# Chapter 7

# Association between age at diagnosis and relative survival in elderly breast cancer patients from the general population

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# Abstract

## Background

Previously it was shown that breast cancer survival decreases with increasing age among a selected population of elderly who participated in a trial. However, patients who participate in a trial differ from patients in the general population. Therefore, the aim of this study was to evaluate the association between age and breast cancer outcome in an unselected group of elderly breast cancer patients.

## Methods

We included patients of the population-based FOCUS study, which comprises all incident breast cancer patients aged 65 years or older at diagnosis, who were diagnosed in the South Western part of The Netherlands between 1997 and 2004. All patients with non-metastasized breast cancer who received breast surgery were included. Age was categorized as 65-75 years and ≥75 years. Primary outcome was relative survival, which is an approximation of disease specific survival and the preferred way to describe the prognosis of elderly cancer patients in population-based studies. In addition, the relative excess risk of death was estimated.

## Results

Overall, 3,124 patients were included (1,617 aged 65-75 years; 1,507 aged ≥75 years), with a median age of 74.6 years. The five-years relative survival was 92.6% (95% CI 90.5-94.5) in patients aged 65-75 years, and 86.4% (95% CI 82.5-90.2) in patients aged ≥75 years. The lower relative survival in the oldest patients corresponded with a higher relative excess risk of death in patients aged ≥75 years as compared to patients aged 65-75 years (multivariable relative excess risk of death was 1.72 (95% CI 1.21-2.44)).

## Conclusions

Breast cancer outcome, in terms of relative survival, deteriorates with increasing age among unselected elderly patients from the general population.

# Introduction

Breast cancer is the most frequently diagnosed malignancy in females in the Western world, with over 40% of new diagnoses occurring in women aged 65 years and older[1]. It is often assumed that breast cancer phenotype is less aggressive in older women. Although elderly breast cancer patients more often present with larger tumors[2] and positive lymph nodes at diagnosis[3], they more often have hormone receptor positive disease and lower tumor differentiation grades[4]. In addition, a higher competing risk of death among elderly, in which a patient dies from causes unrelated to breast cancer, may affect breast cancer mortality[5].

However, recently we showed that breast cancer mortality increased with increasing age among 9,766 postmenopausal women with hormone receptor positive breast cancer who participated in a randomized clinical trial[6]. Moreover, elderly patients had a higher risk of breast cancer recurrence, and distant recurrence in particular[7].

Regardless of the disease and the age of the patients under study, it has been shown that the outlook of patients included in a clinical trial is usually better than those who do not participate[8]. In the general population, the risk of competing mortality is likely to be higher. In addition, both treatment[9] as well as implications of treatment may differ from patients who participate in a trial. Therefore it remains unknown whether the association of a worse breast cancer outcome with increasing age is also present in unselected elderly patients from the general population.

The aim of this study was to evaluate the association between age at diagnosis and breast cancer outcome in a large, unselected, population-based cohort of elderly patients with breast cancer.

# Methods

## FOCUS cohort

We included patients of the population-based FOCUS study. The FOCUS study (Female breast cancer in the elderly; Optimizing Clinical guidelines USing clinico-pathological & molecular data) comprises all incident breast cancer patients aged 65 years or older at diagnosis, who were diagnosed in the geographically defined Comprehensive Cancer Center Region West in The Netherlands between 1997 and 2004. Inclusion in the cohort is based on the National Cancer Registry, which contains data of all incident cancer cases. The nationwide Dutch network and registry of histopathology and cytopathology regularly submits reports of all newly diagnosed malignancies to the Regional Cancer Registries. The national hospital discharge data bank, which receives discharge diagnoses of admitted patients from all Dutch hospitals, completes case ascertainment. Trained personnel reviewed charts of these patients and collected information on patient, tumor, treatment and outcome characteristics. Vital

status was established either directly from the patient's medical record or through linkage with the municipal population registries, which record information on vital status (follow-up until January 1st 2011). Patients with in situ or invasive, non-metastatic breast cancer at diagnosis who received breast surgery were included in the current study.

