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

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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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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 United States in 2008, 41% of these women were aged 65 years or older at diagnosis.[2] Because breast cancer incidence increases with increasing age,[2] changing demographics and continuously increasing life expectancy will further enlarge the number of older women confronted with breast cancer.

In addition to classic 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 considered a competing risk of death, which may be particularly present in older 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, older patients are often not included in clinical trials

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due to age restrictions.[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.[7] The trial was registered (ClinicalTrials.gov NCT00279448, NCT00032136, and NCT00036270; 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.[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 end points between 5 years of exemestane use alone vs the sequence of tamoxifen followed by exemestane.[7] Moreover, death from other causes excluding breast cancer was comparable for both treatment groups.[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 7, 2010. Patients were categorized into 3 age groups (<65 years, 65-74 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 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. Classifica-

Table 1. Patient Characteristics by Age at Diagnosis

	No. (%)			
	<65 Years (n = 5349)	65-74 Years (n = 3060)	≥75 Years (n = 1357)	*P* Value
Histological grade and differentiation				
G1, well	911 (17.0)	550 (18.0)	216 (15.9)	.06
G2, moderate	2580 (48.2)	1537 (50.2)	679 (50.0)	
G3, G4, poor	1377 (25.7)	732 (23.0)	329 (24.2)	
Gx, unknown	481 (9.0)	241 (7.9)	133 (9.8)	
T stage				
T0, Tis	6 (0.1)	0	0	<.001
T1	3291 (61.5)	1806 (59.0)	593 (43.7)	
T2	1793 (33.5)	1122 (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	
N stage				
Negative	2799 (52.3)	1622 (53.0)	690 (50.8)	.14
Positive	2518 (47.1)	1419 (46.4)	651 (48.0)	
Unknown	32 (0.6)	19 (0.6)	16 (1.2)	
Estrogen receptor				
Positive	5218 (97.6)	3022 (98.8)	1344 (99.0)	<.001
Negative	128 (2.4)	35 (1.1)	13 (1.0)	
Unknown	3 (0.1)	3 (0.1)	0	
Progesterone receptor				
Positive	4028 (75.3)	2268 (74.1)	1004 (74.0)	.54
Negative	915 (17.1)	554 (18.1)	255 (18.8)	
Unknown	406 (7.6)	238 (7.8)	98 (7.2)	
Country				
Belgium	265 (5.0)	106 (3.5)	43 (3.2)	<.001
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	1428 (26.7)	852 (27.8)	473 (34.9)	
United Kingdom/Ireland	696 (13.0)	413 (13.5)	166 (12.2)	
United States	1159 (21.7)	695 (22.7)	378 (27.9)	

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Table 2. Treatment Characteristics by Patient Age at Diagnosis

	No. (%)			
	<65 Years (n = 5349)	65-74 Years (n = 3060)	≥75 Years (n = 1357)	*P* Value
Most extensive surgery				
Mastectomy	2120 (39.6)	1372 (44.8)	841 (62.0)	<.001
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)	<.001
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)	<.001
No	180 (5.6)	142 (8.4)	64 (12.4)	
Chemotherapy				
Yes	2743 (51.3)	700 (22.9)	71 (5.2)	<.001
No	2605 (48.7)	2357 (77.0)	1284 (94.6)	
Unknown	1 (<0.1)	3 (0.1)	2 (0.1)	
Endocrine therapy				
Tamoxifen followed by exemestane	2667 (49.9)	1546 (50.5)	655 (48.3)	.38
Exemestane	2682 (50.1)	1514 (49.5)	702 (51.7)	
Persistence of endocrine therapy				
Yes	4142 (77.4)	2376 (77.6)	980 (72.2)	<.001
No	1207 (22.6)	684 (22.4)	377 (27.8)	

tion 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 were due to presence of distant metastases at time of death. The majority of these patients (57%, n=24) were formerly categorized as having unknown or other cause of death. The secondary end points of this study were other-cause mortality and breast cancer relapse. Other-cause mortality was calculated as all-cause mortality minus disease-specific mortality; breast cancer relapse was defined as locoregional or distant breast cancer recurrence, or ipsilateral or contralateral breast cancer. Ductal carcinoma in situ was not judged to be evidence of relapse.

