Chapter 3

The external validity of a clinical trial comprising elderly patients with hormone receptor positive breast cancer

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Abstract

Background

Despite comprising a large proportion of all breast cancer patients, elderly are underrepresented in clinical trials. Moreover, inclusion is likely to be selective. The aim of this study was to investigate to what extent elderly breast cancer patients in a randomized clinical trial are selected as compared to breast cancer patients from the general population.

Methods

We compared characteristics and outcome of breast cancer patients who participated in a randomized clinical trial (Tamoxifen Exemestane Adjuvant Multinational trial) with unselected breast cancer patients of corresponding age from the general population. Dutch patients aged ≥65 years at diagnosis of hormone receptor positive breast cancer without distant metastases, with either nodal involvement, a tumor >3cm, or a 1-3cm histological grade III tumor, who completed local therapy were included. Analyses were stratified by age (65-75 years; ≥75 years). Primary outcome was overall mortality.

Results

We included 1,325 breast cancer patients who participated in a trial and 1,056 breast cancer patients from the general population. Irrespective of age, patients who participated in the trial had fewer comorbid diseases, a higher socio-economic status, and smaller tumors (all p-values <0.001). In patients aged 65-75 years, those who participated in the trial had a similar overall mortality as patients from the general population after adjustment for patient, tumor, and treatment characteristics (hazard ratio 1.08 (95% confidence interval (CI) 0.73-1.60)). Contrary, in patients aged ≥75 years, those who participated in the trial had a lower overall mortality (multivariable hazard ratio 0.72 (95% CI 0.55-0.95)).

Conclusion

Breast cancer trial participants aged ≥75 years do not represent elderly breast cancer patients of corresponding age from the general population. This may be explained by selective inclusion into a trial, which hampers the external validity of the trial. Hence, breast cancer trial results may not necessarily be extrapolated to the general elderly breast cancer patient aged ≥75 years.

Introduction

In developed countries, over 40% of all breast cancer patients is 65 years or older[1;2]. Different factors may play a role in the evaluation of breast cancer treatment in elderly as compared to younger patients. Elderly 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, while 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 which were obtained in younger patients.

Despite comprising a large proportion of all breast cancer patients, 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 the current study was to evaluate to what extent elderly breast cancer patients in a trial are selected as compared to breast cancer patients from the general population. Therefore, characteristics and outcome of elderly breast cancer patients who participated in a large trial without upper age limit, were compared with those of 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 Adfuvant Multinational trial[9;10] were eligible for inclusion in the current study. Because five-years results of the TEAM trial showed no significant differences in efficacy endpoints between both treatment arms[9], we were able to conduct the current study regardless of randomized treatment. Between January 2001 and January 2006, 9,766 postmenopausal women with hormone receptor positive breast cancer without distant metastases, who completed local therapy with curative intent, were randomized to either exemestane 25 mg daily for 5 years or to a sequential regimen consisting of tamoxifen 20 mg daily for 2.5–3 years, followed by exemestane 25 mg daily for 2.5–2 years. Inclusion for patients in The Netherlands was restricted to those who either had nodal involvement, a tumor of >3cm, or a histological grade III tumor of 1-3cm[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 65 years and 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 either one of the following; a tumor size of >3cm, a histological grade III tumor of 1-3cm, or nodal involvement, were eligible. In addition, they had to have received breast surgery with curative intent.

In all patients, prespecified forms including 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 (ICD-10), namely endocrine, nutritional and metabolic diseases (chapter IV); mental and behavioural disorders (chapter V); diseases of the nervous system (chapter VI); diseases of the circulatory system (chapter IX); diseases of the respiratory system (chapter X); diseases of the digestive system (chapter XI); and diseases of the musculoskeletal and connective tissue (chapter XIII)[12]. In addition, comorbid diseases were categorized by number (0-1; 2-4; 5 or more comorbid diseases). Socio-economic status (SES) was assigned using an area-based measure according to place of residence at the time of diagnosis. The area-based SES was provided by the Netherlands Institute for Social Research, and is based on data concerning income, employment, and education[13]. In the current study, SES was categorized in tertiles (low, intermediate and high SES respectively).

