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Original Research

Ten-year conditional recurrence risks and overall and relative survival for breast cancer patients in the Netherlands: Taking account of event-free years

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Abstract ***Background:*** Survival estimates from diagnosis are of limited importance for (ex-) breast cancer patients who survived several years, as it includes information on already deceased patients. This study analysed the 10-year conditional risk of recurrent breast cancer in specific prognostic subgroups. Second, we investigated 10-year conditional overall survival (OS) and relative survival (RS), adjusted for confounding.

Patients and methods: All women diagnosed in 2005 with operated T1-2N0-1 breast cancer were selected from the Netherlands Cancer Registry. Patients were classified into T1N0, T1N1, T2N0 and T2N1 stage. Ten-year conditional recurrence rates were calculated from diagnosis, and for patients without an event (local [LR], regional recurrence [RR], distant metastasis [DM] or death) every year following diagnosis. Ten-year conditional OS was calculated using multivariable Cox regression. RS was estimated by dividing patient survival rates by those of the general Dutch population.

Results: We included 7969 patients: 52.3% had T1N0, 15.3% T1N1, 19.9% T2N0 and 12.5% T2N1 stage. For T1N0, 10-year LR rates changed from 4.6% at diagnosis to 0.5% in year 10. RR rates changed from 2.3% to 0.2%, and DM rates changed from 7.8% to 0.6%. For T2N1 stage, the LR, RR and DM rates changed from 6.2% to 0.8%, 5.2%–0.4% and 19.6%–1.5%, respectively. For the luminal A subtype, LR, RR and DM rates changed from

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3.9% to 0.4%, 1.7%–0.5% and 7.3%–1.1%, while for triple negative, these rates changed from 5.6% to 0.7%, 4.9%–0.2% and 16.7%–0%, respectively. Differences between subgroups attenuated over time, and all recurrence rates became ≤1.5% in year 10. Ten-year OS and RS, adjusted for confounding, showed declining risk differences between subgroups over time.
Conclusion: Differences in recurrence rates, OS and RS between prognostic subgroups declined as years passed by. These results highlight the importance of taking into account disease-free years to more accurately predict (ex-)breast cancer patients' prognosis over time.

1. Introduction

The incidence of breast cancer is rising [1]. Meanwhile, due to improved treatment and diagnostic procedures, mortality rates are declining [2]. This results in an increasing number of breast cancer survivors. In 2017, the 10-year prevalence of women with breast cancer in the Netherlands was 131,383 [1]. A patient's prognosis is often communicated by physicians based on available survival and recurrence rates, usually calculated from diagnosis. However, survival estimates from diagnosis are of limited importance for (ex-)breast cancer patients who survived several years, as these analyses only include patients who are still alive or disease-free at a certain time point after diagnosis [3,4]. Conditional survival analyses are more relevant, as they calculate the probability of surviving an additional number of years, given that someone has already survived x years [3]. Taking into account that survival and recurrence rates vary over time, conditional survival analyses will result in more accurate prognostic information for breast cancer patients and survivors. Several studies have reported conditional survival rates for breast cancer in different populations [3,5–8], showing that these survival rates ameliorate with increasing time from diagnosis. Importantly, it has been shown that conditional survival is especially of relevance for patients with an initial poor prognosis, as for most of these patients, the chance to survive a number of years is lower than for patients with an initial better prognosis. Patients who do survive x years have to be provided with updated information regarding their prognosis [3]. In general, female breast cancer survivors in the Netherlands have a good prognosis, which improves as years pass by. However, a small, but significant excess mortality during the whole 20 years of follow-up has been observed compared to the general population, which may among others be due to (late) recurrences [9]. As fear of recurrent cancer is very common in breast cancer survivors [10], most likely caused by substantial overestimation of recurrence risks [11], it is relevant to get insight in time-dependent recurrence risks.

Long-term follow-up is rarely available in population-based research. As a consequence, no studies have been performed yet that investigate the 10-year conditional risk of local recurrence (LR), regional recurrence (RR), and distant metastasis (DM) in breast cancer patients. This study aimed to analyse the breast cancer recurrence risk over time in specific prognostic subgroups according to T and N stage and breast cancer subtype, conditional on the number of years survived, in T1-2N0-1 stage breast cancer patients in the Netherlands. As a second objective, we investigated 10-year conditional overall survival (OS) and relative survival (RS) for all subgroups, adjusted for confounding.

2. Methods

2.1. Study population

For this population-based cohort study, patients were selected from the Netherlands Cancer Registry (NCR). This registry contains prospectively recorded patient-, tumour-, and treatment-related characteristics of all newly diagnosed malignancies from 1989 on. We included all women diagnosed in 2005 with pathologically staged T1-2N0-1 breast cancer treated with either breast-conserving therapy or mastectomy. Patients were classified into T1N0, T1N1, T2N0 and T2N1 stage and according to breast cancer subtype.

2.2. Data collection

Data on patient-, tumour, and treatment-related characteristics were retrieved from the NCR. Tumour topography and morphology were coded according to the International Classification of Diseases for Oncology [12]. Staging was coded using the tumour, node and metastasis classification system of the International Union Against Cancer, 6th edition [13]. Additional data on vital status and date of death were derived from the Municipal Personal Records database, completed up to February 2017. Data on recurrences (including LR, RR and DM) were retrospectively gathered from patient files.

2.3. Outcomes and definitions

The primary outcomes of interest were conditional 10-year LR, RR and DM rates. These were defined by the probability of being diagnosed with a LR, RR or DM within 10 years following diagnosis, taking into account

the number of event-free years that passed. An event was defined as death, LR, RR or DM. By calculating the remaining risk on a recurrence within 10 years after diagnosis at a certain time point, more insight in the distribution of recurrences over the years could be obtained. As secondary outcomes, 10-year conditional OS and RS were investigated, adjusted for confounding. Crude 10-year OS was defined as the probability of being alive within 10-years from diagnosis, taking into account the number of years survived. RS was used as a measure for disease-specific survival and was calculated by dividing the observed survival of the patient population by the expected survival of the general Dutch population. All outcomes were calculated per T and N subgroup and breast cancer subtype as both factors are very important prognostic factors. Breast cancer subtypes were defined as luminal A (ER or PR positive, HER2 negative and grade 1 or 2), luminal B (ER or PR positive, HER2 positive, or HER2 negative with grade 3), HER2 positive (ER and PR negative and HER2 positive) and triple negative (ER, PR and HER2 negative). ER or PR positivity was defined as at least 10% positive nuclei. Less than 10% was regarded as negative. HER2 positivity was defined as a positive immunohistochemistry (3 positive, at least 10% of cells with strong intensity membrane staining). It was negative when less than 10% showed membrane staining. In case of an immunohistochemistry score of 2 (at least 10% of cells stained with moderate intensity), an amplification test was performed that overruled the results of the immunohistochemistry. Recurrences were defined according to existing consensus-based definitions for recurrence classification [14]. Contralateral breast cancer was not counted as event; any subsequent recurrence was included in the analysis.

