cancer outside of the screening program, more than 24 months after screening, were not included in this study. Positive predictive values were estimated as the percentage of screen-detected cancer among women recalled (PPV-1), and among all biopsies performed (PPV-3).

For invasive cancers, we presented histological type, tumor diameter, histological grade, lymph node status, and estrogen receptor and progesterone receptor status (22).

Statistical analysis

Study sample characteristics are presented using descriptive statistics. Means and standard deviations (SD) or median and interquartile range (IQR) are presented for continuous variables, while frequencies and proportions are presented for categorical variables.

Due to binary outcomes and dependency between observations, we used mixed effects logistic regression with a random intercept for each woman to analyze the odds of recall, biopsy, screen-detected cancer, and interval cancer. Results from unadjusted and adjusted analysis are presented. Odds ratios (OR) with 95% confidence intervals (CI) are presented for the adjusted models. The adjusted model included age at screening as a covariate. Tumor characteristic variables were tested with bivariate tests. We used STATA version 17.0 for Windows (StataCorp, TX, USA) for all statistical analyses.

Results

The final study sample included data from 3,302,396 screening examinations performed among 794,334 women (Figure 1). Of these, 3,070,068 were performed with regular intervals and 232,328 irregular intervals. Among the irregular screening examinations, 51,534 had a short, 131,483 had a medium, and 49,311 had a long interval.

Overall, the median number of days between dates of sending two consecutive ordinary invitations was 735 days (IQR: 41), while median number of days between two consecutive screening examinations was 735 days (IQR: 34). Following ordinary invitations, the median time between two consecutive screening examinations was 734 days (IQR: 29) while it was 843 days (IQR: 121) after a reminder.

For regular screening examinations, the median number of days between two screening examinations was 733 days (2 years and 3 days, IQR: 28 days) while it was 1464 days (4 years and 3 days, IQR: 200 days) for irregular examinations (Figure 1). For irregular examinations, the median

number of days for short interval was 957 (2 years and 7 months, IQR: 104), while it was 1464 (4 years and 3 days, IQR: 44) for medium interval and 2220 (6 years and 29 days, IQR: 746) for long interval. The distribution of months between screening examinations is displayed in Figure 2.

The recall rate was 2.4% (72,429/3,070,068) for regular examinations and 3.5% (8217/232,328) for irregular examinations (Table 1). The biopsy rate was 1.0% (29,197/3,070,068) for regular and 1.7% (3825/232,328) for irregular examinations, while the rate of screen-detected cancers was 0.51% (15,664/3,070,068) versus 0.86% (2003/232,328), respectively. There was no statistically significant difference in the interval cancer rate. Recall and biopsy rate as well as the rate of screen-detected cancer increased by length of the interval. There were increasing rates of recall, biopsy, and screen-detected cancers from short interval to medium and long interval irregular examinations (Table 2).

Using regular examinations as reference and adjusting for age at screening, the OR was 1.53 (95% CI: 1.49-1.56) for recall, 1.73 (95% CI: 1.68-1.80) for biopsy, and 1.68 (95% CI: 1.60-1.76) for screen-detected cancer after irregular examinations (Figure 3). The odds of recall, biopsy and screen-detected cancers were significantly higher for all three irregular examination groups compared to regular examinations (Table 3).

Median tumor diameter of invasive screen-detected cancer was 12 mm (IQR: 9) for regular examinations and 14 mm (IQR: 11) for irregular examinations (Table 4). The proportion of screen-detected tumors with a diameter of 21-50 mm was 15.9% (2033/12,751) for regular examinations and 22.1% (366/1655) for irregular examinations. The proportion of lymph node positive tumors was 20.1% (2553/12,719) for regular examinations and 25.6% (426/1662) for irregular examinations. No statistically significant differences were observed between the irregular short, medium and long interval groups with regard to the different tumor characteristic variables (Supplementary Table 1).

Discussion

Our study showed higher rates of recall, biopsy, and screen-detected cancer for irregular versus regular examinations. We observed larger diameter and a higher percentage of lymph node positive status for cancers detected after irregular compared to regular examinations, which indicates that these cases have less prognostically favorable histopathologic tumor characteristics. To our knowledge, this is the first study demonstrating major differences in rates of recall, biopsies, and screen-detected cancer by length of the screening interval.

