Impact of age on breast cancer mortality and competing causes of death at 10 years follow-up in the adjuvant TEAM trial

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Impact of age on breast cancer mortality and competing causes of death at 10 years follow-up in the adjuvant TEAM trial M.G.M. Derks MD[1], E. Bastiaannet PhD[1,2], W. van de Water MD PhD[1], N.A. de Glas MD PhD[2], C. Seynaeve MD PhD[3], H. Putter PhD[4], J.W.R. Nortier MD PhD[2], D. Rea MD PhD[5], A. Hasenburg MD PhD[6], C. Markopoulos MD PhD[7], L.Y. Dirix MD PhD, J.E.A. Portielje MD PhD[2], C.J.H. van de Velde MD PhD[1] , G.J. Liefers MD PhD[1]

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Abstract

Aim of study: Due to increasing life expectancy, patients with breast cancer remain at risk of dying due to breast cancer over a long time. This study aims to assess the impact of age on breast cancer mortality and other cause mortality ten years after diagnosis.

Methods: Postmenopausal patients with hormone-receptor positive breast cancer were included in the Tamoxifen and Exemestane Adjuvant Multinational (TEAM) trial between 2001 and 2006. Age at diagnosis was categorized as <65 years (n=3369), 65 to 74 years (n=1896) and ≥75 years (n=854). Breast cancer mortality was assessed considering other cause mortality as competing event using competing risk analysis.

Results: After a median follow-up of 9.8 years (interquartile range 8.0-10.3), cumulative incidence of breast cancer mortality increased with increasing age (age <65 years 11.7% (95% CI 10.2-13.2), 65-74 years 12.7% (11.2-14.2), ≥ 75 years 15.6% (13.1-18.0). Univariate subdistribution Hazard Ratio (sHR) increased with increasing age (age 65-74 years sHR 1.08, 95% confidence interval (CI) 0.92-1.27, ≥75 years sHR 1.30, 95% CI 1.06-1.58, *P*= 0.013). Multivariable sHR adjusted for tumour and treatment characteristics increased with age but did not reach significance (age 65-74 years sHR 1.11, 95% CI 0.94-1.31; ≥75 years sHR 1.18, 95% CI 0.94-1.48, *P*= 0.055).

Conclusion: Ten years after diagnosis, older age at diagnosis is associated with increasing breast cancer mortality in univariate analysis but it did not reach significance in multivariable analysis. This is not outweighed by a substantially increasing other cause mortality with older age. This underlines the need to improve the balance between undertreatment and overtreatment in older patients with breast cancer.

The trial was registered in international trial databases (ClinicalTrials.gov NCT00279448, NCT00032136, and NCT00036270; the Netherlands Trial Registry NTR267).

Key words: breast neoplasms; geriatric oncology; age; risk factor; mortality; competing risk analysis

Highlights:

- With increasing life expectancy there is a longer period to die due to breast cancer
- Breast cancer mortality increased with age despite higher competing mortality
- Even at older age breast cancer remains an important cause of death
- Older patients are at risk of both undertreatment and overtreatment
- Clinicians should aim to accurately balance harms and benefits of treatment in elderly

Introduction

Age is the strongest predictor for the development of breast cancer (1). Due to aging of the population, the number of older patients diagnosed with breast cancer is rapidly growing. With increasing life expectancy, older patients remain at risk of dying of breast cancer over a longer time period. At the same time, the risk of dying from other causes than breast cancer increases substantially with advancing age (2). Survival estimates that take these competing causes of death into account are essential for individual decision making to balance between benefits and toxicities of cancer therapy (3).

As older patients are poorly represented in clinical trials (4), the relation between age at diagnosis and breast cancer mortality was mostly investigated in observational studies, reporting a higher breast cancer mortality with increasing age (5-9). Due to lack of information on cause of death, most studies use relative survival as a measurement of breast cancer-related survival. The Tamoxifen and Exemestane Adjuvant Multicenter (TEAM) trial included a large number of older postmenopausal patients, and contains reliable information on cause of death. A previous analysis after five years of follow-up observed higher breast cancer mortality with increasing age, despite that increasing age was also associated with a higher proportion of other cause mortality (9).

