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ARTICLE

External Validity of a Trial Comprised of Elderly Patients With Hormone Receptor–Positive Breast Cancer

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Background Inclusion in trials is selective, and thus results may not be generalizable to the general population. The aim of this study was to investigate the external validity of randomized clinical trial outcomes for elderly breast cancer patients.

Methods We compared characteristics and outcomes of breast cancer patients (n = 1325) who participated in a randomized clinical trial (Tamoxifen Exemestane Adjuvant Multinational trial) with unselected breast cancer patients of corresponding age from the general population (n = 1056). Dutch patients aged 65 years or older at diagnosis of hormone receptor–positive breast cancer without distant metastases, with either nodal involvement, a tumor greater than 3 cm, or a 1 to 3 cm histological grade III tumor, who completed local therapy were included. Analyses were stratified by age (65–74 years; ≥75 years). Primary outcome was overall mortality. Multivariable Cox proportional hazards models were used to assess the association between covariables and overall mortality. All statistical tests were two-sided.

Results Irrespective of age, patients who participated in the trial had fewer comorbid diseases, a higher socioeconomic status, and smaller tumors (all $P < .001$). In patients aged 65 to 74 years, those who participated in the trial had a similar overall mortality to patients from the general population (multivariable hazard ratio [HR] = 1.08; 95% confidence interval [CI] = 0.73 to 1.60). Alternatively, in patients aged 75 years or older, those who participated in the trial had a lower overall mortality (multivariable HR = 0.72; 95% CI = 0.55 to 0.95; $P = .02$) than patients in the general population.

Conclusions Breast cancer trial participants aged 75 years or older do not represent elderly breast cancer patients of corresponding age from the general population, which hampers the external validity of a trial.

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In developed countries, more than 40% of all newly diagnosed breast cancer patients are aged 65 years or older (1,2). Different factors may play a role in the evaluation of breast cancer treatment in elderly patients as compared with younger patients. Elderly patients suffer from a higher risk of competing mortality (3) and have a lower remaining life expectancy. Consequently, the absolute benefit of anticancer therapy may be smaller, whereas long-term adverse events may be less relevant. Moreover, concurrent disease and medication use may directly affect tolerability of treatment and increase toxicity (4,5). Therefore, it is important to evaluate treatment efficacy and outcomes specifically in elderly patients and not to extrapolate results obtained in younger patients.

Despite comprising a large proportion of all breast cancer patients, the elderly are frequently underrepresented in clinical trials (6–8). This underrepresentation might not be problematic. As long as the included elderly are representative of the general population of elderly breast cancer patients, age-specific subgroup analyses can be extrapolated. However, inclusion of elderly patients is likely to be selective (7).

The aim of this study was to evaluate characteristics and outcomes of elderly breast cancer patients included in a large trial without upper age limit compared with breast cancer patients of corresponding age from the general population.

Methods

We included elderly patients who participated in a clinical trial and elderly breast cancer patients from the general population. To ensure a valid comparison, similar inclusion criteria with regards to tumor and treatment characteristics were applied to all patients.

Patients Who Participated in a Trial

Patients who participated in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial (9,10) were eligible for

inclusion in our study. Because 5-year results of the TEAM trial showed no statistically significant differences in efficacy endpoints between the two treatment arms (9), we were able to conduct our study regardless of randomized treatment. Between January 2001 and January 2006, 9766 postmenopausal women with hormone receptor–positive breast cancer without distant metastases, who completed local therapy with curative intent, were randomly assigned to either exemestane for 5 years or to a sequential regimen consisting of tamoxifen followed by exemestane for a total of 5 years. Inclusion for patients in the Netherlands was restricted to those who either had nodal involvement, a tumor greater than 3 cm, or a histological grade III tumor of 1 to 3 cm (10).

Patients From the General Population

From the Netherlands Cancer Registry, we identified all incident breast cancer patients aged 65 years or older who were diagnosed in the geographically defined Comprehensive Cancer Center Region West in the Netherlands between January 1997 and December 2004. By means of chart review by trained personnel, additional information on patient characteristics, tumor characteristics, treatment, follow-up, and outcome were recorded (11).

Inclusion Criteria

For a proper comparison between patients who participate in a trial and patients from the general population, similar inclusion criteria were applied to all patients. Hence, we restricted inclusion of patients who participated in a trial to patients from the Netherlands who were aged 65 years or older at diagnosis. Likewise, the inclusion criteria that were used in the trial were applied to patients from the general population; those who had hormone receptor–positive disease without distant metastases and a tumor size greater than 3 cm, a histological grade III tumor of 1 to 3 cm, or nodal involvement were eligible. In addition, they had to have received breast surgery with curative intent.

