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Impact of the COVID-19 pandemic on breast cancer incidence and tumor stage in the Netherlands and Norway: A population-based study

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ABSTRACT

Background: Comparing the impact of the COVID-19 pandemic on the incidence of newly diagnosed breast tumors and their tumor stage between the Netherlands and Norway will help us understand the effect of differences in governmental and social reactions towards the pandemic.
Methods: Women newly diagnosed with breast cancer in 2017–2021 were selected from the Netherlands Cancer Registry and the Cancer Registry of Norway. The crude breast cancer incidence rate (tumors per 100,000 women) during the first (March-September 2020), second (October 2020-April 2021), and Delta COVID-19 wave (May-December 2021) was compared with the incidence rate in the corresponding periods in 2017, 2018, and 2019. Incidence rates were stratified by age group, method of detection, and clinical tumor stage.
Results: During the first wave breast cancer incidence declined to a larger extent in the Netherlands than in Norway (27.7% vs. 17.2% decrease, respectively). In both countries, incidence decreased in women eligible for screening. In the Netherlands, incidence also decreased in women not eligible for screening. During the second wave an increase in the incidence of stage IV tumors in women aged 50–69 years was seen in the Netherlands. During the Delta wave an increase in overall incidence and incidence of stage I tumors was seen in Norway.

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Conclusion: Alterations in breast cancer incidence and tumor stage seem related to a combined effect of the suspension of the screening program, health care avoidance due to the severity of the pandemic, and other unknown factors.

1. Introduction

As of December 31st, 2022 a total of 65.5 million people have been infected with SARS-CoV-2, the virus causing COVID-19, worldwide [1]. A total of 6.7 million people have died from the virus. The severity of the pandemic, i.e., SARS-CoV-2 infection rates and COVID-19 death rates (number of infections/deaths per 100,000 inhabitants), differed widely between countries. It could therefore be expected that the reaction of the society and government towards the pandemic also differed between countries. Comparisons of countries will help to understand the results of those different reactions on variables such as breast cancer incidence and tumor stage.

The Netherlands and Norway are both high-income countries with comparable primary care-based health care systems. The Netherlands has 17.5 million inhabitants (504 inhabitants per km^2) and Norway 5.4 million (15 inhabitants per km^2). The first COVID-19 case was detected (approximately) at the same date in both countries (Fig. 1) [2,3]. The severity of the COVID-19 pandemic markedly differed between the two countries. Up to December 31st, 2021, the COVID-19 infection rate in the Netherlands was 2.4 times higher than in Norway (175,672 vs. 71, 898 per million people, respectively), and the COVID-19 death rate was 4.7 times higher (1193 vs. 256 per million people, respectively [4]. In both countries, measures were taken to mitigate the spread of the virus and to preserve equipment needed for COVID-19 patients. However, the level of political regulation seemed to be less extensive in Norway compared to the Netherlands [5]. Both countries suspended their national breast cancer screening program mid-March 2020. In the Netherlands, the national screening program gradually restarted at the beginning of July 2020 with a capacity of 40%, and they reached 80% of their capacity in October. In Norway, the first screening units restarted mid-May 2020 [3]. All screening units had restarted in August 2020 in Norway, with a screening capacity ranging between the 55% and 121%. Capacity even ranged between the 87% and 129% in November. Both the Netherlands and Norway invite women biennially for screening. The women invited for screening are aged 50–74 in the Netherlands and 50–69 in Norway.

In both countries the suspension of the screening program led to a decrease in the incidence of screen-detected breast tumors [6,7]. The incidence of non-screen-detected breast tumors decreased at the start of the pandemic in the Netherlands, but not in Norway [6,7]. However, the study of the Netherlands included data till August, 2020, and the report from Norway included data till December 2020. To investigate the long-term impact of the pandemic on the incidence of newly diagnosed breast cancer and its tumor stage, longer follow-up is needed.

The current explorative study aimed to investigate the impact of the COVID-19 pandemic on the incidence of newly diagnosed breast tumors and its tumor stage at diagnosis in the Netherlands and Norway. Changes in incidence were linked to policy measures and the severity of the pandemic. Based on the impact in these countries, we aimed to formulate recommendations to advance health policy during future similar circumstances.

2. Methods

2.1. Study population

Women, aged 18 years or older, diagnosed with either ductal carcinoma in situ (DCIS) or invasive breast cancer between 2017 and 2021 were selected from the Netherlands Cancer Registry (NCR) and the Cancer Registry of Norway (CRN) (Fig. 2). Women with a history of breast cancer were excluded. For patients with a synchronous tumor (diagnosed within 91 days of each other), the tumor with the highest clinical tumor stage was included. The NCR and CRN are both nationwide population-based registries that include data on all newly diagnosed malignancies. Since 1989, new malignancies have been notified to the NCR through the Nationwide Histopathology and Cytopathology Data network and Archive (PALGA). Subsequently, trained registration clerks report patient, tumor, and treatment characteristics from the patients' files. The CRN receives their data via institutions diagnosing or treating cancer patients. These institutions are obliged to report this data to the CRN. The use of data from the NCR for the current study was approved by the Privacy Review Board of Netherlands Cancer Registry (reference number K22.049) and the use of data from the CRN was approved by the Regional committees for medical and health research ethics in Norway (reference number 478240).

2.2. Definitions

The period from March 1st 2020 till December 31st 2021 was regarded as the COVID-19 period. The COVID-19 period was divided in three approximately equal periods based on COVID-19 related events: March-September 2020 (first wave), October 2020-April 2021 (second wave, this started mid-September 2020 in the Netherlands and mid-October in 2020 in Norway), May-December 2021 (Delta wave) (Fig. 1). Data from the COVID-19 period was compared with data of the corresponding reference periods in 2017, 2018, and 2019: March-September 2017–2019, October-April 2017–2019, May-December 2017–2019.

