Patterns of care and prognosis of older women with breast cancer

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PATTERNS OF CARE AND PROGNOSIS OF OLDER WOMEN WITH BREAST CANCER

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Chapter 1

General introduction

INTRODUCTION

Breast cancer is the most frequently diagnosed malignancy among women worldwide, especially in developed countries.[1]

The ageing population results in an absolute increase in older women diagnosed with breast cancer.[2] This specific population is underrepresented in the available evidence about the treatment of cancer.[3,4] Therefore, there is no solid evidence on how to treat older women with breast cancer. Exactly this group is such a complex patient group, for several reasons. When we consider chronological age, we have to deal with a very heterogeneous population. For young breast cancer patients, in most of the cases, we can assume that breast cancer is the only disease to be treated at that moment. However, older women have a higher chance to already have been diagnosed with other diseases, like cardiovascular diseases and diabetes.[5] On the other hand, there is also a large group of older women who are very fit and furthermore healthy, who we can consider as biologically young. There are a few studies performed considering other diseases in relation to the treatment and prognosis of breast cancer.[6-9]

Another reason of the complexity of the population of older women with breast cancer is one of the most important consequences of comorbidity: death from another cause than breast cancer. In an undefined number of cases, comorbidity has a greater impact on the life expectancy than breast cancer itself. For instance, when we consider a patient suffering from advanced stage cardiac failure and a new diagnosis of early stage breast cancer. It is imaginable that in this specific patient, the comorbid disease has a higher chance to result in early death, than the breast cancer. When a study is performed with the aim to investigate breast cancer specific prognosis, in this case the cardiac failure can blur the results, because there is a considerable chance that this patient will die of cardiac problems, before a breast cancer recurrence would have occurred. This issue is called competing mortality, and in current literature, this issue is underexposed.

Due to the underrepresentation of older patients in most of the breast cancer studies, it is questionable if the results of the most important breast cancer trials can be extrapolated to the older population. It would be very valuable to repeat important therapeutic studies among older women. However, this would be a very time consuming and difficult mission to undertake. Therefore, novel study designs using population based data sources would be very efficient to solve this problem. One of the most important challenges to handle in population based, retrospective, studies is the issue of *confounding by indication*.[10] This type of bias arises when outcomes of different therapies are directly compared in a retrospective database. In these studies, in contrast to clinical trials, different therapies are used, or not

used, on an individual basis. The reason of choosing for a specific therapy can be related to the outcome. For instance, we consider the patient with advanced stage cardiac failure again. When she is diagnosed with (early stage) breast cancer, the cardiac failure is probably a contraindication for surgery, so she does not undergo breast surgery. Also, she has a relatively short life expectancy. But when she dies (from cardiac failure), there is no causal relationship between the omission of breast surgery and death. However, it is not impossible to draw conclusions on prognosis from population based studies. For example, the instrumental variable might provide a solution. A variable that is related to the treatment choice, but not directly to the outcome.[10] When there are considerable international differences between treatment strategies, country can be a good instrumental variable, when health care systems are similar and when there are no reasons to assume general life expectancy of the populations differ.

In this thesis, the aim is to investigate international patterns of care for older women with breast cancer, and also the impact of these differences on prognosis. Furthermore, we had the objective to assess the impact of different specific co-morbid diseases, but also the use of non-cancer drugs on breast cancer prognosis. Finally, we aim to develop a new predictive model, specifically for older women with breast cancer, in which as well patient-related as tumour-related factors are included. The model could be used in clinical decision making in the treatment of breast cancer in older women.

DATA SOURCES

This thesis is part of the FOCUS project: Female breast cancer in the elderly: Optimizing Clinical guidelines USing clinico-pathological and molecular data. This program was initiated after receiving a program grant from the Dutch Cancer Society in 2007. For this project, the largest, most detailed population-based database of older women with breast cancer was built. This database consists of all 3,672 consecutive breast cancer patients, aged 65 years or older at the time of diagnosis, diagnosed between 1997 and 2004 in the South West region of The Netherlands. In addition to the standard data included in the cancer registry, very detailed information was gathered about the tumour, treatment, but also on the occurrence of a recurrence during follow-up. Also, patient-related information was registered, including comorbidity and social economic status. Probably most innovative of the database was the additional gathering of tumour tissues of a very large part of the included patients, which resulted in the linkage of detailed clinical data to validated pathological information from our own laboratory.