In all patients, prespecified forms that included free-text fields were used for data collection. Comorbidity was defined as presence of comorbidity at time of diagnosis. Comorbid diseases were categorized into presence or absence of the main categories included in the 10th edition of the *International Statistical Classification of Diseases and Related Health Problems*—namely, endocrine, nutritional and metabolic diseases (chapter 4); mental and behavioral disorders (chapter 5); diseases of the nervous system (chapter 6); diseases of the circulatory system (chapter 9); diseases of the respiratory system (chapter 10); diseases of the digestive system (chapter 11); and diseases of the musculoskeletal and connective tissue (chapter 13) (12). In addition, comorbid diseases were categorized by number (n = 0–1, 2–4, or ≥5 comorbid diseases). Socioeconomic status was assigned using an area-based measure according to place of residence at the time of diagnosis. The area-based socioeconomic status was provided by the Netherlands Institute for Social Research and is based on data about income, employment, and education (13). In our study, socioeconomic status was categorized in tertiles (low, intermediate, and high socioeconomic status, respectively).

For the patients included in the TEAM trial, appropriate approvals from the ethical committee were obtained. All patients provided written informed consent.

Statistical Analyses

Statistical analyses were performed using SPSS 20.0 (SPSS, Chicago, IL) and Stata SE 12.0 (StataCorp LP, College Station, TX). In line with previous publications and with recommendations of the International Society of Geriatric Oncology (SIOG) (14,15), the analyses were stratified by age at diagnosis (65–74 years; ≥75 years). To compare proportional differences in patient, tumor, and treatment characteristics between patients who participated in a trial and patients from the general population, the Pearson χ^2 test was used.

Primary outcome was overall mortality, defined as death from any cause. Vital status was established either directly from the patient's medical record or through linkage with the municipal population registries (follow-up until January 1, 2011). Follow-up was truncated at 5 years to accommodate differences in total follow-up duration. Cumulative incidence of death was estimated by $1-\hat{S}(t)$ where $\hat{S}(t)$ is the Kaplan–Meier estimator for the probability of survival at time (t), based on the life tables (16). Corresponding 95% confidence intervals (CIs) were calculated as the cumulative incidence at t(x) ± 1.96 × standard error. Cox proportional hazard models were used to evaluate the association between covariables and overall mortality. For both age groups, the proportional hazard assumption was evaluated by the link test ($P = .45$; $P = .89$, respectively) and based on the analysis of the Schoenfeld residuals ($P = .20$; $P = .75$, respectively) (17).

Because breast cancer mortality contributes to overall mortality, disparities in breast cancer outcome may affect the primary endpoint. Therefore we evaluated distant breast cancer recurrence, which was defined as recurrence in skeleton, skin, liver, lung, brain, or other distant localization, as a secondary endpoint. We focused on distant recurrence because cause of death is more difficult to attribute to a certain cause with increasing age (18,19) and distant recurrence is a valid proxy for death due to breast cancer (20). Detection method of a breast cancer recurrence was similar for all patients. Cause-specific outcomes may be influenced by the risk of competing endpoints; for example, an individual who dies is no longer at risk for a distant breast cancer recurrence. This risk of competing endpoints may be particularly present in older populations (3). Therefore, distant breast cancer recurrence was estimated by regression analyses according to Fine and Gray (21,22). A Fine and Gray analysis is used to assess the risk of a distant breast cancer recurrence while taking into account the risks of reaching other, competing endpoints. Competing endpoints were a locoregional recurrence (recurrence in the ipsilateral breast or chest wall, ipsilateral axillary, or supraclavicular lymph node[s]), contralateral breast cancer, and death due to any cause.

Covariables were included in the multivariable model if they were judged to be clinically relevant, regardless of statistical significance. The fully adjusted multivariable model included tumor characteristics (histological grade [Bloom Richardson grade I, II, III, unknown], T stage [T1/T2, T3/T4, unknown], nodal stage [negative, positive, unknown]), treatment characteristics (most extensive surgery [breast conserving surgery, mastectomy], radiotherapy [yes, no, unknown], endocrine therapy [yes, no], and chemotherapy [yes, no, unknown]), and patient characteristics (age [continuous], year of diagnosis [continuous], socioeconomic status [in tertiles, unknown], and number of comorbidities [0–1, 2–4, ≥5]). Sensitivity analyses were performed excluding missing values. All statistical tests were two-sided; *P* values less than .05 were considered to be statistically significant.

