Association Between Age at Diagnosis and Disease-Specific Mortality Among Postmenopausal Women With Hormone Receptor–Positive Breast Cancer

Willein van de Water, MD
Christos Markopoulos, MD, PhD
Cornelis J. H. van de Velde, MD, PhD
Caroline Seynaeve, MD, PhD
Annette Hasenburg, MD, PhD
Daniel Rea, MD
Hein Putter, PhD
Johan W. R. Nortier, MD, PhD
Anton J. M. de Craen, MD, PhD
Elyse´e T. M. Hille, PhD
Gerrit-Jan Liefers, MD, PhD
Anton J. M. de Craen, MD, PhD
Christos Markopoulos, MD, PhD, Leiden University Medical Center, Albinus-dreef 2, PO Box 9600, 2300 RC Leiden, the Netherlands (c.j.h.van_de_velde@lumc.nl).

Context In addition to classic tumor-related prognostic factors, patient characteristics may be associated with breast cancer outcome.

Objective To assess the association between age at diagnosis and breast cancer outcome in postmenopausal women with hormone receptor–positive breast cancer.

Design, Setting, and Patients Study analysis of 9766 patients enrolled in the TEAM (Tamoxifen Exemestane Adjuvant Multinational) randomized clinical trial between January 2001 and January 2006. Age at diagnosis was categorized as younger than 65 years (n=5349), 65 to 74 years (n=3060), and 75 years or older (n=1357).

Main Outcome Measures Primary end point was disease-specific mortality; secondary end points were other-cause mortality and breast cancer relapse.

Results During median follow-up of approximately 5.1 years, there were a total of 1043 deaths. Disease-specific mortality, as a proportion of all-cause mortality, decreased with categorical age group (78% [<=65 years], 56% [65-74 years], and 36% [=>75 years]; P<.001). In multivariable analyses, compared with patients younger than 65 years, disease-specific mortality increased with age for patients aged 65 to 74 years (hazard ratio [HR], 1.25; 95% CI, 1.01-1.54); and patients aged 75 years or older (HR, 1.63; 95% CI, 1.23-2.16) (P<.001). Similarly, breast cancer relapse increased with age for patients aged 65-74 years (HR, 1.07; 95% CI, 0.91-1.25 and patients aged 75 years or older (HR, 1.29; 95% CI, 1.05-1.60) (P=.06). Other-cause mortality increased with age in patients aged 65 to 74 years (HR, 2.66; 95% CI, 1.96-3.63) and patients aged 75 years or older (HR, 7.30; 95% CI, 5.29-10.07) (P<.001).

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

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due to age restrictions.\textsuperscript{6} The TEAM (Tamoxifen, Exemestane, Adjuvant, Multinational) 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 this 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 relapse were evaluated.

METHODS

The TEAM trial is a randomized, phase 3, multinational, open-label study conducted in postmenopausal breast cancer patients with estrogen receptor–positive tumors, progesterone receptor–positive tumors, or both. Patients were randomized to receive either exemestane, 25 mg once daily for 5 years, or tamoxifen, 20 mg once daily for 2.5 to 3 years, followed by exemestane, 25 mg once daily for 2 to 2.5 years, for a total of 5 years. Participants in Belgium, the Netherlands, United Kingdom, Ireland, United States, Japan, Greece, Germany, and France (N=9766) were enrolled and included between January 2001 and January 2006. Appropriate approvals from the ethical committees and written informed consent from all patients were obtained.\textsuperscript{7} The trial was registered (ClinicalTrials.gov NCT00279448, NCT0032136, and NCT0036270; the Netherlands Trial Registry NTR 267; Ethics Commission Trial 27/2001; and the University hospital Medical Information Network C000000057).

Similar protocols were used in the 9 participating countries with minor differences to accommodate local treatment guidelines.\textsuperscript{7,8} In short, postmenopausal patients with histologically confirmed breast carcinoma who completed local therapy with curative intent (ie, without evidence of metastatic disease) were eligible. Participants were randomized to receive endocrine treatment 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 5 years, an Eastern Cooperative Oncology Group (ECOG) performance status of more than 2, or 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 5 years of exemestane use alone vs the sequence of tamoxifen followed by exemestane.\textsuperscript{7} Moreover, death from other causes excluding breast cancer was comparable for both treatment groups.\textsuperscript{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 2009 and in line with other publications.\textsuperscript{10,11} Primary end point 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 into 1 of 10 prespecified groups. Classification...
Most extensive surgery
- Mastectomy: 2120 (39.6), 1372 (44.8), 841 (62.0)
- Wide local extension: 3222 (60.2), 1685 (55.1), 515 (38.0)
- No resection: 2 (<0.1), 1 (<0.1), 0
- Unknown: 5 (0.1), 2 (0.1), 1 (0.1)

