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Breast cancer in elderly compared to younger patients in the Netherlands;

Stage at diagnosis, treatment and survival in 127,805 unselected patients

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Abstract

Background. Breast cancer is the most common type of cancer in several parts of the world and the number of elderly patients is increasing. The aim of this study was to describe stage at diagnosis, treatment and relative survival of elderly patients compared to younger patients in the Netherlands.

Methods. Adult female patients with their first primary breast cancer diagnosed between 1995-2005 were selected. Stage, treatment and relative survival were described for young and elderly (≥65 years) patients and within the cohort of elderly patients according to 5-year age groups.

Results. Overall, 127805 patients were included. Elderly breast cancer patients were diagnosed with a higher stage of disease. Moreover, within the elderly differences in stage were observed. Elderly underwent less surgery (99.2% to 41.2%); elderly received hormonal treatment as monotherapy more frequently (0.8% to 47.3%) and less adjuvant systemic treatment (79% to 53%). Elderly breast cancer patients with breast cancer had a decreased relative survival. Although relative survival was lower in the elderly, the percentage of patients who die of their breast cancer less than 50% above age 75.

Conclusions. Relative survival for the elderly is lower as compared to their younger counterparts while the percentage of deaths due to other causes increases with age. This could indicate that the patient selection is poor and fit patients could suffer from “under treatment”. In the future, specific geriatric screening tools are necessary to identify fit elderly patients who could receive more “aggressive” treatment while best supportive care should be given to frail elderly patients.

INTRODUCTION

Breast cancer is the most common type of cancer in Western societies and will increasingly become a disease affecting the lives of elderly women. Worldwide, nearly a third of breast cancer occurs in patients ≥65 years, and in more developed countries this proportion increases to over 40%.[1;2] Despite these numbers, few prospective trials exist have included elderly patients. The population of elderly breast cancer patients is characterized by large individual variation in physical and mental conditions. Combined with the fact that there is limited evidence from Randomized Controlled Trials (RCT), the strong influence of personal preferences in the decision-making process complicates the development of guidelines for the treatment of elderly breast cancer patients.[3;4] Consequently, up to date there are no generally agreed guidelines for the treatment of elderly females with breast cancer and variation in treatment is large.

Elderly patients are usually diagnosed with more favorable tumor biology: hormone receptor-positive which increase hormone treatment sensitivity, no Her2/neu overexpression, and lower grades and proliferative indices.[5] However, elderly patients are more likely to present with larger and more advanced tumors and are less likely to be treated according to accepted guidelines, which may have a negative effect on survival.[1;6] Observational studies are suitable to assess achievements in daily medical practice and are useful to study prognosis.[7-9] Cancer registry data, in addition to RCTs, show actual patterns of staging, treatment and survival by age and therefore offer a possible scope for improvement of care. A recently published review of the population-based literature regarding diagnosis, treatment and prognosis of breast cancer patients showed that the proportion of patients with unknown stage and advanced disease is higher among elderly patients compared to younger patients and that their treatment is generally less aggressive.[3] Besides, survival of elderly patients is generally lower and the prevalence of (serious) comorbid conditions is usually higher.[10] The possible explanation for the age-related differences regarding treatment is complex; it reflects decisions based on the view of physicians, patients, relatives and caregivers and on psychosocial issues and costs, but also proximity to an oncology and radiotherapy centre.[1] Because comorbidities and functional status significantly affect prognosis and treatment choices, thorough consideration must be given to the overall health of the elderly patients. However, elderly women are still less likely to have surgery for operable breast cancer, even after accounting for comorbidity, functional status, pretreatment stage,

social deprivation and type of hospital.[11] Comorbidity does not always predict standard treatment; some studies have found an effect of comorbidity, other studies have been contradictory. Studies suggest that treatment decisions for elderly women with breast cancer are still based largely on age rather than health status or potential benefit.[11]

A sizeable proportion of patients older than 70 years with operable breast cancer dies of non-cancer related causes.[1] Consequently, relative survival is the preferred way to describe the prognosis of elderly breast cancer patients, as it takes into account the risk of dying from other causes than the breast cancer. The recent review of Louwman *et al* evaluated all available population-based data concerning elderly with breast cancer and showed several age-related aspects.[3] However, most of the 20 population-based studies that were included in this review were from the SEER database and for the Netherlands only regional data from one regional Cancer Registry were available. Therefore, the aim of this study was to describe stage at diagnosis, treatment and relative survival of the elderly patients with breast cancer as compared to the younger patients in the Dutch population.

