Coming of age : treatment and outcomes in older patients with breast cancer

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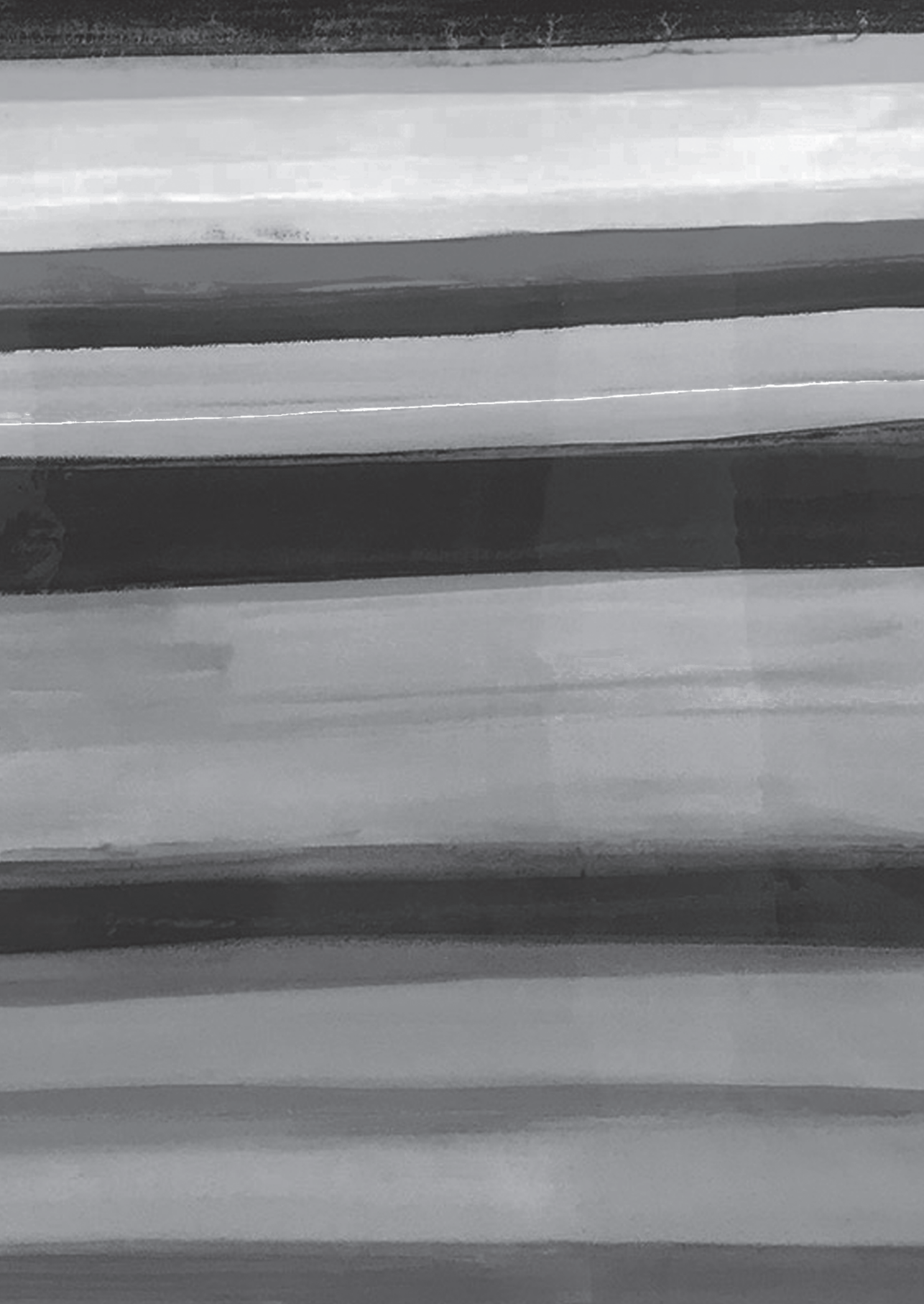

CHAPTER 6

Impact of comorbidities and age on cause specific mortality in postmenopausal patients with breast cancer

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Revisions, the Oncologist

ABSTRACT

Background: Increasing life expectancy leads to increasing numbers of older patients diagnosed with breast cancer. The aim of this study was to determine the long-term impact of comorbidities and age at time of breast cancer diagnosis on breast cancer mortality when taking into account competing causes of death.