However, as patients above 75 years currently have an anticipated life expectancy of 12 years and breast cancer can recur until 20 years after initial diagnosis (10), it is relevant to investigate how breast cancer mortality and other cause mortality compete over a longer time period after breast cancer. Therefore, the aim of this study was to assess the relation between age at diagnosis and breast cancer mortality and other cause mortality ten years after diagnosis among postmenopausal patients with hormone receptor-positive early breast cancer included in the TEAM trial.

Patients and methods

The TEAM study is a randomized controlled trial including postmenopausal patients with non-metastatic estrogen and/or progesterone positive breast cancer. Details of the trial have been extensively described in previous publications (11, 12). In short, patients were included between 2001 and 2006 and randomized to receive exemestane for five years, or tamoxifen followed by exemestane for a total duration of five years. If patients had an Eastern Cooperative Oncology Group (ECOG) performance status higher than two, a previous malignancy with a disease-free interval of fewer than five years or significant cardiac or other diseases interfering with study participation they were ineligible. Cause of death was indicated on a case report form and categorized into 10 pre-specified groups (Table 2). Classification of cause of death was verified centrally by the TEAM datacenter. The database was locked on February 19, 2016 for the study endpoints after ten years of follow-up.

For the current analysis, only patients from countries that completed ten years of follow-up were included (The Netherlands, Belgium, Luxembourg, United Kingdom, Ireland, Greece and Germany). After ten years of follow-up there was no difference in the primary endpoint between the two treatment arms (11).

The trial was registered in international trial databases (ClinicalTrials.gov NCT00279448, NCT00032136, and NCT00036270; the Netherlands Trial Registry NTR267; Ethics Commission Trial 27/2001; and the University hospital Medical Information Network C000000057). Approvals from ethical committees and written informed consent from all patients were obtained (12).

Outcomes

For age at diagnosis patients were categorized into three categories (<65 years (reference group), 65-74 years and ≥75 years) according to the guidelines of the International Society of Geriatric Oncology (SIOG) (13). Breast cancer mortality was defined as time from randomization to death due

to breast cancer. Deaths that occurred after distant recurrence were defined as death due to breast cancer with other cause mortality as a competing event. Other cause mortality was defined as all other causes of death than breast cancer, and in the analyses breast cancer mortality was considered as competing event. Distant recurrence was classified according to the Tumour-Node-Metastasis classification (6^{th} edition) (14). If patients died due to breast cancer, the presence of distant recurrence was assumed and other cause mortality was considered as competing event.

Statistical Analyses

Pearson X^2 test was used to compare proportional differences between age groups. Cumulative incidences of breast cancer mortality, other cause mortality and distant recurrence were calculated using the Cumulative Incidence Competing Risk Methods (15, 16). The Fine and Gray model was used to calculate the effect of prognostic factors for the cause-specific incidences of death or distant recurrence taking into account the effect of competing causes of death (16). The effect of prognostic factors is expressed as subdistribution hazard ratio's (sHR) (15, 16). *P*- values for trend over increasing age were reported. The multivariable model included clinically relevant covariates (histological grade, tumour size, lymph node status, progesterone receptor status, Her2 receptor status, most extensive breast surgery, radiotherapy, chemotherapy, type of endocrine therapy and country of residence). Multiple imputation by chained equation was performed to account for missing values, assuming that data were missing at random (17). Analyses were based on pooled results of five imputed data sets using Rubin's rules. All statistical tests were two-sided. *P*-values of less than 0.05 were considered statistically significant. All analyses were performed in R version 3.3.0 using the survival, cmprsk and mice packages.

