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Breast Cancer

Impact of Older Age and Comorbidity on Locoregional and Distant Breast Cancer Recurrence: A Large Population-Based Study

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Breast cancer • Geriatric oncology • Locoregional recurrence • Distant recurrence • Competing risk

Abstract

Background. Studies have demonstrated worse breast cancer-specific mortality with older age, despite an increasing risk of dying from other causes due to comorbidity (competing mortality). However, findings on the association between older age and recurrence risk are inconsistent. The aim of this study was to assess incidences of locoregional and distant recurrence by age, taking competing mortality into account.

Materials and Methods. Patients surgically treated for non-metastasized breast cancer between 2003 and 2009 were selected from The Netherlands Cancer Registry. Cumulative incidences of recurrence were calculated considering death without distant recurrence as competing event. Fine and Gray analyses were performed to characterize the impact of age (70–74 [reference group], 75–79, and ≥80 years) on recurrence risk.

Results. A total of 18,419 patients were included. Nine-year cumulative incidences of locoregional recurrence were 2.5%, 3.1%, and 2.9% in patients aged 70–74, 75–79, and ≥80 years, and 9-year cumulative incidences of distant recurrence were 10.9%, 15.9%, and 12.7%, respectively. After adjustment for tumor and treatment characteristics, age was not associated with locoregional recurrence risk. For distant recurrence, patients aged 75–79 years remained at higher risk after adjustment for tumor and treatment characteristics (75–79 years subdistribution hazard ratio [sHR], 1.25; 95% confidence interval [CI], 1.11–1.41; ≥80 years sHR, 1.03; 95% CI, 0.91–1.17).

Conclusion. Patients aged 75–79 years had a higher risk of distant recurrence than patients aged 70–74 years, despite the higher competing mortality. Individualizing treatment by using prediction tools that include competing mortality could improve outcome for older patients with breast cancer. ***The Oncologist*** 2020;25:e24–e30

Implications for Practice: In this population-based study of 18,419 surgically treated patients aged 70 years or older, patients aged 75–79 years were at higher risk of distant recurrence than were patients aged 70–74 years. This finding suggests that patients in this age category are undertreated. In contrast, it was also demonstrated that the risk of dying without a recurrence strongly increases with age, and patients with a high competing mortality risk are easily overtreated. To identify older patients who may benefit from more treatment, clinicians should therefore take competing mortality risk into account. Prediction tools could facilitate this and thereby improve treatment strategy.

Introduction

Over 30% of all newly diagnosed patients with breast cancer are 70 years or older, and this proportion is likely to increase even further because of the aging of Western populations [1]. For this growing patient population, treatment decisions can prove challenging given the lack of evidence caused by underrepresentation of older patients in clinical trials. Generally, older patients tend to receive less extensive treatment compared with younger patients [2]. As ageing comes with comorbid diseases, the risk of dying from other causes than breast cancer, so-called competing mortality risk, strongly increases with age [3, 4]. Therefore, it is essential to take competing mortality risks into account when estimating breast cancer outcomes and the benefit of treatment in the older population.

It has been suggested that age is an independent risk factor for worse breast cancer outcome [5–7]. Several

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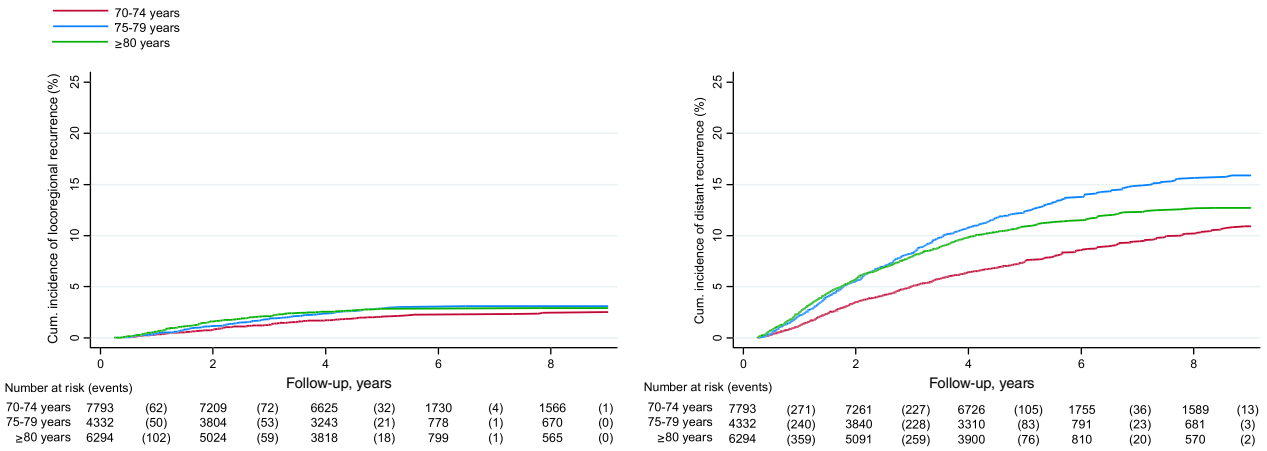