Patients and Methods: Cohort analysis of Dutch and Belgian patients with hormone receptor-positive breast cancer included in the Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial between January 2001 and January 2006. Patients were categorized by number of comorbidities (no comorbidities, 1-2 comorbidities and >2 comorbidities) and age (<70 years and ≥70 years). Main outcome was breast cancer mortality considering other cause mortality as competing event.

Results: Use of chemotherapy was lower in older patients (1%, irrespective of the number of comorbidities) compared to younger patients (50%, 44% and 38% for patients with no, 1-2 or >2 comorbidities, $P<0.001$). Cumulative incidence of breast cancer mortality was higher among patients ≥70 without comorbidities (22.2%, 95% CI 17.5-26.9) compared to patients <70 without comorbidities (15.6%, 13.6-17.7, reference group), multivariable subdistribution Hazard Ratio (sHR) 1.49 (1.12-1.97, $P=0.005$) after a median follow-up of 10 years. Breast cancer mortality in other subgroups was not higher compared to the reference group.

Conclusion: Older patients without comorbidities have a higher risk of dying due to breast cancer than younger patients, even when taking into account higher competing mortality, while use of chemotherapy in this group was low. These findings underline the need to take into account comorbidities, age and competing mortality in the prognosis of breast cancer for accurate decision making.

INTRODUCTION

Increasing life expectancy and decreasing birth rates are important factors contributing to rapid ageing of the population.[1] As increasing age is an important predictive factor for the development of breast cancer, it is expected that the number of older patients diagnosed with breast cancer will increase concomitantly.[2] In older patients, breast cancer occurs against a background of other diseases.[3] On the other hand, studies have shown that increasing longevity may be accompanied by an extended period of good health, resulting in a relevant population of older patients with breast cancer and minimal comorbidity.[4] This diversity in health status in older patients is challenging for clinicians when balancing the benefits and toxicities of breast cancer treatment.

To provide optimal decision making in older patients it is important to consider breast cancer prognosis as well as the chance of dying due to other causes than breast cancer for the forthcoming years. Accurate estimation of breast cancer mortality risk in this group should take into account other cause mortality by applying competing risk analysis.[5] Increasing age and comorbidity are independently associated with reduced life expectancy,[6,7] and this influences the risk of other cause mortality in patients diagnosed with breast cancer. While several studies have shown that increasing age at diagnosis is associated with worse breast cancer outcomes,[8,9] this association for comorbidities remains a matter of debate.[6]

The Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial compared two types of adjuvant endocrine therapy (exemestane monotherapy versus tamoxifen followed by exemestane) in postmenopausal patients with hormone receptor-positive early breast cancer, and recently our group reported no difference in outcomes between both treatment groups after ten years of follow-up.[10,1]. Data on comorbidities at time of diagnosis and long-term follow-up were collected in enrolled TEAM patients in two countries (The Netherlands, and Belgium). In this analysis, we studied the impact of comorbidities and age at diagnosis on breast cancer mortality and other cause mortality after ten years of follow-up, taking into account competing causes of death.

PATIENTS AND METHODS

The TEAM study is a randomized controlled trial of which the details have previously been described.[10,11] In summary, postmenopausal, early hormone receptor-positive breast cancer patients who had completed local treatment with curative intent were included between January 2001 and January 2006, and randomized to receive exemestane (25 mg, once daily) for five years, or sequential treatment of tamoxifen (20 mg, once daily) followed by exemestane for a duration of five years. Patients with a previous malignancy five years before

breast cancer diagnosis, significant cardiac or other diseases that interfered with study participation, or an Eastern Cooperative Oncology Group (ECOG) performance status >2 were considered ineligible. Information on the type of surgery, radiotherapy and chemotherapy was collected at the case report form (CRF) at time of inclusion. During follow-up information was registered on disease recurrence and cause of death. The database was locked on February 19th, 2016. Patients were censored at date of last follow-up or at database lock for event-free patients. After ten years of follow-up no difference was observed for the primary endpoint (disease-free survival) between the two treatment arms[10] and thereafter the cohort has been used for observational research to explore determinants and outcomes of breast cancer.