An extended screening interval provides longer time for a tumor to develop. This might result in larger and more advanced tumors, which in turn require more extensive treatment at a higher cost compared to early detected cancer (23). Our findings are in line with the Dutch study, where irregular

attendance was associated with increased risk of advanced breast cancer (9), and might also support the study by Duffy et al., showing lower breast cancer mortality among regular versus irregular attendees (8).

Long versus short screening intervals increase the likelihood of tumor development. Comparison of prior mammograms is mandatory in the screen reading process. If the most recent priors are being used, older priors will be used among the irregular attendees compared to the regular attendees. This could possibly contribute to detection of more slow growing cancers in irregular attendees. Being aware of this, some centers favor the use of 4-year-old images (two screening rounds earlier) for comparison as standard for all women. The reduced proportion, not statistically significant, of node positive tumors at longer intervals (Supplementary Table 1) might be a length bias phenomenon, and one would tend to miss the fast-disseminating tumors but capture a lot of the slow ones.

Reasons for irregular attendance in mammographic screening might be multifactorial and include lack of awareness and information related to the benefits of regular screening. Studies have shown that false positive screening results can cause transient and long-term anxiety and depression, and this might influence women's decision to participate in consecutive screening rounds (24-28). Some women might consider themselves to have low risk of breast cancer and skip screening, while other women might experience symptoms or anxiety of breast cancer, and therefore decide to attend screening after a longer period of non-attendance. At the same time, less health-conscious women or women with lower health literacy could be expected to skip screening more often. Also, systematic reviews have shown that higher socioeconomic status, income, being born in the country of residence (non-immigrant), and home ownership (versus renting) are factors associated with higher rates of mammographic screening attendance (29). Finally, opportunistic screening at private clinics could have slightly diluted the differences in our study population. Information about opportunistic screening is not available in Norway but assumed to be limited among women in the target group of BreastScreen Norway, particularly in rural areas (30).

Major strengths of this study are the large study sample and the high-quality individual register data. This made us able to apply a rigorous definition of screening regularity with the time interval between screening examinations. However, a limitation is lack of information about the reason for not attending BreastScreen Norway regularly. Neither do we know what motivated women to attend screening after dropping out for one or more screening rounds. Factors associated with attendance and attendance patterns are diverse and interrelated (6, 7, 31). Finally, the study did not analyze the

cumulative risk of the different events after irregular attendance, which is an aspect that should be investigated in future studies.

In conclusion, the present study found that irregular attendance in BreastScreen Norway was associated with higher rates of recall, needle biopsies, and cancer detection. Tumors detected among women attending irregularly were also found to be slightly larger and more frequently lymph node positive. Measures for increasing regular attendance might be an effective and simple augmentation for early detection. Given these findings, women should be made aware of the benefits of regular attendance, and the increased risks associated with irregular screening attendance. Furthermore, screening programs should make it easy to rebook appointments to maintain regular screening intervals.

Data sharing statement

Research data used in the analyses can be made available on request to https://helsedata.no/, given legal basis in Articles 6 and 9 of the GDPR and that the processing is in accordance with Article 5 of the GDPR.

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Declaration of conflicting interests

The authors have no conflicts of interest to declare.

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Table 1. Early performance measures after regular and irregular screening examinations[Ω] in BreastScreen Norway, 1998-2021.

	Total		**Regular examinations**		**Irregular examinations**		
	n=3,302,396		n=3,070,068		n=232,328		
	n	%	n	%	n	%	*p-value**
Recall	80,646	2.4	72,429	2.4	8217	3.5	<0.001
Needle biopsy	33,022	1.0	29,197	1.0	3825	1.7	<0.001
Screen-detected cancer	17,667	0.53	15,664	0.51	2003	0.86	<0.001
PPV-1[♦]	17,667/80,646	21.9	15,664/72,429	21.6	2003/8217	24.4	<0.001
PPV-3[α]	17,667/33,022	53.5	15,664/29,197	53.7	2003/3825	52.4	0.101
Interval cancer[ᵗ]	5071	0.17	4734	0.17	337	0.18	0.289

[Ω] Regular; 2 years +/- 6 months (730 +/-182 days) after the prior screening examination; irregular: >2 years and 6 months (>911 days) after the prior screening examination.