## Outcome measures

Primary outcome measure was relative survival, which is an approximation of disease-specific survival. Relative survival is the preferred method for estimating disease-specific outcome in a population-based setting without requiring information on the cause of death[10;11].

Secondary outcome measures were time from diagnosis to occurrence of a locoregional recurrence, (recurrence in the ipsilateral breast or chest wall, or recurrence in ipsilateral axillary or supraclavicular lymph node(s); distant recurrence (recurrence in bone, skin, liver, lung, brain or other distant localization); or contralateral breast cancer, whichever came first. For patients with synchronously recurrent disease at more than one site, the localization most likely determining prognosis was used as endpoint. Ductal carcinoma in situ was not judged to be evidence of recurrence.

## Statistical analysis

Statistical analyses were performed using SPSS statistical software, version 20.0 (SPSS Chicago, IL) and STATA SE 12.0. Age at diagnosis was categorized as 65-74 years and ≥75 years, as discussed at the meeting of the International Society of Geriatric Oncology in 2009[12] and in line with other publications[6;13]. To compare proportional differences among age categories, the Pearson $\chi 2$ test was used.

Relative survival was calculated as the observed overall survival among patients in the study, divided by the expected overall survival in the sex-, age-, and year matched general population, using the 'strs' command in Stata[11]. Expected survival was obtained from population life-tables according to the Ederer II method[14]. An estimate of the five-years relative survival of less than 100% means that the survival of patients in the study is lower than expected, when compared to survival in the corresponding general population. This means that patients in the study had an excess risk of death, which can be attributed to breast cancer or breast cancer treatment.

The excess risk of death can be calculated as the observed number of deaths minus the expected number of deaths, divided by the total person-years. To compare whether the excess risk of death differed by age at diagnosis, we calculated the relative excess risk of death, which is the excess risk of death in patients aged ≥75 years divided by the excess risk of death in patients aged 65-75 years. The relative excess risk of death is estimated by a multivariable generalized linear model with a Poisson distribution, based on collapsed relative survival data based on exact survival times[14], and can be interpreted as the risk of death from breast cancer in patients aged ≥75 years as compared to the risk of death from breast cancer in patients aged

65-75 years. To assess the robustness of the results, the analyses were also stratified by stage (early stage: in situ, I, II; advanced stage: III)[15].

The relation between age at diagnosis and the secondary endpoints were evaluated by competing risk regression analyses according to Fine and Gray[16], since cause-specific outcomes may be influenced by the risk of competing endpoints. For example, an individual who dies, is no longer at risk for breast cancer recurrence. A Fine and Gray analysis is used to assess the risk of locoregional recurrence, distant recurrence and contralateral breast cancer, respectively, taking into account the risk of reaching competing endpoints. Competing endpoints for locoregional recurrence were distant recurrence, contralateral breast cancer, and death; competing endpoints for distant recurrence were locoregional recurrence, contralateral breast cancer, and death; and competing endpoints for contralateral breast cancer were locoregional recurrence, distant recurrence, and death. Sensitivity analyses were performed for overall recurrence, which was defined as either a locoregional recurrence, distant recurrence or contralateral breast cancer as a first event, with death as competing endpoint.

Covariates were included in the multivariable model if they were judged to be clinically relevant and comprised histological grade (Bloom Richardson G1; G2; G3; unknown), histological subtype (ductal; lobular; other), hormone receptor status (positive; negative; unknown), combined TNM stage (I; II; III; unknown), most extensive breast surgery (mastectomy; wide local excision), most extensive axillary surgery (axillary lymph node dissection; sentinel lymph node biopsy; none), radiotherapy (yes; no), chemotherapy (yes; no), endocrine therapy (yes; no); and comorbid disease (0-1; 2-4; 5 or more). All statistical tests were 2-sided. P values of less than 0.05 were considered to be statistically significant.