Results

Overall, we included 1325 breast cancer patients who participated in a trial and 1056 unselected breast cancer patients from the general population. The mean age of patients who participated in a trial was 73.5 years (standard deviation [SD] = 5.7 years) vs 76.7 years (SD = 7.1 years) for patients from the general population ($P < .001$). First, we investigated whether the phenotype of patients who participated in a clinical trial differs from the phenotype of patients from the general population (Table 1). In both age groups, patients who participated in a trial had fewer comorbid diseases and more often had a high socioeconomic status. Moreover, patients who participated in a trial had smaller tumors (all $P < .001$).

Second, we investigated whether treatment of patients who participated in a clinical trial differs from treatment of patients from the general population (Table 2). Needless to say, all patients who participated in the trial received endocrine therapy, whereas in both age groups of patients from the general population 82% received endocrine therapy despite having hormone receptor–positive disease and an indication for endocrine therapy. In patients aged 75 years or older, patients who participated in a trial more often had breast-conserving surgery as definitive breast surgery ($P < .001$).

Figure 1, A and B, shows the unadjusted cumulative incidence of death for patients who participated in a trial and for patients from the general population by age at diagnosis. In patients aged 65 to 74 years, 5-year cumulative incidence of death was 14% (95% CI = 9 to 16) for patients who participated in a trial and 19% (95% CI = 16 to 23) for patients from the general population. For patients aged 75 years or older, 5-year cumulative incidence of death was 28% (95% CI = 23 to 32) for patients who participated in a trial and 48% (95% CI = 44 to 52) for patients from the general population.

Overall mortality of patients aged 65 to 74 years was lower for patients who participated in a trial (univariate hazard ratio [HR] = 0.65; 95% CI = 0.50 to 0.86). To explore whether this difference in mortality could be explained by unequal distributions in patient, tumor, and treatment characteristics, multivariable analyses were performed. The fully adjusted model (Table 3) showed

Table 1. Patient and tumor characteristics of elderly breast cancer patients who participated in a trial, as compared with those of elderly breast cancer patients from the general population*

Patient and tumor characteristics	Aged 65–74 years					Aged ≥75 years				
	Trial participants (n = 852)		General population (n = 467)		P†	Trial participants (n = 473)		General population (n = 589)		P†
	No.	%	No.	%		No.	%	No.	%	
Socioeconomic status, tertiles					<.001					<.001
1, lowest	200	23.5	205	43.9		108	22.8	250	42.4	
2	177	20.8	96	20.6		106	22.4	122	20.7	
3	419	49.2	165	35.3		238	50.3	217	36.8	
Unknown	56	6.6	1	0.2		21	4.4	0	0	
Number of comorbidities					<.001					<.001
0–1	655	76.9	273	58.5		306	64.7	262	44.5	
2–4	193	22.7	171	36.6		165	34.9	263	44.7	
≥5	4	0.5	23	4.9		2	0.4	64	10.9	
Presence of comorbidity										
Endocrine	178	20.9	130	27.8	.005	105	22.2	188	31.9	<.001
Psychiatric	4	0.5	41	8.8	<.001	7	1.5	72	12.5	<.001
Neurological	31	3.6	38	8.1	<.001	38	8.0	79	13.4	<.001
Circulatory	334	39.2	225	48.2	.002	220	46.5	334	39.2	<.001
Respiratory	54	6.3	48	10.3	.01	30	6.3	67	11.4	.005
Gastrointestinal	24	2.8	54	11.6	<.001	16	3.4	83	14.1	<.001
Musculoskeletal	104	12.2	86	18.4	.002	100	21.1	167	28.4	.008
Histological grade, BR					<.001					<.001
Grade 1	133	15.6	37	7.9		69	14.6	67	11.4	
Grade 2	380	44.6	138	29.6		225	47.6	172	29.2	
Grade 3	286	33.6	181	38.8		134	28.3	193	32.8	
Unknown	53	6.2	111	23.8		45	9.5	157	26.7	
T stage					<.001					<.001
T1, T2	794	93.2	404	86.5		429	90.7	466	79.1	
T3, T4	58	6.8	61	13.1		44	9.3	120	20.4	
Unknown	0	0	2	0.4		0	0	3	0.5	
Nodal status					.09					.53
Negative	269	31.6	126	27		149	31.5	181	307	
Positive	583	68.4	340	72.8		322	68.1	402	68.3	
Unknown	0	0	1	0.2		2	0.4	6	1	

* BR = Bloom Richardson.

† To test for statistical differences in proportions, the Pearson χ^2 test was used. All statistical tests were two-sided. *P* values less than .05 were considered statistically significant.