Statistical analyses

Statistical analyses were performed using SPSS 20.0 (SPSS, Chicago, IL) and Stata SE 12.0. In line with previous publications and in line with SIOG recommendations[14;15], the analyses were stratified by age at diagnosis (65-75 years and 75 years or older). 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.

The 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 1st 2011). Follow-up was truncated at five years to accommodate differences in total follow-up duration. Cumulative incidence of death was estimated by $1 - \widehat{S}(t)$ where $\widehat{S}(t)$ is the Kaplan–Meier estimator for the probability of survival at time (t), based on the life tables[16]. Corresponding 95% confidence intervals were calculated as the cumulative incidence at t(x) ± 1.96 * standard error. Cox proportional hazard models were used to evaluate the association between covariates and overall mortality. For both age groups, the proportional hazard assumption was evaluated by the link test (p=0.45; p=0.89 respectively) and based on the analysis of the Schoenfeld residuals[17] (p=0.20; p=0.75 respectively).

As breast cancer mortality contributes to overall mortality, disparities in breast cancer outcome may affect the primary endpoint. Therefore we evaluated distant breast cancer recurrence as secondary endpoint, which was defined as recurrence in skeleton, skin, liver, lung, brain, or other distant localization. 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 present in older populations in particular[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.

Covariates were included in the multivariable model if they were judged to be clinically relevant. 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], socio-economic 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 <.05 were considered to be statistically significant.

Results

Overall, we included 1,325 breast cancer patients who participated in a trial, and 1,056 unselected breast cancer patients from the general population. Mean age of patients who participated in a trial was 73.5 years, (standard deviation (SD) 5.7 years), versus 76.7 years (SD 7.1 years) in patients from the general population (p<0.001). First, we investigated whether the

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

	Age 65-75 years					Age ≥75 years				
	Trial participants (n=852)		General population (n=467)		p	Trial participants (n=473)		General population (n=589)		p
	n	%	n	%		n	%	n	%	
Socio-economic status (tertiles)					**<0.001**					**<0.001**
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					**<0.001**					**<0.001**
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	**0.005**	105	22.2	188	31.9	**<0.001**
Psychiatric	4	0.5	41	8.8	**<0.001**	7	1.5	72	12.5	**<0.001**
Neurological	31	3.6	38	8.1	**<0.001**	38	8.0	79	13.4	**<0.001**
Circulatory	334	39.2	225	48.2	**0.002**	220	46.5	334	39.2	**<0.001**
Respiratory	54	6.3	48	10.3	**0.013**	30	6.3	67	11.4	**0.005**
Gastro-intestinal	24	2.8	54	11.6	**<0.001**	16	3.4	83	14.1	**<0.001**
Musculoskeletal	104	12.2	86	18.4	**0.002**	100	21.1	167	28.4	**0.008**
Histological grade (BR)					**<0.001**					**<0.001**
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					**<0.001**					**<0.001**
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					0.092					0.525
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.

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 socio-economic status. Moreover, patients who participated in a trial had smaller tumors.

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 82% of patients from the general population 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 the most extended type of breast surgery.

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

	Age 65-75 years					Age ≥75 years				
	Trial participants (n=852)		General population (n=467)		p	Trial participants (n=473)		General population (n=589)		p
	n	%	n	%		n	%	n	%	
Most extended surgery					0.164					**<0.001**
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					0.446					0.052
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					**<0.001**					**<0.001**
Yes	852	100	384	82.2		473	100	480	81.5	
No	0	0	83	17.8		0	0	109	18.5	
Chemotherapy					0.054					**<0.001**
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.

Figure 1a and b show 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 65-75 years, five-years cumulative incidence of death was 14% (95% CI 9-16) for patients who participated in a trial and 19% (95% CI 16-23) for patients from the general population. For patients aged 75 years or older, five-years cumulative incidence of death was 28% (95% CI 23-32) and 48% (95% CI 44-52), respectively.