Radiotherapy
- Yes: 3980 (74.4), 2030 (66.3), 687 (50.6)
- No: 1330 (24.9), 994 (32.5), 651 (48.0)
- Unknown: 39 (0.7), 36 (1.2), 19 (1.4)

Radiotherapy after wide local excision
- Yes: 3042 (94.4), 1543 (91.6), 451 (87.6)
- No: 180 (5.6), 142 (8.4), 64 (12.4)
- Unknown: 1 (<0.1), 3 (0.1), 2 (0.1)

Chemotherapy
- Yes: 2743 (51.3), 700 (22.9), 71 (5.2)
- No: 2605 (48.7), 2357 (77.0), 1284 (94.6)
- Unknown: 5 (0.1), 2 (0.1), 1 (0.1)

Endocrine therapy
- Tamoxifen followed by exemestane: 2667 (49.9), 1546 (50.5), 655 (48.3)
- Exemestane: 2682 (50.1), 1514 (49.5), 702 (51.7)
- No: 1207 (22.6), 684 (22.4), 377 (27.8)

Persistence of endocrine therapy
- Yes: 3042 (94.4), 1543 (91.6), 451 (87.6)
- No: 180 (5.6), 142 (8.4), 64 (12.4)
- Unknown: 1 (<0.1), 3 (0.1), 2 (0.1)

Overall, 9766 patients (age range, 35-96 years; median age, 64 years) were included in the multinational TEAM trial, of which 5349 were younger than 65 years at diagnosis (55%; median age, 58 years), 3060 were aged 65 to 74 years (31%; median age, 69 years), and 1357 were aged 75 years or older (14%; median age, 79 years). Overall, 778 patients (8.0%) were lost to follow-up, 429 (8.0%) in patients younger than 65 years, 214 (7.0%) in patients aged 65 to 74 years, and 135 (9.9%) in patients who were aged 75 years or older. Table 1 and Table 2 show baseline characteristics by age at diagnosis. We observed a significant age-associated increase in larger tumors and estrogen receptor–positive breast cancer. In addition, the proportion of mastectomy increased significantly with age, whereas administration of chemotherapy and administration of radiotherapy after a wide local excision significantly decreased.

At database lock, median follow-up (interquartile range) from randomization was 5.1 years (4.3-6.0) in patients younger than 65 years, 5.1 years (4.2-6.0) in patients aged 65 to 74 years, and 5.0 years (3.8-5.8) in patients aged 75 years or older. The number of deaths was 391 (7.3%), 341 (11.2%), and 311 (22.9%), respectively. The figure illustrates cumulative incidence of death due to breast cancer, other causes excluding breast cancer, and all causes by age at diagnosis. Cumulative incidence of death due to breast cancer increased from 5.7% in patients younger than 65 years, 6.3% in patients aged 65 to 74 years, to 8.3% in patients aged 75 years or older. Cumulative incidence of other-cause death excluding breast cancer 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, 77.5%; 65-74 years, 56.3%; ≥75 years, 36.3%; P < .001). Deaths categorized as other (n = 100) were recorded to be due to 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; gastrointestinal perforation, urogenital disorders, malignancy-related disorders, suicide).

Univariate Cox regression analysis showed a higher risk of disease-specific mortality with increasing age (reference standard, patients <65 years [hazard ratio [HR] for patients aged 65-74 years, 1.12; 95% CI, 0.94-1.34; HR for patients aged ≥75 years, 1.66; 95% CI, 1.34-2.06; P < .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, 8030 patients (82.2%) were included in the multivariable model. Again, disease-specific mortality increased with age (HR for patients aged 65-74 years, 1.25; 95% CI, 1.01-1.54; and HR for patients aged ≥75 years, 1.63; 95% CI, 1.23-2.16; P < .001).

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 10-year increase in age (univariate HR per 10 years, 1.20; 95% CI, 1.10-1.31; P < .001; and multivariable HR per 10 years, 1.21; 95% CI, 1.08-1.36; P = .001).

