# Management of elderly patients with breast cancer : towards evidence based medicine

Water, W. van de

# Chapter 5

# Association between age at diagnosis and disease specific mortality among postmenopausal women with hormone receptor positive breast cancer

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# Abstract

## Background

In addition to classical tumor related prognostic factors, patient characteristics may be associated with breast cancer outcome. The aim of this study was to assess the association between age at diagnosis and breast cancer outcome in postmenopausal women with hormone receptor positive breast cancer.

## Methods

Patients who were enrolled in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) randomized clinical trial were included in the current study. Primary endpoint was disease specific mortality; secondary endpoints were other cause mortality and breast cancer recurrence. Age at diagnosis was categorized as <65 years, 65-75 years, and ≥75 years.

## Results

Overall, 9,766 patients were included; 5,349 were <65 years, 3,060 were 65-75 years, and 1,357 were ≥75 years. Disease specific mortality as a proportion of all cause mortality decreased with age (78%, 56%, 36% respectively; p<0.001). Disease specific mortality increased with age (multivariable analyses, patients aged <65 years functioned as a reference, hazard ratio for patients aged 65-75 years was 1.25 (95% CI 1.01-1.54); hazard ratio for patients aged ≥75 years was 1.63 (95% CI 1.23-2.16); p<0.001). Similarly, breast cancer recurrence and other cause mortality increased with age (patients aged <65 years functioned as a reference, breast cancer recurrence: hazard ratio for patients aged 65-75 years was 1.07 (95% CI 0.91-1.25); hazard ratio for patients aged ≥75 years was 1.29 (95% CI 1.05-1.60); p=0.061 – other cause mortality: hazard ratio for patients aged 65-75 years was 2.66 (95% CI 1.96-2.63); hazard ratio for patients aged ≥75 years was 7.30 (95% CI 5.29-10.07); p<0.001).

## Conclusion

Among postmenopausal women with hormone receptor positive breast cancer, increasing age was associated with a higher disease specific mortality.

# Introduction

Breast cancer is the leading contributor to cancer incidence and cancer mortality in women worldwide, with 1,383,500 new cases in 2008[1]. In the US in 2008, 41% of these women were 65 year or older at diagnosis[2]. As breast cancer incidence increases with increasing age[2], changing demographics and continuously increasing life expectancy will further enlarge the number of elderly women confronted with breast cancer.

In addition to classical tumor related prognostic factors, patient characteristics may be associated with breast cancer outcome; an individual who dies from causes unrelated to breast cancer is no longer at risk for progression of breast cancer or death due to breast cancer. The risk of death from another cause that is unrelated to either breast cancer or its therapy is termed a competing risk of death, and may be particularly present in elderly populations[3].

Observational data in breast cancer patients hint at an age specific association with mortality[4]. Observational data often lack data regarding treatment[5] and in retrospective studies cause of death is not always traceable. Clinical trials generally do not have these problems. Unfortunately, elderly patients are often not included in clinical trials due to age restrictions[6]. As one of few breast cancer trials, the Tamoxifen, Exemestane, Adjuvant, Multinational (TEAM) trial had no upper age limit, thereby providing a unique opportunity to focus on the association between age and disease specific mortality in postmenopausal patients diagnosed with hormone receptor positive breast cancer.

The aim of the current study was to assess disease specific mortality among age groups in postmenopausal patients with hormone receptor positive breast cancer. Secondarily, age specific other cause mortality and age specific breast cancer recurrence were evaluated.

# Methods

The TEAM trial is a randomized, phase 3, multinational, open label study conducted in postmenopausal breast cancer patients with estrogen and/or progesterone receptor positive tumors. Patients were randomized to receive either exemestane 25 mg once-daily for five years or tamoxifen 20 mg once-daily for 2.5–3 years, followed by exemestane 25 mg once-daily for 2.5–2 years, for a total of five years. Participants were enrolled in Belgium, The Netherlands, United Kingdom, Ireland, United States of America, Japan, Greece, Germany, and France (N=9766), and included between January 2001 and January 2006. Appropriate approvals from the ethical committee, and written informed consent from all patients were obtained[7]. The trial was registered with ClinicalTrials.gov, NCT00279448, NCT00032136, and NCT00036270; NTR 267; Ethics Commission Trial 27/2001; and UMIN, C000000057.

Similar protocols were used in the nine countries, with minor differences to accommodate local treatment guidelines[7;8]. In short, postmenopausal patients with histologically confirmed breast cancer, who completed local therapy with curative intent, i.e. without evidence of metastatic disease, were eligible. Participants commenced endocrine treatment assigned at random within 10 weeks of completion of surgery and chemotherapy, if indicated. Patients were ineligible if they had a previous malignancy with a disease free interval of less than five years, an Eastern Cooperative Oncology Group (ECOG) performance status of more than 2, or a significant cardiac disease or other illness interfering with study participation.