METHODS

Study population

PALGA, the nationwide Dutch network and registry of histo- and cytopathology regularly submits reports of all diagnosed malignancies to the regional cancer registries. The national hospital discharge databank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. Trained registry personnel collect data on diagnosis, staging, and treatment from the medical records, including pathology and surgery reports, using the registration and coding manual of the Dutch Association of Comprehensive Cancer Centers. All data from the regional cancer registries are merged into the Netherlands Cancer Registry (NCR). From the NCR database, adult female patients with their first primary breast cancer diagnosed between 1995-2005 were selected. Patients with a history of other malignancy were excluded. The mass mammographic screening program in the Netherlands started between in 1990 and 1991 for females aged 50-70 years; in 1997 the upper age limit of the screening program was increased to 75 years.

Statistical analysis

Stage was classified according to version of the TNM classification that was used in at the year of diagnosis. Pathological T, N and M stage was used; clinical stage was used if pathology was missing. Vital status was established either directly from the patient's medical record or through linkage of cancer registry data with the municipal population registries (until January 1st, 2008) which record information on their inhabitant's vital status. Relative survival was calculated by the Hakulinen method as the ratio of the survival observed among the cancer patients and the survival that would have been expected based on the corresponding (age, sex and year) general population. National life tables were used to estimate expected survival. Relative Excess Risks of death (RER) were estimated using a multivariable generalized linear model with a Poisson distribution, based on collapsed relative survival data, using exact survival times. Finally, mortality in the cohort was compared to the overall mortality in the Dutch general population according to age for the total period of follow-up. The estimated percentage of patients that died of breast cancer within the total number of deceased patients was calculated as ((Observed deaths-Expected deaths)/Observed deaths)*100 in the specific age groups.

RESULTS

Table 1 shows the characteristics of the 127805 patients that were included in our study. Almost 40% of the patients were 65 years and older at time of diagnosis. There was a gradual increase in the number of patients over the years 1995-2005. Most breast cancer had a ductal morphology (70.0%), were invasive (91.8% versus 8.2% in situ) and were grade 2 (29.4%) or 3 (27.3%).

Stage at diagnosis

Figure 1 shows the stage at diagnosis according to age. Elderly patients were more often diagnosed with a higher stage of disease with an increase from 27.1% for stage IIA for the 15-64 year old patients to 32% for the 90+ and an increase from 8% to 18% for stage III. The proportion of patients with stage IV disease increased from 3.7% for the 15-64 year old patients to 8.5% for the 80-84 years old, but did not further increase for the oldest elderly (6.7% for 85-89 years and 4.4% for 90+). Besides, the fraction of patients with an unknown stage of disease was also higher in elderly with an increase from 1.5% for 15-64 year olds to 13.3% for the 90+. These trends were also present in the elderly above the age of 75 outside the mass screening program. Besides, for patients in the screening program, differences in stage distribution were observed. It is not clear whether the oldest elderly present more often with positive lymph nodes since the nodal status is frequently unknown in the oldest elderly; 10.4% for patients aged 80-84, 16.1% for 85-89 and 24.2% for the patients older than 90 years, respectively. Patients aged 75-89 presented more often with distant metastases (stage IV), while for the oldest elderly the stage of disease was usually not known.