Additional analyses

An additional analysis was performed to assess the impact of age at diagnosis on breast cancer mortality in those patients who were diagnosed with a distant recurrence during follow-up.

Furthermore, two sensitivity analyses were performed to test the validity of the study endpoints (Supplementary Material).

Results

Overall, 6119 postmenopausal patients were included. 3369 patients (55%) were aged <65 years, 1896 were 65-74 years (31%), and 854 patients (14%) were aged ≥75 years at diagnosis. Median follow-up was 9.8 years (interquartile range 8.0-10.3). Table 1 shows the baseline characteristics by age group. Patients aged ≥75 years were more likely to present with larger tumours, no difference was observed in nodal status or differentiation grade. The proportion of patients undergoing a mastectomy increased significantly with increasing age, whereas administration of radiotherapy and adjuvant chemotherapy decreased significantly with increasing age.

During follow-up, 551 of 3369 (16%) patients aged <65 years at diagnosis, 467 of 1896 (25%) patients aged 65 to 75 years and 443 of 854 (52%) patients aged ≥75 years at diagnosis died. Breast cancer was the leading cause of death among all age groups, but proportionally decreased with increasing age at diagnosis (Table 2). Ten-year cumulative incidence of breast cancer mortality increased from 11.7% in patients aged <65 years, to 12.7% in patients aged 65-74 years and 15.6% in patients aged ≥75 years (Table 3, Figure 1). In univariate analysis, increasing age was associated with a higher breast cancer mortality (age group 65-74 years sHR 1.08, 95% CI 0.92-1.27; age group ≥75 years sHR 1.30, 95% CI 1.06-1.58, *P*= 0.013, Table 3). In multivariable analysis, breast cancer mortality increased with advancing age although it did not reach statistical significance (age group 65-74 years sHR 1.11, 95% CI 0.94-1.31; age group ≥75 years sHR 1.18, 95% CI 0.94-1.48, *P*= 0.055, Table 3).

Ten-year cumulative incidence of other cause mortality increased with older age at diagnosis (patients aged <65 years 3.7%; 65-74 years 10.6%; ≥75 years 33.4%, Figure 1). Both models showed a strong association between age and other cause mortality (Table 3).

Cumulative incidence of distant recurrence increased between five and ten years in all age groups. In both models, age was not associated with a higher risk of distant recurrence after ten years (age group 65-74 years multivariable sHR 1.05, 95% CI 0.90-1.23, age group ≥75 years 0.97, 95% CI 0.79-1.20, *P*= 0.462, Table 3).

Additional analyses

Older patients that developed a distant recurrence during follow-up were at higher risk of dying due to breast cancer compared to younger patients (patients aged 65-74 years multivariable sHR 1.30, 95% CI 1.09-1.56; patients aged ≥75 years sHR 2.18, 95% CI 1.70-2.78, *P*<0.001).

When not assuming breast cancer as the cause of death after diagnosis of distant recurrence, 39 deaths originally classified as death due to breast cancer were now considered as death due to other causes (Table S1). A similar trend for the effect of age at diagnosis and breast cancer mortality in univariate analysis was observed while there was no clear trend between increasing age and breast cancer mortality in multivariate analysis (Table S2). Outcomes of further sensitivity analyses are described in the Supplementary Material.

Discussion

After ten years of follow-up, increasing age at diagnosis is associated with higher breast cancer mortality and this is not outweighed by a substantially higher other cause mortality. After adjusting for breast cancer and treatment characteristics, a similar trend was observed although this did not reach significance. Moreover, distant recurrences occurred at a similar rate between younger and older patients, despite substantially higher other cause mortality among the oldest patient group. In those patients that developed distant recurrence, increasing age was associated with increasing breast cancer mortality subsequently. These findings indicate the need to develop prediction tools that include both breast cancer and other cause mortality to balance harms and benefits of treatment.