Figure 1. Cumulative incidence of locoregional recurrence and distant recurrence by age group.

studies have demonstrated that increasing age was associated with worse breast cancer-specific mortality, despite increasing competing mortality risks [3, 5, 6]. One would expect the worse breast cancer-specific mortality to be accompanied with a higher risk of disease recurrence. However, research findings on the association between age and recurrence risk are inconsistent, as some studies demonstrate a higher recurrence risk with age, whereas other studies do not find such association [3, 5–9]. Different handling of competing mortality risks could play a role in the discrepant findings.

Therefore, the aim of this study was to assess the incidences of locoregional and distant recurrence by age at diagnosis among patients aged ≥70 years while taking competing mortality risks into account.

Materials and Methods

All surgically treated patients diagnosed with nonmetastasized invasive breast cancer aged 70 years or older between 2003 and 2009 were selected from The Netherlands Cancer Registry (NCR), which is hosted by The Netherlands Comprehensive Cancer Organisation (IKNL). The NCR receives reports of diagnosed malignancies from the nationwide network and registry of histo- and cytopathology in The Netherlands (PALGA), which are completed by the national hospital discharge databank.

Trained data managers of the IKNL collect data on diagnosis, staging, and treatment directly from the medical records using international coding rules. Breast cancer stage was defined using the TNM Classification of Malignant Tumours (6th edition) [10]. Clinical stage was used if pathological T or N stage was unknown. Estrogen receptor and progesterone receptor status were considered positive if ≥10% of tumor cells demonstrated positive nuclear staining. For the current project, additional information on comorbidity at time of diagnosis and recurrences was retrospectively collected from the medical records. Five-year follow-up was available for the total cohort, and longer follow-up was available for a subcohort of 5,115 patients diagnosed between 2007 and 2009. Vital status was obtained through linkage of NCR data with the Municipal Personal Records database.

Patients were categorized into three groups based on age at diagnosis (70–74 [reference group], 75–79, and ≥80 years) following recommendations of the International Society of Geriatric Oncology [11]. Comorbidity was aggregated using the Charlson Comorbidity Index (CCI) [12]. Study endpoints were time from diagnosis to locoregional (ipsilateral breast, chest wall, axillary lymph nodes, and supraclavicular lymph nodes) and distant recurrence by age group [13]. If a patient had both a locoregional and distant recurrence, the event was defined as distant recurrence.

Statistical Analysis

The statistical analysis was performed with SPSS 23.0 and STATA 12.1. Multiple imputation by chained equation was performed to account for missing values, assuming that data were missing at random [14]. For each imputed variable, imputation models were applied that included incomplete and complete variables. Analyses were based on the pooled results of 25 imputed sets (according to Rubin's rules) [15]. Differences between the age groups were assessed by means of Pearson's chi square tests. Cumulative incidences of recurrence were calculated using the Cumulative Incidence Competing Risk method with death without distant recurrence as competing event [16]. For locoregional recurrence, distant recurrence was also a competing event. Graphically depicted were cumulative incidences of locoregional and distant recurrence by age group, distant recurrence, and competing mortality within each age group and competing mortality by age and comorbidity status (CCI score, 0 and ≥1). In addition, distant recurrence risk was graphically depicted by age and comorbidity in supplemental online Figure 1 as exploratory analysis. The association between age and recurrence risk was assessed by performing univariable and multivariable Fine and Gray analysis using all available follow-up data, and the effect was expressed as subdistribution hazard ratio (sHR) [16]. Covariates were included in the multivariable model if judged to be clinically relevant. Tumor characteristics (histologic grade, tumor size, nodal status, hormone-receptor status, Her2Neu overexpression) were included, as older patients generally present with more advanced disease. Furthermore, patients up to 75 years were included in the Dutch mass screening program, which accounts for the

