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Prolonged screening interval due to the COVID-19 pandemic and its association with tumor characteristics and treatment; a register-based study from BreastScreen Norway

Anouk H. Eijkelboom [a,b,*], Marthe Larsen [c], Sabine Siesling [a,b], Jan F. Nygård [d], Solveig Hofvind [c,e], Linda de Munck [b]

[a] Department of Health Technology and Services Research, University of Twente, Drienerlolaan 5, 7522 NB, Enschede, the Netherlands
[b] Department of Research and Development, Netherlands Comprehensive Cancer Organisation (IKNL), Godebaldkwartier 419, 3511 DT, Utrecht, the Netherlands
[c] Section for Breast Cancer Screening, Cancer Registry of Norway, P.O. Box 5313, 0304, Oslo, Norway
[d] Department of Register Informatics, Cancer Registry Norway, P.O. Box 5313, 0304 Oslo, Norway
[e] Department of Health and Care Sciences, UiT The Arctic University of Norway, P.O. 6050, 9037, Tromsø, Norway

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ABSTRACT

Objective: During the COVID-19 pandemic Norway had to suspend its national breast cancer screening program. We aimed to investigate the effect of the pandemic-induced suspension on the screening interval, and its subsequent association with the tumor characteristics and treatment of screen-detected (SDC) and interval breast cancer (IC).

Methods: Information about women aged 50–69, participating in BreastScreen Norway, and diagnosed with a SDC ($N = 3799$) or IC ($N = 1806$) between 2018 and 2021 was extracted from the Cancer Registry of Norway. Logistic regression was used to investigate the association between COVID-19 induced prolonged screening intervals and tumor characteristics and treatment.

Results: Women with a SDC and their last screening exam before the pandemic had a median screening interval of 24.0 months (interquartile range: 23.8–24.5), compared to 27.0 months (interquartile range: 25.8–28.5) for those with their last screening during the pandemic. The tumor characteristics and treatment of women with a SDC, last screening during the pandemic, and a screening interval of 29–31 months, did not differ from those of women with a SDC, last screening before the pandemic, and a screening interval of 23–25 months. ICs detected 24–31 months after screening, were more likely to be histological grade 3 compared to ICs detected 0–23 months after screening (odds ratio: 1.40, 95% confidence interval: 1.06–1.84).

Conclusions: Pandemic-induced prolonged screening intervals were not associated with the tumor characteristics and treatment of SDCs, but did increase the risk of a histopathological grade 3 IC. This study provides insights into the possible effects of extending the screening interval.

1. Introduction

Mammographic screening aims to detect asymptomatic breast cancer at an earlier and more curable stage than symptomatic breast cancer. The implementation of regular mammographic screening has resulted in a reduction of breast-cancer specific mortality (Paci, 2012; Zielonke et al., 2020). Several national and international health organizations are thus recommending regular mammographic screening for women aged 50–69 years, but also for younger and older age groups (Cancer Australia, 2015; Cardoso et al., 2019; Oeffinger et al., 2015; Qaseem et al., 2019; Schünemann et al., 2020; World Health Organization, 2014).

The majority of guidelines recommend biennial screening mammography for women aged 50–69 years (European Commission Initiative on Breast Cancer. Recommendations from the European Breast Guidlines, 2022; Ren et al., 2022). However, little is known about the association between the time between two subsequent screening examinations and breast cancer outcomes. A systematic review, published

* Corresponding author at: Department of Health Technology and Services Research, University of Twente, Drienerlolaan 5, 7522, NB, Enschede, the Netherlands.
E-mail addresses: a.h.eijkelboom@utwente.nl (A.H. Eijkelboom), maln@kreftregisteret.no (M. Larsen), s.siesling@iknl.nl (S. Siesling), jfn@kreftregisteret.no (J.F. Nygård), sshh@kreftregisteret.no (S. Hofvind), l.demunck@iknl.nl (L. de Munck).

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in 2022, made an overview of studies comparing the effect of annual, biennial, and triennial screening intervals (Canelo-Aybar et al., 2022). The five observational studies included in this review showed no difference in mortality or risk of a stage IIB-IV tumor between women with different screening intervals (Coldman et al., 2008; Duffy and Blarney, 2008; Miglioretti et al., 2015; O'Meara et al., 2013; Parvinen et al., 2011). In contrast, five modeling studies included in the review showed lower mortality for women with a shorter screening interval (Mandelblatt et al., 2016; Miglioretti et al., 2016; Tsunematsu and Kakehashi, 2015; Vilaprinyo et al., 2014; Yaffe et al., 2015).