*Overall p-value for irregular- versus regular examinations are calculated from unadjusted mixed effects logistic regression.

[♦] Positive predictive value of recall.

[α]Positive predictive value of needle biopsy.

[ᵗ] Calculations based on 2,952,892 and 185,234 screening examinations performed before 1998-2019 to ensure 2 years' follow up.

Table 2. Early performance measures by length of the irregular examinations (short, medium and long)[β] in BreastScreen Norway, 1998-2021

	Short irregular		**Medium irregular**		**Long irregular**		
	n=51,534		n=131,483		n=49,311		
	n	%	n	%	n	%	*p-value**
Recall	1597	3.1	4360	3.3	2260	4.6	<0.001
Needle biopsy	726	1.4	1998	1.5	1101	2.2	<0.001
Screen-detected cancer	366	0.71	1070	0.81	567	1.15	<0.001
PPV- 1[♦]	366/1597	22.9	1070/4360	24.5	567/2260	25.1	0.283
PPV -3[α]	366/726	50.4	1070/1998	53.6	567/1101	51.5	0.277
Interval cancer[ᵗ]	60	0.22	200	0.17	77	0.18	0.241

[β] Intervals of irregular screening attendance: Short: from 2.5 to 3.5 years, 912-1276 days; Medium: from 3.5 to 4.5 years, 1277-1641 days; and Long: >4.5 years, 1642 days or more

*Overall p-value for short irregular, medium irregular and long irregular examinations are calculated from unadjusted mixed effects logistic regression.

[♦] Positive predictive value of recall.

[α]Positive predictive value of needle biopsy.

[ᵗ] Calculations based on 2,952,892 and 185,234 screening examinations performed before 1998-2019 to ensure 2 years' follow up.

Table 3. Odds ratio (OR)* and 95% confidence intervals (CI) for recall, needle biopsy, screen-detected cancers and interval cancers across three intervals of irregular screening attendance: short, medium and long intervals[#], in BreastScreen Norway, 1998-2021.

	Recall		Needle biopsy		Screen-detected cancer		Interval cancer	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Regular examinations	1	Ref.	1	Ref.	1	Ref.	1	Ref.
Short irregular examinations	1.32	1.26-1.39	1.50	1.39-1.62	1.41	1.27-1.57	1.29	1.00 - 1.67
Medium irregular examinations	1.43	1.38-1.48	1.60	1.53-1.68	1.59	1.49-1.69	1.00	0.87 - 1.15
Long irregular examinations	2.02	1.93-2.11	2.34	2.20-2.50	2.18	2.00-2.37	1.08	0.86 - 1.35

*Adjusted for age at screening.

[#] Intervals of irregular screening attendance: Short: from 2.5 to 3.5 years, 912-1276 days; Medium: from 3.5 to 4.5 years, 1277-1641 days; Long: >4.5 years, 1642 days or more.

Table 4. Histopathologic tumor characteristics of screen-detected cancers among regular and irregular screening examinations [Ω] in BreastScreen Norway, 1998-2021.

	Total		**Regular examinations**		**Irregular examinations**		
Age at diagnosis, mean (SD)	68.8 (5.7)		68.8 (5.7)		69.3 (5.4)		
All tumors	n=17,667		n=15,664		n=2003		
	n	%	n	%	n	%	*p-value**
Histological type							0.368
Ductal carcinoma in situ	2952	16.7	2644	16.9	308	15.4	
Invasive ductal carcinoma NST	12,509	70.8	11,064	70.6	1445	72.1	
Invasive lobular carcinoma	1535	8.7	1364	8.7	171	8.5	
Other Invasive	671	3.8	592	3.8	79	3.9	
Invasive tumors	n=14,715		n=13,020		n=1695		
Tumor diameter mm, median (IQR)	12 (9)		12 (10)		14 (11)		<0.001
≤10 mm	5446	37.8	4912	38.5	534	32.3	
11-20 mm	6423	44.6	5688	44.6	735	44.4	
21-50 mm	2399	16.7	2033	15.9	366	22.1	
>50 mm	138	1.0	118	0.9	20	1.2	
Data not available	309		269		40		
Histologic Grade							0.280
1	4293	29.6	3816	29.7	477	28.6	
2	7140	49.2	6287	49.0	853	51.1	
3	3067	21.2	2727	21.3	340	20.4	
Data not available	215		190		25		
Lymph node status							<0.001
Positive	2979	20.7	2553	20.1	426	25.6	
Data not available	334		301		33		
ER status							0.392
Positive	12,881	89.7	11,374	89.6	1507	90.3	
Data not available	354		328		26		
PR status							0.018
Positive	10,143	71.1	8925	70.8	1218	73.6	
Data not available	445		406		39		