2.4. Statistical analysis

Patient-, tumour-, and treatment-related characteristics were summarised and compared between subgroups using the Chi-squared or Fisher's exact test. For each T and N subgroup and breast cancer subtype, 10-year conditional recurrence risks from diagnosis were determined. The 10-year conditional risks were calculated for all patients from diagnosis and on patients who were event-free after 1 to 9 years following diagnosis. This risk was calculated as percentage of patients that was diagnosed with a LR, RR, or DM within 10-years from diagnosis at the specific time point following diagnosis. Crude 10-year conditional OS was calculated as the proportion of patients that was still alive at 10 years following diagnosis as part of the entire study population. To calculate 10-year RS, this OS proportion was divided by the average survival rate of the general Dutch population, where patients were matched to the general population on age, sex and calendar year. This procedure was performed by making use of the -strs- command in Stata, developed by Dickman and Coviello [15]. Multivariable Cox proportional hazard analyses were performed to obtain hazard ratios (HRs) with 95% confidence intervals (CIs) of 10-year OS from diagnosis, and conditional on 1 to 9 years survived. For confounding adjusted 10-year RS was estimated by calculating excess mortality ratios (EMRs) using general linear models with Poisson distribution, with life tables of the general population as a reference. EMRs with 95% CIs were determined using the Ederer II method [16]. The probability of being alive 10 years following diagnosis was calculated at 0 to 9 years from diagnosis. The conditional analyses at 1 to 9 years from diagnosis were calculated exclusively on patients alive at the start of every analysis. Potential confounding variables were first tested in univariable analysis, where after all significantly contributing variables ($P < 0.1$) were included in the multivariable model. Subsequently, variables that did not significantly contribute to the multivariable model were eliminated using manual backward selection. Potential confounding variables tested for all T and N subgroups were: age, social economic status, region of diagnosis, lateralisation and sublocalisation of the tumour, histological subtype, grade, multifocality, hormonal receptor status, HER2 status, type of surgery, axillary lymph node dissection, use and type of adjuvant systemic therapy and targeted therapy. For Cox regression, the proportional hazards assumption was tested by plotting the log of the −log survival function {log[−log(S(t))]} against the log of the survival time [log(t)]. When producing linear graphs, the proportional hazards assumption was considered to be met. No deviations were found. A P-value <0.05 was considered as statistically significant. All statistical analyses were performed in Stata/SE, version 14.1 (StataCorp LP).

3. Results

3.1. Study population and characteristics

In 2005, 13,023 women in the Netherlands were diagnosed with invasive breast cancer. For this study, we excluded patients with a history of breast cancer (n = 902), unknown stage disease (n = 106), metastatic breast cancer (n = 622), no pathologically established tumour (n = 162), synchronous breast cancer (defined as second breast cancer within 90 days, n = 276), no surgery (n = 602) or incomplete 10-year follow-up (n = 24). In total, 10,329 patients were identified of whom 10-year follow-up was available. We additionally excluded patients with pT3-4pN2-3 stage disease (n = 2035) and patients treated with breast conservation without radiation therapy or mastectomy with radiation therapy (n = 329), to obtain a homogeneous

population. The final study population consisted of 7969 patients, of whom 4166 (52.3%) had T1N0, 1223 (15.3%) T1N1, 1583 (19.9%) T2N0 and 997 (12.5%) T2N1 stage breast cancer (Fig. 1). Patients in the T1N0 and T1N1 subgroup more often had a low-grade tumour as compared to patients in the T2N0 and T2N1 subgroup. Patients with a T1N0 tumour were the least often treated with adjuvant systemic therapy (Table 1). Of all patients, 1702 patients (21.4%) had an unknown breast cancer subtype due to lacking data on receptor status or grade. These patients were consequently excluded from the analyses according to breast cancer subtype. Of the remaining 6267 patients, 3774 (60.2%) had luminal A, 1465 (23.4%) had luminal B, 314 (5.0%) had HER2 positive and 714 (11.4%) had triple negative disease (Fig. 1). Patient-, tumour-, and treatment-related characteristics per breast cancer subtype are shown in Table 2. The median follow-up from date of diagnosis to date of death or censoring was 11.4 years (interquartile range 10.9–11.7 years).

3.2. Ten-year conditional recurrence risks per T and N subgroup

At diagnosis, the lowest risks on LR and RR within 10 years were found in T1N1 stage (2.4% and 2.2%, respectively), while the lowest risk on DM (7.8%) within 10 years was found in T1N0 stage. T2N1 stage showed the highest risks on 10-year LR, RR and DM (6.2%, 5.2% and 19.6%, respectively) at time of diagnosis. The total 10-year conditional risks on any recurrence declined as time passed, even as the differences between the prognostic subgroups. For T1N0 stage, the percentage of 10-year LR declined from 4.6% at diagnosis to 0.5% in the last year. For 10-year RR, the risk declined from 2.3% at diagnosis to 0.2% in the last year. For 10-year DM, it ranged from 7.8% at diagnosis to 0.6% in the last year. For T2N1 stage, the group with the highest risk from diagnosis, these percentages declined as follows: from 6.2% to 0.8%, from 5.2% to 0.4% and from 19.6% to 1.5% for LR, RR and DM,