At the start of the COVID-19 pandemic, many countries suspended their national screening program to limit the spread of the virus and to increase the capacity needed to treat COVID-19 patients (Perin et al., 2021). As a result the screening interval increased. The few studies which have reported on the long-term effects of the COVID-19 pandemic on tumor stage showed no evidence of a stage-shift in Norway (Eijkelboom et al., unpublished results), Wales (Greene et al., 2022), and Quebec (Ramanakumar et al., 2023), and a temporary increase in the incidence of stage IV tumors in Dutch women aged 50–69 years (Eijkelboom et al., unpublished results). All mentioned countries/regions suspended their national screening program during the pandemic. However, no distinction was made in the mentioned studies between women with normal versus extended screening intervals. Hence, the individual association between prolonged screening intervals and tumor characteristics was not clear. In addition, none of the mentioned studies included information about treatment. It could be hypothesized that prolonged screening intervals would result in larger tumors, which need more invasive treatment.

In Norway, biennial mammography screening has been offered to women aged 50–69 since 1996. The program was suspended on March 12th, 2020 (Bjørnson et al., 2022). Screening resumed gradually on May 2020. The suspension of the screening program resulted in a "natural experiment" which gave us the opportunity to investigate the impact of the COVID-19 pandemic on the screening interval of women diagnosed with breast cancer. Subsequently, we explored the association between pandemic-induced prolonged screening intervals and tumor characteristics and breast cancer treatment.

2. Methods

This retrospective registry study was based on data from BreastScreen Norway, the national breast cancer screening program offering all women aged 50–69 two-view mammographic screening, biennially (Bjørnson et al., 2022). The program started in 1996 and became nationwide in 2005. The Cancer Registry of Norway administers the program and is responsible for, among others, data collection, monitoring and quality assurance of the program. BreastScreen Norway targets about 650,000 women in 2023 and the annual participation rate is 75%. Women invited for a screening mammogram receive an invitation with a specific time and place for the screening examination. All screening mammograms are independently read by two breast radiologists and all mammograms with suspicious findings indicated by at least one radiologist are discussed in a consensus meeting where it is decided whether the women should be recalled. Recalls, and work-up including supplemental imaging and biopsies, take place at dedicated breast units, mainly at University Hospitals. All screening activity in BreastScreen Norway, including cancer detection, is reported to the Cancer Registry of Norway. Reporting of cancer cases is mandated by a law, set in 1952, and the Cancer Registry of Norway is considered almost complete for solid, malignant tumors (Helse- og omsorgsdepartementet, 2001). This study has legal basis in accordance with Articles 6 (1) (e) and 9 (2) (j) of the General Data Protection Regulation (General Data Protection Regulation, 2016). The study was approved by the Regional Committee for Medical and Health Research Ethics (REC #478240), and the data were disclosed with legal basis in the Cancer Registry Regulations section 3–1 and the Personal Health Data Filing System Act section 19 a to 19 h) (Helse- og omsorgsdepartementet, 2001, 2021).

2.1. Study population

Information about women invited to BreastScreen Norway and diagnosed with breast cancer between 2018 and 2021 was extracted from the Cancer Registry of Norway if 1) the last screening examination in BreastScreen Norway was registered ≤31 months before diagnosis, 2) the woman had attended at least one screening examination in BreastScreen Norway which did not result in breast cancer diagnosis. We chose for the study period 2018–2021 as this allowed us to compare screening intervals, tumor characteristics and treatment of women diagnosed before and during the COVID-19 pandemic. Women with non-COVID-19-induced prolonged screening intervals were excluded. This meant that women with a screen-detected breast cancer (SDC) were excluded if they had not responded to the screening invitation prior to the screening invitation leading to breast cancer diagnosis (i.e., they skipped the screening round immediately prior to the screening round leading to tumor diagnosis). Additionally, women were excluded if their SDC was diagnosed after responding to a reminder invitation, as the tumors of those women are known to have unfavorable tumor characteristics compared to those detected after a regular invitation (Thy et al., 2022). For women with a synchronous tumor (diagnosed within 91 days of each other), the tumor with the highest clinical TNM-stage was included.

2.2. Definitions

Breast cancer was defined as histologically confirmed ductal carcinoma in situ (DCIS) or invasive cancer. A SDC was defined as breast cancer diagnosed within six months after a positive screening examination. Interval breast cancer (IC) was defined as breast cancer diagnosed after a negative screening examination or more than six months after a false-positive screening examination and within 31 months after screening (Hofvind et al., 2018). Usually ICs are defined as being diagnosed within 24 months after screening, but in the current study the period was extended due to COVID-19 induced delays. We defined the screening examination leading to breast tumor diagnosis as the index screen, and the screening examination prior to the index screen as the pre-index screen. The screening interval of SDCs was defined as the number of months between the pre-index screen and the index screen. For ICs, time between index screen and the diagnosis of breast cancer was termed screen-diagnosis interval.

