Double trouble: exploring risk factors to better predict contralateral breast cancer

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APPENDIX 1

Comprehensive trends in incidence, treatment, survival and mortality of first primary invasive breast cancer stratified by age, stage and receptor subtype in the Netherlands between 1989–2017

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Abstract

This study aimed to provide a comprehensive overview of trends in incidence, survival, mortality and treatment of first primary invasive breast cancer (BC), according to age, stage and receptor subtype in the Netherlands between 1989–2017. Data from all women diagnosed with first primary stage I–IV breast cancer (N=320,249) were obtained from the Netherlands Cancer Registry. BC mortality and general population data were retrieved from Statistics Netherlands. Age-standardized incidence and mortality rates were calculated with annual and average annual percentage change statistics (APC and AAPC). The relative survival (RS) was used as estimator for disease-specific survival. The BC incidence for all BC patients combined increased until 2013 from 126 to 158 per 100,000 person-years, after which a declining trend was observed. Surgery became less extensive, but (neo)adjuvant systemic treatments and their combinations were given more frequently. The RS improved for all age groups and for most stages and receptor subtypes, but remained stable for all subtypes since 2012–2013 and since 2000–2009 for stage IV BC at 15–years of follow-up. Overall, the five- and ten-year RS increased from 76.8% (95% confidence interval [CI]:76.1, 77.4) and 55.9% (95%CI:54.7, 57.1) in 1989–1999 to 91.0% (95%CI:90.5, 91.5) and 82.9% (95%CI:82.2, 83.5), respectively, in 2010–2016. BC mortality improved regardless of age and overall decreased from 57 to 35 per 100,000 person-years between 1989–2017. In conclusion, the BC incidence in the Netherlands has steadily increased since 1989, but the latest trends show promising declines. Survival improved markedly for most patients and the mortality decreased regardless of age.

Introduction

Breast cancer (BC) is the most common cancer and leading cause of cancer related death among women in most countries worldwide[1]. It accounts for almost one in four cancers (24.2%) in women, with an estimated 2.1 million new cases globally in 2018[1]. The incidence of BC has been rising for decades in most developed countries and is expected to continue to rise[1]. Meanwhile, mortality rates have been steadily decreasing in most European, American and other high-income countries, while weak-to-moderate increases in mortality have been observed in some lower-to-middle income countries[2-4]. Worldwide, BC is responsible for 15.0% of all cancer-related deaths in women, with an estimated 627,000 deaths in 2018[1]. However, BC survival has improved significantly in recent decades for all age groups in most countries[4].

The rising trends in BC incidence are attributed to the increased presence of known risk-factors, including early age at menarche, late age at menopause, low parity, nulliparity, not breastfeeding, use of oral contraceptives, hormone replacement therapy and older age at first childbearing[5,6]. Other factors that have been implicated to influence BC incidence include changes in lifestyle factors such as excessive alcohol intake, increasing prevalence of obesity and a decrease in physical activity[5,7,8]. Moreover, screening programmes could influence incidence, but can also influence stage distribution and improvements in BC survival and eventually mortality[4]. Improvement in survival could also be explained by earlier detection outside screening, improvements in treatment, access to appropriate healthcare and increasing disease awareness[4,5].

In the Netherlands, incidence, survival and mortality trends of BC are generally comparable to those observed globally, as shown by various studies[9-13]. However, studies describing and interpreting these endpoints simultaneously are scare and many of the currently available trend studies in the Netherlands or elsewhere in Europe are no longer up-to-date. Additionally, receptor subtype specific trends have remained largely unexplored, while these subtypes have become increasingly important in recent years as targets of new personalised ([neo-]adjuvant) treatment strategies[13-15]. Comprehensive trend analyses are useful for medical doctors to better inform patients about their disease and are of great interest to breast cancer researchers, policy makers, and patient advocates. Therefore, this study aimed to provide an up-to-date and comprehensive overview of first primary invasive breast cancer trends in incidence, treatment, survival and mortality in the Netherlands between 1989–2017. Trend evaluation was performed for all BC patients combined and stratified by age group, stage and receptor subtype.

Materials and Methods

Data sources

Data from all women aged ≥18 years, diagnosed with tumour, node and metastasis (TNM) stage I–IV first primary invasive BC between 1989–2017 were obtained from the nationwide population-based Netherlands Cancer Registry (NCR), hosted by the Netherlands Comprehensive Cancer Organisation (IKNL). The NCR contains records on pathologically confirmed cancers after notification by the National Pathology Archive (PALGA). Yearly linkage with the national discharge register data ensures high completeness. All tumours in the registry are coded according to the International Classification of Diseases for Oncology (ICD-O). Patient-, tumour- and treatment-related characteristics were collected from medical records from all Dutch hospitals by trained tumour registrars from the NCR. Information on vital status and date of death is regularly obtained through linkage with the Dutch Municipal Personal Records database and was updated until 31 January 2018. Data on invasive BC mortality cases and data on the general Dutch female population were obtained from Statistics Netherlands[16,17].

Tumour stage, receptor subtype and treatment

The Union for International Cancer Control (UICC) TNM classification of malignant tumours was used to categorize BC stage. From 1989 to 2017, various editions have been introduced, ranging from the 4th to the 8th edition, and resulted in changes in the definition of tumour stage[18]. Most noticeably, going from the 5th to the 6th edition in 2003, a shift from stage II to stage III BC occurred as tumours with more than three positive lymph nodes were categorized as stage III according to the 6th edition, whereas they were previously categorized as stage II disease. All tumours were classified according to the TNM classification valid at the date of diagnosis. If pathological stage was missing, clinical stage was used.

Oestrogen receptor (ER) and progesterone receptor (PR) status were determined by immunohistochemistry (IHC) and were actively registered by the NKR since 2005. Tumours were defined as ER/PR-positive (ER+/PR+) when >10% of the tumour cells stained positive (from 2011 the threshold was ≥10%). Human epidermal growth factor receptor 2 (HER2) was introduced and registered since 2006. Tumours were defined HER2-positive (HER2+) if IHC was 3+ (at least 10% of cells showed strong intensity membrane staining) or when confirmed positive with in situ hybridization (FISH/CISH). HER2-negativity (HER2-) was declared by IHC when less than 10% of the cells showed membrane staining or when FISH/CISH test outcome was negative. Tumours with IHC 2+ without FISH/CISH confirmation available were considered unknown. For the analyses, we grouped receptor subtypes into: hormone receptor (HR)+/HER2- (e.g., ER+ and/or PR+ and HER2-), HR+/HER2+ (i.e., ER+ and/or PR+ and HER2+), HR-/HER2+ (i.e., ER-/PR-/HER2+) and HR-/HER2- (i.e., ER-/PR-/HER2-).

Treatment data on surgery, radiotherapy, chemotherapy and endocrine therapy were included in the NCR since 1989 on an aggregated level. Type of chemotherapy (e.g. taxane-based and/or anthracycline-based) and endocrine therapy (e.g. tamoxifen and/or aromatase inhibitors) were specified by the NCR since 2003. Targeted therapy was included in the NCR since 2005 and almost exclusively existed of trastuzumab (~99%). Treatment proportions were determined based on specific treatments received by patients at any time during their treatment process, irrespective of duration or whether it was completed. Type of endocrine therapy (tamoxifen and/or aromatase inhibitors) was specified based on the first administered treatment, as information on treatment in the NCR was only available up to one year after diagnosis.