Table 2. Treatment characteristics of elderly breast cancer patients who participated in a trial, as compared with elderly breast cancer patients from the general population*

Treatment characteristics	Aged 65–74 years					Aged ≥75 years				
	Trial participants (n = 852)		General population (n = 467)			Trial participants (n = 473)		General population (n = 589)		
	No.	%	No.	%	P†	No.	%	No.	%	P†
Most extended surgery					.16					<.001
BCS	383	45.0	191	40.9		114	24.1	75	12.7	
Mastectomy	469	55.0	276	59.1		359	75.9	514	87.3	
Radiotherapy					.45					.052
Yes	500	58.7	288	61.7		211	44.6	227	38.5	
No	351	41.2	179	38.3		262	55.4	362	61.5	
Unknown	1	0.1	0	0		0	0	0	0	
Endocrine therapy					<.001					<.001
Yes	852	100	384	82.2		473	100	480	81.5	
No	0	0	83	17.8		0	0	109	18.5	
Chemotherapy					.054					<.001
Yes	63	7.4	52	11.1		0	0	19	3.2	
No	788	92.5	415	88.9		473	100	570	98.6	
Unknown	1	0.1	0	0		0	0	0	0	

* BCS = breast-conserving surgery.

† To test for statistical differences in proportions, the Pearson χ^2 test was used. All statistical tests were two-sided. *P* values less than .05 were considered statistically significant.

that after adjustment for tumor, treatment, and patient characteristics, the hazard ratio attenuated toward 1 (HR = 1.08; 95% CI = 0.73 to 1.60). The adjusted cumulative incidence of death is depicted in Figure 1C.

Patients aged 75 years or older who participated in a trial also had a lower overall mortality as compared with patients of corresponding age from the general population (univariate HR = 0.49; 95% CI = 0.39 to 0.60). These differences could not be explained by unequal distributions in patient, tumor, and treatment characteristics; multivariable analysis consistently showed a lower overall mortality (HR = 0.72; 95% CI = 0.55 to 0.95; *P* = .02). The adjusted cumulative incidence of death is depicted in Figure 1D.

To explore whether differences in overall mortality could be explained by differences in breast cancer outcome, we evaluated the risk of a distant recurrence (Table 4). Irrespective of age, multivariable analyses did not reveal any differences. Of note, in both age groups, the absolute number of patients who developed a distant recurrence was exceeded by the number of patients who died. Among patients aged 75 years or older, 124 trial participants and 281 patients from the general population died during 5 years of follow-up. Fifty-four trial participants and 74 patients from the general population developed a distant recurrence. These data confirm that in those aged 75 years or older, the observed difference in overall mortality between patients who participated in a trial and patients from the general population is likely to resemble a non–breast-cancer-driven difference in overall fitness.

Discussion

To warrant the internal validity of a clinical trial, inclusion of patients into a trial is often selective, although this may compromise the external validity of the trial (23). Indeed, we showed that patients who participated in a clinical trial had more favorable patient and tumor characteristics than patients from the general population. In patients aged 65 to 74 years, those who participated in the trial had a similar overall mortality as patients from the general population after adjustment. Thus, selective inclusion can be overcome by taking into account patient, tumor, and treatment characteristics. Selection of patients into a trial may be more pronounced with increasing age, given the larger heterogeneity of patients with increasing age. This hypothesis was confirmed in our study; we showed that in patients aged 75 years or older, differences in overall mortality could not be explained by patient, tumor, and treatment characteristics. Therefore other, unmeasured mechanisms may have played a role in the selection of elderly patients into a trial.

A selective inclusion of patients into a trial is multifactorial. First, eligibility criteria may hamper inclusion of elderly patients in general and inclusion of certain elderly in particular. Patients were ineligible for the TEAM trial if they had a malignancy within 5 years before breast cancer diagnosis, an Eastern Cooperative Oncology Group performance status of greater than 2, substantial cardiac disease, or other illness interfering with study participation and follow-up (10). Others have published about the impact of eligibility criteria on the inclusion in trials (24). Of all clinical trials published in 2008 in five major medical journals, 20% excluded patients based on age (7). In the remaining trials, almost half of the studies excluded patients with age-related diseases, which could disproportionally impact inclusion of certain elderly patients. Next to eligibility criteria hampering inclusion of elderly patients, physician factors (25–27), patient factors (26), and factors related to trial logistics may affect participation (25). From a patient point of view, age has not been shown to be a statistically significant predictor as