Age at diagnosis was grouped into four categories, based on the ages of women eligible for screening in the Netherlands and Norway (<50, 50–69, 70–74, >74 years). Method of detection was defined as screen-detected, i.e., the tumor was detected by the national breast cancer screening program, or non-screen-detected. Clinical TNM-stage was defined according to the TNM-staging system [8]. Estrogen receptor

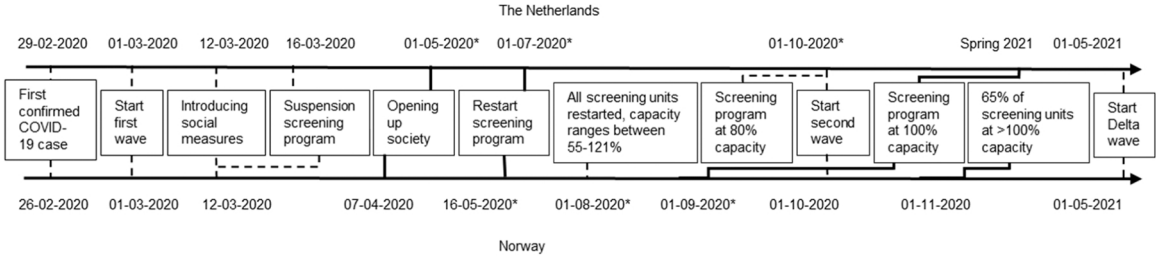

Fig. 1. COVID-19 timeline for the Netherlands and Norway. * approximate date.

(ER) and progesterone receptor (PR) expression of < 10% were classified as hormone receptor (HR)-negative tumors [9]. Tumors with ER and/or PR expression of ≥ 10% were classified as HR-positive tumors. HR-status and HER2-status were grouped into four histopathological subtypes, adapted from the St Gallen International Expert Consensus [10]: luminal A (HR-positive, HER2-negative, grade 1 or 2), luminal B (HR-positive, HER2-positive or HER2-negative with grade 3), HER2 positive (HR-negative and HER2-positive), and triple negative (HR- and HER2-negative).

2.3. Statistical analysis

Descriptive statistics were used to report the characteristics of patients diagnosed in the COVID-19 and reference periods. The crude incidence rate of newly diagnosed breast cancer was expressed as the number of breast cancer diagnoses per 100,000 women of the age group of interest living in the Netherlands or Norway during the period of interest, using data from Statistics Netherlands and Statistics Norway [11,12]. The breast cancer incidence rate was calculated for each COVID-19 period and for each reference period. Incidence rates were stratified by age group, method of detection, and tumor stage. Only women eligible for screening were included in the analyses concerning method of detection. The incidence rates per tumor stage were further stratified by age group and tumor subtype. The monthly breast cancer incidence rate during the COVID-19 and the reference periods was calculated to enable visual comparison over time.

As some patients had missing values on tumor stage, tumor subtype, and/or method of detection, multiple imputation by chained equations (MICE) was used to impute missing values [13]. Missing values were considered to be missing at random. The variables cT, cN, cM, HR, HER2, tumor grade, method of detection, age category, and period of diagnosis were used in the imputation procedure. Clinical tumor stage was subsequently determined by using the variables cT, cN, and cM. Tumor subtype was determined by using the variables HR, HER2, and tumor grade. Imputation was repeated 25 times, and the estimates were pooled using Rubin's rules [14]. The imputed datasets were used to determine the number of patients per tumor stage, subtype, and method of detection. This number was then used to compare the incidence rates in the COVID-19 period with the incidence rates in the corresponding period in 2017–2019, using the IRI-command in Stata (which is an incidence rate ratio calculator). For comparison, complete-case analyses were performed. It was assumed that the breast cancer incidence and age structure in the Netherlands and Norway stayed constant over the study period. This assumption was based on the age-standardized incidence rates of the Netherlands and Norway, which were rather constant over the recent years [15,16], and because of the relatively small study period of the current study.

To correct for multiple testing, we controlled for the false discovery rate. The false discovery rate was set to 5%. The results from the Netherlands and Norway were corrected for multiple testing separately. A total of 144 tests were performed on both the Dutch and Norwegian data. The p-values of all performed analyses were entered in the tool developed by Menyhart O, et al. [17]. Subsequently, the tool calculated the first significant p-value, according to the formula described in the article of Menyhart O, et al. [17]. All p-values below this value were also considered statistically significant. This means that although a confidence interval of a certain risk ratio does not include 1.00, the results could still be insignificant as the corrected p-value was no longer significant. This method of correction for multiple testing is often used for explorative analyses [17]. All analyses were performed for the Netherlands and Norway separately. All data were analyzed using Stata version 16.0 (StataCorp, College Station, Texas, USA).

3. Results

In the Netherlands, 7152 women were diagnosed with a breast tumor during the first wave. During the second wave and the Delta wave 9976 and 11,500 women were diagnosed, respectively (Supplementary Table S1). In the corresponding reference periods, 29,125, 28,915, and 33,218 women were diagnosed, respectively. In Norway, 1892, 2607, and 2964 women were diagnosed during the first, second, and Delta wave, respectively. In the corresponding reference periods, 6727, 7246, and 7883 women were diagnosed, respectively. Detailed baseline characteristics can be found in Supplementary Table S2 and S3.

3.1. First wave

Compared to the reference period, the relative decline in breast cancer incidence was largest in the Netherlands during the first wave, with a total decline of 27.7% (Fig. 3a, Table 1, incidence rate ratios (IRR) and 95% confidence intervals (CI) can be found in Table 2). Breast cancer incidence declined with 17.2% in Norway (Fig. 4a, Table 1, Table 2). In both countries, incidence was significantly lower in women eligible for screening (i.e., those aged 50–74 years in the Netherlands, and those aged 50–69 years in Norway) (Table 2). In the Netherlands, incidence was also significantly lower in women not eligible for screening (i.e., those aged <50 and >74 years).