Statistical analyses

Annual crude and age-standardized incidence and mortality rates for the period 1989–2017 were calculated per 100,000 person-years (PY) using the general population size, as obtained from Statistics Netherlands, as person-time denominator[19]. Crude rates were calculated as three-year moving averages with two-year moving averages calculated at both ends of the study period and rates were age-standardized (European Standardized Rates, ESR) to the 2013 European Standard Population 95+ (2013 ESP 95+)[20,21].

Trend changes over time were evaluated with joinpoint regression analyses, with each model representing a series of connected straight lines on a log scale and with each joinpoint denoting a statistically significant change in trends. Annual Percentage Changes (APC) were determined for each trend segment and provide an overview of all trend changes over time. The Average Annual Percentage Change (AAPC) provides a good summary measure of the overall trend and was determined over the whole period[22,23]. Both APCs and AAPCs were calculated from the slope coefficients of the underlying joinpoint models and were determined with the freely available Joinpoint Regression Program version 4.7.0.0 and based on the previously determined age-standardized incidence and mortality rates[24]. Two-sided significance was determined at an α=0.05 level. Analyses were performed using the "Uncorrelated Error Model" and the "Grid Search Method" setting, with the number of points placed between observed x-values set at 3. For model selection, the recommended Bayesian Information Criteria 3 method was used[23]. The minimum allowed number of joinpoints was set at zero. The maximum allowed number of joinpoints to be tested was based on the algorithmic recommendation table included in the Joinpoint help manual 4.7.0.0 (available at https://surveillance.cancer.gov/joinpoint), allowing a maximum of five joinpoints for overall, age- and stage-specific rates and a maximum number of two joinpoints for the subtype-specific rates. The parametric method was used to calculate 95% Confidence Intervals (CI). Further programme parameters were kept at their default settings.

The relative survival (RS) was used as an estimator of disease-specific survival

and is the ratio between the observed BC survival of the patients and the expected survival in the general Dutch population, matched by attained age, sex and calendar year. Expected survival was determined using nationwide lifetables of the general Dutch population adapted from Statistics Netherlands, containing survival probability data of women aged 0–99 years in 1989 to 2018. Outcomes were age-standardized using the traditional method with cumulative weights based on the age-distribution in the 2013 ESP 95+[20]. Used weights were 0.47, 0.14, 0.30 and 0.09 for the <40, 40–49, 50–74, and ≥75 age groups, respectively[25]. The RS was calculated using the Ederer II approach[26]. Brenner's period analysis was used to derive more up-to-date estimates of the RS by exclusively considering the survival time data of patients during a (recent) time period of interest by left-truncating all observations at the start of the time period and right-censoring them at its end. This in contrast with the traditional cohort methodology, which provides outdated long-term survival estimates based on patients that were diagnosed many years ago without consideration of ongoing improvements. A more detailed description of the period analysis methodology is provided elsewhere[27]. End of follow-up was defined as year of death, year of emigration or 2016, whichever came first. We limited survival analyses to 2016 to avoid potential overestimation of long-term survival outcomes following period analyses[27].

All data analyses were performed using the Stata Software Package, version 14.2 and are presented for all BC patients combined and stratified by age group (<40, 40–49, 50–74, and ≥75), stage and receptor subtype when sample size allowed. Patients with missing or unknown values were excluded from the analyses. Likewise, women with unavailable treatment data (e.g. due to not receiving any treatment or incomplete registration) were excluded. To overcome difficulties in trend recognition over time due to the changes in tumour stage classification, stages II and III BC were analysed individually as well as grouped together. Cut-off points for the age groups were based on the age at invitation to the current Dutch national mammographic screening programme (50–74 years), with younger and older women grouped separately.

Results

Study population

In total, 320,249 women were diagnosed with first primary invasive BC in the Netherlands between 1989–2017 and of all women who died (N=2,027,353), 97,187 died from BC (4.8%). The median age at diagnosis was 61 years (range 18–107 years). All population characteristics are presented in Table 1. Data on the yearly number of BC deaths are included in supplementary Table S1.

Incidence

The BC incidence for all BC patients combined significantly increased from 126 to 153 per 100,000 PY (AAPC=0.7% [95%CI:0.6, 0.9]) between 1989–2017 (Figure 1A and Table S2). Age-specific results showed an increase in BC incidence from 15 to 20 (AAPC=1.0% [95%CI:0.5, 1.5]) in women aged <40 years, 150 to 176 (AAPC=0.5% [95%CI:0.2, 0.7]) for 40-49 years, and 237 to 315 per 100,000 PY (AAPC=1.1% [95%CI:0.8, 1.3]) in women aged 50-74 years at time of diagnosis. In women aged ≥75, the incidence decreased from 300 to 269 per 100,000 PY (AAPC=−0.3% [95%CI:−0.5, −0.2]) between 1989–2017.

In some sub-periods, significant declines in BC incidence were observed for all BC patients combined; in the period 1993–1997 the incidence declined from 145 to 141 (APC=−1.3% [95%CI:−2.1, −0.5]) and in the period 2013-2017 from 158 to 153 per 100,000 PY (APC=−0.8% [95%CI:−1.1, −0.5]). In women aged 40–49 years, the BC incidence significantly declined from 2006 onward from 182 to 176 per 100,000 PY (APC=−0.4% [95%CI:−0.6, −0.2]) and in women aged 50–74 years it declined from 330 to 315 per 100,000 PY (APC=−1.1% [95%CI:−1.6, −0.7]) between 2013 and 2017. In women aged ≥75, BC incidence decreased since 1998 from 339 to 269 per 100,000 PY (APC=−1.2% [95%CI:−1.3, −1.1]) in 2017 (Table S2).

Tumour stage

The stage-specific incidence rates of stage I BC for all BC patients combined increased from 36 to 72 per 100,000 PY (AAPC=2.6% [95%CI:2.1, 3.0]) between 1989–2017. In the same period, the combined incidence of stages II and III BC decreased from 80 to 72 per 100,000 PY (AAPC=−0.3% [95%CI:−0.5, −0.1]). The incidence of stage IV BC remained stable around 8 per 100,000 PY (AAPC=−0.2% [95%CI:−0.6, 0.2]) (Figure S1 and Table S3).

Prior to the shift from the 5th to 6th edition of the TNM classification, the incidence of stages II and III combined increased from 80 to 84 per 100,000 PY (AAPC=0.5% [95%CI:0.2, 0.7]) between 1989 and 2003 and declined from 84 to 72 per 100,000 PY (AAPC=−1.1% [95%CI:−1.3, −0.8]) after the shift in 2003–2017. Similar declines after the shift were observed for stages II and III individually (Table S4).