For this analysis, all Dutch and Belgian patients were selected from the central TEAM database, as these countries collected information on comorbidities at inclusion and on long-term follow-up. Selected patients were categorized into two age categories for age at diagnosis (<70 years and ≥70 years) according to the International Organization for Geriatric Oncology (SIOG) recommendations.[12] Information on comorbidities at diagnosis was extracted from medical charts and registered on the CRF in free text areas. For further analysis, comorbidities were classified according to the ICD-10 classification of diseases.[13] The number of comorbidities was categorized into three categories (no comorbidities, 1-2 comorbidities, >2 comorbidities). Cause of death was indicated on the CRF and later verified and categorized into ten prespecified groups defined in the protocol (Supplementary Table 1) by the central TEAM datacentre.

Endpoints in the current study were breast cancer mortality and other cause mortality. Breast cancer mortality was defined as time from randomization to death due to breast cancer, considering other cause mortality as a competing event. As defined in the protocol, death that occurred after distant recurrence was defined as caused by breast cancer. Other cause mortality was defined as all other causes of death than death due to breast cancer whereby breast cancer mortality was considered as a competing event.

The study was performed in compliance with the guidelines of the Declaration of Helsinki, International Conference on Harmonization, and Good Clinical Practice. Approvals from the respective ethical committees were obtained. All patients provided written informed consent. The TEAM trial was registered in the Netherlands and Belgium (the Netherlands Trial Registry NTR267; Ethics Commission Trial 27/2001).

Statistical analyses

Pearson χ^2 test was used to compare proportional differences of tumor and treatment characteristics between subgroups. Cumulative incidences of breast cancer-related mortality

and other cause mortality were calculated using the Cumulative Incidence Competing Risk Methods (CICRM),[14,15] which assumes that patients who experienced a competing event remain in the risk set calculation for the event of interest and, as a consequence, estimates actual probabilities of reaching different endpoints.[5] The Fine and Gray model was used to calculate the effect of risk factors for the cause-specific incidences of death, thereby taking into account the effect of competing causes of death.[15] The effect of risk factors is expressed in terms of subdistribution hazard ratio's (sHR).[14,15] The multivariable model included the covariates that were included in the PREDICT+ prognostication tool (tumor size (in millimeters), histological grade, lymph-node stage according to the Tumour-Node-Metastasis classification, estrogen (ER) receptor status, Human epidermal growth receptor (Her2) status).[16] Missing values were addressed by multiple imputation by chained equation (MICE) using five imputed data assuming that distribution of missing data is at random (MAR).[17] Results were based on pooled results of the imputed data using the Rubin's rules. All statistical analyses were performed in R statistics version 3.3.3 using the survival, cmprsk and mice packages.[18] Results were considered statistically significant when two-sided P-value was less than 0.05.

Additional analysis

Sensitivity analysis was performed to test the robustness of the "breast cancer mortality" endpoint definition as described in the TEAM protocol. For this additional analysis, breast cancer mortality was defined as death due to breast cancer following the information as registered on the CRF (and not assuming that deaths that occurred after distant recurrence were defined as breast cancer related deaths).

RESULTS

Overall, 3159 Dutch and Belgian patients were included in the TEAM trial of which 2203 (69.7%) patients were aged <70 years and 956 (30.3%) were aged ≥70 years at diagnosis. Median follow up in was 10.2 years (IQR 9.9-10.8). Table 1 shows the baseline characteristics overall and by age group. Median age at diagnosis was 60 years (IQR 56-64) and 75 years (IQR 72-79) in de the younger and older cohort respectively. Tumor size was significantly higher in patients aged ≥70 years at time of diagnosis. Older patients were more likely to have a higher number of comorbidities at diagnosis (Table 1). For both younger and older patients, hypertension, arthrosis and diabetes were the most prevalent types of comorbidities, although the proportions of patients having these comorbidities were higher in older patients (Table 2).