Since increasing age was associated with larger tumors (Table 1 and Table 2), additional analyses were performed to exclude residual confounding by tumor size. Multivariable survival analyses adjusted for tumor size in centimeters instead of T category revealed similar results (HR for patients

Figure. Cumulative Incidence of Death Due to Breast Cancer, Other Causes, and All Causes by Age at Diagnosis

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, 77.5%; 65-74 years, 56.3%; ≥75 years, 36.3%; P < .001). Deaths categorized as other (n = 100) were recorded to be due to 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; gastrointestinal perforation, urogenital disorders, malignancy-related disorders, suicide).

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Other-cause death is defined as all causes except breast cancer (second primary tumor, endometrial cancer, cardiac disorder, thromboembolism, pulmonary disorder, cerebral disorder, vascular disorder, other causes, and unknown causes).

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Moreover, within strata of tumor size in centimeters, increasing age was consistently associated with a higher disease-specific mortality (eTable 1, available at http://www.jama.com).

As disease-specific mortality may be underestimated because of increased other-cause mortality with increasing age, we performed additional survival analyses using a Fine and Gray model, accounting for the risk of competing mortality. Multivariable analyses yielded results comparable with those presented in Table 4 (HR for patients aged 65-74 years, 1.22; 95% CI, 1.00-1.48; and HR for patients aged ≥75 years, 1.50; 95% CI, 1.16-1.94; P < .001). Additionally, one may argue that comorbidity, 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 (eTable 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 7 groups (eTable 3). Disease-specific mortality was similar for patients younger than 70 years. For patients aged 70 years and older, disease-specific mortality increased stepwise with increasing age.

Next, we studied whether other-cause mortality and breast cancer relapse were different among age categories (Table 5). Mortality from other causes increased with age (using multivariable analyses, HR for patients aged 65-74 years was 2.66; 95% CI, 1.96-3.63; and HR for patients aged ≥75 years was 7.30; 95% CI, 5.29-10.07; P < .001). Increasing age was also associated with a higher risk of breast cancer relapse (using multivariable analyses, HR for patients aged 65-74 years was 1.07; 95% CI, 0.91-1.25; and HR for patients aged ≥75 years was 1.29; 95% CI, 1.05-1.60; P = .06).

### Table 3. Causes of Death by Age at Diagnosis

<table>
<thead>
<tr>
<th>Age at Diagnosis</th>
<th>No. (%)</th>
<th>Mortality at 5 y.</th>
<th>Multivariable HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 Years (n = 391)</td>
<td>303 (77.5)</td>
<td>243 (6)</td>
<td>1 (Reference)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>65-74 Years (n = 341)</td>
<td>192 (56.3)</td>
<td>149 (6)</td>
<td>1.25 (1.01-1.54)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥75 Years (n = 311)</td>
<td>113 (36.3)</td>
<td>92 (8)</td>
<td>1.63 (1.23-2.16)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Histological grade (BR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>27 (2)</td>
<td>25 (7.3)</td>
<td>1 (Reference)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>G2</td>
<td>191 (5)</td>
<td>13 (3.8)</td>
<td>1.86 (1.28-2.70)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>G3,4</td>
<td>226 (10)</td>
<td>39 (12.5)</td>
<td>3.23 (2.21-4.72)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>T category</td>
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<td></td>
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</tr>
<tr>
<td>T1</td>
<td>151 (3)</td>
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<tr>
<td>T2</td>
<td>282 (9)</td>
<td>42 (12.7)</td>
<td>1.91 (1.55-2.35)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>T3,4</td>
<td>49 (12)</td>
<td>39 (12.5)</td>
<td>2.01 (1.44-2.81)</td>
<td>&lt;.001</td>
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<td>Nodal category</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>360 (9)</td>
<td>337 (10.6)</td>
<td>2.31 (1.85-2.87)</td>
<td>&lt;.001</td>
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<tr>
<td>Positive</td>
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<td></td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td>Positive</td>
<td>459 (6)</td>
<td>1 (Reference)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Negative</td>
<td>25 (15)</td>
<td>16 (5)</td>
<td>2.18 (1.44-3.31)</td>
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<td>1 (Reference)</td>
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<tr>
<td>Negative</td>
<td>138 (9)</td>
<td>27 (8.7)</td>
<td>1.64 (1.35-2.00)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Most extensive surgery</td>
<td>Mastectomy</td>
<td>316 (8)</td>
<td>1 (Reference)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Wide local extension</td>
<td>168 (4)</td>
<td>70 (20.6)</td>
<td>0.59 (0.46-0.74)</td>
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<tr>
<td>Radiotherapy</td>
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<td>1 (Reference)</td>
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<td>Chemotherapy</td>
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<td>&lt;.001</td>
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<tr>
<td>No</td>
<td>271 (2)</td>
<td>113 (20.3)</td>
<td>0.97 (0.77-1.20)</td>
<td>&lt;.001</td>
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<tr>
<td>Endocrine therapy</td>
<td>Tamoxifen followed by exemestane</td>
<td>246 (6)</td>
<td>1 (Reference)</td>
<td>&lt;.001</td>
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<tr>
<td>Exemestane</td>
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<tr>
<td>Nonpersistent</td>
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<td>19 (2.4)</td>
<td>0.64 (0.50-0.84)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: HR, hazard ratio.

