

Small but significant excess mortality compared with the general population for long-term survivors of breast cancer in the Netherlands

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Background: Coinciding with the relatively good and improving prognosis for patients with stage I–III breast cancer, late recurrences, new primary tumours and late side-effects of treatment may occur. We gained insight into prognosis for long-term breast cancer survivors.

Patients and methods: Data on all 205 827 females aged 15–89 diagnosed with stage I–III breast cancer during 1989–2008 were derived from the Netherlands Cancer Registry. Conditional 5-year relative survival was calculated for every subsequent year from diagnosis up to 15 years.

Results: For stage I, conditional 5-year relative survival remained ~95% up to 15 years after diagnosis (a stable 5-year excess mortality rate of 5%). For stage II, excess mortality remained 10% for those aged 15–44 or 45–59 and 15% for those aged 60–74. For stage III, excess mortality decreased from 35% at diagnosis to 10% at 15 years for those aged 15–44 or 45–59, and from ~40% to 30% for those aged ≥60.

Conclusions: Patients with stage I or II breast cancer had a (very) good long-term prognosis, albeit exhibiting a small but significant excess mortality at least up to 15 years after diagnosis. Improvements albeit from a lower level were mainly seen for patients who had been diagnosed with stage III disease. Caregivers can use this information to better inform (especially disease-free) cancer survivors about their actual prognosis.

Key words: conditional survival, breast cancer, long-term survivors, excess mortality, late side-effects

introduction

In Western countries, breast cancer is the most frequent cancer among females [1, 2]. Overall prognosis is good with a survival rate of at least 80% at 5 years and over 70% at 10 years [2]. In 2015, about 190 000 Dutch females are estimated to be alive after a former diagnosis of breast cancer in the preceding 10 years, representing ~1.5% of the total female adult population [3]. Breast cancer recurrences can occur many years after diagnosis [4–6]. In addition, breast cancer patients have a higher risk for new primary cancers [7] and cardiac diseases may occur as a late side-effect of treatment [8]. This may all lead to excess mortality compared with the general population.

Traditionally, survival estimates for cancer patients are reported from the time of diagnosis. These survival projections are not valid for patients who have already survived a period of time after initial diagnosis and treatment. Conditional survival analysis estimates the survival rate, given the pre-condition of having already survived for some time, and can be used by caregivers for informing cancer survivors about their estimated actual prognosis during follow-up [9, 10].

Although some authors have published on conditional survival for breast cancer patients, most of them restricted the analyses to patients who had survived only 1 year or up to 5 years after diagnosis, or did not report on detailed combinations of age and stage groups [10–15].

In this study, we calculated conditional 5-year relative survival rates for breast cancer patients, for each subsequent year survived up to 15 years after primary diagnosis.

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methods

data collection

Population-based data from the nationwide Netherlands Cancer Registry (NCR), which started in 1989 and is maintained and hosted by the Comprehensive Cancer Centres, was used. The NCR is based on the notification of all newly diagnosed malignancies by the automated national pathological archive (PALGA). Additional sources are the national registry of hospital discharge diagnoses, which account for up to an extra 8% of new cases. Information on patient and tumour characteristics is routinely collected from the medical records within about 9 months after diagnosis. The quality of the data is high, thanks to thorough training of the registrars and computerized consistency checks. Completeness is estimated to be at least 95%. In addition to the active and passive follow-up via the hospitals, date of death is also retrieved from the Municipal Personal Records Database (GBA). This database contains all deaths and emigrated persons in the Netherlands since October 1994. For patients diagnosed before October 1994, follow-up was completed by merging the database with the municipality death records and/or with the Central Bureau for Genealogy, which registers all deaths in the Netherlands.