A considerable part of this thesis is established with data from the FOCUS database. Also, data from the Tamoxifen Exemestane Adjuvant Multinational (TEAM) study were used. This is a large randomized clinical trial among breast cancer patients investigating different adjuvant endocrine therapy regimens. This trial is special because of the broad inclusion criteria, without upper age limit. Therefore, relatively much older women were included in this study. Furthermore, we used data from national cancer registries from several countries. For one study we had the opportunity to use the database of the European Society of Breast Cancer Specialists (EUSOMA), which consists of more than 40.000 breast cancer patients across six different European countries.

OUTLINE

Part 1 of this thesis describes patterns of care across different countries. In **chapter 2**, treatment and survival of older women with breast cancer is crudely compared between several European countries and the US. **Chapter 3** highlights two countries from the former chapter, Ireland and The Netherlands. In this chapter a more detailed comparison of treatment and survival is described. The European Society of Breast Cancer Specialists (EUSOMA) defined a set of quality indicators for the management of breast cancer. In **chapter 4**, compliance to these indicators is assessed according to age.

In **Part 2**, the impact of non-cancer related factors are studied to find out if there is an impact on the cancer specific prognosis. Especially in older patients, there is a substantial chance of the presence of any comorbidities at the time of diagnosing breast cancer. It is hypothesized that there could be a interaction between the existence of specific diseases and the prognosis of breast cancer. Therefore, in **chapter 5** a study assessing the impact of comorbidity on the prognosis of older breast cancer patients is described. In **chapter 6**, one specific comorbidity, diabetes, is explored to find out if there is an association between having this disease and the prognosis of breast cancer patients. Concerning the co-existence of diabetes at the time of breast cancer diagnosis, it has been hypothesized that the use of metformin could have a positive effect on the prognosis of breast cancer. Also, other drugs, that have not been registered as anti-cancer medication, have been suggested to have a probable impact on cancer-prognosis. In **chapter 7**, the impact of the use of three commonly used non-cancer medications on the cancer-specific prognosis is assessed among the patients included in the TEAM trial.

Part 3 consists of studies in which the prognosis of older patients is assessed. **Chapter 8** assesses the external validation of the results of a clinical trial for older

women with breast cancer. In this chapter a study is described in which the older patients included in the TEAM study, a large international multicenter trial, are compared to older breast cancer patient from the general population.

Older women with a diagnosis of breast cancer, do have a significant risk to die from another reason than breast cancer. In **chapter 10**, we show a clinical example of the use of competing risk analyses in older women with breast cancer, to highlight the importance of taking into account the risk of dying from another cause than breast cancer, when assessing a disease specific endpoint.

Finally, in **chapter 11**, all results of the studies in this thesis are discussed in a general discussion.

REFERENCES

1. Jemal A, Bray F, Center MM, et al: Global cancer statistics. CA Cancer J. Clin 61:69-90, 2011
2. Torre LA, Bray F, Siegel RL, et al: Global cancer statistics, 2012. CA Cancer J Clin 65:87-108, 2015
3. Hutchins LF, Unger JM, Crowley JJ, et al: Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N. Engl. J Med 341:2061-2067, 1999
4. Hurria A, Dale W, Mooney M, et al: Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. J. Clin. Oncol 32:2587-2594, 2014
5. Barnett K, Mercer SW, Norbury M, et al: Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 380:37-43, 2012
6. Ring A, Sestak I, Baum M, et al: Influence of comorbidities and age on risk of death without recurrence: a retrospective analysis of the Arimidex, Tamoxifen Alone or in Combination trial. J Clin Oncol 29:4266-4272, 2011
7. Janssen-Heijnen ML, Houterman S, Lemmens VE, et al: Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. Crit Rev Oncol Hematol 55:231-40, 2005
8. Louwman WJ, Janssen-Heijnen ML, Houterman S, et al: Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. Eur J Cancer 41:779-85, 2005
9. Yancik R, Wesley MN, Ries LA, et al: Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 285:885-92, 2001
10. Vandenbroucke JP: When are observational studies as credible as randomised trials? Lancet 363:1728-1731, 2004

Chapter 2

Surgical treatment of early stage breast cancer in elderly: an international comparison

Kiderlen M, Bastiaannet E, Walsh PM, Keating NL, Schrodi S, Engel J, van de Water W, Ess SM, van Eycken L, Miranda A, de Munck L, van de Velde CJ, de Craen AJ, Liefers GJ.