The final results of the TEAM trial showed no significant differences in efficacy endpoints between five years of exemestane alone versus the sequence of tamoxifen followed by exemestane[7]. Moreover, death from non breast cancer causes was comparable for both treatment arms[7]. Therefore we were able to investigate disease specific mortality for all patients regardless of randomized treatment.

The design of the current post hoc analysis was developed in December 2010. The database was locked on October 7th 2010. Patients were categorized in three age groups (<65 years, 65-75 years, ≥75 years) as discussed at the Meeting of the International Society of Geriatric Oncology (SIOG) in 2009[9] and in line with other publications[10;11]. Primary endpoint of this study was disease specific mortality, which was defined as time from randomization to death due to breast cancer, as indicated on the Case Report Form. Cause of death was ascertained by medical record review and categorized in one of ten prespecified groups. Classification was verified by the TEAM Central Statistical and Data-Center. Patients with distant metastases at time of death were considered to have died due to breast cancer. Overall, 7% (n=42) of deaths attributed to breast cancer was accounted to presence of distant metastases at time of death. The majority of these patients (57%, n=24) were formerly categorized as 'unknown' or 'other' cause of death. The secondary endpoints of this study were other cause mortality and breast cancer recurrence. Other cause mortality was calculated as all cause mortality minus disease specific mortality; breast cancer recurrence was defined as locoregional or distant breast cancer recurrence, or ipsi- or contralateral breast cancer. Ductal carcinoma in situ was not judged to be evidence of recurrence.

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL) and R statistical package (R Development Core Team, 2008). To compare proportional differences among age categories, the Pearson chi-square test was used. Cumulative incidences of competing causes of death were calculated[12] using the mstate package in R[13]. Cox proportional hazard models were used to evaluate associations between covariates and cause specific hazards of disease specific mortality and other cause mortality. Additional regression analyses according to Fine and Gray[14] were performed in order to assess the risk of disease specific mortality and other cause mortality respectively, taken into account the risk of reaching the other endpoint. Covariates were included in the multivariable model if they were judged to be clinically

relevant, and comprised country, histological grade (G1; G2; G3,4), T stage (T0,Tis,T1; T2; T3,4), nodal stage (negative; positive), estrogen receptor (negative; positive), progesterone receptor (negative; positive), surgery, (mastectomy; wide local excision) radiotherapy (yes; no), chemotherapy (yes; no), endocrine therapy (tamoxifen followed by exemestane; exemestane) and persistence of endocrine therapy (discontinuation of allocated endocrine therapy because of either adverse events, intercurrent illness, patient refusal or other reasons; continuation of allocated endocrine therapy, or having an event while on study medication). All statistical tests were two-sided. P values <0.05 were considered to be statistically significant.

# Results

Overall 9,766 patients (age range 35-96, median age 64 years) were included in the multinational TEAM trial, of which 5,349 were <65 years at diagnosis (55%, median age 58 years), 3,060 were 65-75 years (31%, median age 69 years) and 1,357 were ≥75 years (14%, median age 79 years). Overall, 778 patients (8.0%) were lost to follow-up, 429 (8.0%) in patients aged <65 years, 214 (7.0%) in patients aged 65-75 years, and 135 (9.9%) in patients aged ≥75 years. Table 1 shows patient characteristics by age at diagnosis. We observed an age associated increase in larger tumors and estrogen receptor positive breast cancer. As shown in Table 2, the proportion of mastectomy increased significantly with age, whereas administration of chemotherapy, and administration of radiotherapy after a wide local excision an decreased.

At database lock, median follow-up (interquartile range) from randomization was 5.1 years (4.3; 6.0 years) in patients aged <65 years, 5.1 years (4.2; 6.0 years) in patients aged 65-75 years, and 5.0 years (3.8; 5.8 years) in patients aged ≥75 years. The number of deaths was 391 (7.3%), 341 (11.2%), and 311 (22.9%) respectively. Figure 1 illustrates cumulative incidence of death due to breast cancer, non breast cancer, and all causes by age at diagnosis. Cumulative incidence of death due to breast cancer increased from 5.7% in patients aged <65 years, 6.3% in patients aged 65-75 years, to 8.3% in patients aged ≥75 years. Cumulative incidence of non breast cancer death was 1.6%, 4.9% and 14.6% respectively.

Table 3 shows causes of death by age at diagnosis. Increasing age was associated with a lower number of deaths due to breast cancer as a proportion of all cause mortality (<65 years 78%, 65-75 years 56%, ≥75 years 36%; p<0.001). Deaths categorized as 'other' (n=100) were recorded to have died of old age, dementia, weakness or cachexia (n=41), infection or sepsis (n=20), sudden death not otherwise specified (n=7), accidents (n=6), a combination of recorded reasons (n=6), and other infrequent causes (n=20; gastro-intestinal perforation, urogential disorders, malignancy related disorders, suicide).