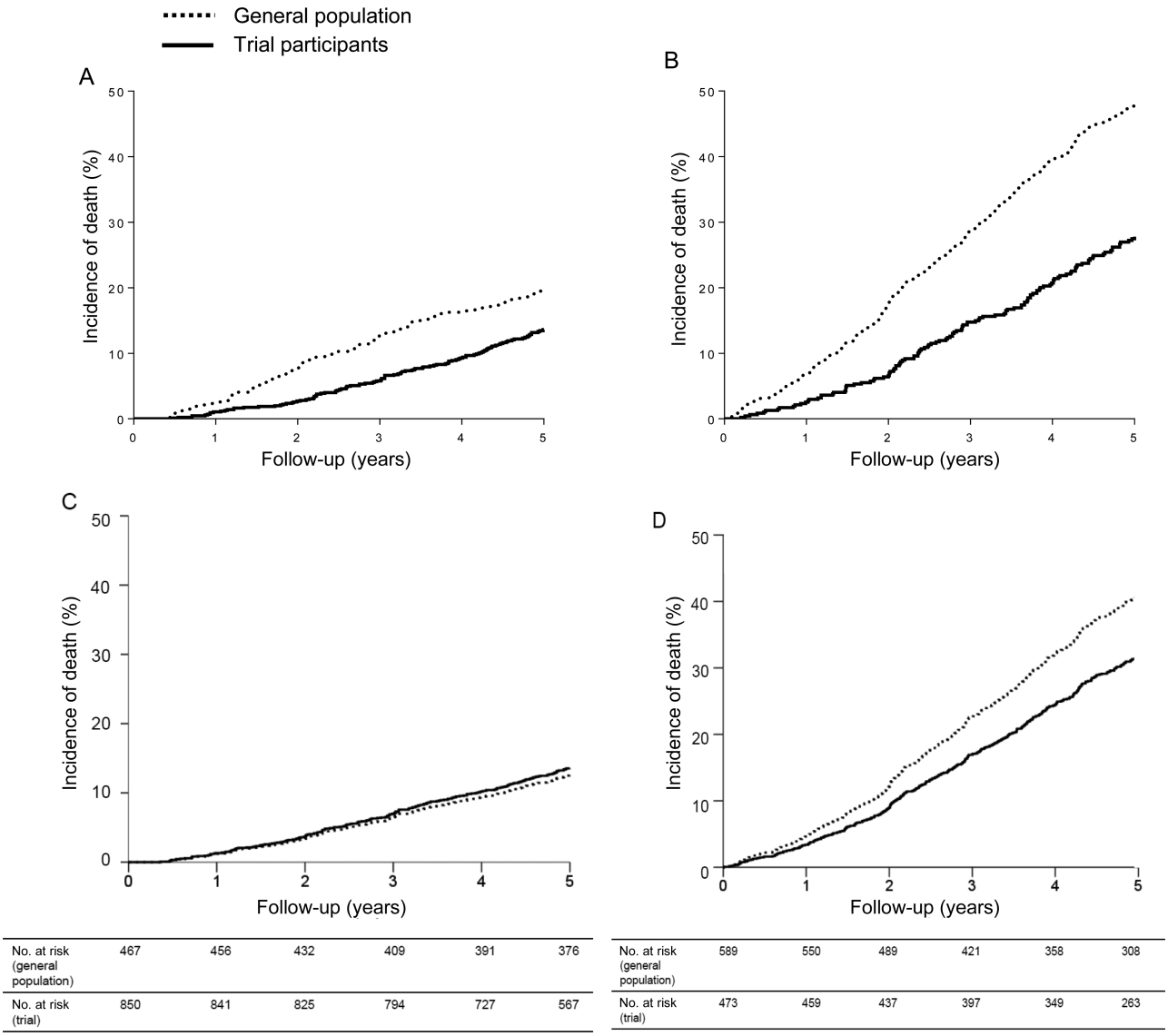

Figure 1. Univariate and multivariable cumulative incidence of death in elderly patients who participated in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial compared with those in the general population. **A**) Unadjusted cumulative incidence of death of elderly breast cancer patients aged 65 to 74 years who participated in a trial, as compared with elderly breast cancer patients from the general population. Cumulative incidence of death was estimated by $1-\hat{S}(t)$ where $\hat{S}(t)$ is the Kaplan–Meier estimator for the probability of survival at time (t), based on the life tables. **B**) Unadjusted cumulative incidence of death of elderly breast cancer patients aged 75 years or older who participated in a trial, as compared with elderly breast cancer patients from the general population. Cumulative incidence of death was estimated by $1-\hat{S}(t)$ where $\hat{S}(t)$ is the Kaplan–Meier estimator for the probability of survival at time (t), based on the life tables. **C**) Adjusted cumulative incidence of death of elderly breast cancer patients aged 65 to 74 years who participated in a trial, as compared with elderly breast cancer patients from the general population, based on multivariable Cox regression analysis. **D**) Adjusted cumulative incidence of death of elderly breast cancer patients aged 75 years or older who participated in a trial, as compared with elderly breast cancer patients from the general population, based on multivariable Cox regression analysis. All statistical tests were two-sided.

to whether a patient would participate once the patient has been offered a trial (26,28).