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ABSTRACT

Introduction. Over 40% of breast cancer patients are diagnosed above the age of 65. Treatment of these elderly patients will probably vary over countries. The aim of this study was to make an international comparison (several European countries and the US) of surgical and radiation treatment for elderly women with early-stage breast cancer. Survival comparisons were also made.

Methods. Data were obtained from national or regional population-based registries in the Netherlands, Switzerland, Ireland, Belgium, Germany and Portugal. For the US patients were selected from the Surveillance, Epidemiology, and End Results (SEER) database. Early-stage breast cancer patients aged ≥65 diagnosed between 1995 and 2005 were included. An international comparison was made for breast and axillary surgery, radiotherapy after breast conserving surgery (BCS), and relative or cause-specific survival.

Results. Overall, 204.885 patients were included. The proportion of patients not receiving any surgery increased with age in many countries; however differences between countries were large. In most countries more than half of all elderly patients received breast conserving surgery (BCS), with the highest percentage in Switzerland. The proportion of elderly patients that received radiotherapy after BCS decreased with age in all countries. Moreover, in all countries the proportion of patients who do not receive axillary surgery increased with age. No large differences in survival between countries were recorded.

Conclusion. International comparisons of surgical treatment for elderly women with early stage breast cancer are scarce. This study showed large international differences in treatment of elderly early-stage breast cancer patients, with the most striking result the large proportion of elderly who did not undergo surgery at all. Despite large treatment differences, survival does not seem to be affected in a major way.

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer worldwide, accounting for 23% of all new cancer cases in women and 14% of all female cancer deaths in 2008[1]. A high incidence of breast cancer is observed in women aged 65 years and older, comprising over 40% of all breast cancer patients in developed countries.[2] Given the aging population and constantly improving screening and diagnostic tools, the number of elderly patients with breast cancer is expected to grow in the coming decades.[3]

Clinical trials indicate that the choice of mastectomy versus breast conserving surgery (BCS) followed by radiotherapy (RT) for early stage breast cancer does not affect overall mortality or breast cancer mortality.[4,5] However, patients who receive BCS+RT have a small but significant increase in local recurrences. Elderly patients have been under-represented in breast cancer treatment trials, based on their age, comorbid diseases and logistic barriers.[2,6] Consequently it is questionable if trial results can be generalized to patients of all ages. Despite guideline recommendations, several observational studies from different countries show that with increasing age, treatment of early stage breast cancer more often consists of mastectomy; moreover, omission of RT after BCS increases with increasing age.[3,7-11] In addition, older breast cancer patients are more likely than younger patients to not undergo breast surgery, even though mortality caused by breast surgery is shown to be low among elderly.[12]

The different treatment approaches to elderly breast cancer patients could have consequences. Several observational studies showed worse overall, breast cancer specific and disease-free survival for 'undertreated' elderly patients (not treated according to guidelines).[13,14] An international study comparing breast surgery among countries for patients participating in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial showed large differences in surgical treatment approach to early-stage breast cancer in postmenopausal women.[15] The EUROCARE group recently published a population-based study on the surgical treatment of early stage breast cancer (T1N0M0) across Europe. They found considerable differences in the use of BCS followed by RT. Of all surgically treated patients across the participating countries, 55% received BCS+RT, with a range from 9% in Estonia to 78% in France.[11] However, none of these studies specifically compared treatment of the elderly patient with breast cancer. The aim of this study is to make an international comparison of breast and axillary surgery, and radiotherapy after breast conserving surgery in elderly patients with early-stage breast cancer, and its possible influence on survival.