Univariate Cox regression analysis showed a higher risk of disease specific mortality with increasing age (patients aged <65 years functioned as a reference, hazard ratio (HR) for patients aged 65-75 years was 1.12 (95% confidence interval (CI) 0.94-1.34); HR for patients aged ≥75

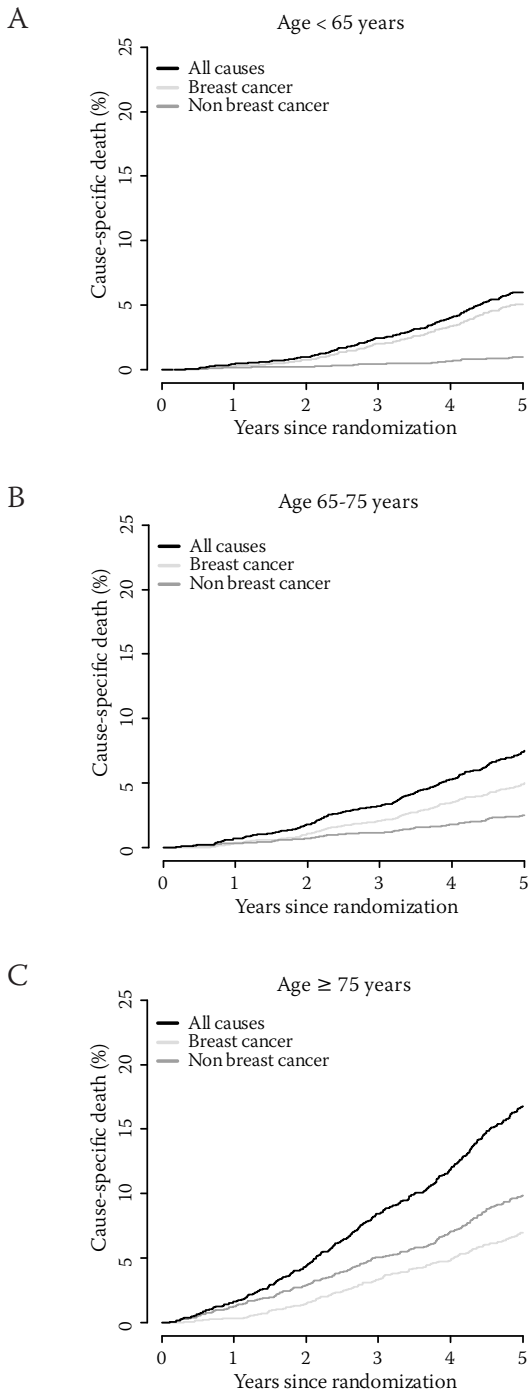


**Figure 1.** Figure 1. Cumulative incidence of death due to breast cancer, non breast cancer and all causes by age at diagnosis. Non breast cancer death is defined as death due to all causes except breast cancer (second primary tumor, endometrial cancer, cardiac disorder, thromboembolism, pulmonary disorder, cerebral disorder, vascular disorder, other causes, and unknown causes).

**Table 1.** Patient characteristics by age at diagnosis.

| | <65 years (n=5,349) | | 65-75 years (n=3,060) | | ≥75 years (n=1,357) | | p |
|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | |
| Histological grade | | | | | | | 0.06 |
| G1 (well) | 911 | (17.0) | 550 | (18.0) | 216 | (15.9) | |
| G2 (moderate) | 2,580 | (48.2) | 1,537 | (50.2) | 679 | (50.0) | |
| G3, G4 (poor) | 1,377 | (25.7) | 732 | (23.) | 329 | (24.2) | |
| Gx, unknown | 481 | (9.0) | 241 | (7.9) | 133 | (9.8) | |
| T stage | | | | | | | **<0.001** |
| T0, Tis | 6 | (0.1) | 0 | (0.0) | 0 | (0.0) | |
| T1 | 3,291 | (61.5) | 1,806 | (59.0) | 593 | (43.7) | |
| T2 | 1,793 | (33.5) | 1,122 | (36.7) | 676 | (49.8) | |
| T3, T4 | 244 | (4.6) | 125 | (4.1) | 88 | (6.5) | |
| Tx, unknown | 15 | (0.3) | 7 | (0.2) | 0 | (0.0) | |
| N stage | | | | | | | 0.14 |
| Negative | 2,799 | (52.3) | 1,622 | (47.1) | 690 | (50.8) | |
| Positive | 2,518 | (47.1) | 1,419 | (46.4) | 651 | (48.0) | |
| Unknown | 32 | (0.6) | 19 | (0.6) | 16 | (1.2) | |
| Estrogen receptor | | | | | | | **<0.001** |
| Positive | 5,218 | (97.6) | 3,022 | (98.8) | 1,344 | (99.0) | |
| Negative | 128 | (2.4) | 35 | (1.1) | 13 | (1.0) | |
| Unknown | 3 | (0.1) | 3 | (0.1) | 0 | (0.0) | |
| Progesterone receptor | | | | | | | 0.54 |
| Positive | 4,028 | (75.3) | 2,268 | (74.1) | 1,004 | (74.0) | |
| Negative | 915 | (17.1) | 554 | (18.1) | 255 | (18.8) | |
| Unknown | 406 | (7.6) | 238 | (7.8) | 98 | (7.2) | |
| Country | | | | | | | **<0.001** |
| Belgium | 265 | (5.0) | 106 | (3.5) | 43 | (3.2) | |
| France | 722 | (13.5) | 403 | (13.2) | 105 | (7.7) | |
| Germany | 871 | (16.3) | 454 | (14.8) | 146 | (10.8) | |
| Greece | 110 | (2.1) | 71 | (2.3) | 26 | (1.9) | |
| Japan | 98 | (1.8) | 66 | (2.2) | 20 | (1.5) | |
| The Netherlands | 1,428 | (26.7) | 852 | (27.8) | 473 | (34.9) | |
| UK/Ireland | 696 | (13.0) | 431 | (13.5) | 166 | (12.2) | |
| United States | 1,159 | (21.7) | 695 | (22.7) | 378 | (27.9) | |