A previous report of the TEAM trial after five years of follow-up described a significant association between increasing age and breast cancer mortality, independent of tumour and treatment characteristics(9). In our study cohort, we observed a corresponding trend after adjusting for similar confounders but it did not reach significance. There are some possible explanations for the different outcomes in both analyses. The population in the current ten-year cohort was different from the original population: in the current cohort patients had larger tumours and were more often lymph node-positive and a poorer disease-free survival than in the original TEAM population(11). Furthermore, the authors applied a Cox model for the main analyses while in this study, a competing risk regression model was applied. After the publication of the study in 2012, this study group has gained more experience and knowledge in the application and interpretation of the competing risk model(3). With this current knowledge it was decided that the competing risk model was more appropriate than the Cox model to predict outcomes between age groups. Moreover, in the current study multiple imputation analysis was performed to account for missing values.

In a population with a high probability of competing events it is important to take competing events into account when estimating the risk of breast cancer mortality, as it could otherwise overestimate the risk of breast cancer mortality(3). Unfortunately, previous studies describing the relation

between age at diagnosis and cause of death among patients diagnosed with breast cancer used various statistical techniques. In the ATAC trial, a positive association between increasing age and risk of breast cancer recurrence and death without recurrence was reported using the Cox model (18). However, this effect of age at diagnosis might be overestimated because competing events were not considered (3). In trials from the NCIC Clinical Trials Group, the effect of age at diagnosis on breast cancer mortality and competing causes of death was studied using various competing risk models (19-21). Age was predictive for breast cancer mortality after 3.9 and 4.1 years of follow-up(19, 20), but not after 7.9 years of follow-up(21). These findings suggest that there is need for consensus on appropriate statistical models to assess the impact of age on breast cancer mortality.

It is interesting to elaborate why older patients were at higher risk of breast cancer mortality. In this study we report similar rates of distant recurrence among all age groups despite substantially higher risk of other cause mortality. Older patients had a substantially higher risk to die due to breast cancer than younger patients after diagnosis of distant recurrence. This may explain the trend for higher breast cancer mortality observed in this study. Unfortunately, there is no further information of distant recurrence available and it remains unclear if our results are explained by tumour biology or given treatment. In view of our data, we hypothesize that older patients may receive less intensive treatment of distant recurrences leading to higher breast cancer mortality. Further research hereon is highly warranted. Moreover, in the multivariable analysis, the trend between age and breast cancer mortality did not reach significance, indicating that there is a role for variation in tumour or treatment characteristics at baseline. In our study older patients were more likely to present with larger tumours than younger patients (Table 1). Previous studies have reported that tumour size is directly associated with poorer breast cancer outcomes (22) and that older patients are more likely to present with larger tumours (23). Although this might suggest there is a direct relationship between tumour size, age and breast cancer mortality, another study has described a different relationship between age, tumour size and lymph node involvement among older patients; after the age of 70, patients with smaller tumours appeared to have a higher risk of lymph node

involvement than patients with larger tumours, suggesting a poorer prognosis for older patients with smaller tumours (24).

Furthermore, older patients were less likely to receive chemotherapy despite having larger tumours (Table 1) and this could have influenced the outcomes as well. Previous studies have shown that chemotherapy in older patients is as effective as in younger patients, though risk of toxicity is higher (13, 25). Due to the very low number of older patients receiving chemotherapy, it was impossible to perform further analyses exploring the effect variation of chemotherapy on breast cancer mortality and therefore no firm conclusions regarding overtreatment or undertreatment can be derived from this data.

Obviously, other cause mortality is strongly related to age (26). To provide a full overview of the prognosis of an individual patient it is of vital importance to investigate factors that are prognostic for other cause mortality along with prognostic factors for breast cancer mortality. In patients with breast cancer, it has been reported that comorbidities are strongly related to other cause mortality (18, 27). Unfortunately, in the TEAM study information on comorbidities was only collected for a small subgroup of patients and therefore comorbidities were not included in this analysis. Geriatric indicators and comorbidities could be used to predict the risk of toxicities to provide a profound estimation of breast cancer mortality, other cause mortality and benefits and harms of treatment (28).