METHODS

Patients

Women aged 65 and older, who were diagnosed with early-stage breast cancer (T0-2, N0-1, M0) and recorded in population-based cancer registries in the Netherlands, Ireland, Switzerland, Belgium, Germany, Portugal, and the U.S were included. From the population-based database of the Netherlands Cancer Registry, women diagnosed between 1995 and 2005 were selected. For the US, patients diagnosed between 1998 and 2007 were selected from the Surveillance, Epidemiology, and End Results (SEER) database covering 28% of the US population. In Switzerland, patients diagnosed between 2003 and 2005 were identified from seven population-based cancer registries (Geneva, Valais, Ticino, St Gallen-Appenzell, Grisons-Glarus, Basel city and countryside and Zurich) covering 47% of the Swiss population. In Ireland, patients were selected from the national cancer registry between 1999 and 2007. In Belgium, patients diagnosed between 2001 and 2006 were selected from the national cancer registry. German patients diagnosed between 1995 and 2008 in the Munich region were selected. Finally, patients from the Portugal South regional cancer registry (ROR-Sul) were selected between 2006 and 2008. Patients with a diagnosis of breast cancer on death certificate or at autopsy only or with unknown treatment were excluded.

Statistics

Calculations of treatment percentages and survival were performed for each country and aggregated into tables for the comparison between countries. Patients were categorized in six age groups (65-69, 70-74, 75-79, 80-84, 85-89 and ≥90) for the treatment analyses. Tumor stage was defined by combined TNM stage[16] (categorized as stage I, IIA, IIB), with clinical stage used when pathological stage was missing. Stage I includes T1N0 tumors, stage IIA T1N1 or T2N0 tumors and stage IIB contains T2N1 tumors (also T3N0 tumors but these were excluded from this study). Breast surgery was categorized as mastectomy, breast conserving surgery, or no surgery. Patients who received BCS first, but later received mastectomy, for any reason, were positioned in the mastectomy group. Receipt of radiation in addition to BCS was also assessed. Axillary surgery (either sentinel node biopsy or axillary lymph node sampling or dissection) was documented (yes/no). Descriptive statistics were used, as only aggregated tables were compared, to assess the proportion of patients receiving each treatment; where possible percentages were compared using the chi-square test. A p value of <0.05 was considered statistically significant.

Relative survival was calculated by the Ederer II method as the ratio of the survival observed among the cancer patients to the survival that would have been expected based on the corresponding (age, sex and year of diagnosis) general population. National life tables for each country were used to estimate expected survival. In all countries and regions, vital status was established either directly from the patient's medical record or through linkage with the municipal or national population registries. The SEER database links with the National Death index, which also provided causes of death, and disease specific survival was calculated for patients treated in the US. Survival of Irish patients was mainly based on linkage to national mortality data, sometime supplemented with clinical information on date of death. For the survival analysis age was categorized as 65-74, 75-84 and ≥85.

RESULTS

Overall, 204.885 patients were included in the study. Characteristics of the populations are shown in Table 1. Age distribution was similar (p=0.9).across participating countries. Stage distribution among European countries was comparable (p=0.5), however, US patients more frequently had stage I disease (p=0.06). Grade distribution was significantly different between the countries (p<0.001).

Breast surgery

Figure 1 shows the proportions of patients who did not receive breast surgery in the several countries by age. The proportion of women not undergoing breast surgery varies among countries (p<0.001) from 0.5% (MCR Germany) to 13.4% (Ireland). Overall, the proportion of patients who did not receive surgery increased with age. In the lowest age categories (65-69 and 70-74), proportions of patients without breast surgery were small (<5%) in all countries (difference between countries were small but significant p<0.001). As age increases, larger differences in the omission of breast surgery become apparent (again p<0.001). In the US and Germany, in particular, relatively few patients did not undergo breast surgery. However, in Ireland and The Netherlands more than half of patients aged 90 years and older had no breast surgery.

Figure 2 shows the proportion of patients that received BCS (of all operated patients) in the countries by age. In most countries more than half of the included patients underwent BCS, except for The Netherlands, Ireland and Portugal. The use of breast conserving procedures was highest in Switzerland (70%). In all countries, except for the US and Ireland, the proportion of BCS decreased with age. In the US the proportion of BCS was relatively stable with age and in Ireland the use of BCS increased with age.