3.2. Second wave

Compared to the reference period, the total incidence and the incidence per age group did not significantly differ from the incidence in the reference period in the Netherlands during the second wave (Table 2). In Norway, incidence was significantly higher in women aged 50–69. In the Netherlands, the incidence of screen-detected tumors was significantly lower and the incidence of non-screen-detected tumors was significantly

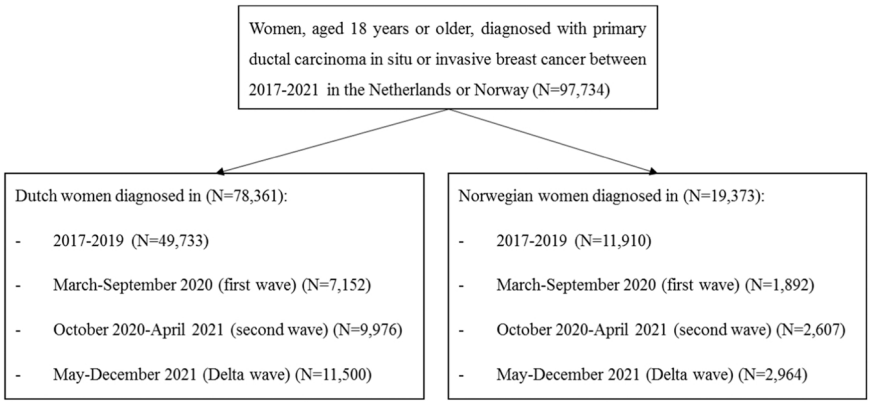

Fig. 2. Flowchart of the study population.

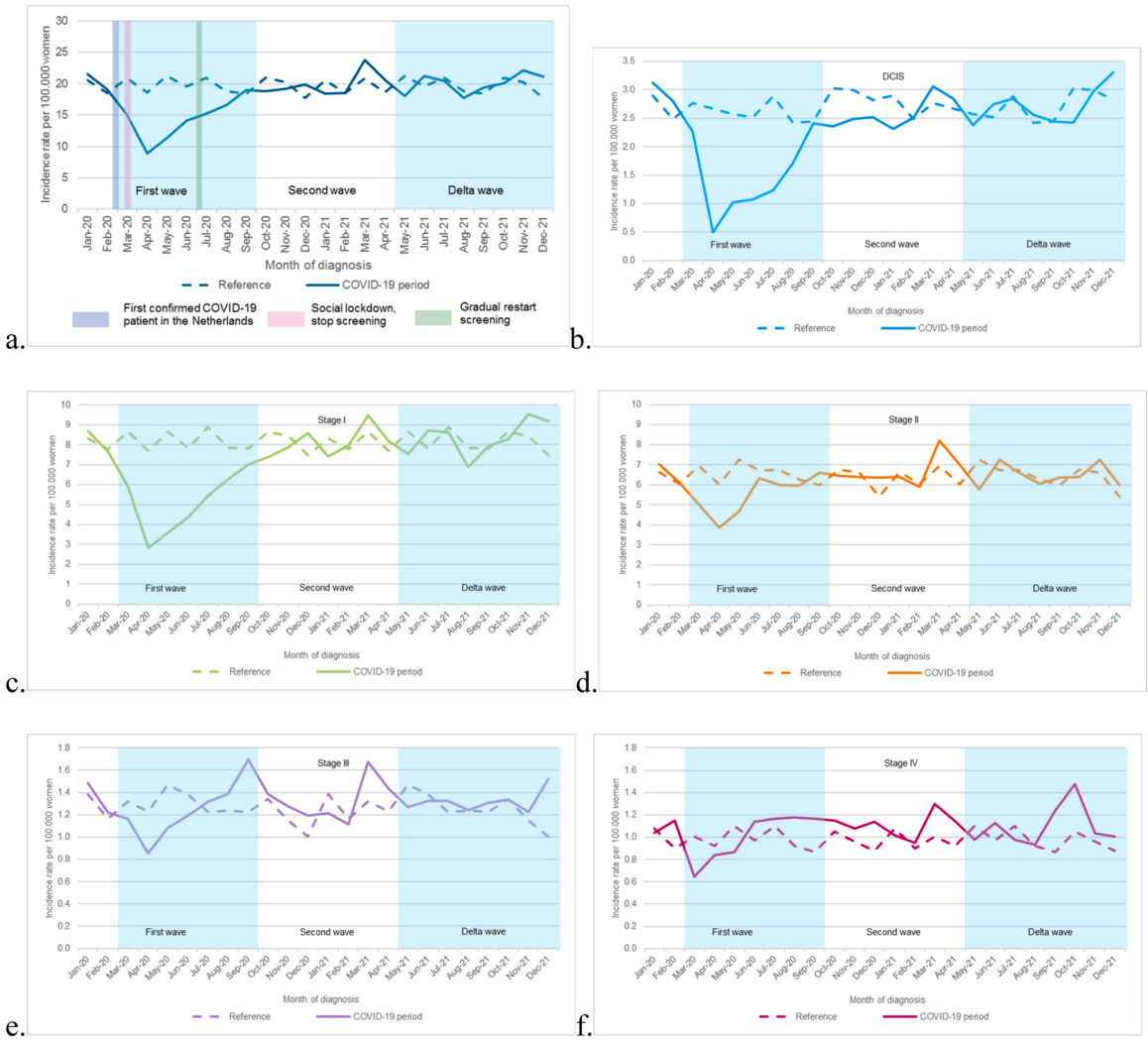

Fig. 3. Breast cancer incidence rates in the Netherlands in 2017–2019 (reference) and 2020–2021 (Covid-19 period), overall (a) and for ductal carcinoma in situ (b), stage I (c), stage II (d), stage III (e), and stage IV tumors (f). The reference incidence rate is the average monthly incidence rate in 2017–2019. Figures are based on the complete cases dataset.

higher, while in Norway the incidence of screen-detected tumors was significantly higher. In the Netherlands, the total incidence of stage IV tumors and the incidence of stage IV tumors in women aged 50–69 was significantly higher. In both countries, the incidence of stage II tumors was significantly higher in women aged 50–69 (Table 3).

Based on the result regarding stage IV a Poisson regression model was specified post-hoc to predict the absolute number of stage IV tumors for each month of 2020 and 2021, using data of 2014–2019. This model allowed to adjust for trends over time. The expected cumulative absolute number of stage IV tumors during the second wave was subtracted from the observed cumulative absolute number of stage IV tumors to estimate cumulative excess of stage IV tumors. The cumulative excess of stage IV tumors during the second wave for the total Dutch population was 58.4 (95%CI: −0.4 to 119.0, p = 0.052) and for Dutch women aged 50–69 years 49.0 (95%CI: 9.6 to 88.9, p = 0.015) (Supplementary Fig. S1 and S2).