Some additional limitations should be mentioned. First, misclassification of cause of death could have occurred and this could possibly influence cause-specific survival outcomes(29). A sensitivity analysis was performed applying a less stringent classification of breast cancer mortality. Consistent with our main results, a similar trend for increasing breast cancer mortality with increasing age was observed. In multivariable analysis, no trend between increasing age at diagnosis and breast cancer mortality was observed. This might be explained due to a loss of power as there were fewer breast cancer mortality events. Moreover, unknown cause of death was more frequently reported among

older patients and this could have influenced our findings. Finally, a previous study has shown that older patients included in the TEAM study were relatively healthy compared to the general population, which may limit the external validity of the present findings (30).

In conclusion, this study shows that breast cancer mortality continues to increase after ten years of follow-up among postmenopausal patients diagnosed with hormone receptor-positive breast cancer regardless of the increasing other cause mortality. In older patients, breast cancer mortality remained higher compared to younger patients and this was not outweighed by substantially higher other cause mortality. A similar trend was observed in multivariable analysis, although this did not reach significance. Moreover, older patients were at a substantially higher risk of dying due to breast cancer after diagnosis of distant recurrence. These findings emphasize the impact of breast cancer on mortality among older patients and underline the need for prediction tools that include both breast cancer and other cause mortality in order to accurately balance harms and benefits of treatment.

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Disclosures

The authors have declared no conflict of interest.

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Table 1. Patient, tumour and treatment characteristics by age at diagnosis

	< 65 years			65-74 years			≥ 75 years			
	n=3369			n=1896			n=854			
	n	%	%*	n	%	%*	n	%	%*	*P*
Histological grade										
G1, well	330	9.8	10.6	200	10.5	11.5	86	10.1	11.6	0.527
G2, modeate	1721	51.1	55.5	1011	53.3	56.9	436	51.1	56.2	
G3, G4, poor	1034	30.7	33.8	553	29.2	31.6	248	29.0	32.2	
Unknown	284	8.4		132	7.0		84	9.8		
T size										
T1	1797	53.3	53.5	954	50.3	50.4	275	32.2	32.2	<0.001
T2	1353	40.2	40.4	830	43.8	43.9	501	58.7	58.7	
T3, T4	208	6.2	6.2	107	5.6	5.7	78	9.1	9.1	
Unknown	11	0.3		5	0.3		0			
N status										
N0	1437	42.7	42.8	818	43.1	43.4	348	40.7	41.1	0.842
N1	1703	50.5	50.7	954	50.3	50.4	442	51.8	52.0	
N2/N3	221	6.6	6.6	117	6.2	6.2	58	6.8	6.9	
Unknown	8	0.2		7	0.4		6	0.7		
Progesterone receptor										
Positive	2431	72.2	72.2	1330	70.1	70.1	616	72.1	72.1	0.275
Negative	938	27.8	27.8	1330	29.9	29.9	238	27.9	27.9	
Her2 receptor										
Positive	328	9.7	13.9	166	8.8	12.4	66	7.7	10.4	0.069
Negative	2000	59.4	86.1	1212	63.9	87.6	612	71.7	89.6	
Unknown	1041	30.9		518	27.3		176	20.6		
Most extensive surgery										
Mastectomy	1395	41.4	41.5	898	47.4	47.4	580	67.9	68.0	<0.001
Wide local excision	1970	58.5	58.5	997	52.6	52.6	273	32.0	32.0	
Unknown	4	0.1		1	0.1		1	0.1		
Radiotherapy										
Yes	2499	74.2	74.4	1247	65.8	66.0	420	49.2	49.3	<0.001
No	861	25.6	25.6	642	33.9	34.0	431	50.5	50.7	
Unknown	9	0.3		7	0.4		3	0.4		
Radiotherapy if wide local excision										0.001
Yes	1873	95.1	-	922	92.5	-	244	89.4	-	
No	94	4.8	-	73	7.3	-	28	10.3	-	
Unknown	3	0.2		2	0.2		1	0.4		
Chemotherapy										
Yes	1855	55.1	55.1	376	19.8	19.8	21	2.5	2.5	<0.001
No	1514	44.9	44.9	1520	80.2	80.2	833	97.5	97.5	
Endocrine therapy										
Tamoxifen followed by exemestane	1689	50.1	50.1	943	49.7	49.7	413	48.4	48.4	0.651
Exemestane	1680	49.9	49.9	953	50.3	50.3	441	51.6	51.6	
Country										
Germany	871	25.9	25.9	454	23.9	23.9	146	17.1	17.1	<0.001
Greece	110	3.3	3.3	71	3.7	3.7	26	3.0	3.0	
Netherlands and Belgium	1692	50.2	50.2	958	50.5	50.5	516	60.4	60.4	
United Kingdom and Ireland	696	20.7	20.7	413	21.8	21.8	166	19.4	19.4	