Table 1: Characteristics of the populations by country

Country		Netherlands		Belgium		Switzerland		Germany (MCR)		Ireland		Portugal (ROR-Sul)		USA		p-value
		cases	%	cases	%	cases	%	cases	%	cases	%	cases	%	cases	%	
Age	**65-69**	10162	28.6	2337	33.1	465	32.1	4539	39.3	1295	30.0	40	32.3	36629	25.3	0.9
	70-74	9636	27.1	1818	25.8	365	25.2	3077	26.7	1142	26.5	40	32.3	35109	24.2	
	75-79	6982	19.6	1503	21.3	273	18.8	2322	20.1	901	20.9	23	18.5	33279	23.0	
	80-84	5260	14.8	907	12.9	171	12.0	1152	10.0	631	14.6	13	10.5	23592	16.3	
	85-89	2687	7.6	340	4.8	100	7.2	376	3.3	271	6.3	7	5.6	11678	8.1	
	90+	853	2.4	153	2.2	50	3.5	73	0.6	72	1.7	1	0.8	4561	3.1	
Stage	**I**	15894	44.7	3331	47.2	657	46.0	5471	47.4	1476	34.2	55	44.4	90402	62.4	0.06[a]
	IIA	13288	37.3	3028	42.9	530	37.2	4120	35.7	1867	43.3	47	37.9	39109	27.0	
	IIB[b]	6398	18.0	699	9.9	237	16.6	1948	16.9	969	22.5	22	17.7	15337	10.6	
Grade	**1**	5316	14.9	1193	16.9	314	22.0	1503	13.0	476	11.0	17	13.7	36182	25.0	**<0.001**
	2	12036	33.8	2983	42.3	794	55.8	6888	59.7	1890	43.8	81	65.3	61178	42.2	
	3 / 4	7383	20.8	2259	32.0	253	17.7	2842	24.6	1188	27.6	11	8.9	35409	24.5	
	missing	10845	30.5	623	8.8	63	4.4	306	2.7	758	17.6	15	12.1	12079	8.3	
Total		35580	100	7058	100	1424	100	11539	100	4312	100	124	100	144848	100	

MCR = Munich Cancer Registry, ROR-Sul = Portugal South Regional Cancer Registry

[a] p=0.06 including US, but p=0.5 among European countries only. [b] But excluding T3N0M0

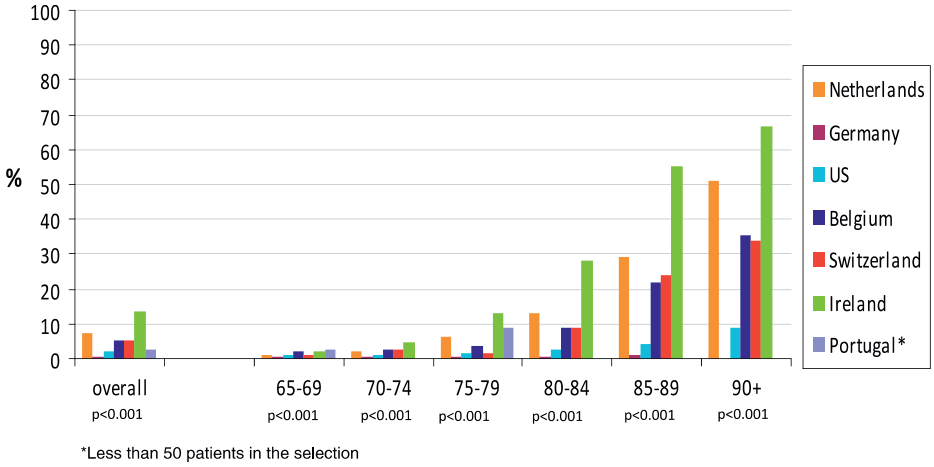

Figure 1: Overall and age-specific percentages of the patients who did not receive breast surgery, by country