The period before March 12th, 2020 was defined as pre-COVID, and the period from March 12th, 2020 to December 31st, 2021 as the COVID-period. Women with a SDC were divided into five subgroups based on their screening interval: women who received their index screen in the pre-COVID-period and with a screening interval of 23–25 months (SDC/23–25) or 26–28 months (SDC/26–28), and women who received their index screen during the COVID-period and with a screening interval of 23–25 months (group SDC-C/23–25), 26–28 months (SDC-C/26–28), or 29–31 months (SDC-C/29–31). Women with a shorter or longer interval than those of the subgroups were excluded from the subgroup-analyses due to low numbers. Women with an IC were divided into two subgroups: women with a screen-diagnosis interval of <24 months (IC/0–23), or 24–31 months (IC/24–31).

Clinical TNM-stage was used to describe tumor size (cT), local lymph node involvements (cN) and distant metastasis (cM) (Brierley et al., 2017). Invasive tumors were considered estrogen receptor-positive if at least 1% of the cells stained positive for estrogen receptors, and progesterone receptor-positive if at least 10% of the cells stained positive for progesterone receptors. Estrogen and/or progesterone receptor-positive tumors were defined as hormone receptor-positive tumors and estrogen and progesterone receptor-negative tumors were defined as hormone receptor-negative tumors. Invasive tumors were considered Ki67 high if at least 30% of the cells stained positive for Ki67 (Coates

et al., 2015). Ki67 is a cellular marker for proliferation and is present during all phases of the cell cycle, but absent in resting cells. The percentage of Ki67 expressing cells is thereby an indicator of the proliferative activity of cancer cells. Neoadjuvant therapy was defined as presurgical treatment with chemotherapy, endocrine therapy, and/or targeted therapy.

2.3. Statistical analysis

Descriptive statistics were used to describe the screening intervals of women diagnosed in the pre-COVID and COVID-period, and to describe characteristics of the different subgroups. Multiple imputation by chained equations (MICE) was used to impute missing values (Azur et al., 2011), using the variables age, cT, cN, cM, hormone receptor-status, HER2-status, Ki67-status, neoadjuvant therapy, and surgical treatment. Missing values were considered to be missing at random. Logistic regression was used to investigate the association between the screening and screen-diagnosis interval and 1) histopathological tumor type (DCIS vs invasive cancer), 2) T-stage (Tis, T1 vs T2, T3, T4), 3) N-stage (N- vs N+), 4) M-stage (M0 vs M1), 5) TNM-stage (stage 0, I, IIA vs stage IIB, III, IV), 6) histopathological tumor grade (grade 1, 2 vs grade 3), 7) hormone receptor-status (hormone receptor+ vs hormone receptor-), 8) HER2-status (HER2+ vs HER2-), 9) Ki67-status (low vs. high), 10) risk of receiving neoadjuvant therapy (no vs yes), 11) risk of receiving lumpectomy (lumpectomy vs mastectomy). Women with a DCIS were only included in the results concerning histopathological tumor type. A complete case analysis was performed to assess whether estimates obtained using imputed datasets were comparable to those obtained after using original datasets. The complete case analysis only included women without missing data on the outcome variable.

A two-sided p-value <0.05 was considered statistically significant. No adjustment for multiple testing was made because of the exploratory nature of the current study (Bender and Lange, 2001). All data were analyzed using STATA version 16.1 (StataCorp, College Station, Texas, USA).

3. Results

Information about 6508 women diagnosed with breast cancer was available for analysis (Fig. 1). Of those women, 903 (13.9%) were excluded, resulting in a total of 5605 women included in the study sample.

3.1. Screening intervals in women with a SDC

A total of 3799 women were diagnosed with a SDC, of which 2298 received their index screen pre-COVID and 1501 during the COVID-period (Fig. 1). Median screening interval of women with a SDC, who received their index screen pre-COVID was 24.0 months (interquartile range (IQR): 23.8–24.5), and 27.0 months (IQR: 25.8–28.5) for women who received their index screen during the COVID-period (Fig. 2). A total of 93.1% (2140/2298) of the women who received their index screen pre-COVID had a screening interval of 23–25 months (SDC/23–25), and 4.6% (105/2298) had a screening interval of 26–28 months (SDC/26–28) (Table 1). In comparison, 29.0% (436/1501) of the women who received their index screen during the COVID-period had a screening interval of 23–25 months (SDC-C/23–25), 53.6% (804/1501) had a screening interval of 26–28 months (SDC-C/26–28), and 16.2% (243/1501) had a screening interval of 29–31 months (SDC-C/29–31). Detailed baseline characteristics of the study population can be found in Supplementary Table 1.