**Table 4. Disease-Specific Mortality by Age at Diagnosis**

<table>
<thead>
<tr>
<th>Age, y</th>
<th>No. (%)</th>
<th>Multivariable HR (95% CI)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>&lt;65</td>
<td>243 (5)</td>
<td>1 (Reference)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>65-74</td>
<td>149 (6)</td>
<td>1.25 (1.01-1.54)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥75</td>
<td>92 (8)</td>
<td>1.63 (1.23-2.16)</td>
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<td>Histological grade (BR)</td>
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Abbreviation: HR, hazard ratio.

**Table 5. Other-Cause Mortality**

<table>
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<tr>
<th>Age, y</th>
<th>No. (%)</th>
<th>Multivariable HR (95% CI)</th>
<th>P Value</th>
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<td>&lt;65</td>
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<tr>
<td>≥75</td>
<td>92 (8)</td>
<td>1.63 (1.23-2.16)</td>
<td>&lt;.001</td>
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</table>
COMMENT

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

Several factors were explored that potentially could have biased our findings. Increasing age was associated with larger tumors at diagnosis. Consequently, disease-specific mortality would be higher in older 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 breast cancer relapse (the secondary end point) revealed similar results. Theoretically, this trial may have been subject to age-specific inclusion bias, in which older patients were included with different tumors compared with younger patients (Table 1 and Table 2). However, since differences in tumor characteristics resemble observational data in postmenopausal patients receiving surgery, 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. 

Bastiaanet et al 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 2 studies, however, others observed an opposite association or no association at all. 

Several possible underlying mechanisms may help to explain the results presented in this study. First, older patients may experience undertreatment. Several studies showed that older breast cancer patients have lower odds of receiving standard care. Increased age at diagnosis predicts deviation from guidelines for surgical therapy, adjuvant radiotherapy, chemotherapy, and endocrine therapy. All patients included in this trial received surgery and endocrine therapy. A previous TEAM study analysis showed that patients aged 75 years or older more frequently discontinued study medication and less often received subsequent therapy. However, discontinuation within the first year of follow-up was not associated with disease-specific mortality thereafter. Radiotherapy after a wide local excision was administered less frequently with increasing age (Table 1 and Table 2). Moreover, although 48% of patients aged 75 years or older had nodal involvement, only 5.2% received adjuvant chemotherapy.

Next, older patients may experience overtreatment, in which adverse events of breast cancer therapy result in mortality attributed to breast cancer. Older patients might have an increased toxicity risk when treated with chemotherapy and to a lesser degree with radiotherapy. In these relatively healthy older trial participants, breast cancer relapse 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 older patients might display a more aggressive tumor biology and thereby increase mortality from breast cancer. In this study, older patients presented more often with larger tumors; however, nodal status was similar in all age categories. 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 and older patients more often present with well-differentiated tumors and positive hormone-receptor status.