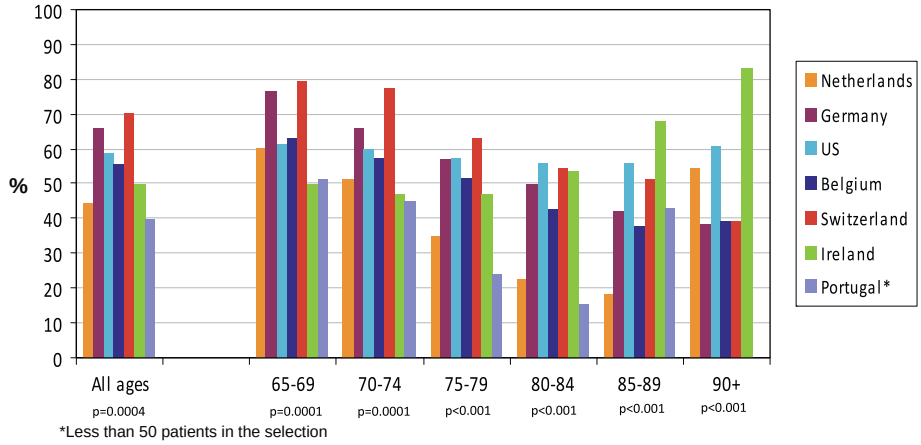

Figure 2: Overall and age-specific percentage of patients that received breast conserving surgery (of all patients that received surgery), by country

Radiotherapy after breast conserving surgery

Figure 3 shows the proportion of patients treated with BCS who received adjuvant RT. This proportion decreased substantially with age in all countries ($p<0.001$), and also varied markedly between countries ($p=0.0005$). The largest overall proportion of BCS followed by RT was observed in Belgium (85%) and the lowest in Portugal (59%) although the sample size was small for the latter.

Axillary surgery

Figure 4 shows proportions of all included patients who did not receive axillary surgery. The national cancer registry of Belgium could not provide this information and in the US, data on axillary staging were missing for 9.8% of patients. In all countries, the percentage of patients who did not undergo axillary surgery increased with age. However, there was major variation among countries ($p<0.001$), from 1.4% (MCR Germany) to 22.6% (Ireland) overall.

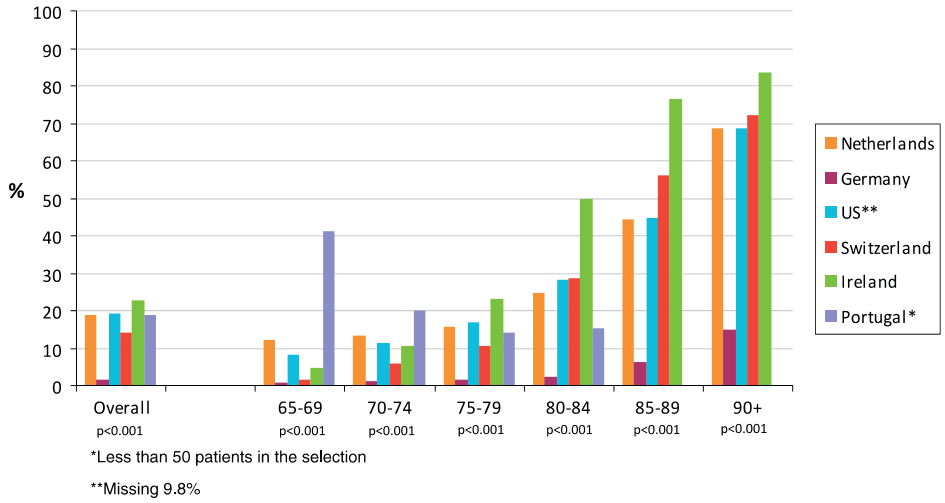

Figure 4: Overall and age-specific percentages of patients that received no axillary surgery, by country

Survival

Figure 5 shows the 5-year survival after diagnosis by age and stage. For all ages combined, there were no major differences in survival between countries, with the highest relative survival for Ireland (99%). Among stage I patients, survival was similar between countries in all age categories. For stage II, patients aged 65-74 years had a similar survival in all countries, but there were differences for patients aged 75-84 and patients aged ≥ 85, where survival was higher for patients in Germany (MCR) and Ireland.