All female patients with invasive stage I–III primary breast cancer (C50, including both unilateral and contralateral breast cancer) diagnosed in the period 1989–2008 in the Netherlands were included ($n = 205\,827$). This study focussed on stage I–III patients, since stage IV patients generally have a limited survival (median survival ~ 2 years). Therefore, conditional survival statistics are less useful and are also less stable due to small numbers. The date of death was completed up to 2009. Patients younger than 15 years and older than 89 years were excluded from the analysis, as well as cases diagnosed at autopsy. Patients aged ≥ 89 years were excluded, because conditional survival estimates are unreliable due to the lack of long follow-up for these patients. Age was divided into four groups (15–44, 45–59, 60–74 and 75–89 years). Age groups 15–29 and 30–44 years were merged, because results became relatively unstable due to the small numbers of patients in the age group 15–29 years, and prognosis does not differ significantly between subgroups of age for those < 40 years [16]. Stage was based on the pathological tumour–node–metastasis (TNM) classification if available. Otherwise, clinical stage was used.

statistical analyses

Relative survival is calculated as the absolute survival among cancer patients divided by the expected survival of a comparable group from the Dutch general population (same period, age and gender) [17]. Period analysis was used to provide up-to-date survival estimates [18]. Furthermore, hybrid analysis was used for situations, in which mortality data (follow-up of the study population) are more up-to-date than incidence data [19]. Five-year relative survival rates were calculated for every subsequent year survived up to 15 years after diagnosis, conditional on being alive at the beginning of that year (conditional 5-year relative survival). Conditional survival was calculated for 15 years age groups, according to the stage of disease. We present only conditional relative survival estimates with a standard error of $\leq 5\%$ of the survival rate.

When conditional 5-year relative survival is at or above the level of 95%, there is minimal excess mortality for that group of patients. For the calculation of conditional 5-year relative survival estimates, a saturated Poisson regression model for period analysis was used [20]. Standard errors of the survival estimates were calculated using the delta method. Calculations were carried out with SAS software (SAS system 9.2, SAS Institute, Cary, NC).

web-based tool

A web-based tool has been constructed to make the conditional relative survival estimates available for caregivers, who can use this tool for counselling

patients with stage I–III breast cancer during follow-up (www.dutchcancersurvival.com).

results

Table 1 shows the numbers of patients available for the analyses, including the last year for which a reliable estimate for the conditional 5-year relative survival could be made, and conditional 5-year relative survival figures at diagnosis and for patients who were alive 5, 10 and 15 years after diagnosis. In none of these cases did the conditional 5-year relative survival rate exceed 95%, meaning that a small but significant 5-year excess mortality remained during follow-up.

conditional relative survival by stage and age

For patients with stage I disease, the 5-year relative survival at diagnosis was 96%, being slightly poorer for patients aged 15–44 years (94%) compared with older patients (96%) (Table 1, $P < 0.05$). This difference remained for conditional 5-year relative survival up to 5 years after diagnosis (Figure 1A). For the total group of patients diagnosed with stage I breast cancer, conditional 5-year relative survival remained $\sim 95\%$ during follow-up, implicating that a 5-year excess mortality rate of $\sim 5\%$ persisted.

For patients with stage II disease, the 5-year relative survival at diagnosis ranged between 82% and 88% for the different age groups (Table 1, $P < 0.05$). Conditional 5-year relative survival slightly increased with every year survived, although a 5-year excess mortality rate of $\sim 10\%$ remained for those aged 15–44 or 45–59 years. This was $\sim 15\%$ for patients aged 60–74 or 75–89 years (Figure 1B).

For patients with stage III disease, conditional 5-year relative survival improved with every subsequent year of survival after diagnosis, but remained clearly poorer for those aged 60–74 and 75–89 years, although increasing from around 60% at diagnosis up to $\sim 70\%$ after 8 years. This coincided with a decrease in excess mortality from $\sim 40\%$ to $\sim 30\%$ compared with a decrease from $\sim 30\%$ to $\sim 10\%$ among younger patients (Figure 1C).