Table 1. Patient, tumour and treatment characteristics of all women diagnosed with first primary invasive breast cancer in the Netherlands between 1989–2017

	1898-1992		1993-1996		1997-2000		2001-2004		2005-2008		2009-2012		2013-2017		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Age at diagnosis																
Median	61.7		61.0		60.1		59.2		59.7		60.5		61.4		60.5	
Range	21.8– 100.3		20.4– 107.3		18.7– 104.2		18.7–100.4		18.9–102.1		19.2–103.1		18.5–103.8		18.5–107.3	
<40	2,364	7.3	2,463	6.6	2,519	6.2	2,829	6.4	2,682	5.7	2,660	5.2	3,378	5.1	18,895	5.9
40–49	6,085	18.8	7,028	18.8	7,639	18.8	8,423	18.9	8,986	19.0	9,160	17.9	10,880	16.3	58,201	18.2
50–74	17,547	54.1	20,492	54.8	22,223	54.7	24,949	56.0	27,385	57.9	30,789	60.3	41,930	62.7	185,315	57.9
≥75	6,440	19.9	7,444	19.9	8,265	20.3	8,333	18.7	8,215	17.4	8,450	16.5	10,691	16.0	57,838	18.1
Tumour stage																
I	9,992	31.4	13,348	36.6	14,972	37.5	16,558	37.6	18,848	40.1	22,816	44.8	31,212	46.7	127,746	40.3
II	16,505	51.8	17,863	49.0	19,430	48.7	20,107	45.7	19,114	40.7	19,046	37.4	24,688	37.0	136,753	43.1
III	3,282	10.3	3,282	9.0	3,401	8.5	5,211	11.8	6,814	14.5	6,673	13.1	7,255	10.9	35,918	11.3
IV	2,083	6.5	1,996	5.5	2,103	5.3	2,145	4.9	2,236	4.8	2,344	4.6	3,633	5.4	16,540	5.2
Unknown	574		938		740		513		256		180		91		3,292	
Tumour size†																
T1	14,190	45.2	18,101	50.2	20,640	52.3	23,797	54.6	26,702	57.2	30,041	59.5	40,559	61.2	174,030	55.4
T2	12,741	40.6	13,491	37.4	14,387	36.5	15,852	36.3	16,264	34.9	16,587	32.9	20,126	30.3	109,448	34.9
T3	1,617	5.1	1,608	4.5	1,616	4.1	1,738	4.0	1,886	4.0	2,125	4.2	3,346	5.0	13,936	4.4
T4	2,866	9.1	2,835	7.9	2,820	7.1	2,232	5.1	1,793	3.8	1,737	3.4	2,291	3.5	16,574	5.3
Unknown	1,022		1,392		1,183		915		623		569		557		6,261	
Lymph node status†																
N0	17,679	56.8	21,621	60.2	23,032	59.0	24,682	57.1	27,959	60.1	31,518	62.3	44,087	66.3	190,578	60.9
N1	12,708	40.8	13,640	38.0	15,427	39.5	15,247	35.3	12,959	27.8	13,849	27.4	17,742	26.7	101,572	32.5
N2	659	2.1	590	1.6	528	1.4	2,125	4.9	3,440	7.4	3,052	6.0	2,545	3.8	12,939	4.1
N3	104	0.3	49	0.1	59	0.2	1,165	2.7	2,199	4.7	2,183	4.3	2,159	3.2	7,918	2.5
Unknown	1,286		1,527		1,600		1,315		711		457		346		7,242	
Histological grade§																
Grade 1	1,022	8.1	1,611	10.3	4,248	16.1	6,988	19.4	9,196	22.7	10,295	24.3	14,031	24.5	47,391	20.6
Grade 2	4,207	33.5	5,824	37.3	11,179	42.3	16,202	45.0	18,032	44.5	19,275	45.6	28,176	49.2	102,895	44.6
Grade 3	7,330	58.4	8,163	52.3	10,997	41.6	12,833	35.6	13,249	32.7	12,723	30.1	15,027	26.3	80,322	34.8
Unknown	19,877		21,829		14,222		8,511		6,791		8,766		9,645		89,641	
ER-status																
Positive									37,675	81.7	41,961	83.9	55,964	84.7	135,600	83.6
Negative									8,433	18.3	8,073	16.1	10,116	15.3	26,622	16.4
Unknown									1,160		1,025		799		2,984	

Table 1. Continued

	1898-1992		1993-1996		1997-2000		2001-2004		2005-2008		2009-2012		2013-2017		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
PR-status																
Positive									29,126	65.9	33,193	67.5	45,736	69.3	108,055	67.8
Negative									15,104	34.1	16,011	32.5	20,269	30.7	51,384	32.2
Unknown									3,038		1,855		874		5,767	
HER2-status																
Positive									6,435	15.3	6,892	14.3	8,766	13.7	22,093	14.3
Negative									35,617	84.7	41,291	85.7	55,143	86.3	132,051	85.7
Unknown									5,216		2,876		2,970		11,062	
Receptor subtype‡																
HR+/HER2-									30,594	73.4	35,865	74.8	48,453	75.9	114,912	74.9
HR+/HER2+									3,929	9.4	4,481	9.3	5,843	9.2	14,253	9.3
HR-/HER2+									2,384	5.7	2,329	4.9	2,908	4.6	7,621	5.0
HR-/HER2-									4,765	11.4	5,287	11.0	6,652	10.4	16,704	10.9
Unknown									5,596		3,097		3,023		11,716	
Surgery + Radiotherapy#																
BCS + RT	8,480	26.1	12,749	34.1	15,315	37.7	19,608	44.0	22,796	48.2	25,494	49.9	36,977	55.3	141,419	44.2
BCS + No RT	486	1.5	781	2.1	1,028	2.5	847	1.9	712	1.5	754	1.5	1,256	1.9	5,864	1.8
Mastectomy + RT	4,433	13.7	5,653	15.1	6,041	14.9	6,063	13.6	5,910	12.5	6,276	12.3	8,579	12.8	42,955	13.4
Mastectomy + No RT	7,609	23.5	13,662	36.5	14,591	35.9	14,105	31.7	13,518	28.6	13,715	26.9	13,215	19.8	90,415	28.2
Surgery (Unspecified) + RT	3,855	11.9	500	1.3	32	0.1	13	0.0	5	0.0	2	0.0	3	0.0	4,410	1.4
Surgery (Unspecified) + No RT	4,416	13.6	610	1.6	82	0.2	11	0.0	3	0.0	4	0.0	8	0.0	5,134	1.6
No surgery + RT	730	2.3	574	1.5	412	1.0	395	0.9	302	0.6	263	0.5	295	0.4	2,971	0.9
No surgery + No RT	2,427	7.5	2,898	7.7	3,145	7.7	3,492	7.8	4,022	8.5	4,551	8.9	6,546	9.8	27,081	8.5
Chemotherapy																
Taxane-containing CT¶	4	0.0	8	0.0	68	0.2	159	0.4	3,589	7.6	5,947	11.6	3,175	4.7	12,950	4.0
Anthracycline-containing CT**	6	0.0	26	0.1	125	0.3	3,673	8.2	3,299	7.0	2,016	3.9	1,195	1.8	10,340	3.2
Taxane- and anthracycline-containing CT††	0	0.0	0	0.0	6	0.0	127	0.3	2,297	4.9	10,521	20.6	22,024	32.9	34,975	10.9
CT (Other/ Unspecified)§§	4,329	13.3	5,483	14.6	9,849	24.2	11,245	25.3	8,804	18.6	4,029	7.9	306	0.5	44,045	13.8
No CT	28,097	86.6	31,910	85.3	30,598	75.3	29,330	65.9	29,279	61.9	28,546	55.9	40,179	60.1	217,939	68.1