Treatment

Table 2 shows several aspects of breast cancer treatment according to age. The percentage of patients who underwent surgery decreased with age. Overall, the proportion of patients who received surgery decreased from 99% (15-65 years) to 41% for the oldest elderly (90+). The percentage of patients who received radiotherapy after breast conserving surgery decreased, especially after age 80, from 91% for the youngest patients to 15% for the 90+. The fraction of patients who received mastectomy was higher in the elderly (45% to 76%); differences were clearer for T1 and T2, however not for *in situ* tumors. The percentage of patients who received a lymph node dissection decreased from 66% for age<65 years to 20% for the 90+. On the contrary, the percentage of patients who

received hormonal treatment as monotherapy increased with age for all stages. Overall, the percentage of patients who received only hormonal treatment increased from 0.8% for patients 15-65 years to 47% for the oldest elderly ($p<0.001$). Finally, the percentage of patients who received any adjuvant systemic treatment decreased with age for all stages; overall, the percentage decreased from 79% for age <65 years to 53% for the 90+.

Survival

Figure 2 shows the proportion of patients who died of breast cancer within the group of patients that died. For younger patients with breast cancer almost 100% of the patients, who died, died as result of their breast cancer. With increasing age, the percentage of patients who died of their breast cancer decreased to almost 20% in the oldest elderly. After the age of 75, more than 50% of the breast cancer patients died due to other causes.

Table 3 shows the 5-years and 10-years Relative Survival (RS) according to age and stage, calculated as the ratio of the survival observed and the survival expected based on the corresponding general population. Survival time was calculated from date of diagnosis to date of death. Overall, the differences between Overall Survival and Relative Survival decreased with age, indicating the excess mortality in the elderly due to other causes than breast cancer (data not shown). For all stages, except RS for *in situ* tumors, there were significant differences between the age categories. Both the Overall Survival and Relative Survival were decreased in elderly. For stage I RS decreased from 96.8% (5-years) to 87.9% for 15-65 versus 90+ ($p=0.004$); for stage II there was a decrease until the age of 89, but an increase of RS for the 90+ ($p<0.001$), for stage III RS decreased from 67.6% to 37.7% for 90+ ($p<0.001$) and for stage IV the RS decreased from 21.4 to 11.6% ($p<0.001$), respectively.

DISCUSSION

Our results confirm the international data that indicate a higher stage at diagnosis, less aggressive treatment, less adherence to guidelines and a decreased survival for the elderly breast cancer patients in the Netherlands. Because of the large number of included subjects, we were able to stratify within the elderly to show that the trends concerning stage and treatment are also present in the patients outside the mass screening program (75+). Although relative survival is lower in the elderly, the percentage of patients who die of their breast cancer is actually low in the elderly.

The field of geriatric oncology has increased in the western countries, although it is still in its early stages.[12] Several population-based studies have shown that elderly patients usually present with more advanced disease, however few have stratified the elderly into different age groups. Recent data show that the stage distribution of patients aged 70-79 years was almost similar to the stage distribution of the younger age groups for the period of diagnosis 2000-2005, which could be due to the extension of the upper age limit of the screening program to 75 years in 1998.[3] Women aged 80 years and older, however, remained at higher risk of being diagnosed with more advanced disease in this study. In the present study we further stratified the age group 70-79 in 2 subgroups and we showed that specifically in the ages 70-74 the stage distribution is similar to the younger patients. After the age of 75, less patients are diagnosed with stage I disease. Moreover, an increasing number of patients were diagnosed with stage III and an unknown stage of disease. This less favorable stage distribution could be due to delay in the diagnosis of breast cancer in elderly patients due to fewer or no screening mammography examinations or patient delay caused by less breast cancer awareness.

Treatment of the elderly population with breast cancer is usually less aggressive than in their younger counterparts. As also shown in the present study, elderly patients receive less surgery as age increases, even in the lower stages of disease, despite the fact that for the elderly population breast cancer surgery-related mortality is low.[5] A recent study of 268 patients above the age of 70 years diagnosed at the Nottingham Breast Institute showed, however, even lower numbers of patients who were operated (60% versus 80.6% in the present study).[13] One of the reason for this is that the elderly patients are thought to be at a higher risk of morbidity and mortality; besides personal preferences of the elderly patients also play a role. Hormonal treatment alone without surgery has been considered as alternative treatment option[14], mainly in the very old. However, as shown in the