Table 1. Tumor and treatment characteristics by age at diagnosis

Characteristics	All patients (*n* = 18,419), *n* (%)	%[a]	70–74 yr (*n* = 7,793), *n* (%)	%[a]	75–79 yr (*n* = 4,332), *n* (%)	%[a]	≥80 yr (*n* = 6,294), *n* (%)	%[a]	*p* value for trend
Charlson Comorbidity Index score									<.001
0	4,459 (24.2)	58.4	2,109 (27.1)	62.9	1,004 (23.2)	57.3	1,346 (21.4)	53.5	
1	1,829 (9.9)	25.1	733 (9.4)	23.1	452 (10.4)	25.6	644 (10.2)	27.2	
≥2	122 (6.6)	16.5	450 (5.8)	14.0	321 (7.4)	17.1	449 (7.1)	19.3	
Unknown	10,911 (59.2)		4,501 (57.8)		2,555 (59.0)		3,855 (61.3)		
Histological grade									<.001
1	4,198 (22.8)	24.6	2,098 (26.9)	28.7	872 (20.1)	22.0	1,228 (19.5)	21.2	
2	8,390 (45.6)	48.9	3,560 (45.7)	48.7	1,902 (43.9)	47.8	2,928 (46.5)	50.0	
3	4,587 (24.9)	26.5	1,649 (21.2)	22.6	1,235 (28.5)	30.2	1,703 (27.1)	28.8	
Unknown	1,244 (6.8)		486 (6.2)		323 (7.5)		435 (6.9)		
T size									<.001
T1	9,827 (53.4)	53.4	5,530 (71.0)	71.1	2,125 (49.1)	49.1	2,172 (34.5)	34.6	
T2	7,421 (40.3)	40.4	1,987 (25.5)	25.5	1,936 (44.7)	44.8	3,498 (55.6)	55.7	
T3/4	1,138 (6.2)	6.2	266 (3.4)	3.4	262 (6.1)	6.1	610 (9.7)	9.7	
Unknown	33 (0.2)		10 (0.1)		9 (0.2)		14 (0.2)		
N status									<.001
Negative	12,133 (65.9)	66.3	5,624 (72.2)	72.4	2,738 (63.2)	63.5	3,771 (59.9)	60.8	
Positive	6,193 (33.6)	33.7	2,153 (27.6)	27.7	1,582 (36.5)	36.6	2,458 (39.1)	39.2	
Unknown	93 (0.5)		16 (0.2)		12 (0.3)		65 (1.0)		
HR status									<.001
ER and/or PR positive	15,053 (81.7)	85.8	6,497 (83.4)	87.3	3,474 (80.2)	84.0	5,082 (80.7)	85.2	
ER and PR negative	2,446 (13.3)	14.2	919 (11.8)	12.7	650 (15.0)	16.0	877 (13.9)	14.9	
Unknown	920 (5.0)		377 (4.8)		208 (4.8)		335 (5.3)		
Her2-receptor status									.008
Negative	11,178 (60.7)	89.1	4,908 (63.0)	90.2	2,594 (59.9)	87.9	3,676 (58.4)	88.6	
Positive	1,302 (7.1)	10.9	508 (6.5)	9.8	340 (7.9)	12.1	454 (7.2)	11.4	
Unknown	5,939		2,377 (30.5)		1,398 (32.3)		2,164 (34.4)		
Most extensive surgery									<.001
Mastectomy	11,111 (60.3)		3,439 (44.1)		2,684 (62.0)		4,988 (79.3)		
BCS	7,308 (39.7)		4,354 (55.9)		1,648 (38.0)		1,306 (20.8)		
Surgical margins									<.001
Free	17,204 (93.4)		7,348 (94.3)		4,052 (93.5)		5,804 (92.2)		
Not free	807 (4.4)		297 (3.8)		192 (4.4)		318 (5.1)		
Unknown	408		148 (1.9)		88 (2.0)		172 (2.7)		
ALND									<.001
Yes	8,560 (46.5)		2,981 (38.3)		2,169 (50.1)		3,410 (54.2)		
No	9,859 (53.5)		4,812 (61.8)		2,163 (49.9)		2,884 (45.8)		
Radiotherapy after BCS									<.001
Yes	6,761 (92.5)		4,243 (97.5)		1,570 (95.3)		948 (72.6)		
No	547 (7.5)		111 (2.6)		78 (4.7)		358 (27.4)		
Adjuvant endocrine therapy in HR+									<.001
Yes	8,026 (53.3)	52.7	2,892 (44.5)	43.9	2,025 (58.3)	57.5	3,109 (61.2)	60.6	
No	7,027 (46.7)	47.3	3,605 (55.5)	56.1	1,449 (41.7)	42.5	1,973 (38.8)	39.4	
Chemotherapy									<.001
Yes	420 (2.3)		319 (4.1)		70 (1.6)		31 (0.5)		
No	17,999 (97.7)		7,474 (95.9)		4,262 (98.4)		6,263 (99.5)		