Although 5-year relative survival at diagnosis for all age groups combined was clearly different between stage I (96%), stage II (86%) and stage III (64%) (Figure 2), the differences became smaller with each subsequent year of survival after diagnosis. After 15 years, the 5-year excess mortality rates decreased to $\sim 5\%$ and $\sim 10\%$ for stages I and II, respectively, while for stage III patients it remained $> 10\%$, notwithstanding the strong decrease in excess mortality since diagnosis (almost 40%) (Figure 2).

discussion

Although long-term prognosis for patients with stage I–III breast cancer is relatively good, a small but significant excess mortality compared with the general population remained for survivors even after prolonged follow-up up to 15 years.

It seems reasonable to assume that patients have minimal to no excess mortality when conditional 5-year relative survival exceeds 95% (survival is then almost similar to the general population with the same age structure). Whereas long-term excess mortality $< 5\%$ has been described for other cancers

Table 1. Conditional survival from breast cancer in the Netherlands 1989–2008 (*n* = 205 827), according to the stage and age at diagnosis

	Age at diagnosis (years)	No. of patients available for survival analysis after year ^a				Reliable estimate up to year ^b	5-year relative survival at diagnosis (%)	Conditional 5-year relative survival (%)		
		0	5	10	15			At 0 years (95% CI)	At 5 years (95% CI)	At 10 years (95% CI)
Stage I	Overall	55 251	30 294	11 878	1576	15	96 (96–97)	94 (93–94)	94 (93–94)	94 (92–95)
	15–44	6640	4355	2167	441	15	94 (93–94)	91 (91–92)	93 (92–94)	94 (93–96)
	45–59	21 056	12 257	5072	685	15	96 (96–97)	94 (94–95)	95 (94–96)	94 (93–96)
	60–74	21 488	11 513	4273	435	15	97 (97–98)	94 (94–95)	93 (92–95)	93 (89–97)
	75–89	6068	2170	367	44	10	96 (94–97)	94 (91–97)	89 (81–97)	–
Stage II	Overall	60 525	30 768	11 755	1752	15	86 (85–86)	85 (85–86)	88 (87–88)	89 (88–91)
	15–44	9897	5558	2516	487	15	84 (83–85)	85 (84–86)	89 (88–90)	93 (91–94)
	45–59	23 524	12 761	5178	817	15	88 (87–88)	87 (86–87)	89 (89–90)	89 (88–91)
	60–74	17 767	9460	3590	435	15	86 (85–87)	84 (83–85)	85 (83–86)	86 (82–90)
	75–89	9337	2990	471	44	11	82 (80–83)	83 (81–85)	90 (83–97)	–
Stage III	Overall	8909	2947	965	159	15	64 (63–65)	70 (68–71)	77 (74–80)	87 (81–92)
	15–44	1399	508	235	47	15	67 (65–69)	76 (73–79)	86 (82–90)	86 (79–93)
	45–59	3226	1090	396	74	15	68 (67–70)	73 (71–75)	83 (79–86)	92 (87–98)
	60–74	2450	903	286	35	11	64 (62–66)	66 (63–68)	66 (61–72)	–
	75–89	1834	446	49	15	6	56 (54–58)	65 (60–70)	–	–

Source: Netherlands Cancer Registry.

^aYear is defined as the time after diagnosis.

^bConditional survival figures are considered reliable when the standard error was ≤ 5% of the survival rate. Year is defined as the last year since diagnosis for which a reliable conditional 5-year relative survival estimate could be provided.

[10, 11, 13, 14, 21–23], 5-year excess mortality for breast cancer patients remained higher than 5%. This means that breast cancer patients—even after prolonged follow-up—continue to have a poorer survival compared with the general population. Potential explanations for excess mortality for breast cancer patients include late recurrences [4–6, 24], second tumours [7, 25, 26] and late side-effects of breast cancer treatment [4, 26, 27].

Recurrences and progression from breast cancer occur (especially among patients with ER and/or PR positive tumours), even many years after diagnosis, but can be treated better systematically nowadays [4–6, 24, 28, 29]. About 25% of all recurrences of breast cancer occur after 5 years of follow-up [4].