present data the increase in the use of only hormonal treatment started already at the age of 65. For fit elderly patients it has been confirmed (Cochrane meta-analysis[14]) that primary hormonal treatment with tamoxifen is inferior to surgery (with or without hormonal treatment) for the local control and progression-free survival of breast cancer, however, no difference in overall survival was shown and data for the frail elderly are not available .[1;14] Most elderly women with early stage breast cancer are candidates for breast conserving treatment; however, available data suggest that older patients are less likely to receive such treatment.[1] The same trend was observed in the present study: elderly patients with T1 or T2 underwent mastectomy more often when compared to younger patients. Besides, if elderly patients did receive breast conserving surgery (BCS) their chances of receiving radiotherapy were significantly decreased. Several studies have specifically assessed the benefits of radiotherapy in elderly patients and have shown a decrease in the relative rate of breast cancer recurrence.[1;15-19] However, the absolute incidence of relapses tended to be low and data on overall survival was generally absent. Finally, elderly patients in the present study received less often a lymph node dissection, also stratified for early and advanced disease. A retrospective study of Aziz et al showed a trend towards survival benefit in elderly women with stage I or II breast cancer who underwent axillary lymph node dissection, however the trend was not significant after adjusting for differences in the probability of receiving a lymph node dissection.[20] Besides, as the authors mention in the discussion, it is difficult to conclude about treatment outcomes in retrospective studies. In conclusion, adherence to guidelines is worse in elderly women; they undergo less surgery and less radiotherapy after breast conserving surgery. A study from Giordano et al showed that even after adjustment for comorbidity score, race, marital status, educational status, clinical stage and tumor characteristics, increased age was independently associated with decreased guideline concordance for surgery, adjuvant chemotherapy and adjuvant hormonal therapy.[21] A significant part of this deviation from the guidelines could be explained by patient preferences, however studies are needed to show the extent to which the difference in management can be explained by differences in preferences.[11] It seems, however, that older patients with cancer appear to prefer a more passive role in treatment decisions and that the disparity in treatment by age is not likely to be the sole function of patient preferences.[22, 11]

The less aggressive treatment of elderly women in the present study seems to be associated with decreased survival. This could especially decrease the survival of fit elderly patients if the selection for treatment was based only on age. However, effects of treatment on survival are hard to determine by observational research due to confounding by indication. Our study shows a decreased relative survival for elderly patients in all stages of disease. As relative survival reflects disease-specific survival, the results cannot be explained by a higher rate of death in the elderly due to other causes, less intense treatment or either tumor or co-morbid conditions may play a role.[23] A recent trial supported the belief that adjuvant chemotherapy can improve survival among fit elderly women with breast cancer and that standard chemotherapy is superior to the oral agent capecitabine.[24] However, differences between OS and RS are larger for the elderly patients, suggesting that more patients die of other causes; actually as shown in the present study the percentage of patients who die of their breast cancer within the group of deceased patients decreases to around 20% for the oldest elderly, meaning that the largest proportion of patients dies due to other causes. After the age of 75, more than 50% of the deceased patients with breast cancer die of other causes than their breast cancer; so a careful, multidisciplinary evaluation of the elderly patient has to take place.

In conclusion, the present study showed that elderly patients in the Netherlands are diagnosed at a higher stage of disease, receive less aggressive treatment, and have a decreased relative survival. Although relative survival was lower in the elderly, the percentage of patients who died of their breast cancer was actually low in the elderly. This could indicate that patient selection is poor and that fit patients suffer from “under treatment”. Future studies should be aimed at designing specific geriatric screening tools for elderly breast cancer patients which assist in choosing adequate treatment; thereby improving breast cancer specific survival (with minimal toxicity) for fit elderly patients and selecting frail elderly patients for best supportive care.