Compared to the reference group (SDC/23–25), women in group SDC/26–28 were statistically significantly more likely to have an invasive cancer (odds ratio (OR): 2.32, 95% confidence interval (95%CI): 1.20–4.49) or a cT2+ tumor (OR: 2.16, 95%CI: 1.37–3.41) and to receive neoadjuvant therapy (OR: 2.95, 95%CI: 1.57–5.54) or an ablatio (OR: 2.03, 95%CI: 1.23–3.36) (Table 2). Women in group SDC-C/23–25 were more likely to have an invasive cancer (OR: 1.40, 95%CI: 1.05–1.86) and a HER2+ tumor (OR: 1.67, 95%CI: 1.26–2.07), and less likely to receive a mastectomy (OR: 0.54, 95%CI: 0.36–0.82). Women in the SDC-C/26–28 group were more likely to have a histopathological grade 3 tumor (OR: 1.30, 95%CI: 1.05–1.59). Finally, no changes in tumor characteristics and treatment were seen between women in the SDC/23–25 and SDC-C/29–31 group. The complete case analysis can be found in Supplementary Table 2.

3.2. Screen-diagnosis intervals in women with an IC

Group IC/0–23 included 81.9% of all women with an IC (1479/1806) and group IC/24–31 18.1% (327/1806) (Table 3). Median age differed between the two subgroups, with women in the IC/0–23 having a median age of 60 (IQR: 54–65), and women in the IC/24–31 group of

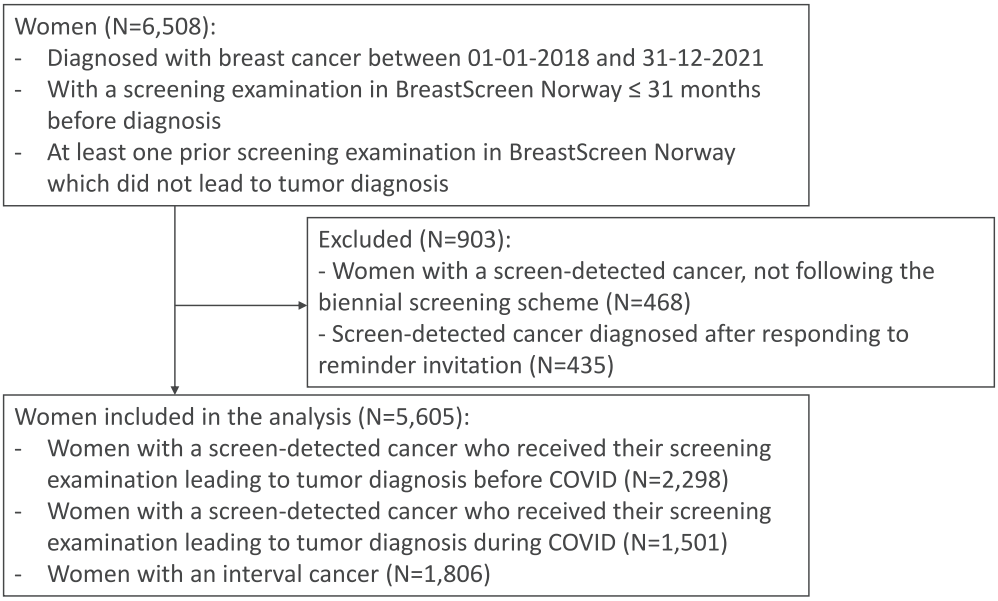

Fig. 1. Flowchart of included Norwegian women diagnosed with breast cancer between 2018 and 2021.