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

	Patients aged 65-75 years			Patients aged ≥75 years		
	5-years death, n	Multivariable* HR (95% CI)	p	5-years death, n	Multivariable* HR (95% CI)	p
Patients			0.693			**0.019**
General population	91	1 (reference)		281	1 (reference)	
Trial participants	110	1.08 (0.73-1.60)		124	0.72 (0.55-0.95)	
Socio-economic status			0.935			0.102
Low	58	1 (reference)		112	1 (reference)	
Intermediate	65	0.97 (0.65-1.43)		124	1.03 (0.78-1.36)	
High	69	0.90 (0.65-1.43)		162	1.27 (1.01-1.60)	
Missing	9	0.87 (0.42-1.80)		7	1.74 (0.80-3.82)	
Number of comorbidities			**0.010**			0.122
0-1	121	1 (reference)		199	1 (reference)	
2-4	75	1.58 (1.18-2.11)		171	1.13 (0.92-1.40)	
≥5	5	1.18 (0.47-2.93)		35	1.46 (1.00-2.12)	
Histological grade (BR)			**<0.001**			**0.007**
Grade 1	18	1 (reference)		50	1 (reference)	
Grade 2	55	0.97 (0.57-1.65)		126	0.90 (0.65-1.26)	
Grade 3	92	2.19 (1.30-3.69)		143	1.32 (0.95-1.84)	
Unknown	36	1.81 (0.99-3.31)		86	0.89 (0.61-1.29)	
T stage			0.656			**0.002**
T1, T2	169	1 (reference)		313	1 (reference)	
T3, T4	31	1.22 (0.80-1.87)		91	1.56 (1.22-2.00)	
Unknown	-	Too low numbers		1	0.70 (0.10-5.09)	
Nodal stage			**0.007**			0.058
Negative	44	1 (reference)		112	1 (reference)	
Positive	156	1.82 (1.26-2.63)		288	1.32 (1.05-1.66)	
Unknown	-	Too low numbers		5	1.25 (0.50-3.16)	
Most extensive surgery			**0.001**			0.518
BCS	58	1 (reference)		49	1 (reference)	
Mastectomy	143	2.03 (1.35-3.04)		356	1.12 (0.80-1.57)	
Radiotherapy			0.448			0.333
Yes	115	1 (reference)		148	1 (reference)	
No	86	1.27 (0.88-1.84)		257	0.89 (0.70-1.13)	
Unknown	-	Too low numbers		-	NA	
Endocrine therapy			**0.048**			0.232
Yes	182	1 (reference)		347	1 (reference)	
No	19	0.59 (0.35-1.00)		58	0.83 (0.61-1.13)	
Chemotherapy			0.568			0.993
Yes	22	1 (reference)		10	1 (reference)	
No	179	1.15 (0.71-1.88)		395	1.00 (0.52-1.91)	
Unknown	-	Too low numbers		-	NA	

* Hazard ratios adjusted for all other covariates mentioned in the Table, and age (continuous) and year of diagnosis (continuous). BR: Bloom Richardson; BCS: breast conserving surgery. Cox proportional hazard models were used to evaluate the association between covariates and overall mortality. All statistical tests were two-sided; p values <.05 were considered to be statistically significant.

Overall mortality of patients aged 65-75 years was lower for patients who participated in a trial (univariate HR 0.65 (95% CI 0.50-0.86)). 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 that after adjustment for tumor, treatment and patient characteristics, the hazard ratio attenuated towards 1 (HR 1.08 (95%CI 0.73-1.60)). Patients aged 75 years or older who participated in a trial also had a lower overall mortality as compared to patients of corresponding age from