Table 1. Patient and tumor characteristics by age group and for all patients

	< 70 years (N=2203)		≥ 70 years (N=956)			All patients (N=3159)	
	N	%	N	%	*P*	N	%
Age at diagnosis, median (IQR)	60 (56-64)		75 (72-79)			64 (58-71)	
Tumor size in mm, median (IQR)	21 (15-30)		25 (18-32)		<0.001	22 (16-30)	
Unknown	11	<1	-	-		11	<1
Histological grade					0.137		
I	310	14	147	15		457	15
II	939	43	425	45		1364	43
III	837	38	314	33		1151	36
Unknown	117	5	70	7		187	6
Nodal stage					0.363		
N0	632	29	327	34		959	30
N1	1404	64	562	59		1966	62
N2/N3	165	8	65	7		230	7
Unknown	2	<1	2	<1		4	<1
Estrogen-receptor status					<0.001		
Negative	57	3	11	1		68	2
Positive	2145	97	945	99		3090	98
Unknown	1	<1	-	-			
Her2-receptor status					0.062		
Negative	1600	73	740	77		2340	74
Positive	231	11	87	9		318	10
Unknown	372	17	129	14		501	16
Number of comorbidities					<0.001		
0	1196	54	314	33		1510	48
1-2	864	39	494	52		1358	43
≥ 2	143	7	148	16		291	9

Figure 1 and Supplementary Table 2 show treatment characteristics by age group and number of comorbidities. Breast-conserving surgery was performed less frequently in case of >2 comorbidities among patients diagnosed <70 years (51%, 52% and 43% in patients without, with 1-2, and more than 2 comorbidities, respectively). Patients aged ≥70 years at diagnosis were less likely to undergo breast-conserving surgery compared to younger patients but this did not vary across the different comorbidity groups (34%, 31% and 32%, respectively). Virtually all patients received radiotherapy after breast-conserving surgery. In patients aged <70 years at diagnosis, the administration of chemotherapy decreased with an increasing number of comorbidities (50%, 44% and 38% in patients without, with 1-2, and more than two comorbidities, respectively), while nearly none of the older patients received chemotherapy, irrespective comorbidity status (1%, <1% and 1%, respectively).

Table 2. Ten most prevalent comorbidities by age group

Age < 70 years (N=2203)		**Age ≥ 70 years (N=956)**	
	N (%)		N (%)
Hypertension	460 (21)	Hypertension	325 (34)
Arthrosis	178 (8)	Arthrosis	146 (15)
Diabetes Mellitus	135 (6)	Diabetes Mellitus	123 (13)
Hypothyroidism	109 (5)	Myocardial infarction	77 (8)
Hypercholesterolemia	106 (5)	COPD[#]	58 (6)
COPD[#]	90 (4)	Hypercholesterolemia	57 (6)
Myocardial infarction	61 (3)	Hypothyroidism	52 (5)
Gastric ulcer	45 (2)	Cardiac arrhythmias	39 (4)
Mood disorder	40 (2)	Transient cerebral ischemic attack	39 (4)
Osteoporosis	36 (2)	Cardiac valve disorders	32 (3)
Rheumatism	34 (2)	Osteoporosis	30 (3)

[#]Chronic obstructive pulmonary disorder

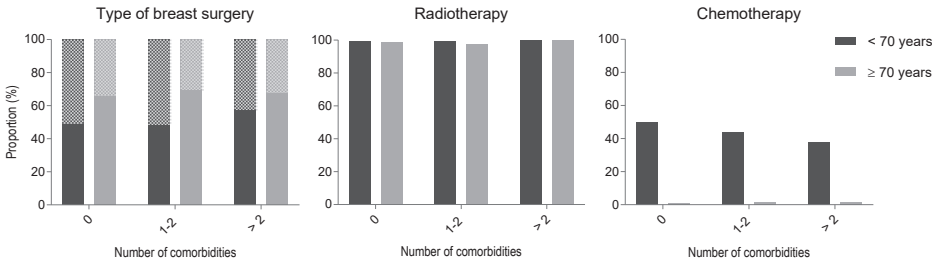

Figure 1 Types of treatment by age group and number of comorbidities
Type of breast surgery: mastectomy (filled bar) and breast conserving surgery (dotted bar); radiotherapy represents the proportion of patients receiving radiotherapy after breast conserving surgery.