[a]Proportional distribution after multiple imputation.

Abbreviations: ALND, axillary lymph node dissection; BCS, breast-conserving surgery; ER, estrogren receptor; HR, hormone receptor; PR, progesterone receptor.

detection of more early stage disease below this age limit. Treatment characteristics that were included in the multivariable model were most extensive surgery, surgical margins, axillary lymph node dissection, radiotherapy, adjuvant endocrine treatment, and chemotherapy. Last, year of diagnosis was included. Sensitivity analyses were performed with truncated 5-year follow-up to test the robustness of our results. All statistical tests were two-sided and a *p* value smaller than .05 was considered statistically significant.

Results

Between 2003 and 2009, 19,748 patients aged 70 years or older were surgically treated for nonmetastasized breast cancer, and 18,419 patients with available follow-up were included in this study. At time of diagnosis, 7,793 patients (42.3%) were aged 70–74, 4,332 patients (23.5%) were aged 75–79, and 6,294 patients (34.2%) were aged ≥80 years, and the proportion of patients with a CCI score of 1 or higher increased with age (37.1%, 42.7%, and 46.5% in patients aged 70–74, 75–79, and ≥80 years, respectively; $p < .001$). Tumor and treatment characteristics by age group are presented in Table 1. With increasing age, patients more often presented with larger tumors and more node-positive disease (27.7%, 36.6%, and 39.2% in patients aged 70–74, 75–79, and ≥80 years; $p < .001$). Furthermore, patients aged 70–74 years more often presented with grade 1 tumors (28.7%) compared with patients aged 75–79 and ≥80 years (22.0% and 21.2%; $p < .001$). With increasing age group, type of surgery was more often a mastectomy rather than a breast-conserving surgery (BCS), and the proportion radiotherapy after BCS was lower in patients aged ≥80 years (72.6%) compared with patients aged 70–74 and 75–79 years (97.5% and 95.3%; $p < .001$). Notably, chemotherapy use was low in all age groups (4.1%, 1.6%, and 0.5% for patients aged 70–74, 75–79, and ≥80 years).

Median follow-up was 5.0 years (interquartile range [IQR], 3.1–5.0) for the total cohort and 6.3 years (IQR, 3.3–8.1 years) for the subcohort with longer follow-up. During follow-up, 815 of 7,793 patients aged 70–74, 693 of 4,332 patients aged 75–79, and 892 of 6,294 patients aged ≥80 years had a locoregional or distant recurrence. Figure 1 shows the cumulative incidences of locoregional and distant recurrence by age group. Nine-year cumulative incidences of locoregional recurrence were 2.5%, 3.1%, and 2.9% in patients aged 70–74, 75–79, and ≥80 years. Nine-year cumulative incidences of distant recurrence were 10.7%, 15.6%, and 12.7%, respectively (Table 2). The stacked cumulative incidences of distant recurrence and competing mortality for each age group are shown in Figure 2, which demonstrates the strong increase in competing mortality with age. Furthermore, Figure 3 confirms that having comorbidity clearly increases the competing mortality risk within each age category. No such trend was seen between having comorbidity and distant recurrence risk (supplemental online Fig. 1).