To summarize, the lower overall mortality of patients aged 75 years or older who participated in a trial may be the result of selective inclusion of patients into a trial. As was shown, those who participated in a trial had, among other characteristics, fewer comorbid diseases. Additionally, participation in a trial in itself may result in lower overall mortality. One may argue that more attention is being paid to treatment of comorbid disease of elderly patients who participate in a trial, as compared with those from the general population, which may decrease overall mortality.

Others have published on the external validity of clinical trials (23). The novelty of our study is that we were able to perform a head-to-head comparison of patients participating in a clinical trial and patients from the general population. This way we could pinpoint that external validity is compromised for patients aged 75 years or older in particular. Our study has some limitations. By

Table 3. Overall mortality for elderly breast cancer patients who participated in a trial, as compared with elderly patients from the general population, fully adjusted model*

Patients and covariables	Patients aged 65–74 years			Patients aged ≥75 years		
	5-years death, No.	Multivariable† HR (95% CI)	*P*‡	5-years death, No.	Multivariable† HR (95% CI)	*P*‡
Patients			.69			.02
General population	91	1.00 (referent)		281	1.00 (referent)	
Trial participants	110	1.08 (0.73 to 1.60)		124	0.72 (0.55 to 0.95)	
Socioeconomic status			.94			.10
Low	58	1.00 (reference)		112	1.00 (referent)	
Intermediate	65	0.97 (0.65 to 1.43)		124	1.03 (0.78 to 1.36)	
High	69	0.90 (0.65 to 1.43)		162	1.27 (1.01 to 1.60)	
Missing	9	0.87 (0.42 to 1.80)		7	1.74 (0.80 to 3.82)	
Number of comorbidities			.01			.12
0–1	121	1.00 (referent)		199	1.00 (referent)	
2–4	75	1.58 (1.18 to 2.11)		171	1.13 (0.92 to 1.40)	
≥5	5	1.18 (0.47 to 2.93)		35	1.46 (1.00 to 2.12)	
Histological grade, BR			<.001			.007
Grade 1	18	1.00 (referent)		50	1.00 (referent)	
Grade 2	55	0.97 (0.57 to 1.65)		126	0.90 (0.65 to 1.26)	
Grade 3	92	2.19 (1.30 to 3.69)		143	1.32 (0.95 to 1.84)	
Unknown	36	1.81 (0.99 to 3.31)		86	0.89 (0.61 to 1.29)	
T stage			.66			.002
T1, T2	169	1.00 (referent)		313	1.00 (referent)	
T3, T4	31	1.22 (0.80 to 1.87)		91	1.56 (1.22 to 2.00)	
Unknown	—	NA		1	0.70 (0.10 to 5.09)	
Nodal stage			.007			.06
Negative	44	1.00 (referent)		112	1.00 (referent)	
Positive	156	1.82 (1.26 to 2.63)		288	1.32 (1.05 to 1.66)	
Unknown	—	NA		5	1.25 (0.50 to 3.16)	
Most extensive surgery			.001			.52
BCS	58	1.00 (referent)		49	1.00 (referent)	
Mastectomy	143	2.03 (1.35 to 3.04)		356	1.12 (0.80 to 1.57)	
Radiotherapy			.45			.33
Yes	115	1.00 (referent)		148	1.00 (referent)	
No	86	1.27 (0.88 to 1.84)		257	0.89 (0.70 to 1.13)	
Unknown	—	NA		—	NA	
Endocrine therapy			.048			.23
Yes	182	1.00 (referent)		347	1.00 (referent)	
No	19	0.59 (0.35 to 1.00)		58	0.83 (0.61 to 1.13)	
Chemotherapy			.57			.99
Yes	22	1.00 (referent)		10	1.00 (referent)	
No	179	1.15 (0.71 to 1.88)		395	1.00 (0.52 to 1.91)	
Unknown	—	NA		—	NA	

* BCS = breast-conserving surgery; BR = Bloom Richardson; CI = confidence interval; HR = hazard ratio; NA = not applicable.

† Hazard ratios adjusted for all other covariables mentioned in the table, and age (continuous) and year of diagnosis (continuous).