Figure 2 shows the cumulative incidences of breast cancer mortality and other cause mortality stratified by age group and number of comorbidities. Cumulative incidence of breast cancer mortality ten years after diagnosis in patients aged <70 years without comorbidities was 15.6% (95% CI 13.6-17.7, reference group, Table 3). Compared to this reference group, the cumulative incidence of breast cancer mortality in patients aged ≥70 years without comorbidities was significantly higher (22.2%, 95% CI 17.5-26.9; sHR 1.45 95% CI 1.09-1.91, *P*= 0.009) which remained significant after adjusting for confounders (sHR 1.49 95% CI, 1.12-1.97, *P*=0.005, Table 3). For patients with 1-2 comorbidities, the cumulative incidence of breast cancer mortality over the ten years period was not higher than that in the reference group, applying for both age cohorts. Further, compared to the reference group, the cumulative incidence of breast cancer mortality appeared to be higher in patients with >2 comorbidities in both age groups, being 21.3% (95% CI 14.4-28.3) in patients <70 years

and 21.3% (95% CI 14.3-28.2) in patients aged ≥70 years, respectively, but this was not statistically significant (Table 3).

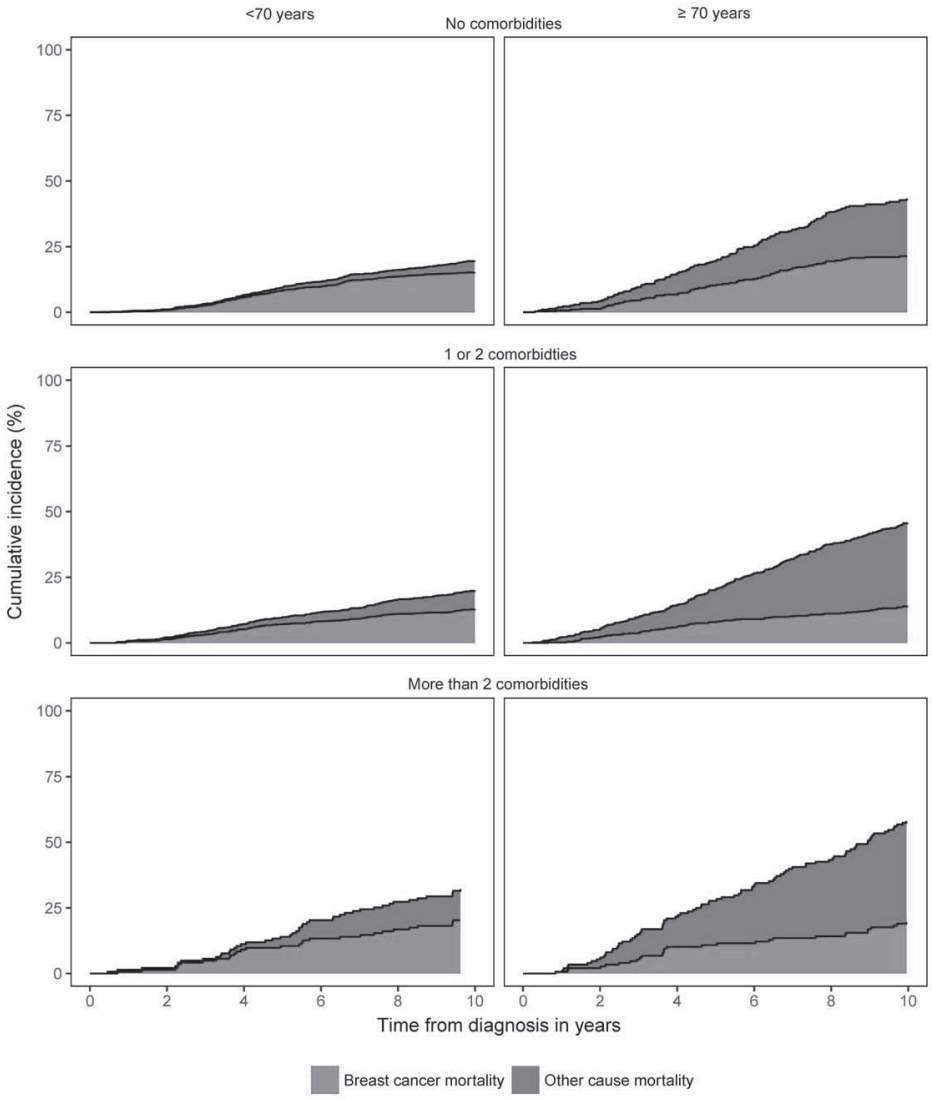

Figure 2 Cumulative incidence of breast cancer mortality and other cause mortality by age group and number of comorbidities

Stacked cumulative incidence of breast cancer mortality (red) and other cause mortality (blue) by age group and number of comorbidities from time since diagnosis in years.