UK: United Kingdom.

years was 1.66 (95% CI 1.34-2.06); p<0.001). Since tumor and treatment characteristics may be associated with disease specific mortality, multivariable analyses were performed in attempt to adjust for unequal distributions among age categories (Table 4). Overall, 8,030 (82.2%) patients were included in the multivariable model. Again, disease specific mortality increased with age (patients aged <65 years functioned as a reference, HR for patients aged 65-75 years was 1.25 (95% CI 1.01-1.54); HR for patients aged ≥75 years was 1.63 (95% CI 1.23-2.16); p<0.001).

**Table 2.** Treatment characteristics by age at diagnosis.

| | <65 years (n=5,349) | | 65-75 years (n=3,060) | | ≥75 years (n=1,357) | | p |
|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | |
| Most extensive surgery | | | | | | | **<0.001** |
| Mastectomy | 2,120 | (39.6) | 1,372 | (44.8) | 841 | (62.0) | |
| WLE | 3,222 | (60.2) | 1,685 | (55.1) | 515 | (38.0) | |
| No resection | 2 | (<0.1) | 1 | (<0.1) | 0 | (0.0) | |
| Unknown | 4 | (0.1) | 2 | (0.1) | 1 | (0.1) | |
| Radiotherapy | | | | | | | **<0.001** |
| Yes | 3,980 | (74.4) | 2,030 | (66.3) | 687 | (50.6) | |
| No | 1,330 | (24.9) | 994 | (32.5) | 651 | (48.0) | |
| Unknown | 39 | (0.7) | 36 | (1.2) | 19 | (1.4) | |
| RT in case of WLE | | | | | | | **<0.001** |
| Yes | 3,042 | (94.4) | 1,543 | (91.6) | 451 | (87.6) | |
| No | 180 | (5.6) | 142 | (8.4) | 64 | (12.4) | |
| Chemotherapy | | | | | | | **<0.001** |
| Yes | 2,743 | (51.3) | 700 | (22.9) | 71 | (5.2) | |
| No | 2,605 | (48.7) | 2,357 | (77.0) | 1,284 | (94.6) | |
| Unknown | 1 | (<0.1) | 3 | (0.1) | 2 | (0.1) | |
| Endocrine therapy | | | | | | | 0.38 |
| Tam → Exe | 2,666 | (49.9) | 1,546 | (50.5) | 655 | (48.3) | |
| Exemestane | 2,682 | (50.1) | 1,514 | (49.5) | 702 | (51.2) | |
| Persistence of ET | | | | | | | **<0.001** |
| Yes | 4,142 | (77.4) | 2,376 | (77.6) | 980 | (72.2) | |
| No | 1,207 | (22.6) | 684 | (22.4) | 377 | (27.8) | |

WLE: wide local excision; RT: radiotherapy; Tam → Exe: tamoxifen followed by exemestane; ET: endocrine therapy.