Second primary tumours occur in up to 15% of breast cancer survivors [7, 25]. Among breast cancer patients younger than 50 years, radiotherapy increases the risk of lung cancer, especially in smokers, whereas the use of chemotherapy and hormonal therapy was followed by a decreased risk of second cancers, especially in the contralateral breast [7]. Among those aged ≥50 years, chemotherapy has been linked to an increased risk of melanoma, uterine cancer and leukaemia, while hormonal therapy contributed to an increased risk of uterine cancer [7].

Whether late side-effects of breast cancer treatment (especially systemic treatment and radiotherapy) translate into long-term excess mortality might be analysed by stratification according to treatment. However, even in our nation-wide database containing more than 200 000 patients, stratification according to treatment (in addition to stage and age) would lead to subgroups that are too small to estimate valid conditional 5-year relative survival rates. Quite a few studies have shown an increased rate of

cardiac morbidity and mortality among patients with breast cancer, especially after radiotherapy at young age and delivered before the 1990s [4, 26, 27]. Cardiovascular diseases have become an important cause of death in breast cancer survivors [28, 30]. Modern techniques for planning and delivery of radiotherapy including respiratory control, conformal therapy with shielding of heart and lungs and intensity modulated radiation therapy (IMRT) have decreased the risk for (late) cardiovascular side-effects [31]. The more widespread use of the cardiotoxic anthracycline-based chemotherapy yet with a lower tumour relapse risk may also lead to an increased rate of cardiac mortality [32–34]. For that reason, non-anthracycline-based regimes have been developed [35], although not all oncologists believe that this provides the highest level of efficacy.

In our study, we found that older women with stage II or III breast cancer had a poorer conditional 5-year relative survival than younger patients, as was also found in previous studies [2]. This might be explained by a higher excess mortality due to comorbidity, second tumours or late side-effects of treatment. On the other hand, the poorer prognosis that was found for younger patients with stage I or II breast cancer might be explained by a unique biologic entity driven by unifying oncogenic signaling pathways and is characterized by less hormone sensitivity and higher HER-2/EGFR expression [16].

Strengths of this study are the size of the population-based cohort, completeness of the cancer registry data, length of follow-up time and the fact that stratified conditional 5-year relative survival rates based on important prognostic factors (age, stage and period of diagnosis) could be carried out.