The cumulative incidence of other cause mortality ten years after diagnosis was higher with increasing numbers of comorbidities and with older age at diagnosis (Figure 2, Table 3).

Table 3. Breast cancer mortality and other cause mortality by age group and number of comorbidities

	Cumulative incidence ten years after diagnosis in % (95% CI)	**Univariate sHR (95% CI)**	***P***	**Multivariable sHR (95% CI)[a]**	***P***
Breast cancer mortality					
< 70 years; no comorbidities	15.6 (13.6-17.7)	Reference		Reference	
< 70 years ; 1-2 comorbidities	13.4 (11.1-15.8)	0.92 (0.73-1.15)	0.450	0.89 (0.69-1.08)	0.203
< 70 years; > 2 comorbidities	21.3 (14.4-28.3)	1.41 (0.96-2.07)	0.080	1.24 (0.83-1.85)	0.301
≥ 70 years; no comorbidities	22.2 (17.5-26.9)	1.45 (1.09-1.91)	0.009	1.49 (1.12-1.97)	0.005
≥ 70 years; 1-2 comorbidities	14.8 (11.6-18.1)	0.91 (0.69-1.19)	0.490	0.93 (0.71-1.23)	0.615
≥ 70 years; > 2 comorbidities	21.3 (14.3-28.2)	1.31 (0.89-1.94)	0.180	1.22 (0.82-1.80)	0.325
Other cause mortality					
< 70 years; no comorbidities	4.6 (3.4-5.9)	Reference		Reference	
< 70 years ; 1-2 comorbidities	7.4 (5.6-9.2)	1.62 (1.14-2.30)	0.007	1.63 (1.15-2.31)	0.006
< 70 years; > 2 comorbidities	12.5 (6.9-18.2)	3.11 (1.88-5.15)	<0.001	3.11 (1.87-5.16)	<0.001
≥ 70 years; no comorbidities	23.3 (18.4-28.2)	5.78 (4.12-8.12)	<0.001	5.76 (4.10-8.09)	<0.001
≥ 70 years; 1-2 comorbidities	33.0 (28.7-37.2)	8.47 (6.31-11.38)	<0.001	8.38 (6.23-11.26)	<0.001
≥ 70 years; > 2 comorbidities	41.5 (33.1-49.9)	12.14 (8.61-17.11)	<0.001	12.05 (8.52-17.04)	<0.001

[a] Covariates included in the model: tumor size, histological grade, lymph-node, ER-receptor status, Her2-receptor status).

Additional analysis

Applying a different definition for breast cancer mortality (see methods), 30 patients previously categorized as having died due to breast cancer were now assumed to have died due to other causes. Univariate and multivariable regression analyses yielded comparable results for breast cancer mortality (Supplementary Table 3).

DISCUSSION

In this subanalysis of Dutch and Belgian TEAM patients, we observed a higher risk of dying due to breast cancer ten years after diagnosis in older patients without comorbidities when compared to younger patients without comorbidities which was independent of tumor characteristics. In the other subgroups, breast cancer mortality was not significantly different. Other cause mortality increased significantly with age as well as the number of comorbidities but this higher other cause mortality did not lead to lower breast cancer mortality. Moreover, administration of adjuvant chemotherapy was more driven by age than by comorbidities.

To our knowledge, long-term follow-up analysis of mortality outcomes in postmenopausal breast cancer patients stratified for both age at diagnosis and comorbidities has not been performed before. Several studies reported an increased risk of breast cancer mortality with increasing age.[8,9,19] In observational studies an increased risk of breast cancer death or breast cancer recurrence was observed in patients with one or more comorbidities (not stratified for age at diagnosis).[7,19-22] On the other hand, the ATAC trial described no impact of comorbidities on breast cancer recurrence.[23] In addition, in most comparable studies the Cox Proportional hazards model was applied,[7,19,20,22,23] whereby patients who died due to other causes were censored and were assumed to have the same risk of breast cancer mortality as non-censored patients. Results described in studies using this methodology are therefore likely to be overestimated.[5] In the study performed by Berglund et al[21] and in our study, competing risk analyses were performed enabling to take into account competing causes of death, which in our opinion is a more optimal method of analysis. In view of the conflicting findings and the importance of the question for clinical practice it is warranted to reach consensus on appropriate statistical models to assess the impact of comorbidities and age on breast cancer mortality.