Table 1. Continued

	1898-1992		1993-1996		1997-2000		2001-2004		2005-2008		2009-2012		2013-2017		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Endocrine therapy‡‡																
Tamoxifen first	18	0.1	38	0.1	143	0.4	9,649	21.7	21,043	44.5	26,104	51.1	29,774	44.5	86,769	27.1
Aromatase inhibitors first	0	0.0	1	0.0	2	0.0	863	1.9	2,335	4.9	3,999	7.8	8,950	13.4	16,150	5.0
Ovarian ablation##	9	0.0	91	0.2	194	0.5	184	0.4	118	0.2	113	0.2	186	0.3	895	0.3
ET (Other/ Unspecified)¶¶	9,708	29.9	11,436	30.6	14,630	36.0	9,145	20.5	0	0.0	0	0.0	4	0.0	44,923	14.0
No endocrine therapy	22,701	70.0	25,861	69.1	25,677	63.2	24,693	55.4	23,772	50.3	20,843	40.8	27,965	41.8	171,512	53.6
Systemic therapy																
Chemotherapy only	3,829	11.8	4,670	12.5	6,683	16.4	6,490	14.6	4,448	9.4	4,633	9.1	5,598	8.4	36,351	11.4
Endocrine therapy only	9,225	28.4	10,719	28.6	11,604	28.5	11,191	25.1	11,747	24.9	14,436	28.3	20,616	30.8	89,538	28.0
Chemotherapy and Endocrine therapy	510	1.6	847	2.3	3,365	8.3	8,605	19.3	9,843	20.8	12,965	25.4	14,105	21.1	50,240	15.7
Targeted therapy***	0	0.0	0	0.0	0	0.0	115	0.3	3,751	7.9	5,075	9.9	7,220	10.8	16,161	5.0
No systemic therapy	18,872	58.2	21,191	56.6	18,994	46.7	18,133	40.7	17,479	37.0	13,950	27.3	19,340	28.9	127,959	40.0
Total	32,436	100.0	37,427	100.0	40,646	100.0	44,534	100.0	47,268	100.0	51,059	100.0	66,879	100.0	320,249†††	100.0

Abbreviations: HR= hormone receptor, HER2= human epidermal growth factor receptor2, ER= oestrogen receptor, PR= progesterone receptor, CT= chemotherapy, ET= endocrine therapy, RT= radiotherapy, NCR= Netherlands Cancer Registry, BCS= breast-conserving surgery, AI= aromatase inhibitor

*****The various elements included in the table were collected by the NCR at different moments in time. ER and PR-status were routinely collected and included in the NCR since 2005 and HER2-status since 2006. Specification of chemotherapy and endocrine therapy regimens in the NCR has been done since 2003. Target therapy was routinely collected and included in the NCR since 2005 (mainly trastuzumab). Treatment data in the NCR is collected up to one year after initial cancer diagnosis. The data may still include 162 in situ BC cases due to discrepancies in registration within the dataset. Percentages may not total to 100% due to rounding.

† Tumour size and Lymph node status are based on the pathological stage, but clinical stage was used if pathological stage was unavailable.

§ Including 502 first primary BCs that were defined as "undifferentiated" in the NCR.

‡ HR+ = ER+ and/or PR+, HR- = ER- and PR-.

Patients that received both BCS and mastectomy were included in the mastectomy group.

¶ The chemotherapy regimen contains taxanes, but no anthracyclines.

** The chemotherapy regimen contains anthracyclines, but no taxanes.

†† The chemotherapy regimen contains both taxanes and anthracyclines.

§§ All other chemotherapy regimens (e.g. cyclophosphamide/cisplatine containing regimes) and/or chemotherapy not further specified.

‡‡ The NCR codes aromatase inhibitors specifically; tamoxifen is coded as hormonal treatment. Both treatments were included when provided as initial treatment.

Ovarian ablation includes LHRH agonist treatment, radiotherapy and/or surgical removal of the ovaries to reduce oestrogen production in pre-menopausal women.

¶¶ All other hormonal treatments (e.g. fulvestrant) and/or not further specified.

*** Patients received targeted therapy either alone or in combination with CT, ET, or both.

††† Total numbers provided do not correspond with those for the ER, PR, HER2 and the receptor subtype groups due to their inclusion since 2005-2009.