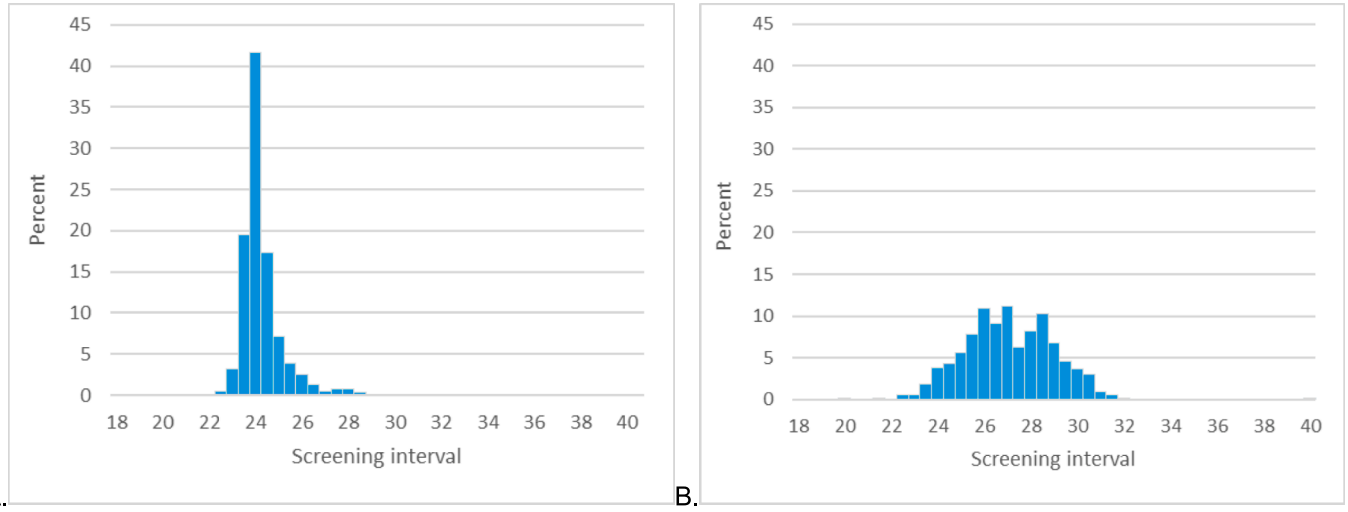

Fig. 2. Number of months between the pre-index screen and the index screen of Norwegian women diagnosed with a screen-detected breast tumor between 2018 and 2021, whose index screen was pre-COVID (A) or during the COVID-period (B). Pre-COVID: <12 March 2020, COVID-period: 12 March 2020–31 December 2021.

Table 1
Clinical and histopathological characteristics of screen-detected breast cancers in Norwegian women diagnosed between 2018 and 2021, by screening interval and period of index screen.

		Index screen before COVID		Index screen during COVID		
	Total	SDC/23–25	SDC/26–29	SDC-C/23–25	SDC-C/26–28	SDC-C/29–31
Patients	3728	2140	105	436	804	243
Age (median, IQR)	62 (57–66)	62 (57–66)	62 (58–66)	62 (57–66)	62 (57–66)	62 (57–66)
Histopathological type (N, %)						
Invasive	3040 (81.6)	1719 (80.3)	95 (90.5)	371 (85.1)	660 (82.1)	194 (80.3)
Clinical tumor size, cT[a] (N, %)						
cT2+	541 (19.6)	291 (18.4)	30 (33.3)	62 (18.8)	120 (20.2)	38 (22.4)
cT0, unknown	276	139	5	41	66	25
Clinical nodal stage, cN[a] (N, %)						
cN+	164 (5.8)	91 (5.8)	6 (6.5)	26 (7.3)	35 (5.6)	6 (3.3)
Unknown	193	136	2	13	31	11
Clinical distant metastasis, cM[a] (N, %)						
cM1	8 (0.3)	3 (0.2)	0 (0.0)	3 (0.8)	2 (0.3)	0 (0.0)
Clinical tumor stage, cTNM[a] (N, %)						
IIB, III, IV	162 (5.9)	90 (5.7)	9 (10.0)	24 (7.3)	32 (5.4)	7 (4.1)
Unknown	269	137	5	40	62	25
Histopathological grade[a] (N, %)						
3	693 (23.1)	388 (22.8)	15 (16.5)	76 (20.9)	179 (27.7)	35 (18.1)
Unknown	42	15	4	7	14	2
Hormone receptor[a] (N, %)						
Positive	2784 (92.5)	1571 (92.4)	90 (94.7)	334 (90.5)	605 (92.9)	184 (94.4)
Unknown	30	19	0	2	9	0
HER2[a] (N, %)						
Positive	697 (23.2)	364 (21.4)	15 (15.8)	113 (30.7)	152 (23.4)	53 (27.2)
Unknown	34	21	0	3	10	0
Ki67[a] (N, %)						
High, ≥30%	662 (23.2)	399 (24.7)	18 (22.0)	76 (21.8)	136 (21.8)	33 (18.2)
Unknown	186	101	13	22	36	14
Neoadjuvant therapy[a] (N, %)						
Yes	174 (5.8)	85 (5.0)	12 (12.8)	20 (5.5)	44 (6.7)	13 (6.8)
Unknown	26	11	1	7	4	3
Surgical treatment[a] (N, %)						
Mastectomy	366 (12.1)	227 (13.2)	21 (22.1)	25 (6.8)	73 (11.1)	20 (10.4)
No, unknown	32	10	3	8	8	3

SDC: screen-detected breast cancer with an index screen pre-COVID (<12 March 2020), SDC-C: screen-detected breast cancer with an index screen during the COVID-period (12 March 2020–31 December 2021).
SDC/23–25: screening interval of 23–25 months.
SDC/26–28: screening interval of 26–28 months.
SDC-C/23–25: screening interval of 23–25 months.
SDC-C/26–28: screening interval of 26–28 months.
SDC-C/29–31: screening interval of 29–31 months.
Percentages are calculated on known values only and women who are not divided in any of the subgroups ($N = 71$) are not included in the baseline table.
a. Only invasive cancers included.