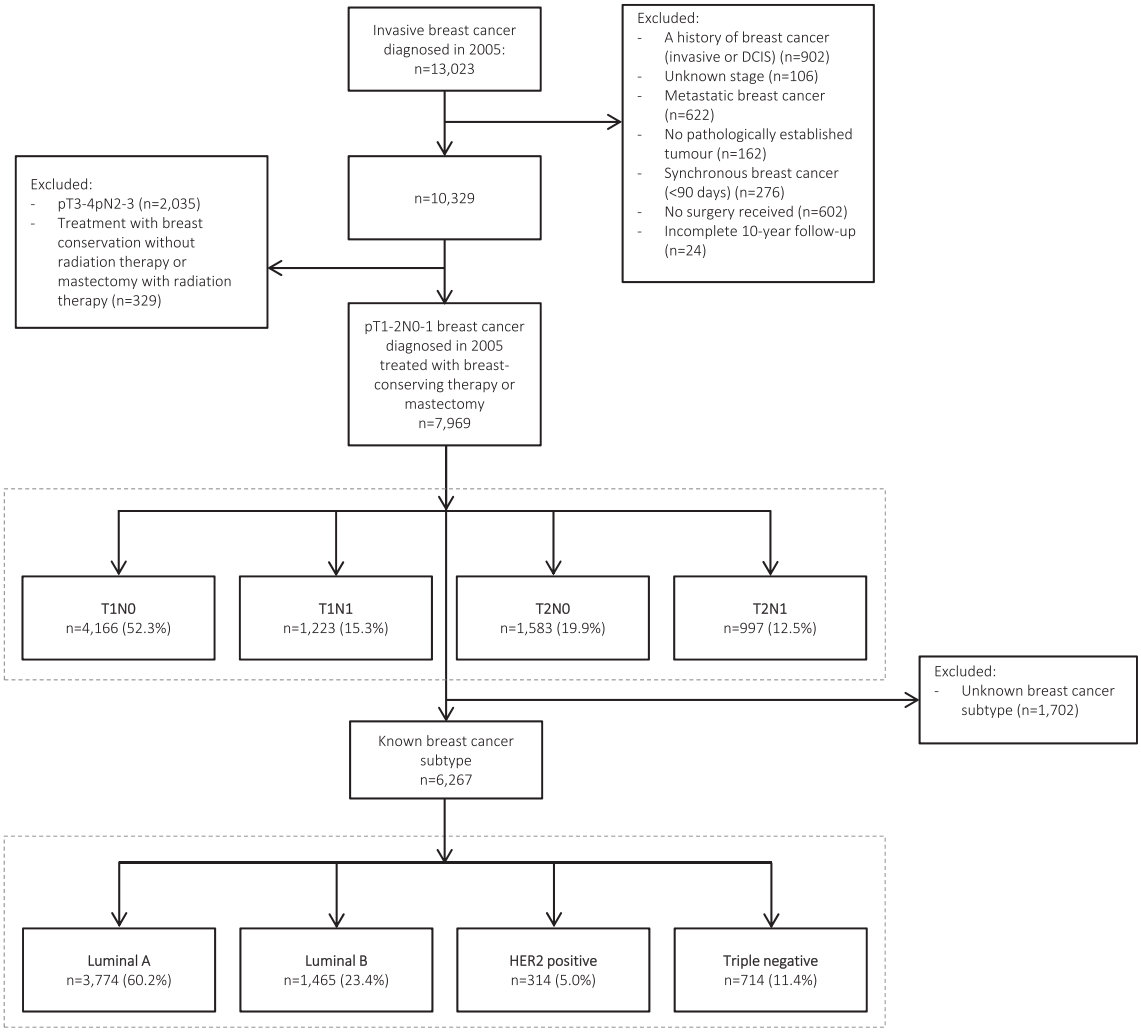

Fig. 1. Consort diagram of included patients.

Table 1
Baseline characteristics of the entire study population according to T and N subgroup (n = 7969). *P-values are calculated on known values only. P-values depicted in bold are considered as statistically significant.

Characteristics	T1N0 (N = 4166)	T1N1 (N = 1223)	T2N0 (N = 1583)	T2N1 (N = 997)	P-value*
Age (years)					
<40	188 (4.5)	95 (7.8)	88 (5.6)	46 (4.6)	**<0.001**
40–49	633 (15.2)	265 (21.7)	316 (20.0)	257 (35.8)	
50–59	1268 (30.4)	371 (30.3)	356 (22.5)	270 (27.1)	
60–69	1164 (27.9)	278 (22.7)	316 (20.0)	187 (18.8)	
70–79	752 (18.1)	155 (12.7)	274 (17.3)	120 (12.0)	
≥80	161 (3.9)	59 (4.8)	233 (14.7)	117 (11.7)	
Social economic status					
Low	1241 (29.8)	366 (29.9)	508 (32.1)	294 (29.5)	0.158
Medium	1676 (40.2)	498 (40.7)	577 (36.5)	412 (41.3)	
High	1249 (30.0)	359 (29.4)	498 (31.5)	291 (29.2)	
Region of diagnosis					
A	552 (13.3)	186 (15.2)	223 (14.1)	138 (13.8)	**0.017**
B	429 (10.3)	106 (8.7)	125 (7.9)	105 (10.5)	
C	275 (6.6)	104 (8.5)	105 (6.6)	78 (16.3)	
D	791 (19.0)	226 (18.5)	286 (18.1)	162 (16.3)	
E	410 (9.8)	108 (8.8)	157 (9.9)	100 (10.0)	
F	557 (13.4)	149 (12.2)	253 (16.0)	134 (13.4)	
G	612 (14.7)	168 (13.7)	207 (13.1)	138 (13.8)	
H	245 (5.9)	90 (7.4)	92 (5.8)	62 (6.2)	
I	295 (7.1)	86 (7.0)	135 (8.5)	80 (8.0)	
Lateralisation					
Left	2169 (52.1)	616 (50.4)	834 (52.7)	531 (53.3)	0.527
Right	1997 (47.9)	607 (49.6)	749 (47.3)	466 (46.7)	
Sublocalisation					
Outer quadrants	2013 (48.3)	595 (48.7)	738 (46.6)	493 (49.5)	**<0.001**
Inner quadrants	889 (21.3)	209 (17.1)	328 (20.7)	153 (15.4)	
Central parts	261 (6.3)	105 (8.6)	126 (8.0)	84 (8.4)	
Overlapping lesions	922 (22.1)	291 (23.8)	367 (23.2)	251 (25.2)	
Unknown	81 (1.9)	23 (1.9)	24 (1.5)	16 (1.6)	
Grade					
1	1241 (29.8)	315 (25.8)	223 (14.1)	129 (12.9)	**<0.001**
2	1871 (44.9)	569 (46.5)	628 (39.7)	437 (43.8)	
3	841 (20.2)	283 (23.1)	681 (43.0)	402 (40.3)	
Unknown	213 (5.1)	56 (4.6)	51 (3.2)	29 (2.9)	
Histological tumour type					
Ductal	3421 (82.1)	1048 (85.7)	1212 (76.6)	803 (80.5)	**<0.001**
Lobular	357 (8.6)	103 (8.4)	210 (13.3)	133 (13.3)	
Mixed	176 (4.2)	47 (3.8)	52 (3.3)	39 (3.9)	
Other	212 (5.1)	25 (2.0)	109 (6.9)	22 (2.2)	
Multifocality					
No	3552 (85.3)	987 (80.7)	1367 (86.4)	814 (81.6)	**<0.001**
Yes	515 (12.4)	214 (17.5)	188 (11.9)	155 (15.6)	
Unknown	98 (2.4)	22 (1.8)	28 (1.8)	28 (2.8)	
Hormonal receptor status					
Positive	2881 (69.2)	907 (74.2)	934 (59.0)	650 (65.2)	**<0.001**
Mixed	658 (15.8)	180 (14.7)	250 (15.8)	170 (17.1)	
Negative	526 (12.6)	129 (10.6)	393 (24.8)	173 (17.4)	
Unknown	101 (2.4)	7 (0.6)	6 (0.4)	4 (0.4)	
HER2 status					
Negative	2821 (67.7)	914 (74.7)	1096 (69.2)	722 (72.4)	**<0.001**
Unclear	522 (12.5)	53 (4.3)	125 (7.9)	45 (4.5)	
Positive	428 (10.3)	161 (13.2)	223 (14.1)	144 (14.4)	
Unknown	395 (9.5)	95 (7.8)	139 (8.8)	86 (8.6)	
Type of surgery					
Mastectomy	1133 (27.2)	451 (36.9)	797 (50.4)	572 (57.4)	**<0.001**
Breast-conserving therapy	3033 (72.8)	772 (63.1)	786 (49.7)	425 (42.6)	
Axillary lymph node dissection					
No	3481 (83.6)	88 (7.2)	1168 (73.8)	55 (5.5)	**<0.001**
Yes	685 (16.4)	1135 (92.8)	415 (26.2)	942 (94.5)	
Adjuvant systemic therapy					
None	3342 (80.2)	176 (14.4)	407 (25.7)	79 (7.9)	**<0.001**
Endocrine therapy	333 (8.0)	423 (34.6)	519 (32.8)	338 (33.9)	