Univariable analysis showed that patients aged 75–79 and ≥80 years had a higher risk of locoregional recurrence (75–79 years sHR, 1.32; 95% CI, 1.05–1.66; ≥80 years sHR, 1.32; 95% CI, 1.07–1.63) and distant recurrence (75–79 years sHR, 1.63; 95% CI, 1.46–1.83; ≥80 years sHR, 1.39; 95% CI,

Table 2. Risk of recurrence by age at diagnosis

Age at diagnosis	Cumulative incidence, % (95% CI)		Competing events, % (95% CI)		Univariable sHR (95% CI)	*p* value	Multivariable sHR (95% CI)[a]	*p* value
	5 yr	9 yr	5 yr	9 yr				
Locoregional recurrence								
70–74 yr	2.1 (1.8–2.4)	2.5 (2.1–3.0)	16.3 (15.5–17.2)	30.9 (29.2–32.6)	Reference		Reference	
75–79 yr	2.8 (2.3–3.3)	3.1 (2.6–3.7)	28.6 (27.3–30.0)	49.0 (46.6–51.4)	1.32 (1.05–1.66)	.018	1.04 (0.82–1.33)	.743
≥80 yr	2.8 (2.5–3.3)	2.9 (2.5–3.4)	44.6 (43.4–45.8)	71.3 (69.3–73.2)	1.32 (1.07–1.63)	.009	0.86 (0.68–1.09)	.219
Distant recurrence								
70–74 yr	7.4 (6.9–8.0)	10.9 (10.0–11.9)	9.5 (8.8–10.1)	21.2 (19.7–22.7)	Reference		Reference	
75–79 yr	12.3 (11.4–13.3)	15.9 (14.5–17.3)	17.4 (16.3–18.5)	35.2 (32.9–37.6)	1.63 (1.46–1.83)	<.001	1.25 (1.11–1.41)	<.001
≥80 yr	10.9 (10.1–11.7)	12.7 (11.8–13.7)	35.4 (34.2–36.6)	61.1 (59.0–63.1)	1.39 (1.25–1.55)	<.001	1.03 (0.91–1.17)	.606

[a]This multivariable analysis included year of diagnosis, histologic grade, tumor size, nodal status, hormone receptor status, Her2Neu overexpression, most extensive surgery, surgical margins, axillary lymph node dissection, adjuvant radiotherapy, adjuvant hormonal therapy, and chemotherapy.
Abbreviations: CI, confidence interval; sHR, subdistribution hazard ratio.

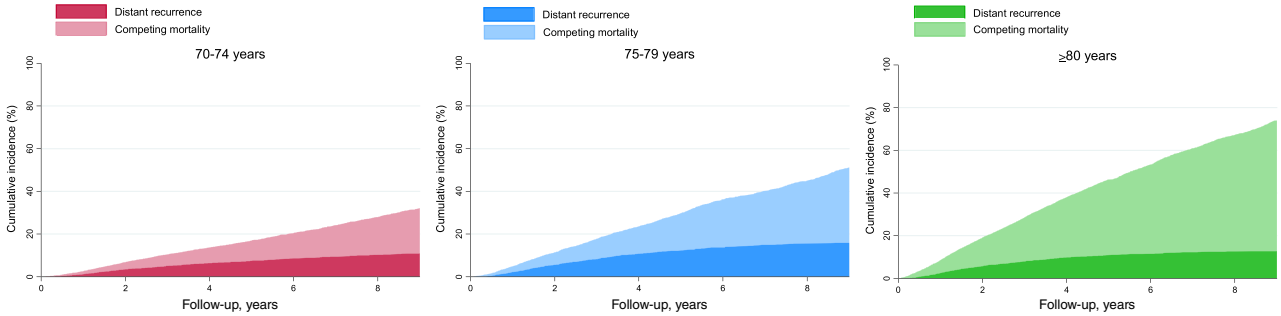

Figure 2. Stacked cumulative incidences of distant recurrence and competing mortality by age group.