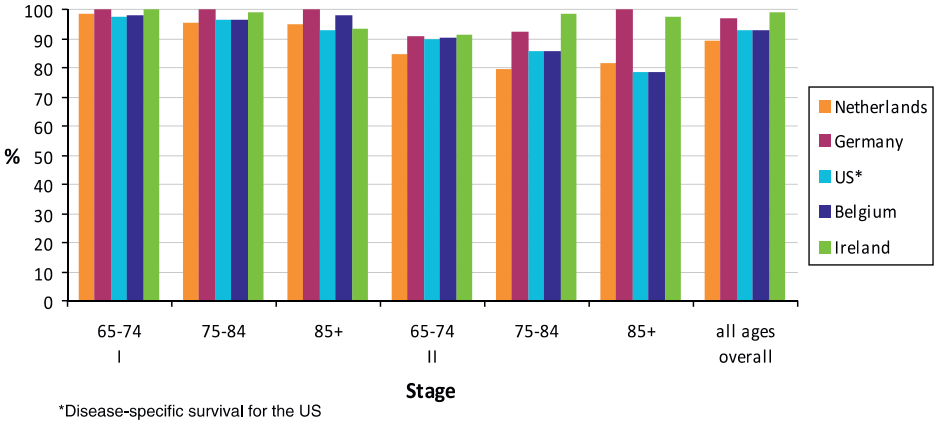

Figure 5: Relative survival (5-years) for Stage I and II disease, by age and country * Disease-specific survival for US

DISCUSSION

Major findings of the present study were the large differences in locoregional treatment across countries, especially in the proportion of elderly breast cancer patients receiving no breast surgery at all. However, despite substantial differences in breast cancer treatment, survival among countries was comparable. International comparisons of surgical treatment for elderly women with early-stage breast cancer are scarce. In the present study we were able to make a comparison between several European countries and the US.

Breast surgery

The international differences in the percentage of elderly early-stage breast cancer patients who did not undergo breast surgery are striking. Whereas, for example, in Ireland the percentage of patients aged ≥90 who did not have surgery was 67%, in the US only 8.8% had no surgery and in Germany all patients in this age category received breast surgery. The findings in the US are consistent with a recently published study from the US in which 98% of all T1 or T2 breast cancer patients aged ≥65 years received at least some surgery.[17] International studies comparing the percentage of breast cancer patients who do not receive surgery are scarce. Most observational studies of survival excluded patients who did not have any surgical treatment, but the few retrospective studies that did include non-surgically treated patients showed poor overall and lower breast cancer specific survival for these patients.[13,17-19] Many descriptive studies from different countries have also showed

less extensive surgical treatment for elderly women with early-stage breast cancer compared with younger patients[2,3,7,11,12]

Radiotherapy

An overview of clinical trial data has shown that BCS should be followed by radiotherapy to achieve results comparable with mastectomy in terms of recurrence and survival.[4] In some elderly women BCS without radiation may be used to minimize potential treatment-related complications. However, the value of RT after BCS in elderly breast cancer patients is still subject of debate, since some studies suggest that radiation may be safely omitted for low-risk tumors in women over age 70.[20,21] The current study shows that the proportion of women who received RT after BCS decreased with age. This trend was found in all participating countries, although specific proportions vary. Notable are the high percentages of elderly patients that received RT after BCS in Switzerland (79%) and Germany (MCR 80%). Possibly, for Switzerland, high accessibility of health services could partly explain this finding. For the selected German region (Munich), a previous study demonstrated that this specific region has a higher percentage of BCS for early-stage breast cancer than five other regions in Germany, so this region may not be completely representative for the whole country.[22] Also interesting are the differences in breast surgery between the Netherlands and Ireland (both national databases). Both countries have a high proportion of patients that receive no breast surgery although it is higher in Ireland. The proportion of BCS decreases with age in the Netherlands but increases in Ireland; the proportion of adjuvant RT decreases with age in both countries. This remarkable difference in locoregional therapy did not influence survival in any way. Information concerning loco-regional recurrences, not routinely collected by most cancer registries, could add some information to these comparisons and should be collected when possible in the future.

Axillary surgery

In all participating countries the proportion of women in whom axillary surgery was not performed increased with age, a finding consistent with another observational study.[23] The largest proportion was found in Ireland, directly followed by the US, Portugal and the Netherlands. Germany stands out on this topic; only 1.4% of the elderly breast cancer patients did not undergo any form of axillary surgery. Axillary staging is part of some guidelines, and these findings suggest that guideline adherence decreased with increasing age. However, several randomized and non-randomized studies showed very low rates of axillary recurrences and comparable disease-free and overall survival between clinical node-negative elderly breast cancer patients with and without axillary surgery.[24,25]

Strengths and limitations

One of the strengths of this comparison is the large number of patients and the population-based datasets that included all elderly patients. This facilitated comparison of treatment strategies in countries with similar health systems by using country as an instrumental variable.