Table 2
Logistic regression analysis to assess the association between the screening interval and tumor characteristics and treatment in Norwegian women diagnosed with a screen-detected breast cancer between 2018 and 2021 (odds ratio (95% confidence interval)).

	Invasive cancer	Clinical tumor size cT2 +[a]	Clinical nodal stage cN +[a]	Clinical distant metastasis cM1[a]	Clinical tumor stage cTNM IIB, III, IV[a]	Grade 3[a]	Hormone receptor -[a]	HER2 +[a]	Ki67 High (≥30%)[a]	Neoadjuvant therapy[a]	Mastectomy[a]
SDC/ 23–25	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
SDC/ 26–28	**2.32 (1.20–4.49)**	**2.16 (1.37–3.41)**	1.25 (0.54–2.89)	–	1.86 (0.90–3.84)	0.70 (0.40–1.24)	0.67 (0.27–1.67)	0.68 (0.39–1.20)	0.95 (0.57–1.60)	**2.95 (1.57–5.54)**	**2.03 (1.23–3.36)**
SDC-C/ 23–25	**1.40 (1.05–1.86)**	1.06 (0.78–1.45)	1.28 (0.82–2.02)	4.72 (0.95–23.51)	1.31 (0.82–2.07)	0.93 (0.71–1.22)	1.28 (0.87–1.89)	**1.62 (1.26–2.07)**	0.90 (0.68–1.17)	1.26 (0.78–2.03)	**0.54 (0.36–0.82)**
SDC-C/ 26–28	1.12 (0.91–1.39)	1.18 (0.93–1.50)	0.98 (0.66–1.47)	1.73 (0.29–10.40)	0.98 (0.65–1.49)	**1.30 (1.05–1.59)**	0.92 (0.65–1.30)	1.12 (0.90–1.39)	0.87 (0.71–1.08)	1.37 (0.95–1.98)	0.83 (0.63–1.10)
SDC-C/ 29–31	1.00 (0.71–1.39)	1.31 (0.89–1.92)	0.57 (0.24–1.31)	–	0.71 (0.33–1.56)	0.75 (0.51–1.11)	0.72 (0.38–1.35)	1.36 (0.97–1.90)	0.72 (0.49–1.06)	1.34 (0.73–2.45)	0.74 (0.46–1.20)

Analyses are adjusted for age. Bold: significant finding.
SDC: screen-detected breast cancer with an index screen pre-COVID (<12 March 2020), SDC-C: screen-detected breast cancer with an index screen during the COVID-period (12 March 2020–31 December 2021).
SDC/23–25: screening interval of 23–25 months.
SDC/26–28: screening interval of 26–28 months.
SDC-C/23–25: screening interval of 23–25 months.
SDC-C/26–28: screening interval of 26–28 months.
SDC-C/29–31: screening interval of 29–31 months.
a. Only invasive cancers included.

Table 3
Clinical and histopathological characteristics of interval breast cancers in Norwegian women diagnosed between 2018 and 2021, by screen-diagnosis interval.

	Total	IC/0–23	IC/24–31
Patients	1806	1479	327
Age (median, IQR)	61 (55–66)	60 (54–65)	64 (57–70)
Period of diagnosis (N, %)			
2018–2019	877 (48.6)	758 (51.3)	119 (36.4)
2020–2021	929 (51.4)	721 (48.8)	208 (63.6)
Histopathological type (N, %)			
Invasive	1649 (91.3)	1347 (91.1)	302 (92.4)
Clinical tumor size, cT[a] (N, %)			
cT2+	768 (51.3)	622 (50.9)	146 (52.9)
cT0, unknown	151	125	26
Clinical nodal stage, cN[a] (N, %)			
cN+	253 (16.7)	203 (16.4)	50 (18.2)
Unknown	134	107	27
Clinical distant metastasis, cM[a] (N, %)			
cM1	35 (2.1)	30 (2.2)	5 (1.7)
Clinical tumor stage, cTNM[a] (N, %)			
IIB, III, IV	302 (20.0)	249 (20.2)	53 (18.9)
Unknown	137	115	22
Histopathological grade[a] (N, %)			
3	531 (34.2)	423 (33.3)	108 (38.7)
Unknown	98	75	23
Hormone receptor[a] (N, %)			
Positive	1338 (83.0)	1104 (83.5)	234 (80.7)
Unknown	36	24	12
HER2[a] (N, %)			
Positive	451 (28.0)	389 (29.4)	62 (21.5)
Unknown	36	23	13
Ki67[a] (N, %)			
High, ≥30%	533 (38.0)	458 (39.4)	75 (31.4)
Unknown	248	185	63
Neoadjuvant therapy[a] (N, %)			
Yes	372 (23.9)	306 (24.1)	66 (23.0)
Unknown	92	77	15
Surgical treatment[a] (N, %)			
Mastectomy	404 (26.0)	327 (25.8)	77 (26.9)
No, unknown	96	80	16

IC: interval breast cancer.
IC/0–23: screen-diagnosis interval of 0–23 months.
IC/24–31: screen-diagnosis interval of 24–31 months.
Percentages are calculated on known values only.
[a] Only invasive cancers included.