# Results

Overall, 3,124 patients with a median age of 74.6 years were included (range 65–98 years); 1,617 were 65-75 years (median age 69.8 years), and 1,507 were 75 years and older (median age 81.0 years). Median follow-up time was 7.3 years (interquartile range 4.2-9.7 years). Patient, tumor and treatment characteristics by age at diagnosis are shown in Table 1. Patients aged ≥75 years had a higher number of comorbid diseases. Moreover, they more often had a higher stage at diagnosis, and more often presented with hormone receptor positive tumors. The proportions of patients who received a mastectomy and endocrine therapy increased with increasing age, whereas axillary surgery, administration of radiotherapy after lumpectomy, and chemotherapy decreased.

When we compared overall survival of the patients in the current study to the expected overall survival as based on the corresponding general population, survival of patients in the study was lower than in the corresponding general population; the five-years relative survival was 92.6% (95% CI 90.5-94.5) in patients aged 65-75 years, and 86.4% (95% CI 82.5-90.2) in patients

**Table 1.** Patient, tumor and treatment characteristics by age at diagnosis.

| | Age 65-75 years (n=1,617) | | Age ≥75 years (n=1,507) | | p |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Comorbid disease | | | | | **<0.001** |
| 0-1 | 919 | 56.8 | 602 | 39.9 | |
| 2 to 4 | 584 | 36.1 | 721 | 47.8 | |
| ≥5 | 114 | 7.1 | 184 | 12.2 | |
| Histological subtype | | | | | 0.116 |
| Ductal cancer | 1,224 | 75.7 | 1,092 | 72.5 | |
| Lobular cancer | 169 | 10.5 | 175 | 11.6 | |
| Other/unknown | 224 | 13.9 | 240 | 15.9 | |
| Histological grade (BR) | | | | | 0.813 |
| Grade 1 | 226 | 14.0 | 195 | 12.9 | |
| Grade 2 | 492 | 30.4 | 468 | 31.1 | |
| Grade 3 | 391 | 24.2 | 358 | 23.8 | |
| Unknown | 508 | 31.4 | 486 | 32.2 | |
| Hormone-receptor status | | | | | **<0.001** |
| Positive | 1,018 | 63.0 | 1,045 | 69.3 | |
| Negative | 256 | 15.8 | 232 | 15.4 | |
| Unknown | 343 | 21.2 | 230 | 15.3 | |
| TNM stage | | | | | **<0.001** |
| In situ | 137 | 8.5 | 61 | 4.0 | |
| I | 685 | 42.4 | 373 | 24.8 | |
| II | 627 | 38.8 | 803 | 53.3 | |
| III | 113 | 7.0 | 204 | 13.5 | |
| Unknown | 55 | 3.4 | 66 | 4.4 | |
| Most extensive breast surgery | | | | | **<0.001** |
| Mastectomy | 786 | 48.6 | 1,161 | 77.0 | |
| Wide local excision | 831 | 51.4 | 346 | 23.0 | |
| Most extensive axillary surgery | | | | | **<0.001** |
| ALND | 870 | 53.8 | 913 | 60.6 | |
| SLNB | 489 | 30.2 | 288 | 19.1 | |
| None | 258 | 16.0 | 306 | 20.3 | |
| Radiotherapy after wide local excision | | | | | **<0.001** |
| Yes | 751 | 90.4 | 238 | 68.8 | |
| No | 80 | 9.6 | 108 | 31.2 | |
| Endocrine therapy | | | | | **<0.001** |
| Yes | 550 | 34.0 | 704 | 46.7 | |
| No | 1,067 | 66.0 | 803 | 53.3 | |
| Chemotherapy | | | | | **<0.001** |
| Yes | 123 | 7.6 | 37 | 2.5 | |
| No | 1,494 | 92.4 | 1,47 | 97.5 | |

BR: Bloom Richardson; ALND: axillary lymph node dissection; SLNB: sentinel lymph node biopsy.

aged ≥75 years. This is depicted in Figure 1. This means that patients in the study had an excess risk of death, which can be attributed to breast cancer. We calculated the excess risk of death of patients in the current study as the difference between the observed and expected number of deaths, divided by the total person-years. Among patients aged 65-75 years, 261