*proportional distribution after multiple imputation

Table 2. Cause of death by age at diagnosis

	< 65 years		65-74 years		≥ 75 years	
All deaths	n=551	%	n=467	%	n=443	%
Breast cancer	412	74.8	250	53.5	134	30.2
Second primary tumour	66	12.0	58	12.4	33	7.4
Endometrial cancer	1	0.2	2	0.4	0	0
Cardiac disorder	13	2.4	37	7.9	56	12.6
Thromboembolism	3	0.5	2	0.4	11	2.5
Pulmonary disorder	5	0.9	18	3.9	15	3.4
Cerebral disorder	4	0.7	14	3.0	21	4.7
Vascular disorder	1	0.2	2	0.4	3	0.7
Other	21	3.8	50	10.7	111	25.1
Unknown	21	3.8	34	7.3	59	13.3

Percentages represent the proportion of all deaths by age group.

Table 3. Survival outcomes by age at diagnosis

	Cumulative incidence (%) (95% CI)					
	Five years after diagnosis	Ten years after diagnosis	Univariate sHR[#] (95% CI)	*P* value[##]	Multivariable sHR[#] (95% CI)	*P* value[##]
Breast cancer mortality						
< 65	6.4 (5.6-7.2)	11.7 (10.2-13.2)	Reference	0.013	Reference	0.055
65-74	6.6 (5.5-7.7)	12.7 (11.2-14.2)	1.08 (0.92-1.27)		1.11 (0.94-1.31)	
≥ 75	8.9 (7.0-10.8)	15.6 (13.1-18.0)	1.30 (1.06-1.58)		1.18 (0.94-1.48)	
Other cause mortality						
< 65	1.2 (0.7-1.5)	3.7 (3.1-4.3)	Reference	<0.001	Reference	<0.001
65-74	4.9 (3.9-5.9)	10.6 (9.2-12.0)	2.88 (2.33-3.56)		2.44 (1.95-3.06)	
≥ 75	14.6 (12.3-17.0)	33.4 (30.2-36.5)	10.53 (8.63-12.86)		7.97 (6.31-10.06)	
Distant recurrence						
< 65	10.2 (9.2-11.3)	17.8 (16.4-19.2)	Reference	0.462	Reference	0.995
65-74	10.0 (8.6-11.3)	18.8 (16.9-20.8)	1.02 (0.89-1.17)		1.05 (0.90-1.23)	
≥ 75	12.3 (10.1-14.5)	18.8 (16.0-21.5)	1.07 (0.89-1.29)		0.97 (0.79-1.20)	

[#] Calculated for complete follow-up time. [##] *P* for trend.

Figures

Figure 1.

Title: Cumulative incidence of mortality by cause of death per age group

Legend: Stacked cumulative incidence of breast cancer mortality (red) and other cause mortality (blue) by age group from time since diagnosis.