‡ Cox proportional hazard models were used to evaluate the association between covariables and overall mortality. All statistical tests were two-sided. *P* values less than .05 were considered to be statistically significant.

applying identical inclusion criteria, we aimed to construct similar groups of patients. However, differences in design and data collection may have influenced our results by misclassification of baseline characteristics and follow-up data. Although prespecified forms that included free-text fields were used for all patients and baseline characteristics were reported extensively in the medical files of patients from the general population, we cannot exclude possible differences due to the prospective and retrospective nature of data collection. A strength of this study is that systematic misclassification of the primary endpoint of overall mortality is unlikely; vital status was established through linkage with the municipal population registries for all patients. Regarding the secondary endpoint, the method of detection of a breast cancer recurrence was similar for all patients. Of note, those who participated in the trial had strict follow-up schemes, whereas this may not always be accomplished in general practice. Therefore, we cannot exclude the possibility of underdiagnosis of breast cancer recurrence among patients from the general population. Regarding overall mortality, sample size was sufficient to detect a difference among patients aged 75 years or older. Among patients aged 65 to 74 years, given the confidence interval of the multivariable analysis (95% CI = 0.73 to 1.60), we cannot exclude that those who participate in a trial do have a different overall mortality than patients from the general population.Regarding the secondary endpoint, sample size may have been insufficient. However, it was also shown that the absolute number of patients who developed a distant recurrence

Table 4. Risk of distant breast cancer recurrence for elderly breast cancer patients who participated in a trial, as compared with elderly breast cancer patients from the general population*

Age group	5-years distant recurrence No.	5-years competing events† No.	Univariate HR (95% CI)	*P*§	Multivariable HR‡ (95% CI)	*P*§
65–74 years				.05		.51
General population (n = 467)	61	59	1.00 (referent)		1.00 (referent)	
Trial participants (n = 852)	84	62	0.72 (0.52 to 1.00)		1.17 (0.73 to 1.87)	
≥75 years				.45		.28
General population (n = 589)	74	228	1.00 (referent)		1.00 (referent)	
Trial participants (n = 473)	54	95	0.87 (0.66 to 1.24)		1.33 (0.79 to 2.34)	

* CI = confidence interval; HR = hazard ratio.

† Competing events are comprised of intercurrent death; locoregional recurrence as first site of recurrence; and contralateral breast cancer.

‡ Multivariable hazard ratios were adjusted for histological grade, T stage, nodal stage, most extensive surgery, radiotherapy, endocrine therapy, chemotherapy, socioeconomic status, comorbidity, age, year of diagnosis.

§ Fine and Gray regression models were used to evaluate the association between covariables and distant breast cancer recurrence. All statistical tests were two-sided. *P* values less than .05 were considered statistically significant.

was greatly exceeded by the absolute number of patients who died, especially in patients aged 75 years or older. Therefore, although the direct comparison of distant breast cancer recurrence between patients who participated in a trial and patients from the general population is possibly underpowered, the secondary endpoint does strengthen the main conclusion that the observed higher overall mortality in patients aged 75 years or older from the general population is likely to resemble a non–breast-cancer-driven difference in overall fitness.

As compared with other randomized clinical trials, the TEAM trial had relatively few eligibility criteria and was without an upper age limitation, enabling enrollment of many elderly patients (9). Therefore it is expected that the discrepancy between trial patients and patients from the general population will be present in other breast cancer trials that include elderly patients. Investigators and clinicians may need to pay more attention to actively including a representative sample of patients aged 75 years or older into clinical trials.

Because treatment guidelines are mainly based on clinical trial results, the evidence base for treatment in patients aged 75 years or older may be limited. However, it is unlikely that clinical trials are sufficient to fill this evidence gap. Even in the absence of eligibility criteria, it is expected that elderly included in a trial will be selected (26,27,29). Moreover, the large heterogeneity in the elderly population makes it difficult to conduct clinical trials that include a representative sample of the general population; even with inclusion of large numbers, it remains a challenge to create comparable study arms. Therefore different study designs may be warranted. Restriction in research topics, design, and analysis may give observational research the chance to be as credible as randomized evidence (30). Moreover, observational, population-based data reflect the heterogeneity of the general population. Among others, international comparisons of treatment strategies, using country as an instrumental variable, may increase insight into adequate treatment for different groups of elderly breast cancer patients.

Inclusion in a breast cancer trial is more selective with increasing age. Breast cancer patients aged 75 years or older who participate in a trial are not representative of breast cancer patients of corresponding age from the general population, which may hamper the external validity of a trial; breast cancer trial results may not necessarily be extrapolated to the general breast cancer patient with corresponding age.