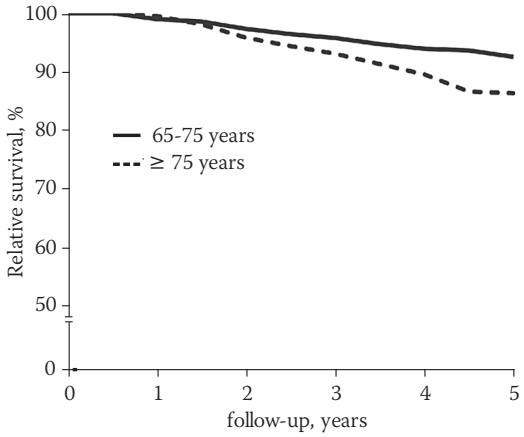



**Figure 1.** Survival of elderly patients with breast cancer as compared to the corresponding general population, by age at diagnosis.

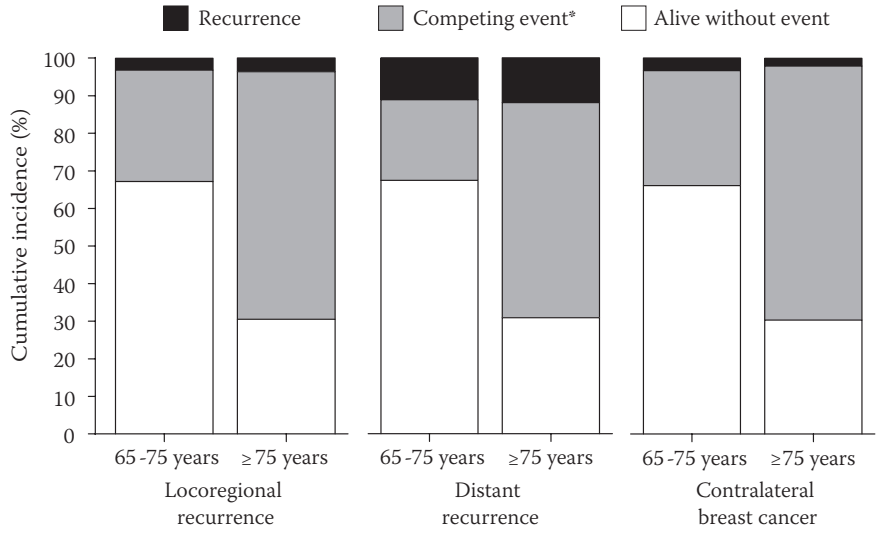
deaths occurred in 7470 person-years; among patients aged ≥75 years, 659 deaths occurred in 5894 person-years. The expected numbers of deaths were 147 and 496, respectively. Hence, the excess risk of death in patients aged 65-75 years was 15.2/1000 person-years, and 27.7/1000 person-years in patients aged ≥75 years. To compare whether the excess risk of death differed between both age groups, we calculated the relative excess risk of death. As shown in Table 2, the relative excess risk of death for patients aged ≥75 years as compared to patients aged 65-75 years was 1.88 (95% CI 1.25-3.83). Multivariable analyses confirmed a higher relative excess risk of death for patients aged ≥75 years (1.72 (95% CI 1.21-2.44)). As patients aged ≥75 years more often presented with a higher stage of disease, additional analyses were stratified by stage (Supplementary table). In patients with early stage breast cancer, again patients aged ≥75 years had a higher relative excess risk of death. Comparable results were observed in patients with advanced stage breast cancer, however these results were not statistically significant.

**Table 2.** Excess risk of death in elderly patients with breast cancer as compared to the corresponding general population, by age at diagnosis.

| | 5-years relative survival % | Excess risk of death / 1000py | Univariate relative excess risk of death (95% CI) | p | Multivariable* relative excess risk of death (95% CI) | p |
|---|---|---|---|---|---|---|
| Age | | | | **0.002** | | **0.003** |
| 65-75 years | 92.6 | 15.2 | 1 (reference) | | 1 (reference) | |
| ≥75 years | 86.4 | 27.7 | 1.88 (1.25-2.83) | | 1.72 1.21-2.44) | |

CI: confidence interval. * Multivariable analyses were adjusted for comorbidity, combined TNM stage, hormone receptor status, histological subtype, histological grade, most extensive breast surgery, most extensive axillary surgery, radiotherapy, endocrine therapy and chemotherapy.