64 (IQR 57–70). A total of 877 women were diagnosed with an IC in 2018–2019 and 929 women were diagnosed with an IC in 2020–2021. Most of the IC in the IC/24–31 group were detected in 2020–2021, with 119 ICs from the IC/24–31 group being detected in 2018–2019 (36.4%) and 208 tumors in 2020–2021 (61.6%). Detailed baseline characteristics can be found in Supplementary Table 3.

Compared to group IC/0–23, women in group IC/24–31 were more likely to have histopathologic grade 3 tumor (OR: 1.40, 95%CI: 1.06–1.84) and were less likely to have a HER2+ tumor (OR: 0.72, 95% CI: 0.52–0.98) (Table 4). The complete case analysis can be found in Supplementary Table 4.

4. Discussion

The current study showed a 3.0 months increase in the median screening interval of women with a SDC receiving their index screen during, compared to before the pandemic. In addition, the tumor characteristics and treatment of women with a SDC, index screen during the pandemic, and a screening interval of 29–31 months, did not differ from those of women with a SDC, index screen before the pandemic and a screening interval of 23–25 months. Women with an IC and a screen-diagnosis interval of 24–31 months had a higher risk of a histological grade 3 tumor compared to women with an IC and a screen-diagnosis interval of 0–23 months. No difference in treatment was seen between those two IC-groups.

Table 4
Logistic regression analysis to assess the association between the screen-diagnosis interval and tumor characteristics and treatment in Norwegian women diagnosed with an interval breast cancer between 2018 and 2021 (odds ratio (95% confidence interval)).

		Invasive cancer	Clinical tumor stage cT2 + [a]	Clinical nodal stage cN + [a]	Clinical distant metastasis cM1[a]	Clinical tumor stage cTNM IIB, III, IV[a]	Grade 3[a]	Hormone receptor - [a]	HER2 + [a]	Ki67 High (≥30%)[a]	Neoadjuvant therapy[a]	Mastectomy[a]
IC/0–23	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
IC/24–31	1.20 (0.76–1.88)	1.14 (0.88–1.49)	1.26 (0.90–1.78)	0.81 (0.31–2.14)	1.05 (0.75–1.46)	**1.40 (1.06–1.84)**	1.31 (0.94–1.83)	**0.72 (0.52–0.98)**	0.93 (0.71–1.24)	1.08 (0.80–1.46)	1.08 (0.81–1.44)

Analyses are adjusted for age. Bold: significant finding.
IC: interval breast cancer.
IC/0–23: screen-diagnosis interval of 0–23 months.
IC/24–31: screen-diagnosis interval of 24–31 months.
[a] Only invasive cancers included.

An English study showed that the screening mammogram of women screened between July 2020 and June 2021 was delayed by 2–7 months due to the suspension of the screening program (Duffy et al., 2022). The authors estimated that the delays in the screening program caused between 2783 and 4564 cancers to shift from screen-detected to clinically-detected. Our study showed that in 2020–2021, 89 extra tumors had a screen-diagnosis interval of 24–31 months compared to 2018–2019. This small increase in extra ICs with a longer screen-diagnosis interval is not necessarily due to the suspension of the screening program. Part of the increase may be because women with symptoms postponed their visit to the GP, shifting from an IC with a screen-diagnosis interval of 0–23 months to one with an interval of 24–31 months. Our study showed that in total 52 more ICs were diagnosed in 2020–2021 compared to 2018–2019, suggesting that only a small number of tumors shifted from screen- to clinically-detected. This small increase in the number of ICs could be due to the short suspension and quick catch-up of the Norwegian screening program (Larønningen et al., 2021).

The current study showed no evidence for an association between pandemic-induced prolonged screening intervals and tumor characteristics and treatment. Previous observational studies performed with data from the United States found no difference in tumor characteristics between women receiving biennial or triennial screening (Kerlikowske et al., 2013; O'Meara et al., 2013). The United States performs opportunistic screening which means that the women in consultation with their general practitioner decide if and when they should be screened (Centers for Disease Control and Prevention, 2022). Most European countries, including Norway, have an organized population-based screening program. This makes it difficult to compare results from the United States and Europe. Comparable to our results, a study with Dutch data, also with an organized screening program, found no difference in tumor characteristics between women receiving biennial or quadrennial screening (Duijm et al., 2022). A higher risk of estrogen receptor-negative and triple negative (i.e., estrogen receptor-, progesterone receptor-, and HER2-negative) tumors was found for women receiving screening once every six years compared to women receiving biennial screening. As we found no associations between COVID-19 induced prolonged screening-intervals and the tumor characteristics of SDCs, future (modeling) studies could investigate the (cost-)effectiveness of increasing the screening interval by three months.