3.3. Delta wave

Compared to the reference period, the total incidence, the incidence per age group, and the incidence per method of detection did not significantly differ from the incidence in the reference period in the Netherlands during the Delta wave (Table 2). In Norway, breast cancer incidence increased with 10.0%, which was mainly caused by an increase in incidence in women aged 50–69 years and by an increase in the incidence of stage I tumors.

Results described above did not differ from the results of the complete case-analyses (Supplementary Table S4 and S5), although in the complete case-analyses the higher incidence of stage I tumors was not seen during the Delta wave in Norway.

4. Discussion

Our results show a decline in the incidence of newly diagnosed breast tumors during the first wave of the pandemic in both countries, with a larger decline in the Netherlands compared to Norway. While breast cancer incidence decreased in all age groups in the Netherlands during the first wave, incidence in Norway only declined in women eligible for screening. During the second wave a partial catch-up was observed in both countries, which was most pronounced in Norway. Furthermore, a higher incidence of stage IV tumors was seen in the Netherlands during the second wave, mainly in women aged 50–69 years. During the Delta wave, an increase in the overall incidence and in the incidence of stage I tumors was seen in Norway.

At the beginning of the pandemic the Dutch and Norwegian government put social measures in place and suspended the national breast

Table 1
Incidence rates of newly diagnosed breast cancer (% change compared to 2017–2019) in the COVID-19 periods and in the corresponding period of 2017–2019 in the Netherlands and Norway, stratified by age group, method of detection and clinical tumor stage.

	Netherlands						Norway					
	March-September		October-April		May-Dec		March-September		October-April		May-Dec	
	2017–2019	2020 First wave	2017–2019	2020–2021 Second wave	2017–2019	2021 Delta wave	2017–2019	2020 First wave	2017–2019	2020–2021 Second wave	2017–2019	2021 Delta wave
Total	138.6	100.3 (−27.7)	137.6	139.4 (1.3)	158.1	160.3 (1.4)	107.9	89.4 (−17.2)	116.2	122.7 (5.5)	126.5	139.1 (10.0)
Age group												
< 50	56.2	47.5 (−15.5)	53.8	52.3 (−2.8)	60.8	57.4 (−5.5)	39.7	39.2 (−1.2)	41.3	41.5 (0.4)	46.6	47.7 (2.5)
59–69	210.9	135.7 (−35.7)	213.7	217.3 (1.7)	245.2	248.2 (1.2)	189.3	128.7 (−32.0)	215.1	238.7 (11.0)	223.3	243.2 (8.9)
70–74	285.7	174.6 (−38.9)	295.8	283.8 (−4.0)	331.3	327.2 (−1.3)	174.9	147.7 (−15.5)	175.9	138.3 (−21.4)	202.6	213.5 (5.4)
> 74	207.7	179.2 (−13.8)	195.6	199.1 (1.8)	235.2	241.3 (2.6)	185.7	189.8 (2.2)	182.8	182.9 (0.1)	214.4	242.5 (13.1)
Method of detection[a]												
Screen-detected	124.1	44.4 (−64.2)	129.5	119.6 (−7.7)	145.7	147.7 (1.4)	118.7	54.6 (−54.0)	140.9	158.0 (12.1)	139.8	152.5 (9.1)
Non-screen-detected	93.0	94.2 (1.2)	91.4	103.8 (13.5)	106.8	109.3 (2.4)	70.6	74.1 (5.0)	74.2	80.8 (8.9)	83.5	90.8 (8.7)
Unavailable	6.0	3.8	6.1	5.5	6.7	4.9	0.0	0.0	0.0	0.0	0.0	0.0
Clinical tumor stage												
DCIS	18.3	10.2 (−44.1)	19.7	18.1 (−8.0)	21.7	21.7 (0.0)	13.4	8.7 (−35.3)	14.0	15.5 (11.0)	15.6	16.0 (2.3)
Stage I	57.3	35.4 (−38.2)	57.0	56.9 (−0.2)	65.6	66.7 (1.7)	41.3	29.2 (−29.2)	46.2	46.7 (1.0)	47.8	52.0 (8.8)
Stage II	45.9	38.4 (−16.2)	44.4	46.7 (5.1)	51.7	51.7 (−0.1)	35.1	34.1 (−2.7)	37.3	39.3 (5.4)	40.9	40.6 (−0.8)
Stage III	9.1	8.7 (−4.4)	8.6	9.3 (8.1)	10.0	10.6 (5.2)	7.3	5.6 (−23.3)	7.1	7.4 (4.9)	8.5	7.6 (−9.7)
Stage IV	6.9	7.0 (1.6)	6.8	7.8 (14.4)	7.8	8.8 (11.7)	2.2	2.6 (16.9)	2.6	2.6 (1.4)	2.8	3.1 (7.4)
Unavailable	1.2	0.5	1.1	0.7	1.3	0.9	8.6	9.2	9.1	11.2	10.8	19.8

Incidence rates are calculated per 100,000 women of the age group of interest living in the Netherlands or Norway during the period of interest.
[a]Only including women eligible for screening, i.e. Dutch patients aged 50–74 and Norwegian patients aged 50–69.

Table 2
Incidence rate ratios (95% confidence intervals) comparing the incidence rate in the COVID-19 periods with the incidence rate in the corresponding period of 2017–2019, by age group, method of detection, and tumor stage, using the imputed datasets.