**Table 3.** Causes of death by age at diagnosis.

| | <65 years (n=391) | | 65-75 years (n=341) | | ≥75 years (n=311) | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| Breast cancer | 303 | (77.5) | 192 | (56.3) | 113 | (36.3) |
| Second primary tumor | 35 | (9.0) | 50 | (14.7) | 31 | (10.0) |
| Endometrial cancer | 1 | (0.3) | 0 | (0.0) | 0 | (0.0) |
| Cardiac disorder | 14 | (3.6) | 25 | (7.3) | 39 | (12.5) |
| Thromboembolism | 0 | (0.0) | 2 | (0.6) | 10 | (3.2) |
| Pulmonary disorder | 5 | (1.3) | 12 | (3.5) | 14 | (4.5) |
| Cerebral disorder | 4 | (1.0) | 13 | (3.8) | 17 | (5.5) |
| Vascular disorder | 1 | (0.3) | 3 | (0.9) | 3 | (1.0) |
| Other | 17 | (4.3) | 26 | (7.6) | 57 | (18.3) |
| Unknown | 11 | (2.8) | 18 | (5.3) | 27 | (8.7) |

**Table 4.** Disease specific mortality by age at diagnosis.

| | 5-years death n | (%) | Multivariable* HR (95% CI) | p |
|---|---|---|---|---|
| Age | | | | **<0.001** |
| <65 years | 243 | (5) | 1 (reference) | |
| 65-75 years | 149 | (6) | 1.25 (1.01-1.54) | |
| ≥75 years | 92 | (8) | 1.63 (1.23-2.16) | |
| Histological grade (BR) | | | | **<0.001** |
| G1 | 27 | (2) | 1 (reference) | |
| G2 | 191 | (5) | 1.86 (1.28-2.70) | |
| G3,4 | 226 | (10) | 3.23 (2.21-4.72) | |
| T stage | | | | **<0.001** |
| T1 | 151 | (3) | 1 (reference) | |
| T2 | 282 | (9) | 1.91 (1.55-2.35) | |
| T3,4 | 49 | (12) | 2.01 (1.44-2.81) | |
| Nodal status | | | | **<0.001** |
| Negative | 121 | (3) | 1 (reference) | |
| Positive | 360 | (9) | 2.31 (1.85-2.87) | |
| Estrogen receptor | | | | **<0.001** |
| Positive | 459 | (6) | 1 (reference) | |
| Negative | 25 | (15) | 2.18 (1.44-3.31) | |
| Progesterone receptor | | | | **<0.001** |
| Positive | 293 | (5) | 1 (reference) | |
| Negative | 138 | (9) | 1.64 (1.35-2.00) | |
| Most extensive surgery | | | | **<0.001** |
| Mastectomy | 316 | (8) | 1 (reference) | |
| WLE | 168 | (4) | 0.59 (0.46-0.74) | |
| Radiotherapy | | | | **0.001** |
| Yes | 335 | (6) | 1 (reference) | |
| No | 146 | (6) | 0.68 (0.54-0.86) | |
| Chemotherapy | | | | 0.76 |
| Yes | 213 | (2) | 1 (reference) | |
| No | 271 | (2) | 0.97 (0.77-1.20) | |
| Endocrine therapy | | | | 0.08 |
| Tam → Exe | 246 | (6) | 1 (reference) | |
| Exe | 238 | (6) | 0.85 (0.71-1.02) | |
| Persistence of ET | | | | **0.001** |
| Persistent | 425 | (2) | 1 (reference) | |
| Nonpersistent | 79 | (2) | 0.64 (0.50-0.84) | |

HR: Hazard ratio; CI: confidence interval. * Hazard ratios adjusted for all other covariates mentioned in the Table, and country. WLE: wide local excision; Tam → Exe: Tamoxifen followed by Exemestane; ET: endocrine therapy.

To test the robustness of the age cut points, additional analyses were performed with age as a continuous variable, which confirmed an increased risk of breast cancer death per ten years increase in age (univariate HR per ten years was 1.20 (95% CI 1.10-1.31), p<0.001; multivariable HR per ten years 1.21 was (95% CI 1.08-1.36), p=0.001). Since increasing age was associated with larger tumors (Table 1), additional analyses were performed to exclude residual confounding by tumor size. Multivariable survival analyses adjusted for tumor size in centimeters instead of T stage revealed similar results (patients aged <65 years functioned as a reference, HR for patients aged 65-75 years was 1.25 (95% CI 1.01-1.55); HR for patients aged ≥75 years was 1.62 (95% CI 1.22-2.14); p=0.003). Moreover, within strata of tumor size in centimeters, increasing age was consistently associated with a higher disease specific mortality (Supplementary table 1).

As disease specific mortality may be underestimated due to increased other cause mortality with increasing age, we performed additional survival analyses using a Fine and Gray model, in which the risk of competing mortality is accounted for. Multivariable analyses yielded comparable results as those presented in Table 4 (patients aged <65 years functioned as a reference, HR for patients aged 65-75 years was 1.22 (95% CI 1.00-1.48); HR for patients aged ≥75 years was 1.50 (95% CI 1.16-1.94); p<0.001). Additionally, one may argue that comorbidity in itself, independent of associated competing mortality, may result in higher disease specific mortality. Data on comorbidity were available for Dutch and Belgian patients (n=3142, 32%). Survival analyses restricted to these patients showed that estimates were not affected by comorbidity (Supplementary table 2).