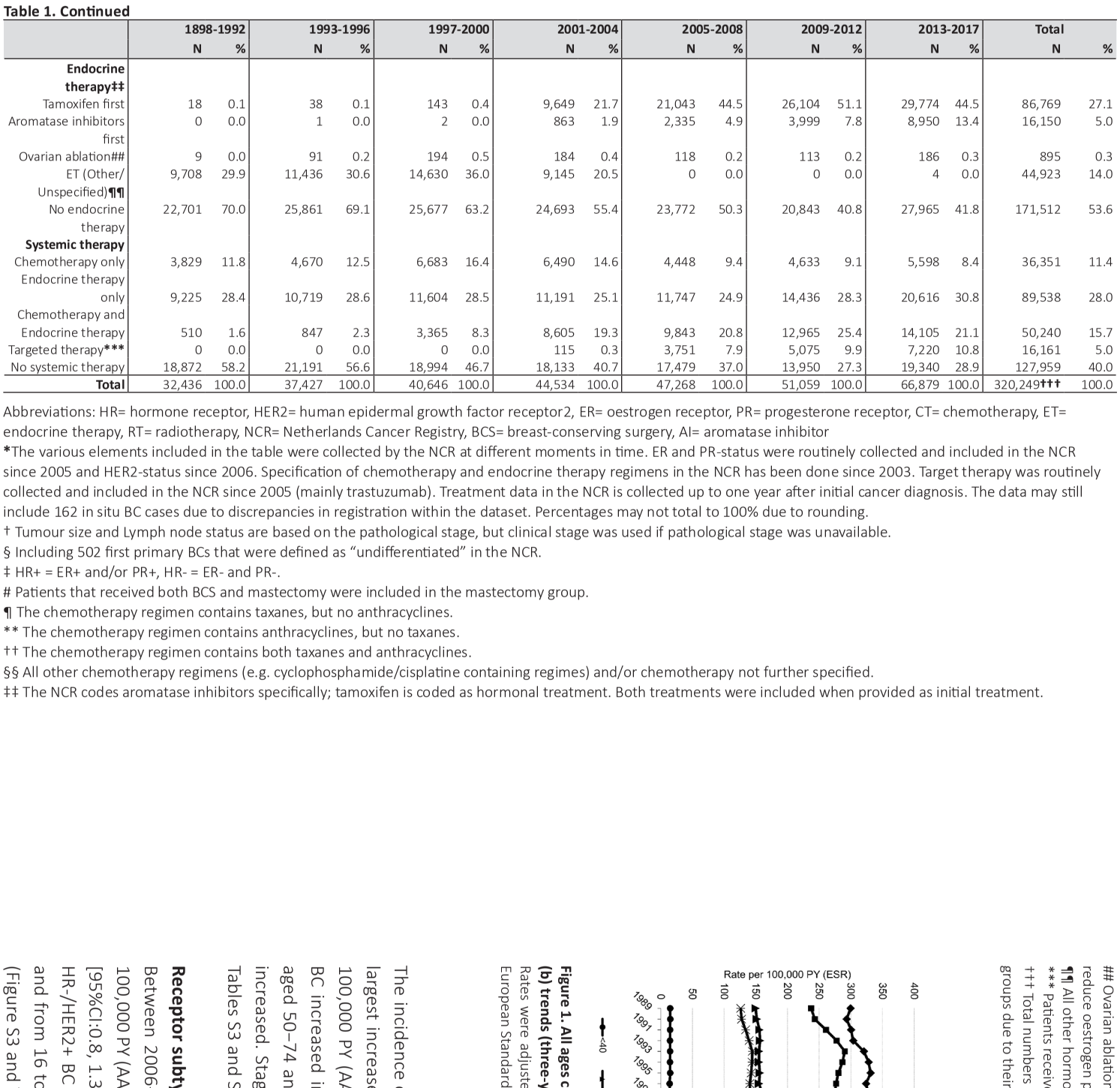


Figure 1. All ages combined and age-specific first primary invasive breast cancer incidence (a) and mortality (b) trends (three-year moving averages) in the Netherlands in the period 1989–2017
Rates were adjusted for age (European Standard Rates, ESR) by direct standardization according to the 2013 European Standard Population 95+ and calculated per 100,000 person-years (PY)

The incidence of stage I BC increased for all age groups between 1989–2017, with the largest increase observed in women aged 50–74 years, increasing from 69 to 176 per 100,000 PY (AAPC=3.5% [95%CI:3.0, 3.9]). The combined incidence of stages II and III BC increased in women aged <40 and 40–49 years, whereas it decreased in women aged 50–74 and ≥75 years. In women aged 40–49 years, the incidence of stage IV BC increased. Stage IV incidence remained stable for the other age groups (Figure S2 and Tables S3 and S4).

Receptor subtype

Between 2006–2017, the incidence of HR+/HER2- BC increased from 104 to 112 per 100,000 PY (AAPC=0.7% [95%CI:0.5, 0.9]) and from 12 to 13 per 100,000 PY (AAPC=1.0% [95%CI:0.8, 1.3]) for HR+/HER2+ BC for all ages combined. Meanwhile, the incidence of HR-/HER2+ BC declined from 8 to 7 per 100,000 PY (AAPC=–0.9% [95%CI:–1.7, –0.2]) and from 16 to 15 per 100,000 PY (AAPC=–0.3% [95%CI:–0.6, –0.0]) for HR-/HER2- BC (Figure S3 and Table S5).

HR+/HER2- BC incidence decreased slightly from 123 to 121 per 100,000 PY (AAPC=−0.3% [95%CI:−0.6, −0.0]) in women aged 40–49 years, whereas it significantly increased among women aged <40 and 50–74 years between 2006–2017. The incidence of HR+/HER2+ BC increased for women aged <40, 40–49 and 50–74 years. No changes in incidence of HR+/HER2- and HR+/HER2+ BC were observed since 1989 among women aged ≥75 years Concurrently, the incidence of HR-/HER2+ BC decreased from 15 to 13 (AAPC=−1.8% [95%CI:−2.3, −1.3]), and HR-/HER2- BC decreased from 29 to 27 per 100,000 PY (AAPC−0.7 [95%CI:−1.1, −0.3]) in women aged 50−74 years. The HR-negative BC incidence remained stable for the remaining age groups (<40, 40–49 and ≥75 years) regardless of HER2-status (Figure 2 and Table S5).

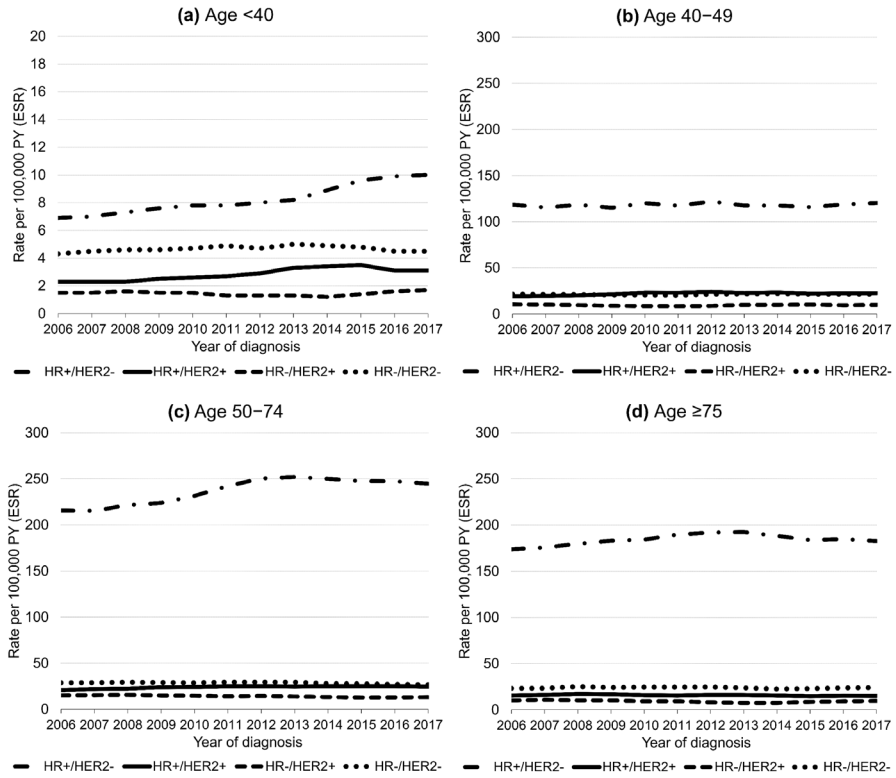


Figure 2. Incidence trends in the Netherlands stratified by receptor subtype between 2006–2017 in women diagnosed with first primary invasive breast cancer

Rates were adjusted for age (European Standard Rates, ESR) by direct standardization according to the 2013 European Standard Population 95+ and calculated per 100,000 person-years (PY). HR+= ER+ and/or PR+, HR-= ER- and PR-. Information on ER/PR and HER2-status was routinely collected by the Dutch cancer registry since 2005 and 2006, respectively. Note the different scaling in (a)

Treatment strategies

Surgery and radiotherapy

The proportion of women with BC that underwent surgery remained stable around 90% since 1989. Breast-conserving surgery (BCS) became the preferred surgical intervention since 2003 with 60.1% of all surgically treated patients undergoing BCS in 2017 (Figure 3). Radiotherapy use increased from 55.4% in 1989 to 70.1% in 2017 and was almost exclusively given in combination with surgical treatment (up to 99.6% in 2013−2017) (Figure 3 and Table 1). The most commonly provided local treatment was BCS followed by radiotherapy, with 55.3% of BC patients receiving this combination in 2013−2017 (Table 1).