	Netherlands			Norway		
	First wave	Second wave	Delta wave	First wave	Second wave	Delta wave
Total	0.72 (0.70–0.74)*	1.01 (0.99–1.04)	1.01 (0.99–1.04)	0.83 (0.79–0.87)*	1.06 (1.01–1.10)	1.10 (1.05–1.15)*
Age group						
< 50	0.85 (0.80–0.89)*	0.97 (0.92–1.02)	0.94 (0.90–0.99)	0.99 (0.88–1.10)	1.00 (0.90–1.12)	1.03 (0.93–1.13)
50–69	0.64 (0.62–0.67)*	1.02 (0.98–1.05)	1.01 (0.98–1.04)	0.68 (0.63–0.73)*	1.11 (1.05–1.18)*	1.09 (1.03–1.15)*
70–74	0.61 (0.57–0.66)*	0.96 (0.90–1.02)	0.99 (0.93–1.05)	0.84 (0.72–0.99)	0.79 (0.66–0.93)*	1.05 (0.92–1.25)
> 74	0.86 (0.81–0.91)*	1.02 (0.96–1.08)	1.03 (0.98–1.08)	1.02 (0.91–1.14)	1.00 (0.89–1.12)	1.13 (1.03–1.25)
Method of detection[a]						
Screen-detected	0.36 (0.34–0.38)*	0.92 (0.89–0.96)*	1.01 (0.98–1.05)	0.46 (0.41–0.52)*	1.12 (1.04–1.21)*	1.09 (1.01–1.17)
Non-screen-detected	1.01 (0.96–1.05)	1.13 (1.08–1.18)*	1.01 (0.97–1.05)	1.05 (0.94–1.17)	1.09 (0.98–1.21)	1.09 (0.99–1.20)
Tumor stage						
DCIS	0.56 (0.52–0.60)*	0.92 (0.86–0.98)*	1.00 (0.94–1.06)	0.65 (0.55–0.76)*	1.11 (0.97–1.26)	1.03 (0.91–1.16)
Stage I	0.62 (0.59–0.64)*	0.99 (0.96–1.03)	1.01 (0.98–1.05)	0.73 (0.67–0.80)*	1.03 (0.96–1.11)	1.17 (1.10–1.25)*
Stage II	0.84 (0.80–0.87)*	1.05 (1.01–1.09)	1.00 (0.96–1.04)	0.99 (0.92–1.08)	1.07 (0.99–1.15)	1.07 (1.00–1.15)
Stage III	0.96 (0.87–1.05)	1.08 (0.99–1.18)	1.05 (0.97–1.14)	0.79 (0.65–0.96)	1.04 (0.87–1.24)	0.96 (0.81–1.13)
Stage IV	1.02 (0.92–1.13)	1.14 (1.04–1.26)*	1.12 (1.02–1.23)	1.17 (0.84–1.61)	1.01 (0.73–1.38)	1.07 (0.80–1.43)

First wave: March – September 2020, second wave: October 2020 – April 2021, Delta wave: May – December 2021
* statistical significant after correction for the false discovery rate. First significant p-value was 0.010 for the Dutch data and 0.006 for the Norwegian data.
[a]Only including women eligible for screening, i.e. Dutch patients aged 50–74 and Norwegian patients aged 50–69.

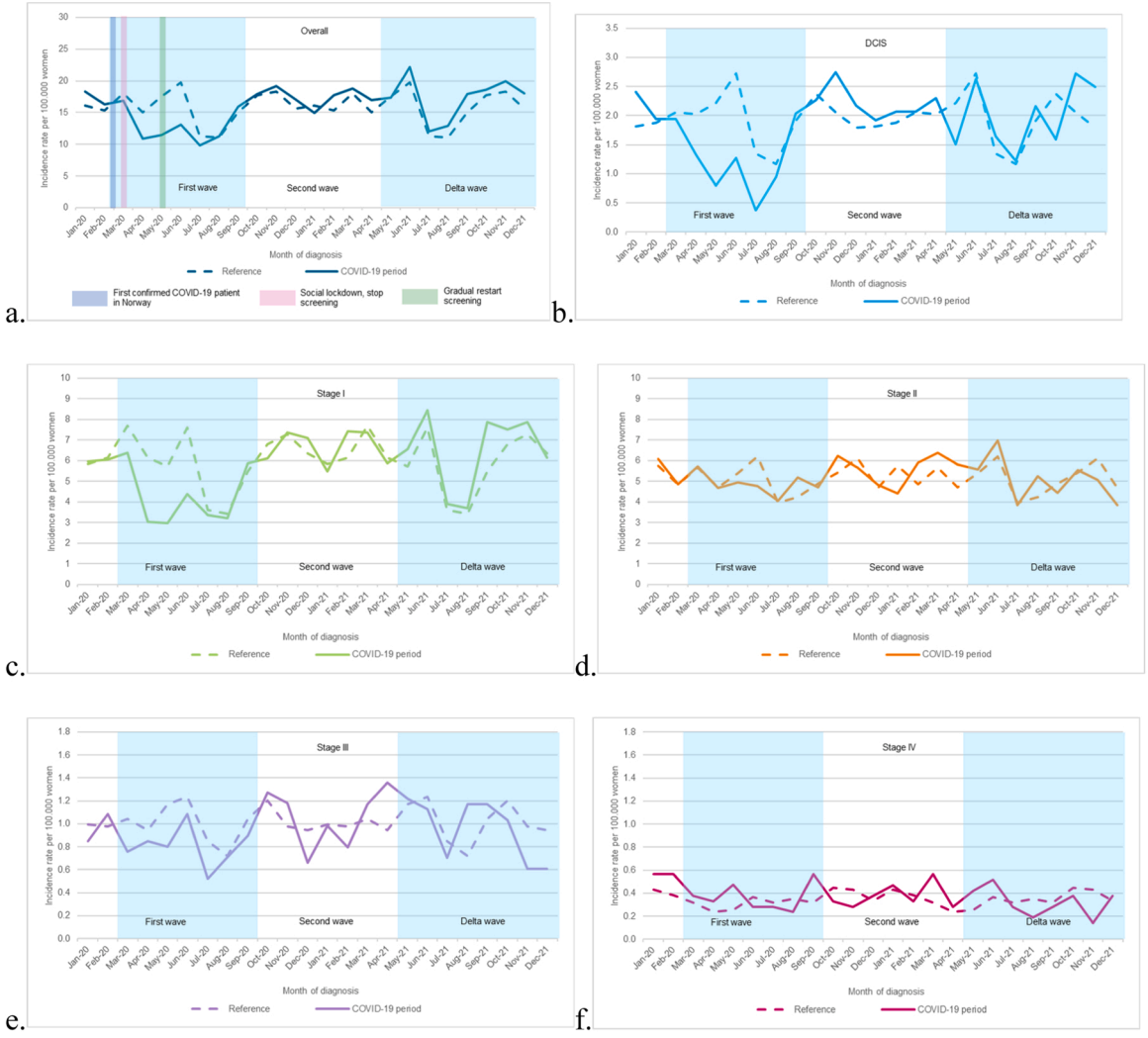

Fig. 4. Breast cancer incidence rate in Norway in 2017–2019 (reference) and 2020–2021 (Covid-19 period), overall (a) and for ductal carcinoma in situ (b), stage I (c), stage II (d), stage III (e), and stage IV tumors (f). The reference incidence rate is the average monthly incidence rate in 2017–2019. Figures are based on the complete cases dataset.