Several factors may explain why older patients without comorbidity, in contrast to patients with comorbidity, had a higher risk of breast cancer mortality than younger patients without comorbidity. Older patients without comorbidity had a lower other cause mortality than older patients with one or more comorbidities (Figure 2, Table 3) and therefore were surviving for a longer time period in which they remained at risk for disease recurrence and breast cancer death. Also, although older patients presented with larger tumors, adjuvant chemotherapy was rarely administered (approximately 1%), compared to 50% of younger patients without comorbidity (Table 1, Supplementary Table 2, Figure 1), which possibly explained an increased risk of disease recurrence. This indicates potential undertreatment of fit older patients and underlines the importance of optimal treatment.

Other factors could also have contributed to higher breast cancer mortality in the healthy older patient group. Previous studies have shown that older patients experience more adverse events during and after adjuvant chemotherapy or radiotherapy.[12] However, as adjuvant chemotherapy was administered in only 1% of older patients overtreatment is not likely to have contributed to the observed higher breast cancer mortality. Lack of compliance of endocrine therapy in the TEAM trial has been reported to be higher among older than among younger patients.[24] However, this was independent of the number of comorbidities and does not explain the higher breast cancer mortality in older patients without comorbidities in our study cohort.

Endocrine therapy might lead to an increased risk of other cause mortality especially among older patients. The BIG 1-98 trial investigating either letrozole or tamoxifen as adjuvant endocrine therapy, reported higher rates of lethal adverse events, all being of cardiovascular origin and more cerebrovascular accidents among patients aged >75 years versus younger patients [25] In the current study cohort, cardiovascular disease was the second cause of death after breast cancer among older patients but it is difficult to estimate to what extent endocrine therapy might have attributed to this risk.

Virtually none of the older patients in this study cohort received adjuvant chemotherapy, irrespective of the presence and the number of comorbidities and despite larger tumors at diagnosis, which was in line with national guidelines. Due to the very low proportion of older patients receiving chemotherapy in our study, further analysis on the potential effect of chemotherapy on breast cancer mortality was not possible. Also, as the number of older patients included in trials investigating chemotherapy strategies is limited due to either eligibility criteria (excluding older patients) or poor accrual in studies for specifically older patients,[26] current guidelines do not contain clear recommendations for chemotherapy in older patients. In a NSABP trial including fit older patients (aged >65 years, good performance score, no major organ dysfunction) standard intravenous chemotherapy (either cyclophosphamide, methotrexate, and fluorouracil (CMF) or cyclophosphamide/doxorubicin (AC)) was compared with oral capecitabine. Better outcomes for disease recurrence and overall survival were observed in the standard chemotherapy group at the cost of moderate to severe toxic effects.[27] In both therapy arms, however, a substantial percentage of patients experienced toxicity, needed dose reduction or stopped therapy prematurely. Weekly paclitaxel in older patients is feasible but the efficacy in hormone-receptor positive breast cancer is not clear.[28,29] Potentially the chemotherapy toxicity tool in older cancer patients as was developed by Hurria and colleagues,[30n] might be helpful in decision making and recommending adjuvant chemotherapy.

In line with other studies, comorbidities were strongly related to other cause mortality.[6,7,19-23,31-34] Our data, however, also indicate that age appears to be a driving factor of other cause mortality (Figure 2, Table 3); patients≥70 years without comorbidities had higher other cause mortality compared to patients <70 years with >2 comorbidities. Therefore, in our opinion it is important to include both age and number of comorbidities in the risk assessment of other cause mortality and also in the toxicity prediction tool.