Statistical analyses were performed using SPSS statistical software, version 17.0 and R statistical package. To compare proportional differences among age categories, the Pearson χ^2 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 to assess the risk of disease-specific mortality and other-cause mortality, respectively, taking into account the risk of reaching the other end point. Covariates were included in the multivariable model if they were judged to be clinically relevant and comprised country, histological grade (G1; G2; G3, G4), T category (T0,Tis,T1; T2; T3,T4), nodal category (negative; positive), estrogen receptor status (negative; positive), progesterone receptor status (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 adverse events, intercurrent illness, patient refusal, or other reasons; continuation of allocated endocrine therapy, or having an event during use of study medication). All statistical tests were 2-sided. *P* values of less than .05 were considered to be statistically significant.

RESULTS

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.

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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, urogential disorders, malignancy-related disorders, suicide).

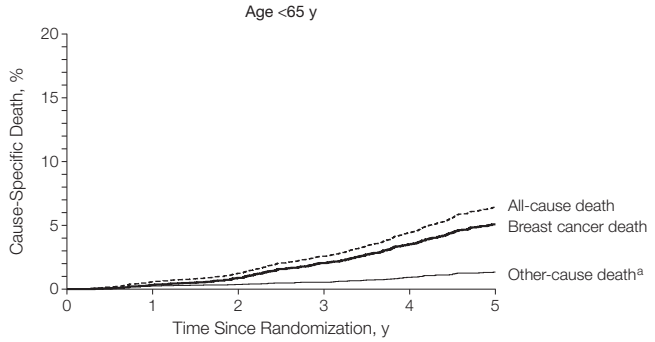
Univariate Cox regression analysis showed a higher risk of disease-specific mortality with increasing age (reference standard, patients <65 years [hazard ratio {HR} for patients aged 65-74 years, 1.12; 95% CI, 0.94-1.34; HR for patients aged ≥75 years, 1.66; 95% CI, 1.34-2.06; $P<.001$]).

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; $P<.001$).

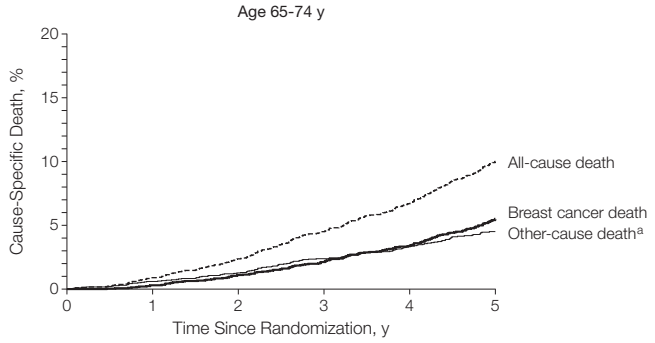
To test the robustness of the age cut points, additional analyses were performed with age as a continuous variable, which confirmed an increased risk of breast cancer death per 10-year increase in age (univariate HR per 10 years, 1.20; 95% CI, 1.10-1.31; $P<.001$; and multivariable HR per 10 years, 1.21; 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

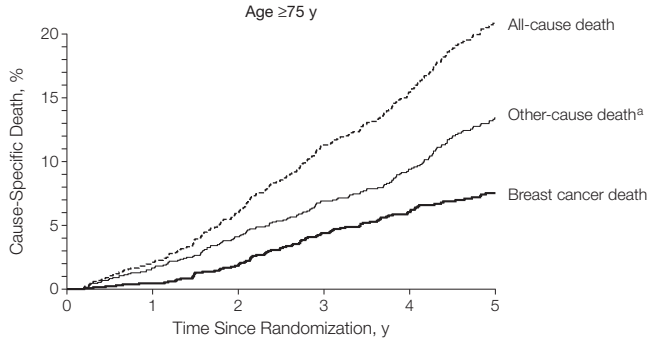
Figure. Cumulative Incidence of Death Due to Breast Cancer, Other Causes, and All Causes by Age at Diagnosis



No. at risk	5349	5243	5129	4966	4413	3254
No. of events						
All-cause death		30	35	69	92	81
Breast cancer death		17	29	60	73	64
Other-cause death[a]		13	6	9	19	17



No. at risk	3060	2982	2903	2805	2516	1821
No. of events						
All-cause death		27	44	63	63	78
Breast cancer death		9	24	30	36	50
Other-cause death[a]		18	20	33	27	28



No. at risk	1357	1292	1219	1128	955	664
No. of events						
All-cause death		28	40	69	50	55
Breast cancer death		6	18	33	20	15
Other-cause death[a]		22	32	36	30	40

[a]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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Table 3. Causes of Death by Age at Diagnosis

	No. (%)		
	<65 Years (n = 391)	65-74 Years (n = 341)	≥75 Years (n = 311)
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
Cardiac disorder	14 (3.6)	25 (7.3)	39 (12.5)
Thromboembolism	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