[Ω] Regular: 2 years +/- 6 months (730 +/-182 days) after prior screening examination; Irregular: >2 years and 6 months (>911 days) after prior screening examination.

* Overall p-value for examination type calculated from bivariate tests.

SD: standard deviation, NST: no special type, IQR: interquartile range, ER: estrogen receptor, PR: progesterone receptor.

Figure legends

Figure 1. Flowchart of the study sample. Time between screening exams is presented with median and interquartile range (IQR). * Intervention studies performed in BreastScreen Norway (15-20).

Figure 2. Distribution of months between screening attendances among women attending BreastScreen Norway, 1998-2021.

Figure 3. Odds ratio (OR) of recall, biopsy, screen-detected cancers, and interval cancers after irregular screening examinations with regular examinations as reference, adjusted for age at screening, in BreastScreen Norway, 1998-2021.

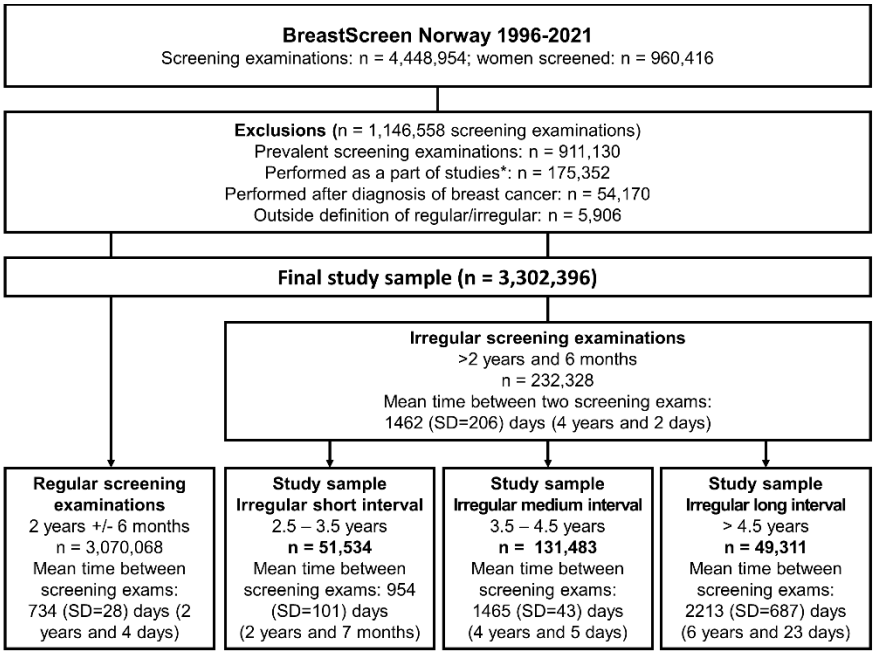
BreastScreen Norway 1996-2021
Screening examinations: n = 4,448,954; women screened: n = 960,416
Exclusions (n = 1,146,558 screening examinations)
Prevalent screening examinations: n = 911,130
Performed as a part of studies*: n = 175,352
Performed after diagnosis of breast cancer: n = 54,170
Outside definition of regular/irregular: n = 5,906
Final study sample (n = 3,302,396)
Irregular screening examinations
>2 years and 6 months
n = 232,328
Mean time between two screening exams:
1462 (SD=206) days (4 years and 2 days)
Regular screening examinations
2 years +/- 6 months
n = 3,070,068
Mean time between screening exams:
734 (SD=28) days (2 years and 4 days)
Study sample
Irregular short interval
2.5 – 3.5 years
n = 51,534
Mean time between screening exams: 954 (SD=101) days
(2 years and 7 months)
Study sample
Irregular medium interval
3.5 – 4.5 years
n = 131,483
Mean time between screening exams:
1465 (SD=43) days
(4 years and 5 days)
Study sample
Irregular long interval
> 4.5 years
n = 49,311
Mean time between screening exams:
2213 (SD=687) days
(6 years and 23 days)