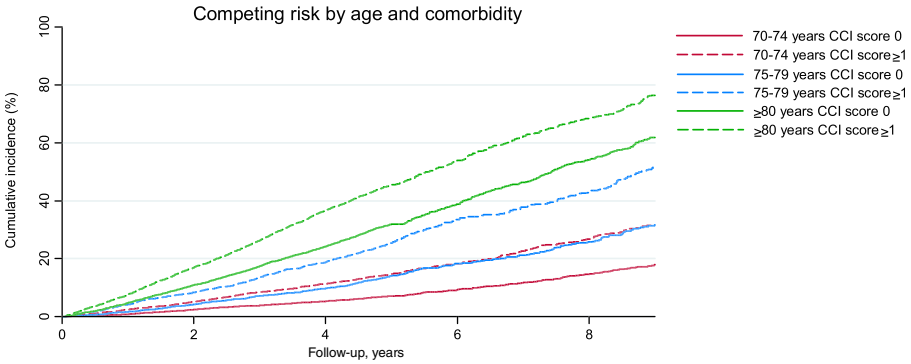

Figure 3. Competing mortality risk by age group and comorbidity status (Charlson Comorbidity Index [CCI] score 0 and ≥1).

1.25–1.55) compared with patients aged 70–74 years (Table 2). The association between age and locoregional recurrence risk was no longer significant after adjustment for tumor and treatment characteristics in multivariable analysis (75–79 years sHR, 1.04; 95% CI, 0.82–1.33; ≥80 years sHR, 0.86; 95% CI, 0.68–1.09), whereas the association between age and distant recurrence risk remained significant for patients aged 75–79 years (75–79 years sHR, 1.25; 95% CI, 1.11–1.41; ≥80 years sHR, 1.03; 95% CI, 0.91–1.17; Table 2). The sensitivity analysis with truncated 5-year follow-up yielded similar results (supplemental online Table 1).

Discussion

The main finding of our study is that patients aged 75–79 years at diagnosis were at higher risk of distant recurrence compared with patients aged 70–74 years after adjustment for tumor and treatment characteristics, despite the higher competing mortality risk.

Our finding that age at diagnosis was not associated with locoregional recurrence risk is in line with previous studies [6–9, 17, 18]. Moreover, cumulative incidences of locoregional recurrence were low in all age groups despite the fact that we included all surgically treated patients with non-metastasized breast cancer, and almost half of the patients was not treated systemically. Plausibly, some of the patients died from other causes than breast cancer before they could get a recurrence. Low locoregional recurrence risks among older patient have prompted research on the de-escalation of locoregional treatments for this population. The CALGB 9343 trial demonstrated that radiotherapy after breast-conserving surgery can be safely omitted in patients aged ≥70 years with stage 1 breast cancer who are treated with endocrine treatment [19]. Ongoing studies may confirm this for broader patient selections or other locoregional treatments such as the axillary treatment. The low cumulative incidences raise the question of how much there is to gain in reducing the locoregional recurrence risk in older patients and whether treatments that only reduce locoregional recurrence risk but do not affect breast cancer-specific survival, such as radiotherapy after BCS, are always appropriate [11, 20].

In contrast to consistent findings regarding the lack of association with locoregional recurrence risk, previous studies have reported inconsistent findings on the association between age and distant recurrence. One study reported an increasing risk of distant recurrence with age [7], whereas other studies reported a nonsignificant trend [3, 6] or no association [8, 9]. Different study populations and statistical models may play a role in the discordant findings. For example, in the randomized phase III Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial in which two endocrine regimens were compared, increasing age was associated with a higher risk of distant recurrence [7]. However, it is questionable whether these findings apply to the general population, as older patients included in trials are generally a healthy selection of the general population and, consequently, the impact of competing mortality is lower [21]. A second study, performed in a regional population-based cohort, demonstrated an association between increasing age and recurrence risk when combining locoregional and distant recurrence, but only a nonsignificant trend when distant recurrence was analyzed separately, possibly as a result of insufficient power [6]. With regard to statistical models, almost all previous studies used the Cox proportional hazards model that

does not take competing mortality into account [6–9]. However, because the influence of competing mortality seems rather large in the older population of patients with breast cancer, the Fine and Gray model is considered more appropriate [22].