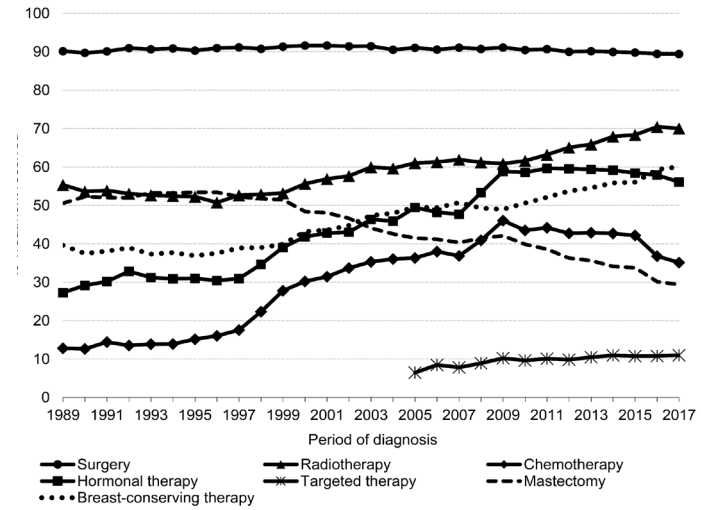


Figure 3. Proportion of treatment received by patients with first primary invasive breast cancer in the Netherlands between 1989–2017

Targeted therapy (mainly trastuzumab) was routinely collected by the NCR since 2005. Cumulative proportion were calculated per treatment strategy and based on treatment received (yes/no). Proportions of mastectomy and breast-conserving surgery were calculated based on the proportion of patients receiving surgery. Patients that received both surgical treatments were included in the mastectomy group

Systemic treatment

The use of any systemic treatment increased from 41.8% in 1989−1992 to 71.1% in 2013−2017. Most women received endocrine therapy only (28.4% in 1989−1992 and 30.8% in 2013−2017). The proportion of women that received both chemotherapy and endocrine therapy increased from 1.6% in 1989−1992 to 25.4% in 2009−2012, but slightly declined to 21.1% in 2013−2017. The use of targeted therapy (mainly trastuzumab) increased from 7.9% in 2005−2008 to 10.8% in 2013−2017 (Figure S4).

Trends in systemic treatment use over time according to age, stage and receptor subtype are included in Figure S5.

Chemotherapy

The overall proportion of women that received chemotherapy increased from 12.8% in 1989 to 46.0% in 2009, and decreased to 35.1% in 2017 (Figure 3). Chemotherapy use likewise decreased since 2009 for most age groups and stages, and for the HR+/HER2- subtype, but remained stable in women aged ≥75 years (2–3%) and in women with stage IV BC (41–43%), as shown in Figure S6. Among all women receiving chemotherapy, the proportion treated with both taxane and anthracycline containing regimens increased from 5.7% in 2003–2005 to 79.3% in 2015–2017 (Figure S7a).

Endocrine therapy

Endocrine therapy use increased from 27.3% in 1989 to 59.6% in 2011, and slightly decreased to 56.1% in 2017 (Figure 3). Most patients received tamoxifen as initial endocrine therapy. Use of tamoxifen for all BC patients combined was stable at 88.2–91.8% between 2003–2005 and 2009–2011, and subsequently decreased to 74.5% in 2015–2017. The use of aromatase inhibitor as initial endocrine therapy increased from 11.2% to 25.0% between 2003–2005 and 2015–2017 (Figure S7b). Endocrine therapy use increased among women of all ages and for most BC stages (stage I–III), as shown in Figure S8.

Relative survival

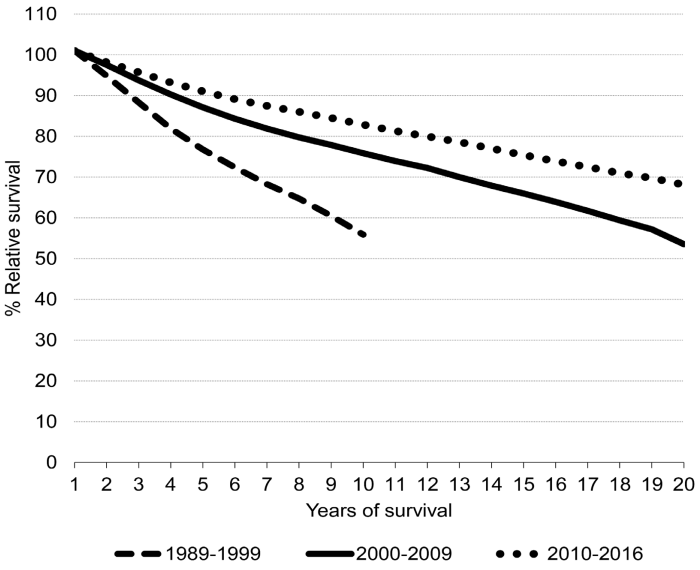
The RS at five and ten years of follow-up for all BC patients combined was 76.8% (95%CI:76.1, 77.4) and 55.9% (95%CI:54.7, 57.1) in 1989–1999, respectively, and increased to 91.0% (95%CI:90.5, 91.5) and 82.9% (95%CI:82.2, 83.5) in 2010–2016. Between 2000–2009 and 2010–2016, the 15-year RS increased from 66.0% (95%CI:65.2, 66.7) to 75.4% (95%CI:74.6, 76.2) and the 20-year RS increased from 53.5% (95%CI:52.2, 54.8) to 68.1% (95%CI:67.1, 69.1) (Figure 4).

The RS improved for all age groups and most stages between 1989–1999 and 2010–2016, but the 15-year RS remained stable for stage IV BC between 2000–2009 (RS=4.6% [95%CI:3.1, 6.4]) and 2010–2016 (RS=7.2% [95%CI:4.6, 10.5]). The survival of all receptor subtypes improved between 2006–2011 and 2012–2013, but no further improvements were observed in the subsequent period 2014–2016 (Figure 5 and Table S6).

The RS improved for all women aged <40, 40–49 and 50–74 years with stages I to III BC between 1989–1999 and 2010–2016 for all years of follow-up. The RS at ten and 15 years of follow-up remained stable for those with stage IV BC since 2000–2009 and likewise did not improve since 2000–2009 in women aged ≥75 years with any stage BC (Figure S9 and Table S7). The five-year RS of all receptor subtypes remained stable since 2012–2013 irrespective of age(Figure S10 and Table S8). Survival outcomes were overall slightly lower in women aged ≥75 years in comparison to other age groups and deteriorated with advancing stage for all age groups (Figures 5 and S9, and Tables S6 and S7).