Figure 1

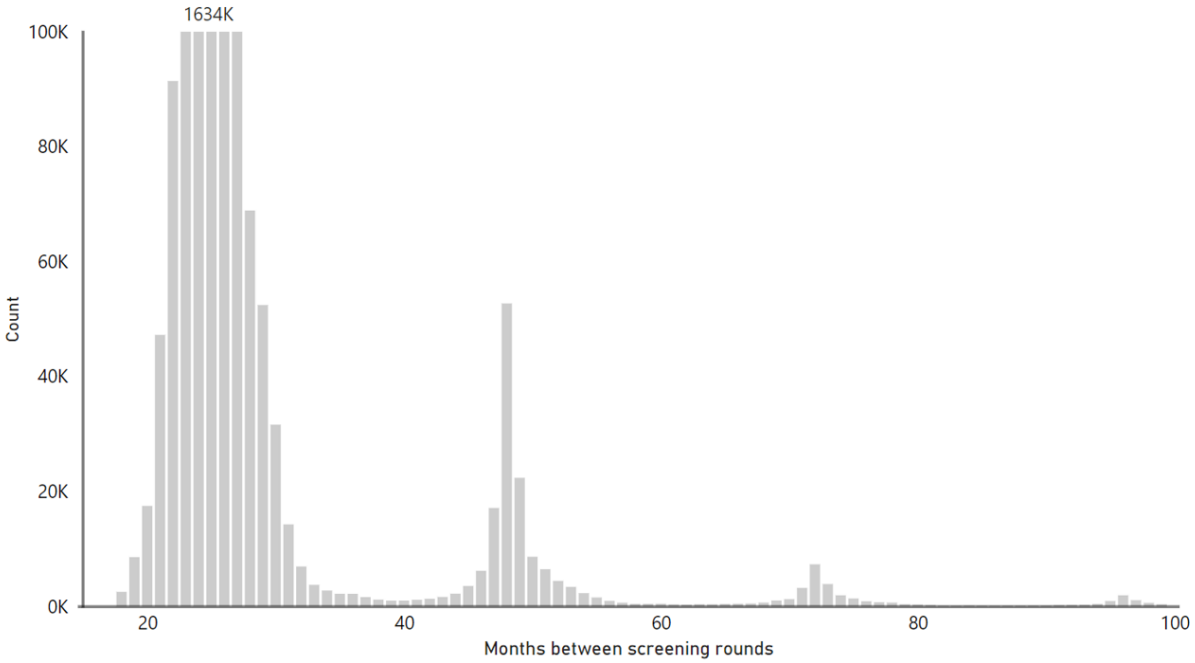
1634K
100K
80K
60K
40K
20K
0K
Count
20
40
60
80
100
Months between screening rounds