References

1. Cancer of the Breast. *SEER Stat Fact Sheets*. http://seer.cancer.gov/statfacts/html/breast.html#incidence-mortality. Accessed September 6, 2012.
2. DeSantis C, Siegel R, Bandi P, Jemal A. Breast cancer statistics, 2011. *CA Cancer J Clin*. 2011;61(6):409–418.
3. Mell LK, Jeong JH, Nichols MA, Polite BN, Weichselbaum RR, Chmura SJ. Predictors of competing mortality in early breast cancer. *Cancer*. 2010;116(23):5365–5373.
4. Aapro M, Bernard-Marty C, Brain EG, et al. Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper. *Ann Oncol*. 2011;22(2):257–267.
5. Sokol KC, Knudsen JF, Li MM. Polypharmacy in older oncology patients and the need for an interdisciplinary approach to side-effect management. *J Clin Pharm Ther*. 2007;32(2):169–175.
6. Lewis JH, Kilgore ML, Goldman DP, et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol*. 2003;21(7):1383–1389.
7. Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA. Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. *J Gen Intern Med*. 2011;26(7):783–790.
8. Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr, Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med*. 1999;341(27):2061–2067.
9. van de Velde CJ, Rea D, Seynaeve C, et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. *Lancet*. 2011;377(9762):321–331.
10. van Nes JG, Seynaeve C, Jones S, et al. Variations in locoregional therapy in postmenopausal patients with early breast cancer treated in different countries. *Br J Surg*. 2010;97(5):671–679.
11. de Glas NA, Kiderlen M, Bastiaannet E, et al. Postoperative complications and survival of elderly breast cancer patients: a FOCUS study analysis. *Breast Cancer Res Treat*. 2013;138(2):561–569.
12. World Health Organization. *The International Statistical Classification of Diseases and Related Health Problems ICD-10*; 2010. http://apps.who.int/classifications/icd10/browse/2010/en. Accessed April 1, 2013.
13. Tesser P, Van Praag C, Van Dugteren F, Herweijer L, Van der Wouden H. *Rapportage minderheden 1995*. Rijswijk/Den Haag, the Netherlands: Sociaal en Cultureel Planbureau/VUGA; 2013.
14. Conference communication: age categorization proposed at oral session, accessible for members only. Paper discussed at International Society of Geriatric Oncology Annual Meeting; October 15–17, 2009; Berlin, Germany.
15. van de Water W, Markopoulos C, van de Velde CJ, et al. Association between age at diagnosis and disease-specific mortality among

postmenopausal women with hormone receptor-positive breast cancer. *JAMA*. 2012;307(6):590–597.
16. Andersen PK, Geskus RB, de WT, Putter H. Competing risks in epidemiology: possibilities and pitfalls. *Int J Epidemiol*. 2012;41(3):861–870.
17. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika*. 1982;69(1):239–241.
18. Lu TH, Shih TP, Lee MC, Chou MC, Lin CK. Diversity in death certification: a case vignette approach. *J Clin Epidemiol*. 2001;54(11):1086–1093.
19. Harteloh P, de Bruin K, Kardaun J. The reliability of cause-of-death coding in the Netherlands. *Eur J Epidemiol*. 2010;25(8):531–538.
20. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365(9472):1687–1717.
21. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;(94):496–509.
22. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. *Stat Med*. 2007;26(11):2389–2430.
23. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?" *Lancet*. 2005;365(9453):82–93.
24. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *JAMA*. 2007;297(11):1233–1240.
25. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol*. 2005;23(13):3112–3124.
26. Kemeny MM, Peterson BL, Kornblith AB, et al. Barriers to clinical trial participation by older women with breast cancer. *J Clin Oncol*. 2003;21(12):2268–2275.
27. Kornblith AB, Kemeny M, Peterson BL, et al. Survey of oncologists' perceptions of barriers to accrual of older patients with breast carcinoma to clinical trials. *Cancer*. 2002;95(5):989–996.
28. Townsley CA, Chan KK, Pond GR, Marquez C, Siu LL, Straus SE. Understanding the attitudes of the elderly towards enrolment into cancer clinical trials. *BMC Cancer.* 2006;6:34.
29. Hamaker ME, Seynaeve C, Nortier JW, et al. Slow accrual of elderly patients with metastatic breast cancer in the Dutch multicentre OMEGA study. *Breast*. 2013;22(4):556–559.
30. Vandenbroucke JP. When are observational studies as credible as randomised trials? *Lancet*. 2004;363(9422):1728–1731.

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Notes

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