We propose two possible explanations for our finding that patients aged 75–79 years were at higher risk of distant recurrence compared with patients aged 70–74 years. First, undertreatment could have played a role. Although the analyses were adjusted for treatment characteristics in the analysis, we lacked details on treatment extensiveness such as specific type and duration. Studies have demonstrated that older age is associated with increased discontinuation of and nonadherence to endocrine treatment [23, 24]. Also, chemotherapy toxicity with subsequent dose reduction or discontinuation increases with age, although this could only have had a limited effect because few patients received chemotherapy [25]. Second, aging of the immune system could have played a role. Several studies have related decreased cellular immunity with decreased tumor defense or worse breast cancer prognosis [26].

As the proposed explanations for the higher risk of distant recurrence in patients aged 75–79 both imply an age-dependent trend, a similar association among patients ≥80 years would be expected. The fact that we did not observe this can be explained by the higher competing mortality risk, but age-selective underdetection of recurrences may also have played a role. It is likely that underdetection increases with age because more patients refrain from visiting a doctor or do not wish to undergo diagnostic testing with age, and clinicians may refrain from diagnostic testing in patients with limited residual life expectancies. A study showed that 33% of nursing home patients with suspected breast cancer are not referred for further testing [27].

The major strength of our study is that the results are applicable to the general population of older patients with breast cancer, as our study was performed in a nationwide population-based cohort. To our knowledge, this is one of the largest population-based cohort with information on comorbidity and recurrence. Furthermore, the prevalence of comorbidity was similar to the prevalence in two large population-based studies performed in the Danish and U.S. populations [28, 29]. Of course, this study also has its limitations. First, no detailed information on treatment extensiveness and adherence was available. Furthermore, because we used observational follow-up data, age-selective underdetection is likely present and could not be taken into account. Notably, this could not have explained the higher distant recurrence risk for patients aged 75–79 years, because underdetection will increase with age.

Our findings suggest that some older patients may be undertreated, but they also demonstrate that older patients have a higher competing mortality risk. Therefore, patient selection for treatment should focus not only on breast cancer outcome but also on distinguishing patients with high from patients with low competing mortality risk, as only the latter may benefit from extensive treatment. In this context, prediction tools could play an important role in improving breast cancer management for older patients, as such tools could predict outcome with and without treatment, while taking into account competing mortality risk by including comorbidity as a predictor because it is well known and demonstrated in our study that having comorbidity increases the competing mortality risk. To facilitate the development of such prediction tools, prognostic studies should focus on the predictive value of comorbidity scores and geriatric parameters from geriatric screenings or assessments in addition to disease characteristics. The ultimate goal is to not only predict recurrence risk and survival but also to predict risk of toxicity, quality of life, and physical functioning, as these outcomes are (more) relevant for older patients.

Conclusion

Our study demonstrated that patients aged 75–79 years were at increased risk of distant recurrence compared with patients aged 70–74 years when differences in tumor and treatment characteristics were taken into account, regardless of the increasing competing mortality risks with age. Individualizing treatment by using prediction tools that include competing mortality could improve outcome for older patients with breast cancer.

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Disclsoures

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References

1. DeSantis CE, Ma J, Goding Sauer A et al. Breast cancer statistics, 2017, racial disparity in mortality by state. CA Cancer J Clin 2017;67:439–448.

2. Bastiaannet E, Liefers GJ de Craen AJ et al. Breast cancer in elderly compared to younger patients in the Netherlands: Stage at diagnosis, treatment and survival in 127,805 unselected patients. Breast Cancer Res Treat 2010;124:801–807.

3. Derks MGM, Bastiaannet E, van de Water W et al. Impact of age on breast cancer mortality and competing causes of death at 10 years follow-up in the adjuvant TEAM trial. Eur J Cancer 2018;99:1–8.

4. Yancik R, Wesley MN, Ries LA et al. Effect of age and comorbidity in postmenopausal breast

cancer patients aged 55 years and older. JAMA 2001;285:885–892.

5. 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;307:590–597.

6. Kiderlen M, van de Water W, Bastiaannet E et al. Survival and relapse free period of 2926 unselected older breast cancer patients: A FOCUS cohort study. Cancer Epidemiol 2015;39:42–47.

7. van de Water W, Seynaeve C, Bastiaannet E et al. Elderly postmenopausal patients with breast cancer are at increased risk for distant recurrence: A tamoxifen exemestane adjuvant multinational study analysis. ***The Oncologist*** 2013;18:8–13.