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Table 1: Characteristics of the Dutch cohort of 127805 breast cancer patients diagnosed between 1995-2005

Characteristic	Number	Percentage
Age (years)		
15-65	78449	61.4
65-69	13029	10.2
70-74	12550	9.8
75-79	9682	7.6
80-84	7883	6.2
85-89	4509	3.5
90-94	1470	1.2
95+	233	0.2
Year of diagnosis		
1995	10183	8.0
1996	10475	8.2
1997	10610	8.3
1998	10944	8.6
1999	11762	9.2
2000	11923	9.3
2001	12314	9.6
2002	12100	9.5
2003	12299	9.6
2004	12652	9.9
2005	12543	9.8
Morphology		
Ductal	89471	70.0
Lobular	13648	10.7
Other*	24686	19.3
Invasive / in situ		
In situ	10518	8.2
Invasive	117287	91.8
Grade		
1	15748	12.3
2	37524	29.4
3	34904	27.3
Unknown	39629	31.0
Overall	127805	100

* includes combined ductal & lobular and “not otherwise specified”

Figure 1: Stage at diagnosis (%) according to TNM classification of the year of diagnosis for the Dutch cohort breast cancer patients 1995-2005.

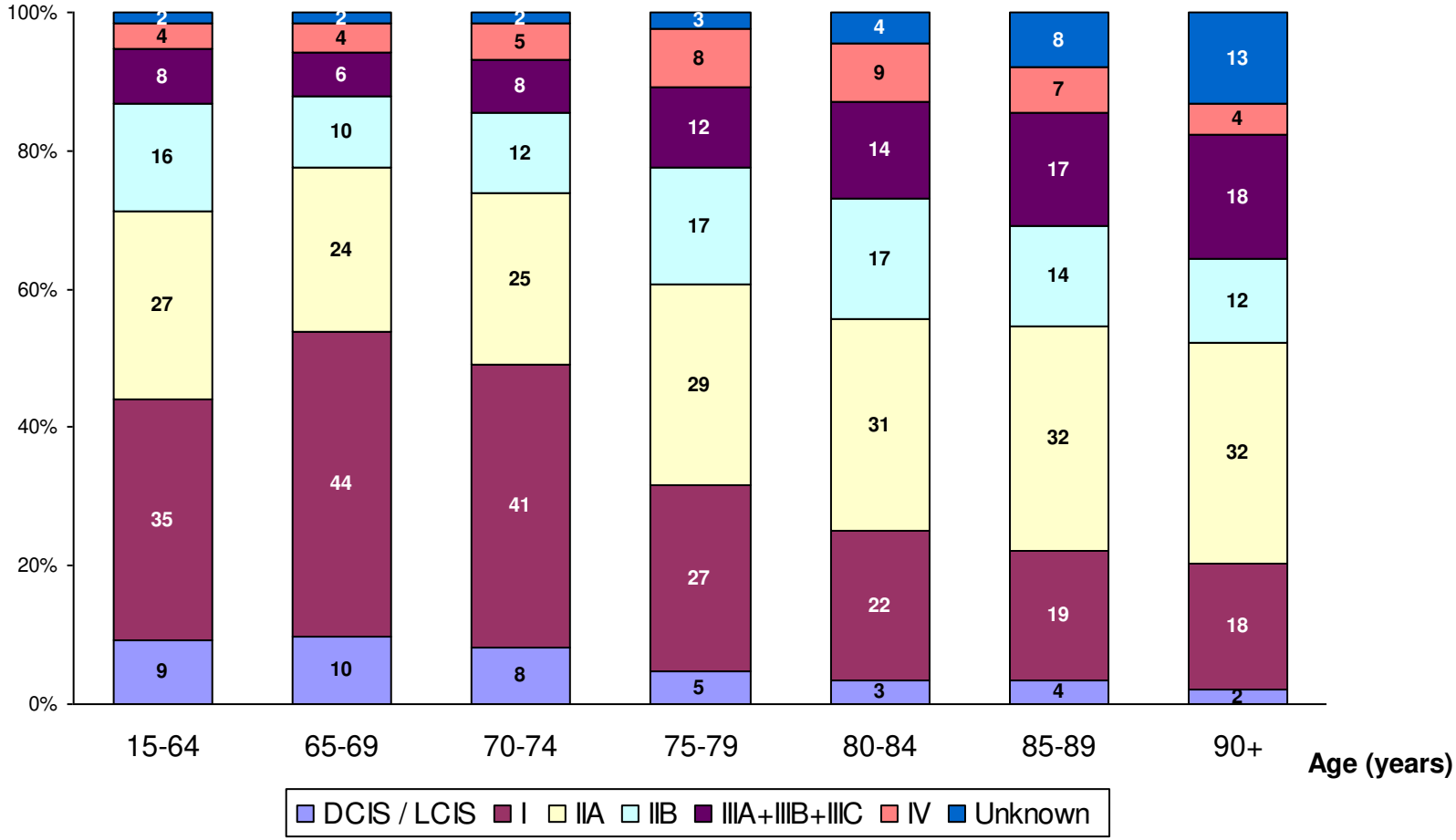

Table 2: Treatment of female breast cancer patients in the Netherlands, according to age.