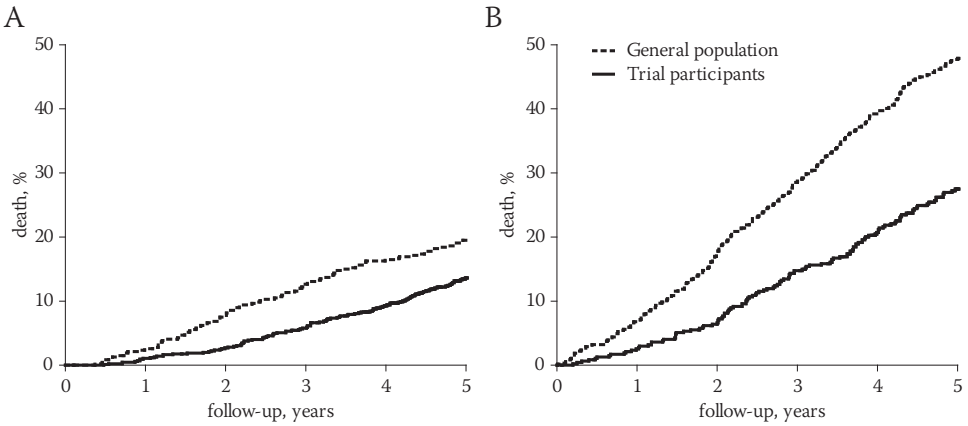

Figure 1. Cumulative incidence of death by age at diagnosis.

the general population (univariate HR 0.49 (95% CI 0.39-0.60)). 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 0.55-0.95)). 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, the number of patients who died during five years of follow-up was 124 and 281. Contrary, the number of patients who developed a distant recurrence was 54 and 74. 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, even though this may compromise the external validity of the trial[23]. Indeed we

showed that patients who participated in a clinical trial had more favourable patient and tumor characteristics as compared to patients from the general population. In patients aged 65-75 years, those who participated in a 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 the current 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.

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

	5-years distant recurrence n	5-years competing events* n	Univariate HR (95%CI)	p	Multivariable HR** (95% CI)	p
65-75 years				0.05		0.737
General population (n=467)	61	59	1 (reference)		1 (reference)	
Trial participants (n=852)	84	62	0.72 (0.52-1.00)		0.94 (0.64-1.37)	
≥75 years				0.447		0.269
General population (n=589)	74	228	1 (reference)		1 (reference)	
Trial participants (n=473)	54	95	0.87 (0.66-1.24)		0.80 (0.53-1.19)	

HR: Hazard ratio. * Competing events comprise intercurrent death; locoregional recurrence as first site of recurrence; contralateral breast cancer. ** Multivariable HRs were adjusted for histological grade, T stage, nodal stage, most extensive surgery, radiotherapy, endocrine therapy, chemotherapy, socio-economic status, comorbidity, age, year of diagnosis. Fine and Gray regression models were used to evaluate the association between covariates and distant breast cancer recurrence. All statistical tests were two-sided; p values <.05 were considered to be statistically significant.

A selective inclusion of patients into a trial may vary by type of study and study drug, and 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 five years preceding breast cancer diagnosis, an Eastern Cooperative Oncology Group performance status of more than two, or a significant cardiac disease or other illness interfering with study participation and adequate follow-up[10]. Others have published about the impact of eligibility criteria on the inclusion in clinical 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. As compared with other randomized clinical trials, the TEAM trial had relatively few eligibility criteria, without an upper age limitation, enabling enrolment of many elderly patients[9]. Therefore it is expected that the discrepancy between trial patients and patients from the general population will also be present in other breast cancer trials including elderly patients. Next to eligibility criteria hampering the 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 been shown to be no significant predictor as to whether a patient would participate, once they have 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 others, fewer comorbid diseases. Additionally, participation in a trial in itself may *result in* a 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 to those from the general population, which may decrease overall mortality.

Others have published on the external validity of clinical trials[23]. The novelty of the current 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 breast cancer patients aged 75 years or older in particular. Our study has some limitations. By applying identical inclusion criteria, we aimed to construct similar groups of patients. However, differences in design and data collection may have influenced our results. Although prespecified forms including 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 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 under diagnosis 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 65-75 years, given the confidence interval of the multivariable analysis (95% CI 0.73-1.60), we cannot exclude that those who participate in a trial do have a different overall mortality as compared to 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 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.

Clinical implications

Since 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 not likely that conduction of clinical trials will be sufficient to fill this 'evidence gap'. Even in the absence of eligibility criteria it is expected that elderly who are 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 including 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 in adequate treatment for different groups of elderly breast cancer patients.

Conclusions

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.

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