To investigate whether the association between age and disease specific mortality was of linear origin, or whether a specific turning point was present, age was categorized in seven groups (Supplementary table 3). Disease specific mortality was similar for patients up to 70 years of age. From this age onwards, disease specific mortality increased stepwise with increasing age.

**Table 5.** Other cause mortality and breast cancer recurrence by age at diagnosis.

| | 5-years events n | (%) | Univariate HR (95% CI) | p | Multivariable* HR (95% CI) | p |
|---|---|---|---|---|---|---|
| Other cause mortality | | | | **<0.001** | | **<0.001** |
| <65 years | 64 | (1) | 1 (reference) | | 1 (reference) | |
| 65-75 years | 126 | (5) | 2.99 (2.29-3.89) | | 2.66 (1.96-3.63) | |
| ≥75 years | 160 | (14) | 9.96 (7.74-12.80) | | 7.30 (5.29-10.07) | |
| Breast cancer recurrence | | | | **0.002** | | 0.061 |
| <65 years | 512 | (10) | 1 (reference) | | 1 (reference) | |
| 65-75 years | 282 | (10) | 1.00 (0.87-1.15) | | 1.07 (0.91-1.25) | |
| ≥75 years | 153 | (13) | 1.34 (1.13-1.59) | | 1.29 (1.05-1.60) | |

HR: Hazard ratio; CI: confidence interval. *Hazard ratios adjusted for country, histological grade, T stage, nodal stage, estrogen receptor, progesterone receptor, surgery, radiotherapy, chemotherapy, endocrine therapy and persistence of endocrine therapy.

Next, we studied whether other cause mortality and breast cancer recurrence were different among age categories (Table 5). Mortality from other causes increased with age (multivariable analyses, patients aged <65 years functioned as a reference, HR for patients aged 65-75 years was 2.66 (95% CI 1.96-3.63); HR for patients aged ≥75 years was 7.30 (95% CI 5.29-10.07); p<0.001). Next, increasing age was associated with a higher risk of breast cancer recurrence (multivariable analyses, patients aged <65 years functioned as a reference, HR for patients aged 65-75 years was 1.07 (95% CI 0.91-1.25); HR for patients aged ≥75 years was 1.29 (95% CI 1.05-1.60); p=0.061).

# Discussion

The major finding in this study is that disease specific mortality is higher in older breast cancer patients, independent of tumor and treatment characteristics. Similarly, breast cancer recurrence increased with increasing age. Disease specific mortality as a proportion of all cause mortality decreased with age.

Several factors were explored which potentially could have biased our findings. Increasing age was associated with larger tumors at diagnosis. Consequently, disease specific mortality would be higher in elderly patients. Multivariable analyses adjusted for treatment and tumor characteristics, and analyses stratified by tumor size did not alter the results. Selective misclassification, in which death is more often attributed to breast cancer with increasing age, is not likely to have biased our results, because additional analyses using the secondary endpoint breast cancer recurrence revealed similar results. Theoretically, this trial may have been subject to age specific inclusion bias, in which elderly were included with different tumors compared to younger patients (Table 1). However, since differences in tumor characteristics resemble observational data in postmenopausal patients receiving surgery[15], this was not likely to have had a major influence.

Our finding that disease specific mortality as a proportion of all cause mortality decreased with age is consistent with several observational studies[3;5;10;16-19]. Bastiaannet et al[4] found that within breast cancer patients the percentage of deaths attributed to breast cancer decreased with age. The decreased proportion of all cause mortality attributed to breast cancer may have led to the conclusion that disease specific mortality decreases with increasing age. Here we provide arguments that disease specific mortality increases with age. There are few studies in the literature addressing this topic. Besides, there are only little data available on disease specific mortality in breast cancer patients by age at diagnosis. Increased risk of disease specific mortality with increasing age is confirmed in two studies[4;20], however others observed an opposite association[5;17;18], or no association at all[16;19;21].

It is tempting to speculate on the underlying mechanisms which could explain the results presented in this study. First, elderly patients may experience undertreatment. Several studies

showed that elderly breast cancer patients have lower odds of receiving standard care[10;22-25]. Increased age at diagnosis predicts deviation from guidelines for surgical therapy[23], adjuvant radiotherapy[10;24;25], chemotherapy[23-25] and endocrine therapy[23;24]. All patients included in this trial received surgery and endocrine therapy. A previous TEAM study analysis showed that patients aged ≥75 years more frequently discontinued study medication, and received less often subsequent therapy. However, discontinuation within the first year of follow-up was not associated with disease specific mortality thereafter[11]. Radiotherapy after a wide local excision was administered less frequently with increasing age (Table 1). Moreover, while 48% of patients aged ≥75 years had nodal involvement, only 5.2% received adjuvant chemotherapy. Next, elderly patients may experience overtreatment, in which adverse events of breast cancer therapy result in mortality attributed to breast cancer. Older patients may have an increased toxicity risk when treated with chemotherapy and to a lesser degree with radiotherapy[26]. In these relatively healthy elderly trial participants, breast cancer recurrence was shown to be higher with increasing age as well. Therefore overtreatment is not likely to play a role in our findings.