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. In addition, older patients might respond differently to a certain therapy. Polypharmacy can cause drug interactions and

Table 5. Other-Cause Mortality and Breast Cancer Relapse by Age at Diagnosis

<table>
<thead>
<tr>
<th>Other-cause mortality, age, y</th>
<th>Death/Relapse at 5 y, No. (%)</th>
<th>Univariate HR (95% CI)a</th>
<th>P Value</th>
<th>Multivariable HR (95% CI)b</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>64 (1)</td>
<td>1 [Reference]</td>
<td></td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>126 (6)</td>
<td>2.99 (2.29-3.89)</td>
<td>&lt;.001</td>
<td>2.66 (1.96-3.63)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥75</td>
<td>160 (14)</td>
<td>9.96 (7.74-12.80)</td>
<td></td>
<td>7.30 (5.29-10.07)</td>
<td></td>
</tr>
</tbody>
</table>

Breast cancer relapse, age, y

| <65                         | 512 (10)                       | 1 [Reference]           |         | 1 [Reference]             |         |
| 65-74                       | 282 (10)                       | 1.00 (0.87-1.15)        | .002    | 1.07 (0.91-1.29)          | .06     |
| ≥75                         | 153 (13)                       | 1.34 (1.13-1.59)        |         | 1.29 (1.05-1.60)          |         |

Abbreviation: HR, hazard ratio.
aHRs adjusted for country, histological grade, T category, nodal stage, estrogen receptor, progesterone receptor, surgery, radiotherapy, chemotherapy, endocrine therapy, and persistence of endocrine therapy.
may alter pharmacokinetics of antican-
cer therapy.30

Summarized, undertreatment, in par-
ticular undertreatment of either che-
motherapy or radiotherapy, may ex-
plain age-specific outcome in this
relatively healthy population. Differ-
ences in tumor biology and age-
specific overtreatment are not likely
to have influenced our findings. We can-
not exclude a potential influence of an
age-specific response to either the tu-
mor or anticancer therapy.

Effects of anticancer treatment can-
not be estimated as precisely in pa-
tients with a high risk of competing
mortality. As a consequence, studies
may be underpowered to detect treat-
ment 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 or older
died of causes other than breast can-
cer, 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 its
ability to study a large group of breast
cancer patients observed as part of a
clinical trial on endocrine therapy. Trial
data comprise highly standardized treat-
ment algorithms and virtually com-
plete follow-up. The TEAM trial had
very few exclusion criteria and there
was no upper age limitation. This en-
abled us to study age-specific mortality.

Because enrollment in the TEAM trial
was restricted to postmenopausal pa-
tients with estrogen receptor–positive
disease, progesterone receptor–
positive disease, or both, these results
may not necessarily be extrapolated to
all breast cancer patients. No data were
available on adherence to nonrandom-
tized therapy. Although analyses were
adjusted for nonrandomized therapy,
residual confounding and bias by non-
compliance cannot be excluded. Al-
though eligibility criteria of the TEAM
trial were quite broad, it is known that
trial populations generally comprise
relatively healthy patients compared
with the general population.32

The results presented in this study
may slightly differ from results in the
general population. Competing mor-
tality is likely to be higher in the gen-
eral population, and administered treat-
ment, as well as implications of treat-
ment, may differ from a trial popu-
lation. Replication of the current analy-
ses in a detailed population-based study
may reveal additional evidence for 1 or
more explanations of the findings pre-
sent in this study.

CONCLUSION

In conclusion, regardless of a higher
risk of other-cause mortality and
independent of tumor and treatment
characteristics, disease-specific mor-
tality increases with age among post-
menopausal women with hormone
receptor–positive breast cancer. These
data underline the need for age-
specific breast cancer studies in
order to improve breast cancer out-
come in patients of all ages. More-
over, future detailed population-
based and translational studies may
increase insight into causal factors of
higher disease-specific mortality and
breast cancer relapse with increasing age.

Author Contributions: Dr van de Water had full ac-
cess to all of the data in the study and takes respon-
sibility for the integrity of the data and the accuracy
of the data analysis.

Study concept and design: van de Water, Markopoulos,
van de Velde, Seynaeve, Rea, Putter, de Craen, Hill,
Bastiaannet, Hadji, Liefers, Jones.

Acquisition of data: van de Velde, Seynaeve, Hasenberg,
Nortier, Hadji, Jones.

Analysis and interpretation of data: van de Water,
Markopoulos, van de Velde, Seynaeve, Rea, Putter,
de Craen, Hill, Bastiaannet, Hadji, Liefers, Jones.

Drafting of the manuscript: van de Water,
Markopoulos, van de Velde, Hasenberg, Westendorp.

Critical revision of the manuscript for important in-
tellectual content: van de Water, Markopoulos,
van de Velde, Seynaeve, Hasenberg, Rea, Putter,
Nortier, de Craen, Hill, Bastiaannet, Hadji, Liefers, Jones.

Statistical analysis: van de Water, Markopoulos,
Putter, Bastiaannet, Westendorp.

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