8. van der Leij F, van Werkhoven E, Bosma S et al. Low risk of recurrence in elderly patients treated with breast conserving therapy in a single institute. Breast 2016;30:19–25.

9. Geiger AM, Thwin SS, Lash TL et al. Recurrences and second primary breast cancers in older women with initial early-stage disease. Cancer 2007;109:966–974.

10. Greene FL, Page DL, Fleming ID et al., eds. AJCC Cancer Staging Manual. 6th ed. New York, NY: Spinger, 2002.

11. Biganzoli L, Wildiers H, Oakman C et al. Management of elderly patients with breast cancer: updated recommendations of the International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA). Lancet Oncol 2012;13:e148–e160.

12. Charlson ME, Pompei P, Ales KL et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–383.

13. Moossdorff M, van Roozendaal LM, Strobbe LJ et al. Maastricht Delphi consensus on event definitions for classification of recurrence in breast cancer research. J Natl Cancer Inst 2014;106.

14. Sterne JA, White IR, Carlin JB et al. Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. BMJ 2009;338:b2393.

15. Marshall A, Altman DG, Holder RL et al. Combining estimates of interest in prognostic modelling studies after multiple imputation: Current practice and guidelines. BMC Med Res Methodol, 2009;9:57.

16. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: Competing risks and multi-state models. Stat Med 2007;26:2389–2430.

17. Truong PT, Lee J, Kader HA et al. Locoregional recurrence risks in elderly breast cancer patients treated with mastectomy without adjuvant radiotherapy. Eur J Cancer 2005;41:1267–1277.

18. Kontos M, Allen DS, Agbaje OF et al. Factors influencing loco-regional relapse in older breast cancer patients treated with tumour resection and tamoxifen. Eur J Surg Oncol, 2011;37:1051–1058.

19. Hughes KS, Schnaper LA, Bellon JR et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: Long-term follow-up of CALGB 9343. J Clin Oncol 2013;31:2382–2827.

20. Mislang AR, Cheung KL, Hamaker ME et al. Controversial issues in the management of older adults with early breast cancer. J Geriatr Oncol 2017;8:397–402.

21. van de Water W, Kiderlen M, Bastiaannet E et al. External validity of a trial comprised of elderly patients with hormone receptor-positive breast cancer. J Natl Cancer Inst 2014;106:dju051.

22. de Glas NA, Kiderlen M, Vandenbroucke JP et al. Performing survival analyses in the presence of competing risks: A clinical example in older breast cancer patients. J Natl Cancer Inst 2016;108.

23. van Herk-Sukel, MP, van de Poll-Franse LV, Voogd AC et al. Half of breast cancer patients discontinue tamoxifen and any endocrine treatment before the end of the recommended treatment period of 5 years: A population-based analysis. Breast Cancer Res Treat 2010;122:843–851.

24. van de Water W, Bastiaannet E, Hille ET et al. Age-specific nonpersistence of endocrine therapy in postmenopausal patients diagnosed with hormone receptor-positive breast cancer: A TEAM study analysis. ***The Oncologist*** 2012;17:55–63.

25. Loibl S, von Minckwitz G, Harbeck N et al. Clinical feasibility of (neo)adjuvant taxane-based chemotherapy in older patients: Analysis of >4,500 patients from four German randomized breast cancer trials. Breast Cancer Res 2008;10:R77.

26. McCoy JL, Rucker R, Petros JA. Cell-mediated immunity to tumor-associated antigens is a better predictor of survival in early stage breast cancer than stage, grade or lymph node status. Breast Cancer Res Treat 2000;60:227–234.

27. Hamaker ME, Hamelinck VC, van Munster BC et al. Nonreferral of nursing home patients with suspected breast cancer. J Am Med Dir Assoc 2012;13:464–469.

28. Schonberg MA, Marcantonio ER, Li D et al. Breast cancer among the oldest old: Tumor characteristics, treatment choices, and survival. J Clin Oncol 2010;28:2038–2045.

29. Land LH, Dalton SO, Jensen MB et al. Impact of comorbidity on mortality: A cohort study of 62,591 Danish women diagnosed with early breast cancer, 1990-2008. Breast Cancer Res Treat 2012; 131:1013–1020.

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