During five years of follow-up, 523 patients developed a secondary endpoint, among which 80 developed a locoregional recurrence; 359 a distant recurrence; and 84 a contralateral breast cancer. Median follow-up time for recurrent disease was 5.9 years (interquartile range 2.9-7.9 years). As shown in Figure 2, for all three endpoints, the cumulative incidence of competing endpoints (death or another type of recurrence) was more than twice as high in patients aged




* Competing events for locoregional recurrence: distant recurrence, contralateral breast cancer, and death due to any cause. Competing events for distant recurrence: locoregional recurrence, contralateral breast cancer, and death due to any cause. Competing events for contralateral breast cancer: locoregional recurrence, distant recurrence, and death due to any cause.

**Figure 2.** Locoregional recurrence, distant recurrence, contralateral breast cancer and competing events, by age at diagnosis.

**Table 3.** Risk of locoregional recurrence, distant recurrence and contralateral breast cancer, by age at diagnosis.

| | 5-years recurrence, n | 5-years competing event, n | Univariate hazard ratio (95% CI) | p | Multivariable* hazard ratio (95% CI) | p |
|---|---|---|---|---|---|---|
| Locoregional recurrence | | | | 0.065 | | 0.293 |
| 65-75 years | 33 | 288 | 1 (reference) | | 1 (reference) | |
| ≥75 years | 47 | 680 | 1.52 (0.97-2.37) | | 1.30 (0.79-2.15) | |
| Distant recurrence | | | | **0.023** | | 0.435 |
| 65-75 years | 179 | 142 | 1 (reference) | | 1 (reference) | |
| ≥75 years | 180 | 547 | 1.30 (1.04-1.65) | | 1.12 (0.84-1.49) | |
| Contralateral breast cancer | | | | 0.061 | | 0.487 |
| 65-75 years | 53 | 268 | 1 (reference) | | 1 (reference) | |
| ≥75 years | 31 | 696 | 0.61 (0.39-0.95) | | 0.80 (0.42-1.51) | |

* Multivariable hazard ratios adjusted for comorbidity, combined TNM stage, hormone receptor status, histological subtype, histological grade, most extensive breast surgery, most extensive axillary surgery, radiotherapy, endocrine therapy and chemotherapy.

≥75 years as compared to those aged 65-75 years. As shown in Table 3, the risk of a distant breast cancer recurrence increased with increasing age in univariate analysis (hazard ratio for patients aged ≥75 years was 1.30 (95% CI 1.04-1.65). However, in multivariable analyses no significant differences were observed. Sensitivity analyses for overall recurrence did not alter the results (data not shown).

# Discussion

The main finding of our study is that the relative survival is lower for breast cancer patients aged ≥75 years as compared to patients aged 65-75 years. Patients aged ≥75 years had a higher excess risk of death. As the excess risk of death can be attributed to breast cancer, these results indicate that patients aged ≥75 years had a higher risk of death from breast cancer as compared to patients aged 65-75 years. We found no age-specific differences in the occurrence of locoregional recurrence, distant recurrence or contralateral breast cancer.

The design of the current study was based on the results of clinical trial data, which demonstrated a higher recurrence risk and worse breast cancer survival with increasing age[6;7;17]. Our main outcome that relative survival is lower among the oldest elderly breast cancer patients is confirmed by a previous study in The Netherlands[2], and by a population-based study in the United States, which showed a decreasing breast cancer specific survival[18]. However, other population-based studies have shown no association between age and breast cancer specific or relative survival[4;19;20] or even a higher breast cancer specific survival among elderly[21;22]. An explanation for the variation in results between our study and other publications could be the discrepancy in choice of endpoints. In the present study, we used relative survival as an approximation of breast cancer specific survival. As mentioned, the relative survival is the ratio of observed overall survival among patients in the study and the expected overall survival in the age-, sex-, and year-matched background file from the general population. Assuming all other factors being similar in the study cohort and the background file, the relative survival approximates breast cancer specific survival. The major advantage of using this endpoint is that there is no need to know the cause of death or cancer specific death data of all patients in the cohort, which is often described to be biased or overestimated in cancer registry data[10;23]. In addition, in population-based studies, relative survival has been shown to be comparable to cancer specific survival derived from death certificates[24].