Treatment	Age (years)							
	15-64	65-69	70-74	75-79	80-84	85-89	90+	p-value**
Surgery in all tumors, except T4 and M1*	99.2	98.8	97.7	93.3	83.2	64.6	41.2	<0.001
Radiotherapy after breast conserving surgery*	91.4	90.9	90.3	86.3	70.8	35.9	14.6	<0.001
Mastectomy for In Situ, Stage I or Stage II	45.0	46.0	54.3	68.6	78.6	82.2	76.2	<0.001
Lymph node dissection	66.2	62.5	61.3	64.3	55.2	39.0	19.9	<0.001
Hormonal treatment as monotherapy	0.8	2.0	3.8	9.5	18.1	31.1	47.3	<0.001
Any adjuvant systemic treatment	78.5	70.7	66.9	63.8	59.7	57.0	53.3	<0.001

* part of the Dutch guidelines, **p for trend

Figure 2: Breast cancer mortality as percentage of the total deaths in the cohort (Observed – Expected) / Observed)).

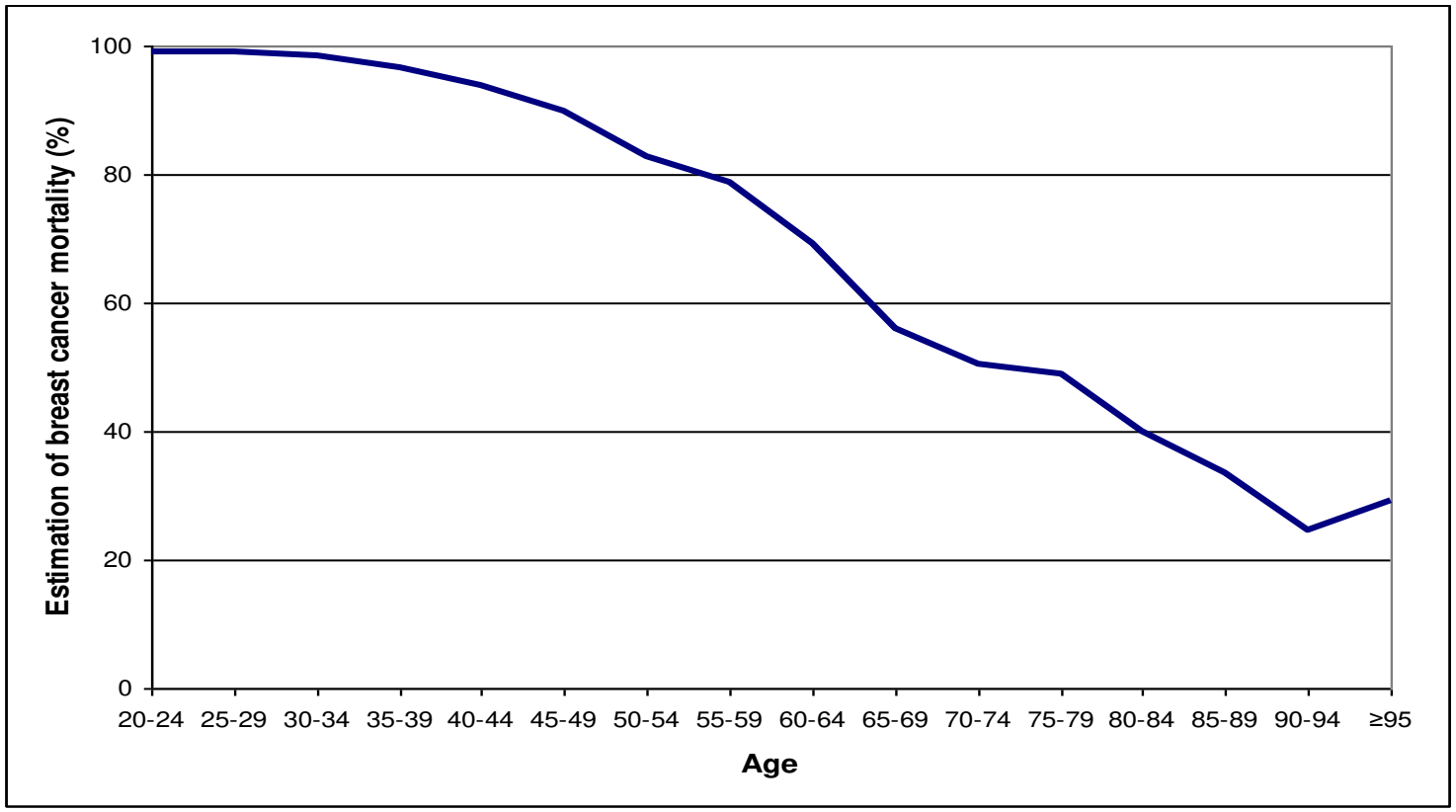

Table 3: Relative survival (5-years and 10-years) of breast cancer patients in the Netherlands according to age and stage.

	In situ (DCIS & LCIS)	**Stage I**	**Stage II**	**Stage III**	**Stage IV**
	Relative Survival (95%CI)	Relative Survival (95%CI)	Relative Survival (95%CI)	Relative Survival (95%CI)	Relative Survival (95%CI)
15-65 years					
5-years	99.6 (99.2-100)	96.8 (96.5-97.1)	87.0 (86.6-87.4)	67.6 (66.2-68.9)	21.4 (19.7-23.0)