	Mortality at 5 y, No. (%)	Multivariable HR (95% CI)[a]	*P* Value
Age, y			
<65	243 (5)	1 [Reference]	<.001
65-74	149 (6)	1.25 (1.01-1.54)	
≥75	92 (8)	1.63 (1.23-2.16)	
Histological grade (BR)			
G1	27 (2)	1 [Reference]	<.001
G2	191 (5)	1.86 (1.28-2.70)	
G3,4	226 (10)	3.23 (2.21-4.72))	
T category			
T1	151 (3)	1 [Reference]	<.001
T2	282 (9)	1.91 (1.55-2.35)	
T3,4	49 (12)	2.01 (1.44-2.81)	
Nodal category			
Negative	121 (3)	1 [Reference]	<.001
Positive	360 (9)	2.31 (1.85-2.87)	
Estrogen receptor			
Positive	459 (6)	1 [Reference]	<.001
Negative	25 (15)	2.18 (1.44-3.31)	
Progesterone receptor			
Positive	293 (5)	1 [Reference]	<.001
Negative	138 (9)	1.64 (1.35-2.00)	
Most extensive surgery			
Mastectomy	316 (8)	1 [Reference]	<.001
Wide local extension	168 (4)	0.59 (0.46-0.74)	
Radiotherapy			
Yes	335 (6)	1 [Reference]	.001
No	146 (6)	0.68 (0.54-0.86)	
Chemotherapy			
Yes	213 (2)	1 [Reference]	.76
No	271 (2)	0.97 (0.77-1.20)	
Endocrine therapy			
Tamoxifen followed by exemestane	246 (6)	1 [Reference]	.08
Exemestane	238 (6)	0.85 (0.71-1.02)	
Persistence of endocrine therapy			
Persistent	425 (2)	1 [Reference]	.001
Nonpersistent	79 (2)	0.64 (0.50-0.84)	

Abbreviation: HR, hazard ratio.
[a] HRs were adjusted for all other covariates mentioned in this table and country.

aged 65-74 years, 1.25; 95% CI, 1.01-1.55; and HR for patients aged ≥75 years, 1.62; 95% CI, 1.22-2.14; $P=.003$). 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; $P=.06$).

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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,[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 2 studies[4,20]; however, others observed an opposite association[5,17,18] or no association at all.[16,19,21]

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

	Death/ Relapse at 5 y, No. (%)	Univariate HR (95% CI)	*P* Value	Multivariable HR (95% CI)[a]	*P* Value
Other-cause mortality, age, y					
<65	64 (1)	1 [Reference]	<.001	1 [Reference]	<.001
65-74	126 (5)	2.99 (2.29-3.89)		2.66 (1.96-3.63)	
≥75	160 (14)	9.96 (7.74-12.80)		7.30 (5.29-10.07)	
Breast cancer relapse, age, y					
<65	512 (10)	1 [Reference]	.002	1 [Reference]	.06
65-74	282 (10)	1.00 (0.87-1.15)		1.07 (0.91-1.25)	
≥75	153 (13)	1.34 (1.13-1.59)		1.29 (1.05-1.60)	

Abbreviation: HR, hazard ratio.
[a] HRs adjusted for country, histological grade, T category, nodal stage, estrogen receptor, progesterone receptor, surgery, radiotherapy, chemotherapy, endocrine therapy, and persistence of endocrine therapy.

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.[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 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.[11] 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 may have an increased toxicity risk when treated with chemotherapy and to a lesser degree with radiotherapy.[26] 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,[27] and older 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 differently to a certain therapy. Polypharmacy can cause drug interactions and

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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 or older died of 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 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 treatment algorithms and virtually complete follow-up. The TEAM trial had very few exclusion criteria and there was no upper age limitation. This enabled us to study age-specific mortality.

Because enrollment in the TEAM trial was restricted to postmenopausal patients 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 nonrandomized therapy. Although analyses were adjusted for nonrandomized 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 with 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 1 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 patients of all ages. Moreover, 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 access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: van de Water, Markopoulos, van de Velde, Putter, Westendorp, Liefers, Jones.
Acquisition of data: van de Velde, Seynaeve, Hasenburg, 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, Hasenburg, Westendorp.
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Statistical analysis: van de Water, Markopoulos, Putter, Bastiaannet, Westendorp.
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Study supervision: Markopoulos, van de Velde, Seynaeve, Rea, Nortier, de Craen, Bastiaannet, Hadji, Westendorp, Liefers, Jones.
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