Table 1 (*continued*)

Characteristics	T1N0 (N = 4166)	T1N1 (N = 1223)	T2N0 (N = 1583)	T2N1 (N = 997)	P-value*
Chemotherapy	218 (5.2)	114 (9.3)	292 (18.5)	141 (14.1)	
Both	273 (6.6)	510 (41.7)	365 (23.1)	439 (44.0)	
Targeted therapy (trastuzumab)					
No	4076 (97.8)	1120 (91.6)	1481 (93.6)	916 (91.9)	**<0.001**
Yes	90 (2.2)	103 (8.4)	102 (6.4)	81 (8.1)	

Numbers are N (%). HER2 = human epidermal growth factor receptor 2.

respectively. Conditional on 9 years survived, the risks on recurrences for the 10th year ranged between 0.5 and 0.8% for LR, between 0.2 and 0.4% for RR and between 0.6 and 1.5% for DM among the different T and N subgroups (Fig. 2).

3.3. Ten-year conditional recurrence risks per breast cancer subtypes

The 10-year risks from diagnosis on LR, RR and DM were lowest for the luminal A subgroup (3.9%, 1.7% and 7.3%, respectively). Patients with triple negative disease showed the highest 10-year risk on LR, RR and DM at diagnosis (5.6%, 4.9% and 16.7%, respectively). The total risk on recurrences declined over time and became as low as 0% for HER2 positive, 0.9% for triple negative, 1.8% for luminal A and 2.2% for luminal B disease in the 10th year. Interestingly, from the fifth year from diagnosis on, HER2 positive tumours displayed a 10-year RR risk of zero, and in the last year, all 10-year recurrence risks were 0% (Fig. 2).

3.4. Ten-year conditional overall and relative survival per T and N subgroup

At 10 years from diagnosis, 78.9% of patients with T1N0 stage were still alive, compared to 77.3%, 65.7% and 63.3% in T1N1, T2N0 and T2N1, respectively. Conditional on 9 years survived, these rates became 97.1%, 97.3%, 96.6% and 95.6% for the 10th year, respectively (Fig. 3). Compared to T1N0 stage, T1N1, T2N0 and T2N1 stage were related to lower 10-year OS, when corrected for confounding. Similar effects were seen conditional on one to seven years survived, although the difference between T and N subgroup became smaller. From year eight on, there was no significant difference in OS for the 9th and 10th year between T and N subgroups anymore (Fig. 4).

When correcting for mortality in the general population, 10-year RS rates were 96.5%, 92.1%, 91.4% and 79.3% for T1N0, T1N1, T2N0 and T2N1 stage, respectively. Conditional on nine years survived, these rates became 98.0%, 98.0%, 97.7% and 96.5%, in the 10th year, respectively (Fig. 3). For confounding-adjusted RS showed similar results as was found for OS (median follow-up was 11.4 years). In the first 3 years, T1N0, T2N0 and T2N1 stage showed a significantly higher excess mortality as compared to T1N0 stage. However, in the subsequent years until 10 years from diagnosis, no significant differences were observed anymore for T1N1 and T2N0 compared to T1N0 stage. The higher excess mortality ratios of T2N1, compared to T1N0, were visible from diagnosis until conditional on seven years survived. However, the interrelationship between the four T and N subgroups declined drastically over time (Fig. 5).

3.5. Ten-year conditional overall and relative survival per breast cancer subtype

Of the entire population, 1702 patients (21.4%) had an unknown breast cancer subtype due to missing data on receptor statuses or grade. These patients were excluded, leaving 6267 patients for analysis. At 10-years from diagnosis, 81.4% of the patients with luminal A disease were still alive, compared to 77.3%, 76.4% and 70.0% in luminal B, HER2 positive and triple negative, respectively. Conditional on 9 years survived, these rates became 97.2%, 96.6%, 98.3% and 96.5%, respectively (Fig. 3). After adjustment for confounders, lower 10-year OS at time of diagnosis was observed for luminal B and triple negative, compared to luminal A. HER2 negative disease was not significantly different from luminal A regarding OS. Similar effects were seen conditional on 1 to 6 years survived. Conditional on 7 and 8 years survived, no significant differences among the subtypes were observed. However, in the last year (conditional on 9 years survived), luminal B was associated with lower OS compared to luminal A (Fig. 4).

When correcting for mortality in the general population, 10-year RS rates were 95.0%, 93.2%, 89.0% and 79.6% for luminal A, luminal B, HER2 positive and triple negative disease, respectively. Conditional on 9 years survived, these rates became 99.6%, 98.5%, 100.6% and 98.3%, in the 10th year, respectively (Fig. 3). For confounding-adjusted RS (median follow-up was 11.4 years) also showed waning differences between the subtypes over time. Conditional on 0 to 3 years survived, clear differences between the subtypes were observed with triple negative disease showing the lowest RS and luminal A showing the highest RS. From 4 years after diagnosis on, no difference in RS between HER2 positive and luminal A were present anymore. For luminal B, compared to luminal A, no

Table 2
Baseline characteristics according to molecular subtype (n = 7969). *P-value was calculated on known values only, patients with unknown molecular subtype were excluded from these analyses. P-values depicted in bold are considered as statistically significant ($P < 0.05$).