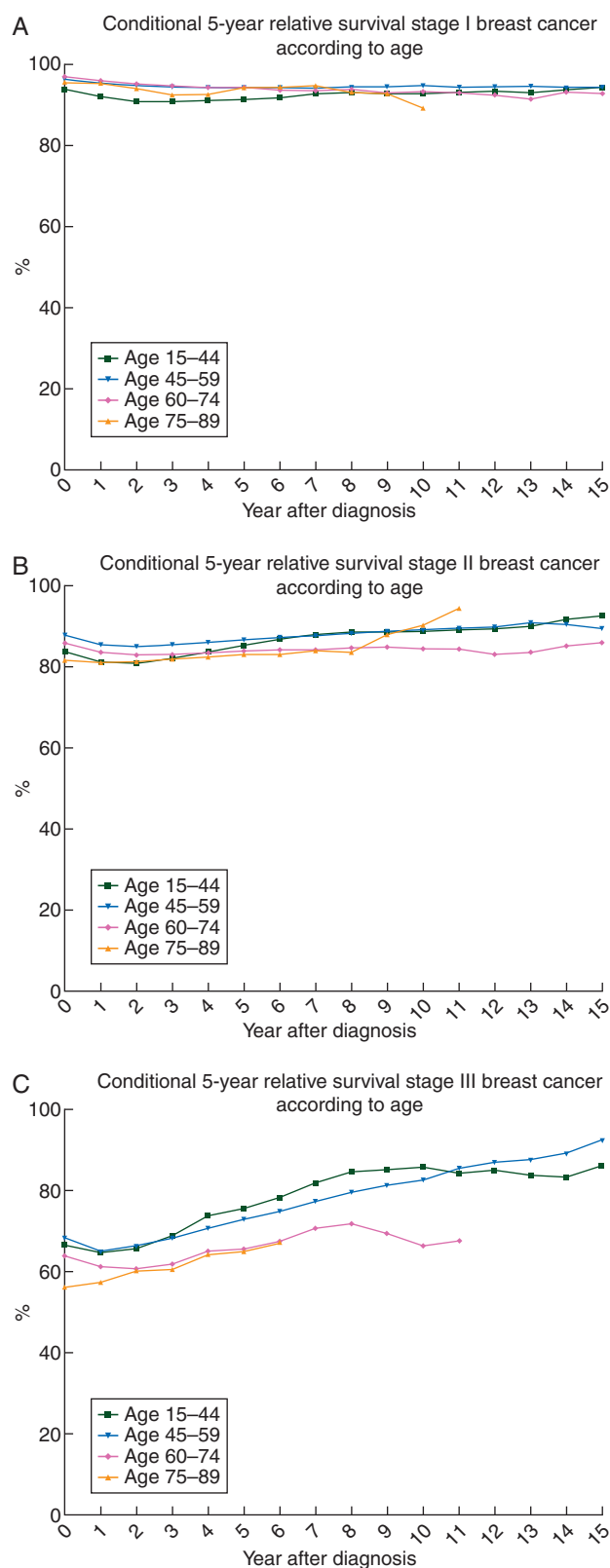


Figure 1. Conditional 5-year relative survival at every subsequent year of survival after initial diagnosis of patients with breast cancer, according to the stage and age. Source: Netherlands Cancer Registry. (A) stage I, (B) stage II, (C) stage III.

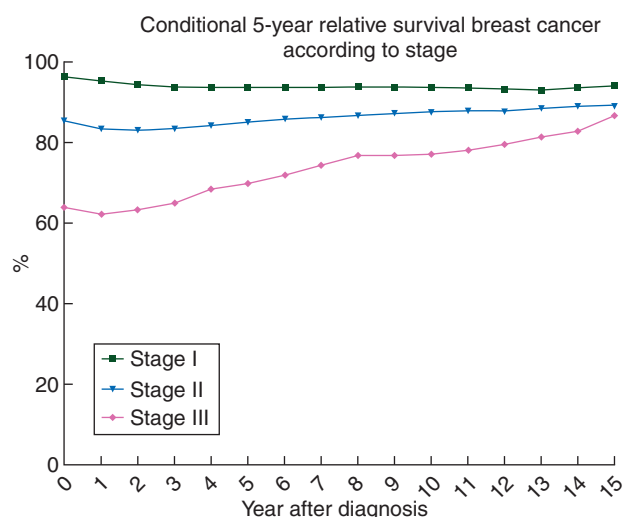


Figure 2. Conditional 5-year relative survival at every subsequent year of survival after initial diagnosis of patients with breast cancer, according to the stage. Source: Netherlands Cancer Registry.

Limitations are the facts that we could not carry out analyses according to some other important prognostic factors such as histological grade and treatment. For example, in the Netherlands, breast cancer screening was introduced between the early 1990s and 1995. This has led to earlier detection and an improved prognosis [36]. In addition, treatment of breast cancer has also become more effective, yet with a higher risk of cardiac mortality [33, 37]. For the interpretation of results, one should take all these changes into account.

In conclusion, patients with stage I or II breast cancer had a (very) good long-term prognosis, albeit exhibiting a small but significant excess mortality at least up to 15 years after diagnosis. Improvements albeit from a lower level were mainly seen for patients who had been diagnosed with stage III disease. The remaining excess mortality is likely to be partially related to late recurrences and second tumours, but can also be explained by late side-effects of breast cancer treatment. Caregivers can use this information to better inform (especially disease-free) cancer survivors about their actual prognosis.

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disclosure

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