10-years	98.8 (97.9-99.6)	91.7 (91.1-92.3)	76.0 (75.3-76.7)	49.9 (47.9-52.0)	10.3 (8.8-11.9)
65-69					
5-years	100 (99.2-100)	98.7 (97.8-99.5)	88.0 (86.7-89.3)	65.1 (60.9-68.9)	15.5 (12.1-19.1)
10-years	99.4 (95.4-100)	93.9 (92.0-95.7)	77.1 (74.8-79.4)	46.6 (40.4-52.7)	*
70-74					
5-years	99.3 (96.7-100)	98.6 (97.4-99.7)	84.9 (83.4-86.4)	61.0 (57.2-64.8)	15.2 (12.2-18.5)
10-years	100 (97.6-100)	94.9 (91.7-98.0)	72.4 (69.5-75.2)	36.7 (31.4-42.3)	4.5 (2.4-7.6)
75-79					
5-years	100 (96.9-100)	96.0 (93.8-98.0)	81.5 (79.6-83.3)	53.1 (49.2-56.9)	19.8 (16.6-23.3)
10-years	98.3 (85.1-100)	92.4 (87.3-97.5)	67.4 (63.8-71.0)	38.7 (32.7-44.9)	7.2 (4.1-11.7)
80-84					
5-years	97.2 (87.2-100)	94.7 (90.9-98.3)	80.8 (78.2-83.3)	57.0 (52.4-61.7)	15.0 (11.4-19.0)
10-years	100 (86.6-100)	89.9 (80.1-100)	64.5 (58.3-70.9)	40.1 (31.5-49.9)	*
85-89					
5-years	99.6 (82.3-100)	93.1 (85.4-100)	77.6 (72.9-82.3)	48.3 (41.4-55.5)	14.1 (8.5-21.6)
10-years	80.1 (37.9-100)	92.4 (68.0-100)	65.5 (51.5-81.5)	34.8 (19.8-55.9)	*
≥90					
5-years	97.7 (47.1-100)	87.9 (69.5-100)	92.8 (80.0-100)	37.7 (24.7-54.0)	11.6 (2.3-35.0)
10-years	*	*	71.7 (27.1-100)	*	*
	p=0.67	***p=0.004***	***p<0.001***	***p<0.001***	***p<0.001***

* less than 10 patients at risk