Characteristics	Luminal A ($N = 3774$)	Luminal B ($N = 1465$)	HER2 positive ($N = 314$)	Triple negative ($N = 714$)	Unknown ($N = 1702$)	P-value*
Age (years)						
<40	142 (3.8)	112 (7.7)	24 (7.6)	87 (12.2)	52 (3.1)	**<0.001**
40–49	650 (17.2)	368 (25.1)	45 (14.3)	159 (22.3)	249 (14.6)	
50–59	1085 (28.8)	405 (27.7)	107 (34.1)	194 (27.2)	474 (27.9)	
60–69	959 (25.4)	301 (20.6)	86 (27.4)	147 (20.6)	452 (26.6)	
70–79	665 (17.6)	186 (12.7)	32 (10.2)	97 (13.6)	321 (18.9)	
≥80	273 (7.2)	93 (6.4)	20 (6.4)	30 (4.2)	154 (9.1)	
Social economic status						
Low	1160 (30.7)	445 (30.4)	86 (27.4)	213 (29.8)	505 (29.7)	0.149
Medium	1518 (40.2)	560 (38.2)	114 (36.3)	280 (39.2)	691 (40.6)	
High	1096 (29.0)	460 (31.4)	1144 (36.3)	221 (31.0)	506 (29.7)	
Region of diagnosis						
A	585 (15.5)	182 (12.4)	32 (10.2)	102 (14.3)	198 (11.6)	**<0.001**
B	284 (7.5)	175 (12.0)	37 (11.8)	63 (8.8)	206 (12.1)	
C	277 (7.3)	87 (5.9)	17 (5.4)	49 (6.9)	132 (7.8)	
D	761 (20.2)	304 (20.8)	70 (22.3)	137 (19.2)	193 (11.3)	
E	376 (10.0)	158 (10.8)	29 (9.2)	68 (9.5)	144 (8.5)	
F	444 (11.8)	167 (11.4)	48 (9.2)	97 (13.6)	337 (19.8)	
G	535 (14.2)	185 (12.6)	35 (11.2)	97 (13.6)	273 (16.0)	
H	240 (6.4)	88 (6.0)	23 (7.3)	50 (7.0)	88 (5.2)	
I	272 (7.2)	119 (8.1)	23 (7.2)	51 (7.1)	131 (7.7)	
Lateralisation						
Left	1920 (50.9)	770 (52.6)	162 (51.6)	386 (54.1)	912 (53.4)	0.383
Right	1854 (49.1)	695 (47.4)	152 (48.4)	328 (45.9)	790 (46.4)	
Sublocalisation						
Outer quadrants	1806 (47.9)	678 (46.3)	150 (47.8)	372 (52.1)	833 (48.9)	0.082
Inner quadrants	740 (19.6)	287 (19.6)	67 (21.3)	151 (21.2)	334 (19.6)	
Central parts	297 (7.9)	104 (7.1)	23 (7.3)	35 (4.9)	117 (6.9)	
Overlapping lesions	865 (22.9)	367 (25.1)	71 (22.6)	151 (21.2)	377 (22.2)	
Unknown	66 (1.8)	29 (2.0)	3 (1.0)	5 (0.7)	41 (2.4)	
T stage						
1	2771 (73.4)	834 (56.9)	177 (56.4)	371 (52.0)	1236 (72.6)	**<0.001**
2	1003 (26.6)	631 (43.1)	137 (43.6)	343 (48.0)	466 (27.4)	
N stage						
0	2679 (71.0)	947 (64.6)	219 (69.8)	547 (76.6)	1357 (79.7)	**<0.001**
1	1095 (29.0)	518 (35.4)	95 (30.3)	167 (23.4)	345 (20.30)	
Grade						
1	1438 (38.1)	65 (4.4)	7 (2.2)	28 (3.9)	370 (21.7)	NA
2	2336 (61.9)	255 (17.4)	82 (26.1)	133 (18.6)	699 (41.1)	
3	–	1125 (76.8)	216 (68.8)	525 (73.5)	341 (20.0)	
Unknown	–	20 (1.4)	9 (2.9)	28 (3.9)	292 (17.2)	
Histological tumour type						
Ductal	2909 (77.1)	1325 (90.4)	293 (93.3)	617 (86.4)	1340 (78.7)	**<0.001**
Lobular	508 (13.5)	63 (4.3)	1 (0.3)	17 (2.4)	214 (12.6)	
Mixed	193 (5.1)	50 (3.4)	3 (1.0)	7 (1.0)	61 (3.6)	
Other	164 (4.4)	27 (1.8)	17 (5.4)	73 (10.2)	87 (5.1)	
Multifocality						
No	3222 (85.4)	1195 (81.6)	255 (81.2)	643 (90.1)	1406 (82.6)	**<0.001**
Yes	476 (12.6)	228 (15.6)	47 (15.0)	52 (7.3)	269 (15.8)	
Unknown	76 (2.0)	42 (2.9)	12 (3.8)	19 (2.7)	27 (1.6)	
Type of surgery						
Mastectomy	1280 (33.9)	610 (41.6)	145 (46.2)	226 (31.7)	692 (40.7)	**<0.001**
Breast-conserving therapy	2494 (66.1)	855 (58.4)	169 (53.8)	488 (68.4)	1010 (59.3)	
Axillary lymph node dissection						
No	2262 (59.9)	787 (53.7)	185 (58.9)	461 (64.6)	1097 (64.5)	**<0.001**
Yes	1512 (40.1)	678 (46.3)	129 (41.1)	253 (35.4)	605 (35.6)	
Adjuvant systemic therapy						
None	2252 (59.7)	290 (19.8)	116 (36.9)	262 (36.7)	1084 (63.7)	**<0.001**
Endocrine therapy	800 (21.2)	465 (31.7)	8 (2.6)	9 (1.3)	331 (19.5)	
Chemotherapy	25 (0.7)	33 (2.3)	181 (57.6)	436 (61.1)	90 (5.3)	

Table 2 (*continued*)

Characteristics	Luminal A (N = 3774)	Luminal B (N = 1465)	HER2 positive (N = 314)	Triple negative (N = 714)	Unknown (N = 1702)	P-value*
Both	697 (18.5)	677 (46.2)	9 (2.9)	7 (1.0)	197 (11.6)	
Targeted therapy (trastuzumab)						
No	3771 (99.9)	1255 (85.7)	174 (55.4)	713 (99.9)	1680 (98.7)	**<0.001**
Yes	3 (0.1)	210 (14.3)	140 (44.6)	1 (0.1)	22 (1.3)	

Numbers are N (%). HER2 = human epidermal growth factor receptor 2, NA = not applicable.

differences in 10-year RS were observed at 7 to 9 years from diagnosis. The difference between triple negative and luminal A disease declined over time; however, conditional on 8 years survived, triple negative disease was associated with lower 10-year RS compared to luminal A (Fig. 5).

4. Discussion

This study showed that 10-year recurrence risks from diagnosis, conditional on the number of event-free years, declined over time for all prognostic subgroups. Remarkably, at diagnosis, clear differences between