It is tempting to speculate on the possible explanations of our finding that breast cancer outcome deteriorates with increasing age. First, elderly breast cancer patients may be undertreated. Less extensive treatment may be the result of careful weighing of the benefits and risk of therapy in patients with comorbid disease, but may also result from underestimation of the disease in elderly patients. As was shown, patients aged ≥75 years received less often axillary surgery, radiotherapy after a lumpectomy, and chemotherapy in particular. Overall, the differences in treatment were relatively small. Therefore it is expected that other mechanisms may play a role.

Although patients aged 75 years and older presented more often with more advances stages of disease, stratified analyse confirmed a worse breast cancer outcome in all stages. Additionally, it has been suggested that older patients may respond different to a tumor as well as to a certain therapy as compared to younger patients. Patients who are biologically older may experience more immunosenescence, and may thereby have an impaired immunoresponse to a tumor, which may impair prognosis[25]. Moreover, concomitant medication use and comorbid disease may alter pharmacokinetics of anticancer therapy[26]. Thus, a biologically older or frailer patient may be at higher risk for breast cancer events. Hence, a higher prevalence of biologically older or frailer patients among those aged ≥75 years may attribute to a worse breast cancer outcome.

We expected that the lower relative survival for the oldest elderly would be accompanied by an increase in breast cancer recurrence. However, after adjusting for patient and tumor characteristics, and after taking into account the risk of competing endpoints, we observed no difference in the occurrence of any type of recurrence. Insufficient power due to the shorter follow-up time for recurrences (median 5.9 years) and the limited number of events may have influenced the results. Another possible explanation could be under registration or under diagnosis of recurrent disease in medical files, especially in the frailest patients. From a clinical point of view, it is understandable that in an old patient with a history of breast cancer who presents with back pain, it is not always desired to further investigate the possibility of bone metastases, because either the patient does not wish to receive any therapy or it is not likely that life expectancy will be increased by administering further therapy. However, there is no literature that reports about this issue, and it would be interesting to investigate this prospectively in a future study.

A major strength of this study is the unselected population-based nature and the large number of consecutively diagnosed patients who were included; to our best knowledge, the FOCUS-cohort is the largest population-based cohort comprising elderly breast cancer patients with such detailed information. However, this study also has some limitations when interpreting the results. As mentioned before, due to the retrospective and observational character of the study we cannot exclude the possibility of under registration of recurrent disease. Next to breast cancer specific endpoints, it remains important to evaluate the impact of the disease and therapy on quality of life and daily functioning. Unfortunately, these data were not available in the current study.

To conclude, breast cancer outcome, in terms of relative survival, deteriorates with increasing age among unselected elderly patients from the general population. Of note, this was not accompanied by an increased risk of breast cancer recurrence.

**Supplementary table.** Excess risk of death in elderly patients with breast cancer as compared to the corresponding general population by age at diagnosis, stratified by stage.

| | 5-years relative survival (%) | Excess risk of death / 1000py | Univariate relative excess risk of death (95% CI) | p | Multivariable* relative excess risk of death (95% CI) | p |
|---|---|---|---|---|---|---|
| Early stage | | | | **0.04** | | **0.03** |
| 65-74 years | 94.5 | 11.1 | 1 (reference) | | 1 (reference) | |
| ≥75 years | 89.9 | 19.9 | 1.86 (1.03-3.36) | | 1.80 (1.07-2.99) | |
| Advanced stage | | | | 0.2 | | 0.2 |
| 65-74 years | 70.7 | 68.7 | 1 (reference) | | 1 (reference) | |
| ≥75 years | 60.1 | 96.4 | 1.39 (0.85-2.30) | | 1.42 (0.82-2.44) | |

CI: Confidence interval. * Multivariable analyses were adjusted for comorbidity, combined TNM stage, hormone receptor status, histological subtype, histological grade, most extensive breast surgery, most extensive axillary surgery, radiotherapy, endocrine therapy and chemotherapy.

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