Table 3
Incidence rate ratios (95% confidence intervals) comparing the incidence rate in the COVID-19 periods with the incidence rate in the corresponding period of 2017–2019 by tumor subtype, and age group, stratified by tumor stage, using the imputed datasets.

	Netherlands			Norway		
	First wave	Second wave	Delta wave	First wave	Second wave	Delta wave
DCIS						
< 50	0.82 (0.68–0.97)	0.92 (0.78–1.09)	0.89 (0.75–1.05)	0.85 (0.59–1.20)	1.02 (0.73–1.41)	0.75 (0.52–1.06)
50–69	0.48 (0.44–0.54)*	0.93 (0.86–1.01)	0.99 (0.92–1.06)	0.52 (0.42–0.65)*	1.11 (0.95–1.29)	1.03 (0.89–1.20)
70–74	0.52 (0.41–0.65)*	0.80 (0.67–0.95)*	0.93 (0.79–1.08)	0.77 (0.41–1.36)	0.68 (0.33–1.30)	1.16 (0.72–1.80)
> 74	0.70 (0.52–0.92)*	0.88 (0.68–1.13)	1.23 (1.01–1.51)	1.08 (0.65–1.76)	1.53 (0.94–2.44)	1.29 (0.82–1.99)
Stage I						
< 50	0.76 (0.68–0.84)*	0.96 (0.87–1.06)	0.98 (0.89–1.07)	0.93 (0.76–1.14)	1.00 (0.82–1.20)	1.02 (0.86–1.22)
50–69	0.55 (0.51–0.58)*	0.98 (0.93–1.03)	0.99 (0.95–1.03)	0.59 (0.52–0.66)*	1.08 (0.99–1.17)	1.15 (1.06–1.25)*
70–74	0.54 (0.48–0.60)*	0.97 (0.89–1.05)	0.96 (0.89–1.04)	0.79 (0.60–1.02)	0.63 (0.47–0.83)*	1.10 (0.88–1.36)
> 74	0.81 (0.73–0.91)*	1.01 (0.91–1.11)	1.08 (0.99–1.19)	1.10 (0.89–1.33)	1.03 (0.84–1.27)	1.36 (1.14–1.61)*
Stage II						
< 50	0.86 (0.79–0.93)*	1.00 (0.92–1.09)	0.91 (0.84–0.98)	1.03 (0.87–1.21)	0.97 (0.82–1.14)	1.13 (0.98–1.31)
50–69	0.81 (0.75–0.86)*	1.09 (1.02–1.16)*	1.06 (1.00–1.12)	0.91 (0.80–1.04)	1.20 (1.07–1.35)*	1.02 (0.91–1.14)
70–74	0.71 (0.61–0.82)*	0.94 (0.83–1.06)	0.99 (0.88–1.11)	0.95 (0.73–1.21)	0.89 (0.69–1.15)	1.00 (0.79–1.25)
> 74	0.88 (0.81–0.96)*	1.02 (0.94–1.11)	0.94 (0.87–1.02)	1.05 (0.90–1.22)	0.96 (0.82–1.12)	1.05 (0.91–1.20)
Stage III						
< 50	1.03 (0.88–1.22)	1.01 (0.85–1.20)	1.03 (0.88–1.20)	1.06 (0.75–1.47)	1.11 (0.79–1.54)	0.94 (0.68–1.28)
50–69	0.94 (0.80–1.09)	1.10 (0.95–1.27)	1.08 (0.94–1.24)	0.77 (0.54–1.09)	0.96 (0.70–1.30)	1.00 (0.75–1.34)
70–74	0.81 (0.57–1.12)	1.20 (0.87–1.62)	0.97 (0.71–1.31)	0.56 (0.25–1.11)	1.45 (0.80–2.55)	0.89 (0.48–1.56)
> 74	0.91 (0.76–1.09)	1.05 (0.87–1.25)	1.02 (0.86–1.20)	0.61 (0.39–0.90)	0.89 (0.61–1.26)	0.88 (0.63–1.21)
Stage IV						
< 50	0.96 (0.75–1.21)	0.84 (0.66–1.06)	0.99 (0.80–1.22)	1.32 (0.58–2.77)	1.33 (0.61–2.72)	0.60 (0.20–1.46)
50–69	1.02 (0.86–1.19)	1.25 (1.07–1.45)*	0.99 (0.85–1.15)	0.98 (0.54–1.69)	0.96 (0.58–1.53)	1.16 (0.73–1.79)
70–74	1.19 (0.86–1.64)	1.41 (1.05–1.89)	1.62 (1.24–2.10)*	1.20 (0.45–2.86)	0.67 (0.16–2.05)	1.42 (0.52–3.50)
> 74	0.97 (0.80–1.18)	1.09 (0.89–1.33)	1.16 (0.97–1.38)	1.27 (0.67–2.31)	0.99 (0.52–1.79)	1.03 (0.59–1.73)
Stage I						
Luminal A	0.60 (0.57–0.63)*	1.01 (0.97–1.05)	1.04 (1.00–1.07)	0.70 (0.63–0.77)*	0.99 (0.90–1.07)	1.14 (1.05–1.23)*
Luminal B	0.68 (0.61–0.76)*	0.90 (0.82–1.00)	0.96 (0.88–1.05)	0.83 (0.70–0.98)	1.17 (1.02–1.33)	1.29 (1.14–1.47)*
HER2 positive	0.52 (0.37–0.73)*	1.17 (0.90–1.52)	0.88 (0.68–1.13)	0.63 (0.34–1.09)	0.90 (0.55–1.41)	0.83 (0.52–1.27)
Triple negative	0.66 (0.56–0.77)*	0.94 (0.82–1.08)	0.93 (0.82–1.05)	0.83 (0.59–1.14)	1.08 (0.82–1.42)	1.29 (0.98–1.67)
Stage II						
Luminal A	0.82 (0.77–0.86)*	1.06 (1.01–1.12)	1.00 (0.95–1.05)	0.96 (0.85–1.07)	0.99 (0.88–1.10)	0.96 (0.87–1.07)
Luminal B	0.85 (0.78–0.92)*	0.99 (0.91–1.07)	0.92 (0.85–1.00)	1.05 (0.91–1.21)	1.20 (1.05–1.36)*	1.23 (1.08–1.39)*
HER2 positive	0.80 (0.65–0.97)	1.19 (1.00–1.41)	1.03 (0.87–1.21)	1.02 (0.71–1.44)	1.05 (0.74–1.46)	1.13 (0.83–1.53)
Triple negative	0.91 (0.81–1.01)	1.05 (0.95–1.17)	1.13 (1.03–1.25)*	0.99 (0.79–1.23)	1.07 (0.86–1.33)	1.09 (0.90–1.33)
Stage III						
Luminal A	0.92 (0.80–1.06)	1.12 (0.98–1.28)	0.96 (0.84–1.09)	0.70 (0.49–0.97)	1.09 (0.81–1.44)	0.92 (0.69–1.20)
Luminal B	0.98 (0.82–1.17)	0.99 (0.83–1.19)	1.11 (0.94–1.30)	0.91 (0.65–1.24)	1.01 (0.74–1.37)	0.89 (0.65–1.21)
HER2 positive	1.03 (0.77–1.36)	1.01 (0.75–1.33)	1.03 (0.79–1.33)	0.63 (0.33–1.14)	0.79 (0.41–1.41)	1.08 (0.67–1.68)
Triple negative	0.98 (0.78–1.21)	1.15 (0.93–1.41)	1.22 (1.00–1.47)	0.90 (0.54–1.46)	1.20 (0.76–1.84)	1.10 (0.71–1.65)
Stage IV						
Luminal A	0.90 (0.77–1.04)	1.21 (1.05–1.39)*	1.04 (0.91–1.19)	1.13 (0.70–1.77)	0.98 (0.61–1.52)	0.76 (0.47–1.19)
Luminal B	1.07 (0.88–1.30)	0.98 (0.80–1.20)	1.18 (0.99–1.41)	1.10 (0.52–2.20)	1.02 (0.56–1.76)	1.75 (1.01–2.98)
HER2 positive	1.37 (0.99–1.88)	1.16 (0.84–1.58)	1.14 (0.83–1.54)	1.13 (0.32–3.39)	1.47 (0.39–4.71)	0.63 (0.12–2.25)
Triple negative	1.16 (0.86–1.56)	1.24 (0.93–1.64)	1.29 (0.98–1.67)	1.47 (0.58–3.45)	0.92 (0.26–2.62)	1.46 (0.69–2.95)