Breast cancer in elderly might display a more aggressive tumor biology and thereby increase mortality from breast cancer. In this study, elderly presented more often with larger tumors, however nodal status was similar over age. Although this hypothesis cannot be tested in detail in this study, other studies suggest the opposite. Advanced age has been associated with a decrease in tumor proliferative factors[27], and elderly patients more often present with well differentiated tumors and positive hormone receptor status[19;28].

Adjustment for both treatment and tumor characteristics did not eliminate the association between age and disease specific mortality. Consequently, other, unknown factors might have contributed to our findings. Older patients might respond differently to a tumor than younger patients[29]. In addition, older patients might respond different to a certain therapy. Polypharmacy can cause drug interactions, and may alter pharmacokinetics of anticancer therapy[30].

Summarized, undertreatment, in particular undertreatment of either chemotherapy or radiotherapy, may explain age specific outcome in this relatively healthy population. Differences in tumor biology and age specific overtreatment are not likely to have influenced our findings. We cannot exclude a potential influence of an age specific response to either the tumor or anticancer therapy.

Effects of anticancer treatment cannot be estimated as precisely in patients with a high risk of competing mortality. As a consequence studies may be underpowered to detect treatment outcome differences in these populations[31]. Fine and Gray analyses accounting for the higher competing mortality with increasing age revealed similar effect sizes; despite the fact that 14.6% of patients aged ≥75 years died from causes other than breast cancer, estimates were

unaffected. These data suggest that competing mortality has to be substantial to affect disease specific outcome as estimated by Cox regression analysis.

## Strengths and limitations

The major strength of this study is the ability to study a large group of breast cancer patients followed as part of a clinical trial on endocrine therapy. Trial data comprise highly standardized treatment algorithms and virtually complete follow-up. The TEAM trial had very few exclusion criteria, among which there was no upper age limitation. This enabled us to study age specific mortality.

As enrollment in the TEAM trial was restricted to postmenopausal patients with estrogen and/or progesterone receptor positive disease, these results may not necessarily be extrapolated to all breast cancer patients. No data were available on compliance to non-randomized therapy. Although analyses were adjusted for non-randomized therapy, residual confounding and bias by noncompliance cannot be excluded. Although eligibility criteria of the TEAM trial were quite broad, it is known that trial populations generally comprise relatively healthy patients compared to the general population[32]. The results presented in this study may slightly differ from results in the general population. Competing mortality is likely to be higher in the general population, and administered treatment as well as implications of treatment may differ from a trial population. Replication of the current analyses in a detailed population based study may reveal additional evidence for one or more explanations of the findings presented in this study.

## Conclusion

In conclusion, regardless of a higher risk of other cause mortality and independent of tumor and treatment characteristics, disease specific mortality increases with age among postmenopausal women with hormone receptor positive breast cancer. These data underline the need for age specific breast cancer studies, in order to improve breast cancer outcome in all ages. Moreover, future detailed population based and translational studies may increase insight in causal factors of higher disease specific mortality and breast cancer recurrence with increasing age.

**Supplementary table 1.** Disease specific mortality by age at diagnosis, stratified by tumor size.

| | 5-years death n | (%) | Univariate HR (95% CI) | p | Multivariable* HR (95% CI) | p |
|---|---|---|---|---|---|---|
| <1 cm | | | | 0.827 | | 0.700 |
| <65 years | 3 | (1) | 1 (reference) | | 1 (reference) | |
| 65-74 years | 0 | (0) | 0.89 (0.16-4.85) | | 1.29 (0.21-7.97) | |
| ≥75 years | 1 | (1) | 1.84 (0.20-16.63) | | 2.82 (0.26-31.21) | |
| 1-2 cm | | | | 0.124 | | 0.073 |
| <65 years | 58 | (3) | 1 (reference) | | 1 (reference) | |
| 65-74 years | 44 | (2) | 1.31 (0.91-1.89) | | 1.52 (0.99-2.32) | |
| ≥75 years | 12 | (4) | 1.61 (0.95-2.74) | | 1.86 (0.97-3.58) | |
| 2-3 cm | | | | 0.208 | | 0.619 |
| <65 years | 80 | (7) | 1 (reference) | | 1 (reference) | |
| 65-74 years | 44 | (6) | 0.93 (0.67-1.29) | | 1.01 (0.69-1.47) | |
| ≥75 years | 76 | (9) | 1.32 (0.91-1.90) | | 1.24 (0.78-1.99) | |
| 3-4 cm | | | | 0.329 | | **0.022** |
| <65 years | 50 | (11) | 1 (reference) | | 1 (reference) | |
| 65-74 years | 21 | (8) | 0.95 (0.62-1.46) | | 1.11 (0.67-1.83) | |
| ≥75 years | 26 | (13) | 1.34 (0.86-2.07) | | 2.15 (1.20-3.82) | |
| 4-5 cm | | | | **0.034** | | 0.136 |
| <65 years | 15 | (9) | 1 (reference) | | 1 (reference) | |
| 65-74 years | 15 | (12) | 1.54 (0.81-2.90) | | 1.48 (0.70-3.14) | |
| ≥75 years | 13 | (20) | 2.51 (1.25-5.02) | | 2.32 (1.02-6.13) | |
| ≥5 cm | | | | 0.241 | | 0.397 |
| <65 years | 19 | (9) | 1 (reference) | | 1 (reference) | |
| 65-74 years | 18 | (18) | 1.51 (0.88-2.58) | | 1.53 (0.79-2.96) | |
| ≥75 years | 8 | (12) | 0.90 (0.43-1.88) | | 1.02 (0.37-2.82) | |