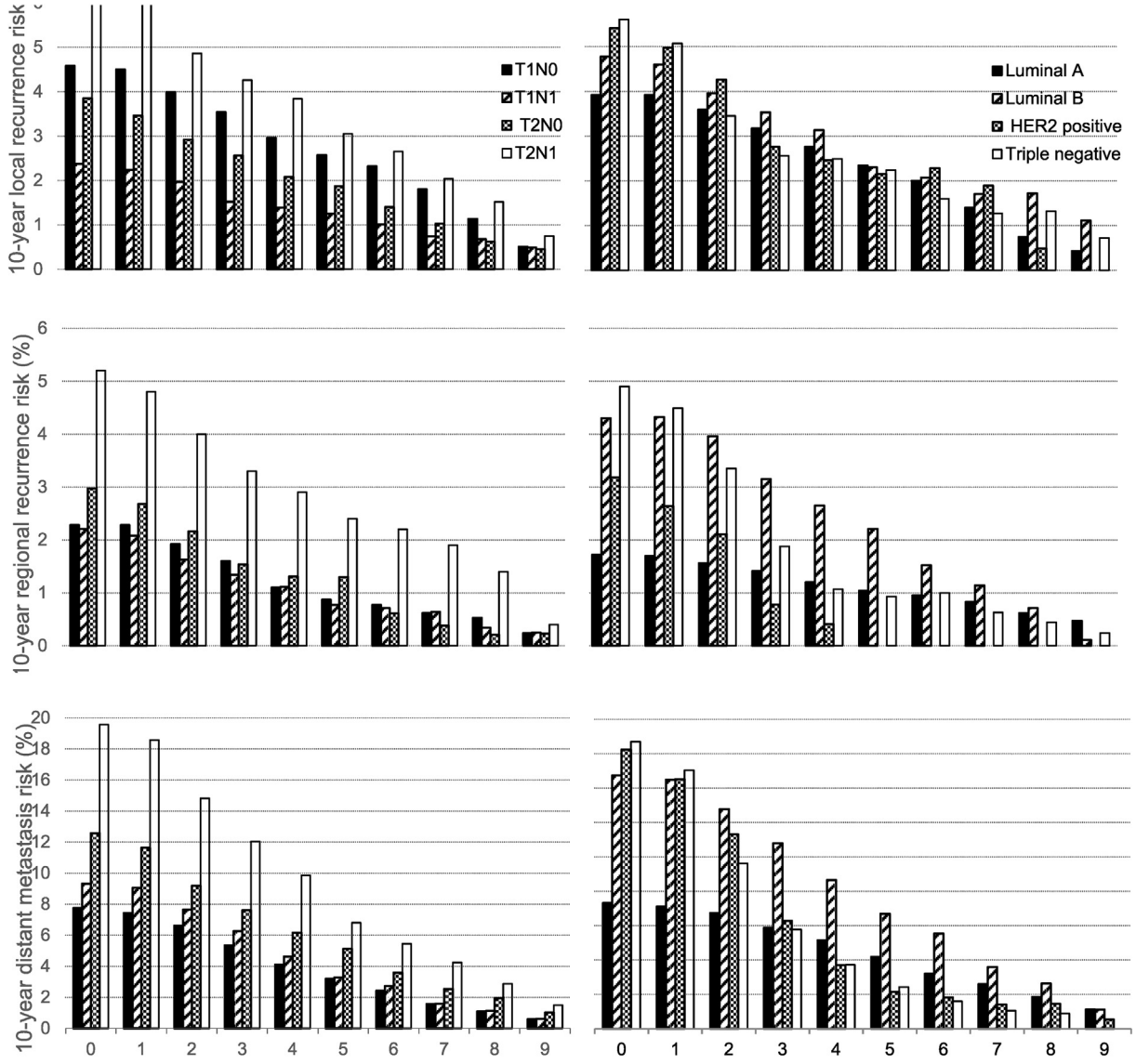

Fig. 2. **Ten-year conditional risk on recurrences, from the first until the tenth year, stratified for T and N subgroup and breast cancer subtype**. Percentages are shown below the graphs. DM = distant metastasis, RR = regional recurrence, LR = local recurrence.

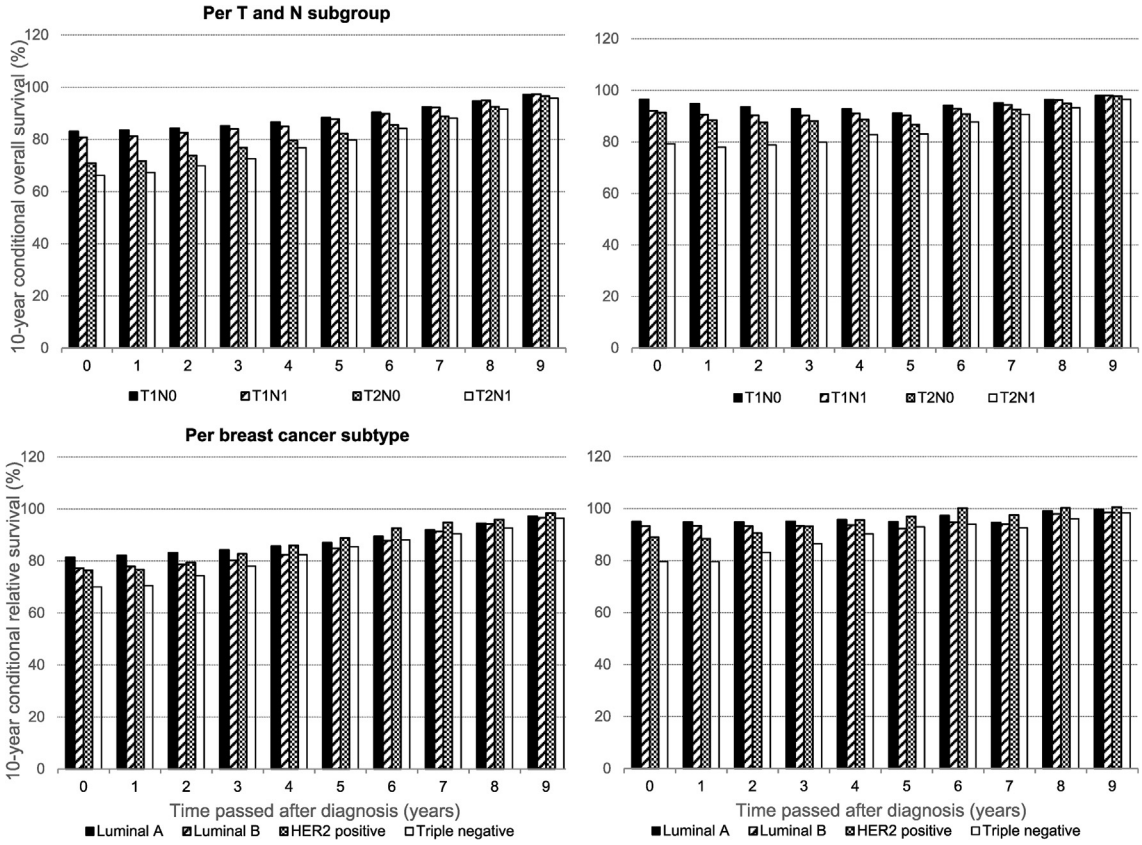

Fig. 3. Ten-year conditional overall and relative survival, from the first until the tenth year, stratified for T and N subgroup and breast cancer subtype.

subgroups were observed regarding recurrences, which attenuated as more years passed. This finding is likely to be explained by the initial prognosis of the patients. Wangchinda et al. showed that larger and node positive tumours were more likely to recur in the first few years following diagnosis [17]. Our study supports these results by showing that the divergent recurrence rates between T and N subgroups attenuated as year passed. Being free of disease at 1 to 9 years following diagnosis increases the chance of being free of disease at 10 years following diagnosis.