Figure 2

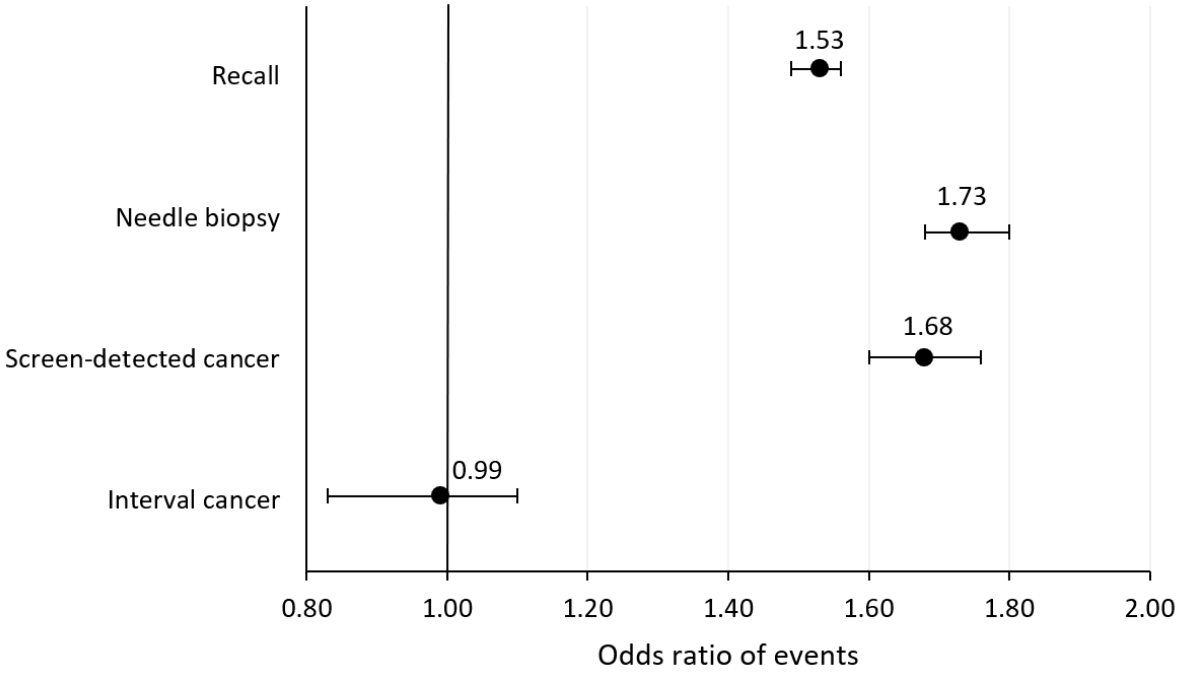
Recall
Needle biopsy
Screen-detected cancer
Interval cancer
1.53
1.73
1.68
0.99
0.80
1.00
1.20
1.40
1.60
1.80
2.00
Odds ratio of events

Figure 3

Supplementary table 1: Histopathological tumor characteristics for cancers detected after irregular screening examinations with short, medium and long intervals in BreastScreen Norway 1996-2021.

	Irregular, short intervals		**Irregular, medium intervals**		**Irregular, long intervals**		
Age at diagnosis, mean (SD)	68.4 (5.9)		69.1 (5.2)		70.1 (5.4)		
All tumors	n=387		n=1087		n=580		
	n	%	n	%	n	%	*p**
Histological type							0.681
Ductal carcinoma in situ	66	17.1	181	16.7	85	14.7	
Invasive ductal carcinoma NST	269	69.5	774	71.2	429	74.0	
Invasive lobular carcinoma	37	9.6	92	8.5	43	7.4	
Other Invasive	15	3.9	40	3.7	23	4.0	
Invasive tumors	n=321		n=906		n=495		
Tumor diameter mm, median (IQR)	15 (13)		14 (12)		15 (11)		<0.001
≤10mm	101	32.2	294	33.2	148	30.8	
11-20mm	127	40.5	405	45.7	218	45.3	
21-50mm	80	25.5	178	20.1	111	23.1	
>50mm	<10	1.9	10	1.1	<10	0.8	
Data not available	<10		19		14		
Histologic Grade							0.079
1	85	26.9	272	30.4	129	26.7	
2	165	52.2	461	51.5	238	49.2	
3	66	20.9	162	18.1	117	24.2	
Data not available	<10		11		11		
Lymph node status							
Positive	101	32.1	224	25.1	124	25.7	<0.001
Data not available	<10		15		12		
ER status							
Positive	283	89.6	809	90.8	439	89.8	0.773
Data not available	<10		15		<10		
PR status							0.085
Positive	238	75.8	651	73.6	348	71.9	
Data not available	<10		21		11		

* Overall p-value for examination type calculated from bivariate tests.
SD: Standard deviation, NST: No special type, IQR: Interquartile range, ER: estrogen receptor, PR: Progesterone receptor