Mortality

The BC mortality for women of all ages decreased from 57 to 35 per 100,000 PY (AAPC=–1.8% [95%CI:–1.9, –1.7]) between 1989–2017. Similar trends were observed for all age groups, as shown in Figure 1B and Table S2.



Time period	1989–1999	2000–2009	2010–2016
Years of survival	% RS (95%CI)		
5	76.8 (76.1, 77.4)	87.1 (86.7, 87.6)	91.0 (90.5, 91.5)
10	55.9 (54.7, 57.1)	75.9 (75.2, 76.5)	82.9 (82.2, 83.5)
15		66.0 (65.2, 66.7)	75.4 (74.6, 76.2)
20		53.5 (52.2, 54.8)	68.1 (67.1, 69.1)

Figure 4. Age-standardized relative survival (RS) outcomes with corresponding 95% confidence intervals (95% CI) of first primary invasive breast cancer in the Netherlands between 1989–2017

Relative survival was adjusted for age by direct standardization according to the 2013 European Standard Population 95+

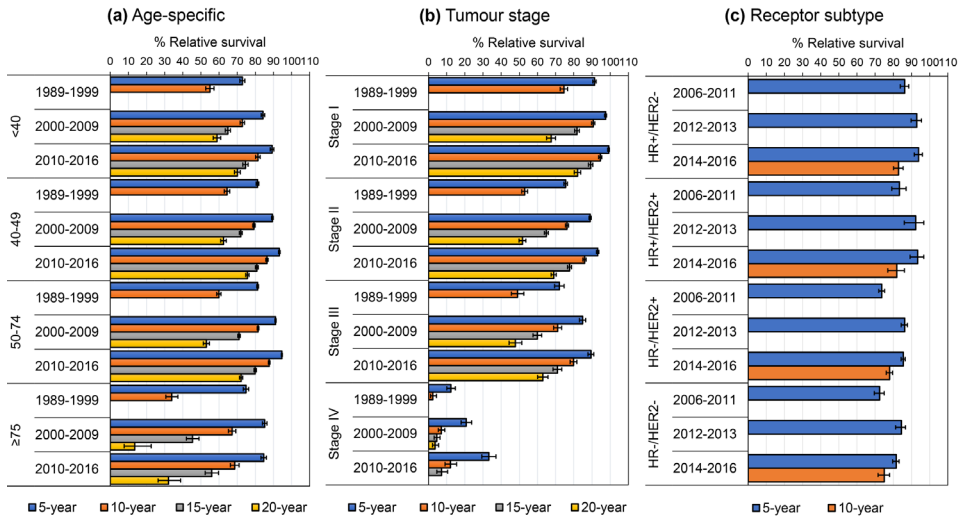


Figure 5. Age-specific (a) and age-standardized stage (b) and receptor subtype-specific (c) relative survival outcomes with corresponding 95% confidence intervals of first primary invasive breast cancer patients in the Netherlands diagnosed between 1989–2016

Relative survival was adjusted for age by direct standardization according to the 2013 European Standard Population 95+. HR+= ER+ and/or PR+, HR-= ER- and PR-. Information on ER/PR and HER2-status was routinely collected by the Dutch cancer registry since 2005 and 2006, respectively. For stage IV BC, the 20-year relative survival in 2010–2016 could not be estimated due low patient numbers

Discussion

This study provides a comprehensive overview of first primary invasive BC incidence, survival, mortality and treatment trends stratified by age, stage and receptor subtype in the Netherlands between 1989–2017, using population-based data on 320,249 women with first primary invasive BC from the NCR. BC incidence in the Netherlands has steadily increased between 1989–2013. However, in recent years the latest time trends (APCs) revealed noticeable declines in BC incidence for the entire patient population, in women aged 40–49 and 50–74 years, and in women with stage I disease. In women aged ≥75 years, BC incidence has been declining since 1998. Systemic treatment increasingly involved a combination of chemotherapy, endocrine therapy and targeted therapy. The relative survival improved markedly over time for all years of follow-up for most patients, but remained stable for all receptor subtypes since 2012–2013 and since 2000–2009 in women with stage IV BC at 15–years of follow-up. BC mortality steadily decreased in women of all age groups since 1989.

Breast cancer incidence

The rising trends in BC incidence are consistent with those found in previous Dutch and global (trend) studies[1,4,5,9-12] and can be attributed in part to changes in the prevalence of known risk and lifestyle factors that have been shown to influence BC incidence[4,5]. In a recent case-control study, the increasingly common use of both oral contraceptives (for more than 10 years) and hormone replacement therapy (for more than three years) has been shown to increase the risk of BC (relative risk=3.2 [95%CI: 1.4, 7.4]) in women aged <55 years[6]. Together with the increased alcohol consumption among younger people this might explain the rising BC incidence in women aged <40 years in this study[7]. The worldwide rise in overweight and obesity in recent decades is also likely to have contributed to the increase in BC incidence in both pre- and post-menopausal women[8]. In the US, decreases in BC incidence in 2002 and 2003 were attributed to the declining use of hormone-replacement therapy in post-menopausal women following unfavourable publicity[28]. However, similar trends were not observed in the Netherlands until 2005 and are likewise not observed now[29].

The observed trends in BC incidence are probably also influenced by the population-based mammography screening programme, which has been operational in the Netherlands since 1989 and for which women aged 50–74 years are invited biennially. Screening is intended to favourably change the stage at diagnosis and leads to a strong temporary increase in BC incidence due to the detection of (mainly) slow growing tumours followed by a decline in more advanced BC stages[4,5]. This corresponds with the observed increase in the incidence of stage I BC and the decline in incidence of stage II/III BC, which was most prominent in women aged 50–74 years. The decline in BC incidence observed since 1998 in women aged ≥75, who are no longer offered screening (compensatory drop), might also reflect screening practices[30].

The decline in BC incidence shown by the latest trends (2013–2017 for all patients combined) might be associated with the transition from screen-film to digital mammography between 2003–2010. In the period when digital mammography was implemented an increase in BC incidence was observed in women aged 50–74 (2004–2013, APC=1.2% [95%CI: 1.0, 1.5]) and in women with stage I BC (2005–2012, APC=3.4% [95%CI: 3.0, 3.8]), whereas no rise in incidence was observed prior to digital mammography implementation. A similar pattern was observed in women aged 50–74 year with HR+/HER2+ BC. In all cases, incidence rates either decreased or remained stable in the subsequent period, which might suggest a temporal increase after implementation of digital mammography[31]. However, in our study, the relation to screening was not directly taken into account in the analyses since mode of detection was not registered in the NCR until 2011. A recent study based on actual screening attendance did show that the incidence of stage III and IV BC was significantly higher in non-screened versus screened women (94 versus 38 per 100,000 PY, respectively; Odds Ratio[OR]=2.86, 95%CI:[2.72, 3.00])[32]. In our data, 56% of all women aged 50–74 years were diagnosed through screening between 2011–2017. Thus, screening has at least partially affected the BC incidence. Alternatively, the observed decline in BC incidence

in women aged 40–49 years might partly relate to the increase in prophylactic bilateral mastectomies, which significantly lowers the BC incidence in unaffected high risk women with *BRCA* mutations (85–100%)[33] and recently showed a significant increase in uptake in women (mean age 41.8 years) who received genetic testing after 2008 (32.7% in the Netherlands)[34].