First wave: March – September 2020, second wave: October 2020 – April 2021, Delta wave: May – December 2021
Luminal A: hormone receptor (HR)-positive, HER2-negative, grade 1 or 2, luminal B: HR-positive, HER2-positive or HER2-negative with grade 3, HER2 positive: HR-negative and HER2-positive, triple negative: HR- and HER2-negative.
* : statistical significant after correction for the false discovery rate. First significant p-value was 0.010 for the Dutch data and 0.006 for the Norwegian data.

cancer screening program. This resulted in a decrease in breast cancer incidence, just as in other countries [18–27]. The suspension of the screening program was probably solely responsible for the decrease in breast cancer incidence in Norway, since incidence only decreased in women eligible for screening. In the Netherlands, breast cancer incidence decreased in women eligible and not eligible for screening. The decrease in incidence in women not eligible for screening can probably be explained by the decreased number of Dutch patients presenting with cancer-related symptoms at the general practitioner (GP), i.e., the gatekeeper for the second line (breast clinic) care, at the start of the pandemic [28,29]. According to a Dutch cross-sectional survey, patients were reluctant to visit their GP because of fear of contracting the virus and to overload the health care system [29]. The health care avoidance seen in the Netherlands could be caused by the relatively high SARS-CoV-2 infection rate and COVID-19 death rate in the Netherlands, compared to Norway. Results from New Zealand, like Norway a country with low SARS-CoV-2 infection rates and COVID-19 death rates, also showed only minimal decreases in the number of breast cancer diagnoses during the start of the pandemic [30]. The stable incidence in Norway could be due to the low severity of the pandemic, resulting in no reluctance to visit the GP among women not eligible for screening.

After the first wave breast cancer incidence quite quickly reached pre-COVID levels in both the Netherlands and Norway, or even exceeded pre-COVID levels. Results from other countries, also experiencing suspensions of the screening program, also showed that breast cancer incidence quite quickly returned to normal after the first wave [18–23]. However, studies from Italy [24], Hungary [25], the United States [27], and Bavaria [26] showed that these countries/regions had more difficulties with reaching pre-COVID levels. The level of political regulation and the number of COVID-19 infections or deaths were comparable between those four countries/regions and other countries [31–33]. Hence, this probably does not explain the difference in incidence. The likely cause for the decline in incidence ranged from women still being hesitant to visit screening [24], to a relatively high number of COVID-19 patients in the hospitals [25] or intensive care units [26]. These cross-country comparisons showed that the cause for the decline in

incidence differed from country to country.

It cannot be concluded that the higher incidence of stage IV tumors, mainly in women aged 50–69 years, in the Netherlands during the second wave, was solely due to the COVID-19 pandemic. Other factors might influence the incidence as well, such as trends over time due to improved diagnostic methods. Although we assumed that the breast cancer incidence and age structure remained constant over time, we decided to specify a Poisson regression model post-hoc to make sure these potential trends over time did not influence the conclusion. The period 2014–2019, instead of 2017–2019, was chosen as a reference period to ensure sufficient observations for secular trend estimation. After adjusting for trends, we continued to find excess incidence in the age group 50–69, indicating that the increase in incidence of stage IV tumors in this age group is not solely driven by secular trends. However, we did not find sufficient evidence of excess incidence when adjusting for trends in the total Dutch population. When interpreting our results it should be kept in mind that our analyses are purely explorative and non-causal. It cannot be excluded that the higher incidence of stage IV tumors is due to chance. The higher incidence of stage IV tumors was only seen during a limited time. Hence, the impact on the absolute numbers of patients with a stage IV tumor is limited. As it cannot be concluded if the increase in incidence is due to delayed diagnosis, either due to delays in screening or delays in presentation at the GP, or to factors not related to the pandemic, women should be encouraged to attend the screening program when invited, and visit the GP in case of breast cancer symptoms, to prevent upstaging due to delays in diagnosis.