The importance of stratifying patients according to T and N stage has been shown in a recent publication of Pan et al. showing that the risk of DM is strongly correlated with T and N stage [18]. The lowest 10-year LR and RR risks from diagnosis were found in T1N1 stage, while this was expected in T1N0 stage (lowest risk group). The difference in RRs between these two subgroups was negligible (2.3 versus 2.2%), but the percentage of LRs in T1N0 was almost doubled as compared to the percentage of LRs in T1N1 stage (4.6 versus 2.4%). A likely explanation is that patients with T1N1 stage breast cancer were treated more intensively than patients with T1N0 stage breast cancer. Indeed, in the studied era, only 20% of T1N0 breast cancer patients received adjuvant systemic therapy, compared to 86% in T1N1. A recent study showed that a larger proportion of T1N0 breast cancers benefited from adjuvant systemic therapy, regardless of molecular subtype, tumour size, age and presence of comorbidities [19], which may explain our results. However, one should realise that the 10-year LR risk is still very low for both T1N0 and T1N1 stage. In addition, the Dutch national guidelines advised adjuvant systemic therapy in case of an absolute risk of 10-year breast cancer-related mortality of 15% or more. As patients with T1N0 stage breast cancer generally have a lower risk of 10-year breast cancer–related mortality, these patients were only advised adjuvant systemic therapy in case of other risk factors. An additional analysis on our data on patients with a known subtype shows that almost 10% of all T1N0 breast cancers were triple negative, compared to 6.5% in the T1N1 group. Triple negative breast cancers are previously shown to be more often classified as N0 [20] and are associated with increased LR risks [21] compared to other subtypes. We showed that patients with triple negative disease had the highest 10-year risk on LR, RR and DM at diagnosis. Over time, differences between breast cancer subtypes became smaller. Of note, luminal B breast cancers showed the highest risk of recurrences, conditional on 2 to 9 years survived. This means that in luminal B disease, recurrences more often occur after some years from diagnosis, while they occur most often in the first few years for the other subtypes

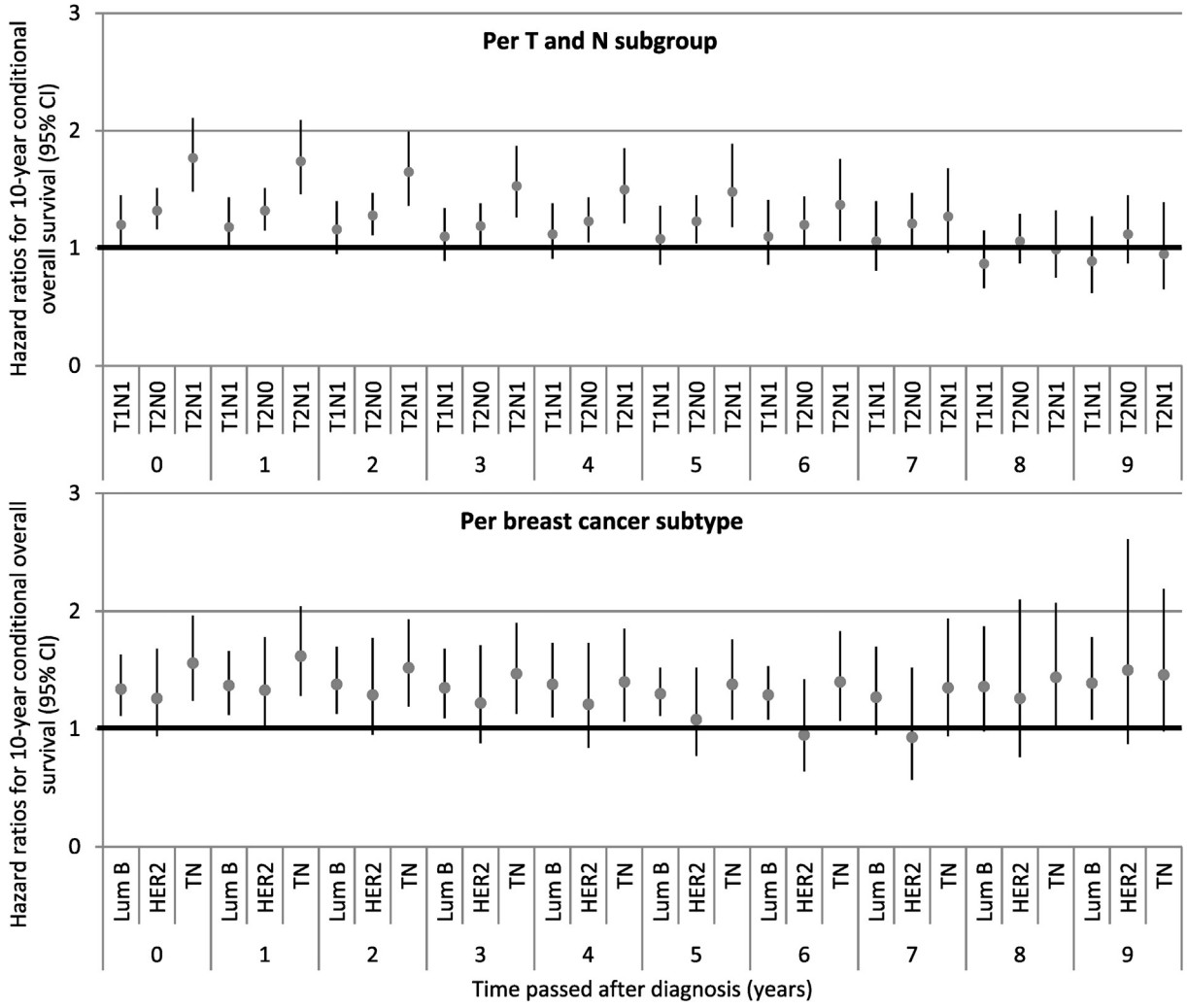

Fig. 4. **Hazard ratios on 10-year conditional overall survival stratified for T and N subgroup and breast cancer subtype**. In this figure, the differences between T and N subgroups in relation to 10-year OS are shown, when correcting for all relevant confounding variables. T1N0 stage was used as a reference for all analyses. CI = confidence interval.

(especially for HER2 positive and triple negative). Our result that the highest recurrence risks from diagnosis were found in triple negative disease confirms a previously performed systematic review, in which results of 7 studies investigating LR and RR according to molecular subtypes were combined [22]. The finding that in HER2-positive disease, no RRs were found from the fifth year from diagnosis on may partly be attributed to the effectiveness of trastuzumab, which is shown to increase the 5-year disease-free survival significantly [23], or the low number of events. Ten-year OS and RS were significantly different between the prognostic subgroups. However, these differences attenuated over time, as shown before [24]. Similar to the waning differences in recurrence risks over time, this can be explained by the initial prognosis of the patients: patients with an initial poorer prognosis are more likely to decease in the first few years. Janssen-Heijnen et al. [9] showed that conditional RS of stage I–III breast cancer patients in the Netherlands remained similar or improved over time. Furthermore, they showed that although long-term prognosis was very good, there was still significant excess mortality in the patient population compared to the general Dutch population, up to 20 years from diagnosis. The authors suggested that this may be due to late recurrences, second tumours or late side-effects of breast cancer treatment. Our study has shown that the conditional risk on recurrences declines over the years, becoming as low as only a few percent in the last years. Whether this small risk may contribute to the described excess mortality rates beyond 10 years is unclear. In our study, we showed that RS rates in the 10th year following diagnosis ranged between 96.5% and 98.0% for the different T and N subgroups, confirming a small but persistent excess mortality compared to the general Dutch population.