HR: Hazard ratio; CI: confidence interval. * Hazard ratios adjusted for country, histological grade, nodal stage, estrogen receptor, progesterone receptor, surgery, radiotherapy, chemotherapy, endocrine therapy and persistence of endocrine therapy.

**Supplementary table 2.** Disease specific mortality in Dutch/Belgian participants, adjusted for comorbidity.

| | 5-years death n | (%) | Multivariable HR (95% CI) | p |
|---|---|---|---|---|
| Model 1* | | | | 0.055 |
| <65 years | 135 | (9) | 1 (reference) | |
| 65-75 years | 74 | (9) | 1.16 (0.86-1.57) | |
| ≥75 years | 51 | (11) | 1.57 (1.09-2.26) | |
| Model 2** | | | | **0.048** |
| <65 years | 135 | (9) | 1 (reference) | |
| 65-75 years | 74 | (9) | 1.16 (0.86-1.58) | |
| ≥75 years | 51 | (11) | 1.60 (1.10-2.32) | |
| Model 3*** | | | | 0.064 |
| <65 years | 135 | (9) | 1 (reference) | |
| 65-75 years | 74 | (9) | 1.16 (0.86-1.57) | |
| ≥75 years | 51 | (11) | 1.55 (1.07-2.25) | |
| Model 4**** | | | | **0.047** |
| <65 years | 135 | (9) | 1 (reference) | |
| 65-75 years | 74 | (9) | 1.17 (0.87-1.59) | |
| ≥75 years | 51 | (11) | 1.59 (1.10-2.31) | |

HR: Hazard ratio; CI: confidence interval. * Hazard ratios adjusted for country, histological grade, T stage, nodal stage, estrogen receptor, progesterone receptor, surgery, radiotherapy, chemotherapy, endocrine therapy and persistence of endocrine therapy. ** Hazard ratios adjusted for variables included in Model 1 and comorbidity categories (cardiac, central nervous system, endocrine, musculoskeletal comorbidities). *** Hazard ratios adjusted for variables included in Model 1 and number of comorbidities (continuous). **** Hazard ratios adjusted for variables included in Model 1 and number of comorbidities (0, 1-2, >2).

**Supplementary table 3.** Disease specific mortality by age at diagnosis (7 groups).

| | 5-years death n | (%) | Univariate HR (95% CI) | p | Multivariable* HR (95% CI) | p |
|---|---|---|---|---|---|---|
| Age at diagnosis | | | | | | |
| <55 years | 63 | (5) | 1 (reference) | | 1 (reference) | |
| 55-60 years | 87 | (5) | 1.08 (0.81-1.44) | 0.611 | 1.02 (0.74-1.41) | 0.908 |
| 60-65 years | 93 | (5) | 1.09 (0.82-1.45) | 0.554 | 1.09 (0.79-1.51) | 0.610 |
| 65-70 years | 75 | (5) | 1.05 (0.78-1.41) | 0.767 | 1.18 (0.84-1.65) | 0.339 |
| 70-75 years | 74 | (7) | 1.38 (1.02-1.87) | **0.035** | 1.48 (1.04-2.11) | **0.029** |
| 75-80 years | 74 | (9) | 1.75 (1.27-2.40) | **0.001** | 1.73 (1.17-2.56) | **0.006** |
| ≥80 years | 29 | (7) | 1.81 (1.23-2.66) | **0.003** | 1.74 (1.11-2.74) | **0.017** |

HR: Hazard ratio; CI: confidence interval. * Hazard ratios adjusted for country, histological grade, T stage, nodal stage, estrogen receptor, progesterone receptor, surgery, radiotherapy, chemotherapy, endocrine therapy and persistence of endocrine therapy.

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