In the Netherlands, no decrease in the incidence of non-screen-detected tumors was seen during the first wave. Other studies of our group did show a decrease in the incidence of non-screen-detected tumors during weeks 12–16 (the beginning of the first wave), after which the incidence returned to normal levels [6,7]. The screening programs restarted during the first wave. Both countries had a different restart of their screening program. In the Netherlands, the screening program restarted at the beginning of July 2020 and reached 80% of its capacity at the beginning of October. In November 2020 the Dutch government decided to allow a maximum screening-interval of three years, due to COVID-19 induced delays and a shortage in mammography technologists (already existing pre-COVID). However, this screening-interval never exceeded an average of 32 months. In Norway, all screening centers had restarted Mid-August 2020, with a screening-capacity ranging between 55% and 121% [3]. The Norwegian breast cancer screening centers tried to catch-up the missed screens by extending their opening hours. This allowed the capacity to range between 87% and 129% in November 2020 [3] and resulted in an increased incidence of screen-detected tumors during the second wave. In the Netherlands an increase in the incidence of non-screen-detected tumors in women aged 50–74 years, was seen during the second wave. This suggests that part of the women experiencing screening delays detected their tumor by symptoms or a breast self-exam instead, or they scheduled their own mammogram [34]. A notable difference between the countries was a higher incidence of stage I tumors in Norway during the Delta wave, which can be attributed to the catch-up strategy of the screening program. During July and August a decrease in incidence was seen in Norway, both before and during the pandemic. This is because the Norwegian screening program does not invite or screen any women during July. The Norwegian data showed no evidence of a stage shift up till December 31st, 2021. Hence, the temporarily suspension of the Norwegian screening program might be a relatively safe measure to temporarily reduce the pressure on health care.

Strengths of this study include the inclusion of a large number of women diagnosed with breast cancer. For both countries all women diagnosed with breast cancer during the study period were included, thereby accurately reflecting the national situation. Limitations of the current study include the large number of Norwegian patients with missing data on tumor stage, with a higher percentage of patients with a missing tumor stage towards the end of the study period. MICE was used to impute missing values to avoid biased results. In addition, the current study did not adjust for trends over time, except in the post-hoc specified Poisson regression model. The crude breast cancer incidence has slowly been increasing in recent years in Norway [12,16]. This might have resulted in an underestimation of the decrease in total breast cancer incidence during the first wave, and an overestimation of the increase in total incidence during the Delta wave. Crude incidence remained constant over the years in the Netherlands, and is unlikely to have biased the results [35]. Finally, some of the patient groups included a small number of patients, thereby limiting the power of the analyses involving those patients.

Based on the results of this study three recommendations can be formulated to advance health policy during similar circumstances such as the COVID-19 pandemic. First of all, maintaining a low COVID-19 infection rate, as seen in Norway, will not only prevent COVID-19 deaths, but also seems to prevent a delay in the diagnosis of non-screen-detected breast cancers. Second, short-term suspension of the breast cancer screening program, as reported for Norway, might be a safe measure to temporarily decrease pressure on health care, as no stage shift was seen up till December 31st, 2021. Third, it is recommended to stimulate women to attend the screening program when invited, and visit the GP in case of breast cancer symptoms (e.g. via cancer campaigns), as a stage shift due to delay in diagnosis cannot be excluded based on the Dutch data. However, it can also not be concluded that this increase was (solely) due to the COVID-19 pandemic. Other factors might influence the incidence as well and the analyses of this study were purely explorative. Future studies should monitor the breast cancer incidence rates and the corresponding distributions of tumor stage, to show whether the Netherlands will also experience a catch-up in breast cancer diagnoses. Moreover, future studies should monitor the survival of breast cancer patients diagnosed during the COVID-19 pandemic as their survival might be affected by the delay in breast cancer diagnosis.

5. Conclusions

The results of the current study indicate that alterations in breast cancer incidence and tumor stage were related to a combined effect of the suspension of the screening program, health care avoidance as a result of the severity of the pandemic, and other unknown factors. A small temporary increase in the incidence of stage IV tumors was observed in the Netherlands, mainly in women aged 50–69 years. However, it cannot be concluded that this is (solely) due to the COVID-19 pandemic. No stage shift was observed in Norway, suggesting that the suspension of the screening program as in Norway is a safe measure to temporarily reduce the pressure on health care.

Ethics approval

Ethical approval for the Norwegian part of this study was obtained from the Regional committees for medical and health research ethics in Norway (reference number 478240). According to the Dutch Central Committee on Research involving Human Subjects, no ethical approval is needed for the Dutch part of this study, as it is a retrospective study, which uses data from the NCR.

CRediT authorship contribution statement

Anouk H. Eijkelboom: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Funding acquisition **Linda de Munck:** Conceptualization, Validation, Writing – review & editing, Supervision **Marthe Larsen:** Validation, Writing – review & editing **Maarten J. Bijlsma:** Methodology, Formal analysis, Writing – review & editing. **Vivianne C.G.:** Writing – review & editing. **Tjan-Heijnen, Carla H. van Gils, Mireille J.M. Broeders, Jan F. Nygård, Marc B.I. Lobbes, Charles W. Helsper,**

Ruud M. Pijnappel, Luc J.A. Strobbe, Jelle Wesseling: Writing – review & editing. **Solveig Hofvind:** Conceptualization, Writing – review & editing, supervision **Sabine Siesling:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

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Data availability statement

All data collected for the study, including a data dictionary defining each field in the set, will be made available via the NCR (https://iknl.nl/en/ncr/apply-for-data) and CRN (https://helsedata.no/en/forvaltere/cancer-registry-of-norway/cancer-registry-of-norway/#nav-heading-3) upon request and after approval of a proposal from the date of publication. The plan for the statistical analysis will be made available by the corresponding author upon request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2023.102481.

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