A strength of this study is the use of a nationwide population-based cancer registry, which increases the

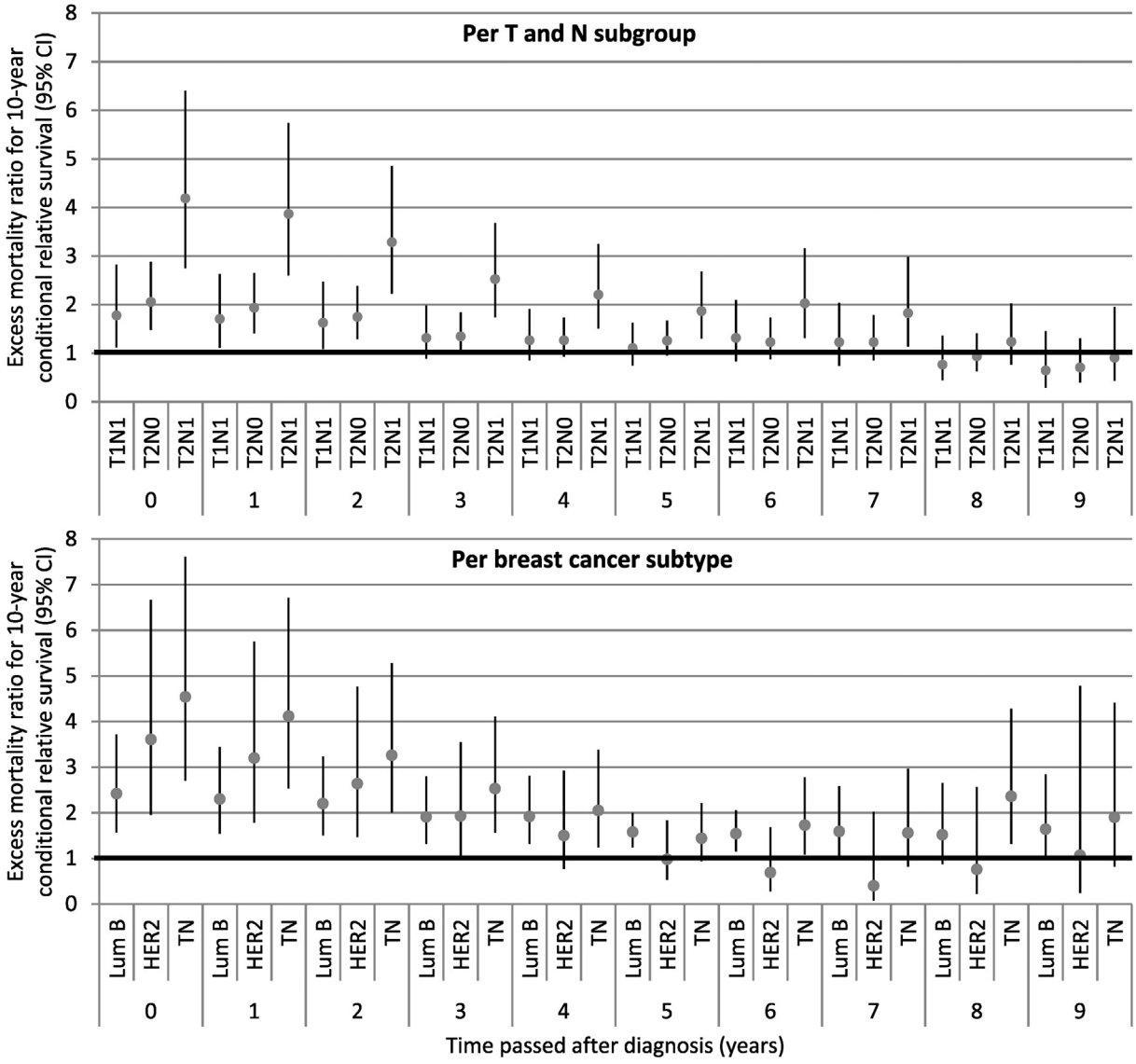

Fig. 5. **Excess mortality ratios on 10-year conditional relative survival stratified for T and N subgroup and breast cancer subtype**. T1N0 stage was used as a reference for all analyses. In this figure, the differences between T and N subgroups in relation to 10-year RS (as a measure for disease-specific survival) are shown, when correcting for all relevant confounding variables. T1N0 stage was used as a reference for all analyses. CI = confidence interval.

generalisability of the results. In addition, follow-up information on recurrences was extracted from patient records in retrospect, thereby ensuring that recurrence data were collected with high accuracy. Furthermore, very little population-based studies have been conducted that investigated the 10-year recurrence risk in breast cancer patients. Baade et al. [3] recommended that knowledge on conditional survival estimates should be incorporated in routine statistical reporting, as these estimates provide more accurate information for patients who survived several years after their diagnosis. Uncertainty has multiple times been reported as a very important factor that negatively affects quality of life in breast cancer survivors [25–27]. Therefore, we would like to emphasise that conditional estimates better reflect the risk of recurrence at a certain time point following diagnosis and that it may help patients dealing with uncertainty about their future. In addition, information on conditional recurrence risks and survival is important to assess the relevance of prolonged endocrine therapy and/or adjuvant chemotherapy.

A limitation of this study is that HER2 status evaluation and the use of trastuzumab was introduced in 2005. As a result, not all patients with HER2 positive disease may have been treated with trastuzumab, which may have led to higher recurrence rates for these patients as compared to patients diagnosed in more recent years. Another limitation is lacking data on Ki-67, which was originally used to classify patients in luminal A or luminal B. However, in this study, we used

grade to classify high risk luminal A tumours into the luminal B group. Furthermore, it is expected that contemporary recurrence risks are lower than the risks observed in our study due to improvements in diagnostics [28], surgical procedures [29] and adjuvant systemic treatment [30]. Especially regarding the latter, our results should be interpreted in light of the increasingly personalised use of adjuvant systemic therapy as a result of the MINDACT [31] and TAILORx [32] trials, both showing specific patient groups in which less or no use of adjuvant systemic treatment is non-inferior to the standard recommendation. Finally, it should be noted that beyond 10 years from diagnosis, recurrences are described to occur at a steady rate in oestrogen receptor positive disease [18,24], which may be related to the concept of tumour dormancy, which is thought to be a possible cause of late recurrences [33] Longer follow-up beyond 10 years should give further information on late recurrences and its relationship with prognostic subgroups.

5. Conclusions

To our knowledge, this is the first study showing conditional 10-year recurrence risks in each subsequent year after diagnosis. Besides, we demonstrated that the difference in recurrence risks and survival between the prognostic subgroups wanes with more disease-free years from diagnosis. This is very important information to be communicated to patients, especially to those remaining free of disease over time. Fear of recurrent cancer has been shown to be related to a high feeling of unmet needs in breast cancer patients [10], even years after their primary treatment [34]. The results of this study may contribute to increased awareness of lower recurrence risks over time, especially for patients with an initial high risk of recurrence. In addition, information on conditional risks may help personalise follow-up, as for some patients less frequent follow-up visits may be sufficient [35,36].

Conflict of interest statement

The authors have declared no conflicts of interest.

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