Treatment strategies

Therapeutic approaches of BC in the Netherlands have changed drastically since 1989. BCS with adjuvant radiotherapy became the preferred treatment over mastectomy after the publication of landmark trials[35,36]. The steep increase in both adjuvant chemotherapy and endocrine therapy use between 2007–2009 can be explained by the broadening of their indications following the 2008 revision of the Dutch evidence-based guidelines and the introduction of the decision tool 'Adjuvant! Online', which was developed to predict the potential benefit of systemic treatment for individual BC patients[37].

The decline in chemotherapy use after 2009 is likely also related to changes in the Dutch evidence-based guidelines for the management of breast cancer (www.oncoline.nl), which now recommends endocrine therapy instead of chemotherapy in post-menopausal women with grade 2 tumours >1.1 cm and ER/PgR >50%. Possibly also related to the decline in chemotherapy use is the increased use of the 70-gene signature (70-GS, "MammaPrint") and other measures used to assess tumour aggressiveness (Ki67 immunohistochemistry, PgR status, etc.), together with a growing focus on shared decision making and a more reluctant attitude of clinicians towards the use of chemotherapy in low risk patients[38,39].

Breast cancer survival and mortality

Advances in treatment and more personalized therapeutic guidelines likely also contributed to the improvements in BC survival and mortality[3-5]. The sharp increase in the proportion of women that received both taxane and anthracycline containing regimens from 2003–2005 to 2015–2017 may provide some explanation for the observed improvements in survival, as use of combination chemotherapy has been shown to improve survival in metastatic BC since the late 1960s[14]. Improvements in survival and mortality may also relate to more personalized therapy (adjuvant endocrine therapy and anti-HER2 therapy) facilitated since the beginning of this century by the use of information on tumour biology (HR and HER2-status), which has improved treatment allocation to patients that will more likely benefit based on their tumour characteristics, even for stage IV disease[40]. The gains in survival and mortality may also in part be attributed to the changed composition of women who receive endocrine therapy, following changes in the Dutch national guidelines. Before 1999, endocrine therapy was given to all post-menopausal women with N+ BC and was provided, irrespective of menopausal status, to all women with N+ and ER+ BC. The similar survival of women with either HER2-positive or HER2-negative BC, irrespective of HR-status, likely relates to the use of trastuzumab, which was recommended in the Netherlands since 2005[15]. When not treated with trastuzumab, the overall survival of HER2-positive BC is poorer compared to HER2-negative BC[41].

Stage at diagnosis has also remained one of the most important determinants for BC survival, with survival becoming increasingly worse with advancing stage. Improvements in stage-specific survival have been described previously[9,11] and may partly be explained by stage migration, due to advances in detecting distant metastases, but also evolutions in TNM classification[42]. In clinical practice, the impact of stage migration has been observed after implementation of FDG-PET in lung cancer care, which resulted in an increase in stage IV classification[43]. Improvements in the detection of distant metastases at time of BC diagnosis likewise resulted in stage migration[44]. It is therefore possible that stage migration contributed to the observed improvements in stage-specific survival observed here. Poorer adherence to treatment guidelines in older patients, together with the fact that these women are no longer included in population screening, may be responsible for the higher stage II–IV rates at diagnosis in women aged ≥75 years and might to some extent explain the lower survival observed in these women compared to the younger age groups[45].

Decreases in BC mortality have been observed previously in most European, North-American and other high-income countries[3-5]. In the south-eastern region of the Netherlands, mortality rates declined annually with 2% between 1995 and 2004[9]. In the current study, a similar annual decline was observed for the entire Netherlands between 1989–2017. The declines in BC mortality and improvements in survival have mainly been related to advances in early diagnosis[3-5]. Worldwide, early detection (mainly due to the more widespread use of mammography screening) has been suggested to be causal in the decline in BC mortality in high-income countries[2,4]. Findings in the Netherlands have led to the same conclusions[12,46,47]. Projections from a simulation study based on six distinct models on BC mortality trends in the US further showed that screening was on average associated with 44% (model range: 35%–60%) and 37% (model range: 26%–51%) of the observed decline in overall BC mortality among women aged 30–79 years in 2000 and 2012, respectively. The remaining decline in mortality in 2012 was on average attributed to chemotherapy; 31% (model range: 22%–37%), endocrine therapy; 27% (model range: 18%–36%) and trastuzumab; 4% (model range: 1%–6%)[48]. However, the data do not support the viewpoint that screening has a substantial effect on breast cancer mortality, as declines in BC mortality in the Netherlands have been present since the late 1980s, prior to the implementation of a nationwide screening programme[49]. Moreover, in this study declines in mortality were slightly higher in women aged <40 and 40–49 years than in older women where organized screening is expected to influence the mortality. Also, declines were already observed in the period shortly after screening implementation, which is not expected due to the usual time lag before screening effects

become apparent[50]. Advances in treatment are therefore more likely to have caused this effect[49].

Strengths and limitations

The major strength of this study was the use of a large population-based dataset from the NCR spanning almost three decades of BC data. Data of all new BC patients were collected by trained registrars, leading to high completeness and ruling out selection bias. This study is among the first to include a detailed description on BC trends according to receptor subtype in Europe, which is another major strength. However, data on receptor subtype was still limited and consequently, we could not detect clear trends based on receptor subtype. Furthermore, we did not have information available on risk and lifestyle factors, and were therefore not able to directly assess trends in incidence according to these factors. We experienced some difficulties in the assessment of trends due to the changing definition of tumour stage. In particular, the change from the 5th to 6th TNM classification resulted in a noticeable shift from stage II to III disease, which complicated trend recognition and comparisons over time. We tried to address this shortcoming by combining both stages for analyses and by assessing pre-shift and post-shift time trends separately with joinpoint regression analyses. Finally, we did not have information available on the BC-specific survival and therefore we used RS as an estimator. Nonetheless, the RS is an appropriate method to use in population-based studies on survival in the absence of cause of death information and does not suffer from misclassification.

Conclusion

This study provides a comprehensive overview of first primary invasive BC trends in the Netherlands since 1989. The incidence of BC for the entire patient population has steadily increased between 1989–2013, but has been declining since. Whether this declining trend continues, should be confirmed by future trend studies covering subsequent time periods. Meanwhile, the relative survival improved for all age groups and for most stages and receptor subtypes, and the the mortality of first primary invasive BC has decreased substantially since 1989. The observed trends in BC incidence, mortality and survival likely result from the combined effect of preventive measures, earlier diagnosis (population screening and better disease awareness), advances in treatment, national implementation of personalized treatment guidelines and changes in the exposure to known risk factors.

Article information

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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Data Availability Statement

The data that support the findings are available from the Netherlands Cancer Registry upon reasonable request (data request study number K18.244, www.iknl.nl).

Ethics statement

The study was reviewed and approved by the Privacy Review Board of the Netherlands Cancer Registry.

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Supplementary Material

For supplementary material see publication