To adequately address the clinical benefit of adjuvant systemic therapy in elderly patients with breast cancer, the following aspects should be considered. First, life expectancy should be evaluated to estimate the risk of other cause mortality using age, comorbidities and other geriatric indicators for prediction.[35] Second, tumor stage and molecular characteristics

including genetic profiling should be considered to estimate breast cancer prognosis. Third, estimation of risk of toxicity or complications of treatment using available tools must be taken into account.[30]

Some limitations of this study should be mentioned. First, classification of cause of death could be subject to misclassification. To address this, we performed a sensitivity analysis using a less stringent definition of breast cancer mortality to estimate the effect of comorbidity and age hereon, but this did not change our findings (Supplementary Table 3). Second, we were not able to code the severity of comorbidities as this was not collected on the CRF. Third, participation in the TEAM trial was restricted by the in- and exclusion criteria (see methods). Especially older patients participating in this trial were relatively healthy compared to the general population and this could hamper the interpretation of our findings.[36]

Overall, this study provides further insight into the role of age at diagnosis and comorbidities on the long-term risk of breast cancer mortality and other cause mortality in postmenopausal patients with early breast cancer, which especially for the older patient cohorts is very relevant. Despite the number of comorbidities or older age, both contributing to increasing other cause mortality, we did not observe a decrease in breast cancer mortality after a follow-up time of ten years. Furthermore, we found that older patients without comorbidities were at increased risk of dying due to breast cancer, despite a higher other cause mortality. In the light of the changing demographics, this group will expand in future years and there is an urgent need to pursue optimal treatment for healthy older patients. Also, this study underlines the clinical challenge with respect to decision making, balancing between undertreatment and overtreatment of older patients, and indicates that assessment of risk for both breast cancer mortality and other cause mortality is indispensable for treatment decision making in older patients. Ideally, future prognostic tools for breast cancer prognosis should incorporate these items as well as risk of toxicity of adjuvant chemotherapy to adequately predict outcomes to optimize personalized treatment for older patients with early breast cancer.

Acknowledgements

We thank all the participating hospitals and patients for participation in the trial. Furthermore, we thank the Datacenter Heelkunde for data collection and preparation of the datasets.

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Supplementary Table 1. Causes of death as defined by the TEAM protocol

Breast cancer
Second primary tumor
Endometrial cancer
Cardiac disorder
Thromboembolism
Pulmonary disorder
Cerebral disorder
Vascular disorder
Other
Unknown

Supplementary Table 2. Proportional distribution of type of treatment by age group and number of comorbidities

Age	**< 70 years**			**≥ 70 years**			
Number of comorbidities	**0**	**1-2**	**>2**	**0**	**1-2**	**>2**	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	*P*
Type of breast surgery							<0.001
Mastectomy	585 (49)	418 (48)	207 (66)	207 (66)	343 (69)	100 (68)	
Breast conserving surgery	611 (51)	446 (52)	61 (43)	107 (34)	151 (31)	48 (32)	
Radiotherapy							0.130
Yes	606 (99)	443 (100)	61 (100)	106 (99)	147 (97)	48 (100)	
No	4 (<1)	2 (<1)	0 (0)	1 (<1)	4 (3)	9 (0)	
Chemotherapy							<0.001
Yes	598 (50)	381 (44)	53 (38)	3 (<1)	7 (1)	2 (1)	
No	598 (50)	483 (56)	89 (62)	311 (99)	487 (99)	146 (99)	

Supplementary Table 3. Breast cancer mortality by age group and number of comorbidities using the definition for breast cancer death as outlined in the sensitivity analysis

	Univariate sHR (95% CI)	*P*	**Multivariable sHR (95% CI)**	*P*
< 70 years; no comorbidities	Reference		Reference	
< 70 years ; 1-2 comorbidities	0.88 (0.70-1.11)	0.300	0.83 (0.66-1.05)	0.116
< 70 years; > 2 comorbidities	1.17 (0.77-1.78)	0.450	1.02 (0.66-1.57)	0.935
≥ 70 years; no comorbidities	1.29 (0.96-1.72)	0.091	1.31 (0.98-1.76)	0.068
≥ 70 years; 1-2 comorbidities	0.84 (0.63-1.12)	0.230	0.86 (0.65-1.15)	0.305
≥ 70 years; > 2 comorbidities	1.23 (0.82-1.85)	0.310	1.14 (0.76-1.71)	0.522