We found that women with SDC, index screen before the pandemic, and a screening-interval of 26–28 months were more likely to have an invasive cancer or cT2+ tumor, and to receive neoadjuvant therapy or a mastectomy compared to women with a screening interval of 23–25 months. This is not in accordance with the results of previous studies, or with the results found in the current study for women with a SDC, index screening during the pandemic, and a screening-interval of 26–28 or 29–31 months. The SDC/26–28 group only included a small number of women ($N = 105$), so in light of the results of other studies, these findings are likely to be a coincidence. However, more research is needed into this subgroup of patients to confirm, or refute, our results.

Previous studies comparing the tumor characteristics of ICs by time since screening found no difference in tumor characteristics between women with an interval of 0–12 versus 13–24 months (Wai et al., 2005), or between women with an interval of <12, 12–23, or 24–47 months (Coldman and Phillips, 2014). Another Norwegian study, including data of women diagnosed between 1996 and 2005, showed a small increase in tumor diameter for women with <13 months versus 13–24 since screening (Kalager et al., 2012). A Dutch study showed that ICs with a 0–12 months interval were less often triple negative (i.e., estrogen receptor-, progesterone receptor-, and HER2-negative) compared to those with a 13–24 months interval (Weber et al., 2016). No other difference in tumor characteristics were reported (Weber et al., 2016). The result of our study suggest that a longer interval might be associated with a higher tumor grade. However, the majority of the tumors in group IC/24–31 were diagnosed during the COVID-period. It might be possible that the COVID-19 pandemic caused a delay in diagnosis in women

experiencing breast cancer symptoms, unrelated to the suspended screening program. More research is needed to investigate the association between the screen-diagnosis interval and tumor characteristics in women with an IC.

To our knowledge this is the first study investigating the association between COVID-19 induced prolonged screening and screen-diagnosis intervals and tumor characteristics and treatment. The current study benefited from the high completeness from the Cancer Registry of Norway, allowing the inclusion of data from a large number of women in the current study. However, some subgroups might still have been too small, resulting in a limited power. A limitation of the current study is that it is unknown whether an IC is detected because of breast cancer-related symptoms or because the women scheduled her own screening appointment at a private clinic. It might be possible that women scheduled their own appointment during the COVID pandemic because of delays in their scheduled screening. This might have led to misclassifying a SDC as an IC, which could have resulted in an underestimation of the differences in tumor characteristics between women with an early and late-IC. In addition, we did not look at the detection rate and IC rate of the screening program in the current study, as our aim was to investigate the association between a prolonged screening or screen-diagnosis interval and tumor characteristics and treatment.

5. Conclusions

The current study showed no evidence for an association between prolonged screening intervals due to the COVID-19 pandemic and tumor characteristics and breast cancer treatment of women with screen-detected breast cancer. In addition, our results suggested that only a limited number of cancers shifted from screen- to clinically-detected, which might be due to the short suspension and quick catch-up of the screening program. For women with an interval breast cancer the association between the screen-diagnosis interval and tumor characteristics was unclear. There was no evidence for an association between the screen-diagnosis interval and treatment. This study provides insight into the possible effects of extending the screening interval. To get a complete image of the potential effects of extending the screening interval, future research should investigate the association between (COVID-19 induced) prolonged screening intervals and the detection rate of both SDCs and ICs. In addition, future studies should investigate the association between COVID-19 induced prolonged screening intervals and the risk of developing a breast cancer recurrence and disease-specific survival.

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Data sharing

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 General Data Protection Regulation (GDPR) and that the processing is in accordance with Article 5 of the GDPR. In addition, the processing must have supplementary basis in Union or Member State law and ethical approval from the Norwegian Regional Committee for Medical and Health Research Ethics (REC). The data can only be made available to a third country or an international organization, subject to the other provisions of GDPR, if the conditions laid down in Chapter V is complied with.

Author contributions

AHE, SS, SH, LdM were involved in conceptualization and investigation. AHE and ML performed data curation. AHE performed the formal analysis and visualization. AHE, ML, LdM, SS wrote the original draft of the paper. AHE, ML, SS, JFN, LdM, SH were involved in reviewing & editing the manuscript.

Disclaimer

Data from the Cancer Registry of Norway has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Solveig Hofvind is the head of BreastScreen Norway. The Cancer Registry has research agreements with ScreenPoint Medical, Lunit and Vara. All other authors have no competing interests.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2023.107723.

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