A limitation of this study is that systemic treatment information was not available for all countries. However, available data indicate that rates of hormonal therapy (HT) were high: for example, among non-surgically treated patients, the proportion receiving HT was 85% in the Netherlands and 69% in Ireland. However, it is questionable if HT can replace surgery in elderly patients. Trials in which women aged ≥70 were randomized to have surgery or HT do not show significant better overall survival for surgery compared to HT alone, although risk of recurrence is significantly larger when operable breast cancer in elderly is treated by tamoxifen alone.[26,27] Another limitation of this study might be that information concerning the extent of "clear margins" after BCS was not available.

Another limitation of the study could be differences in data collection between the participating registries and the absence of national data for several countries (only The Netherlands, Belgium and Ireland are national cancer registries). In countries with regional data, the regions may not be perfectly representative of the whole country. Also the small number of patients included for Portugal may not be representative and in some categories, numbers were insufficient to draw conclusions about treatment. Finally, the years of available data were not completely overlapping, and thus changes in treatment patterns over time could influence our findings.

CONCLUSIONS

Despite the remarkable large differences in locoregional treatment of early breast cancer, the current study showed minimal differences in survival at five years between older breast cancer patients from seven Western countries. These findings raise the question whether more or less aggressive treatment of early stage breast cancer in elderly makes a difference. Future research should be focused on the best therapy for elderly women with respect to survival and quality of life. It may well be that the much criticized "less aggressive therapy" for elderly breast cancer patients does not harm patients with early stage disease, particularly women with comorbid illness that may otherwise limit their life expectancy. To properly investigate this, randomized controlled trials , specifically aimed at the elderly, is considered to give the best evidence. RCT's however, are costly and time

consuming en will not yield practice changing results within years from the start of such a trial. Furthermore, older patients are underrepresented in trials and no direct comparison of different approaches to the local regional treatment of early breast cancer in older women is available. International comparison of specific treatment protocols could serve as a good alternative to select 'best practices' and improve the risk/ benefit ratio in the treatment of older breast cancer patients. This comparative effectiveness research can bridge the knowledge gap specifically in older cancer patient, who are by nature, heterogeneous in patient characteristics and treatment patterns.[28]

REFERENCES

1. Jemal A, Bray F, Center MM et al. Global cancer statistics. CA Cancer J Clin 2011; 61:69-90.
2. Wildiers H, Kunkler I, Biganzoli L et al. Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. Lancet Oncol 2007; 8:1101-1115.
3. Louwman WJ, Vulto JC, Verhoeven RH et al. Clinical epidemiology of breast cancer in the elderly. Eur J Cancer 2007; 43:2242-2252.
4. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. Early Breast Cancer Trialists' Collaborative Group. N Engl J Med 1995; 333:1444-1455.
5. Clarke M, Collins R, Darby S et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 366:2087-2106.
6. Hutchins LF, Unger JM, Crowley JJ et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999; 341:2061-2067.
7. 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.
8. Keating NL, Landrum MB, Brooks JM et al. Outcomes following local therapy for early-stage breast cancer in non-trial populations. Breast Cancer Res Treat 2011; 125:803-813.
9. Jagsi R, Abrahamse P, Morrow M et al. Patterns and correlates of adjuvant radiotherapy receipt after lumpectomy and after mastectomy for breast cancer. J Clin Oncol 2010; 28:2396-2403.
10. Ess S, Joerger M, Frick H et al. Predictors of state-of-the-art management of early breast cancer in Switzerland. Ann Oncol 2011; 22:618-624.
11. Allemani C, Storm H, Voogd AC et al. Variation in 'standard care' for breast cancer across Europe: a EUROCARE-3 high resolution study. Eur J Cancer 2010; 46:1528-1536.
12. Gennari R, Audisio RA. Breast cancer in elderly women. Optimizing the treatment. Breast Cancer Res Treat 2008; 110:199-209.
13. Bouchardy C, Rapiti E, Blagojevic S et al. Older female cancer patients: importance, causes, and consequences of undertreatment. J Clin Oncol 2007; 25:1858-1869.
14. Gajdos C, Tartter PI, Bleiweiss IJ et al. The consequence of undertreating breast cancer in the elderly. J Am Coll Surg 2001; 192:698-707.
15. van Nes JG, Seynaeve C, Jones S et al. Variations in locoregional therapy in postmenopausal patients with early breast cancer treated in different countries. Br J Surg 2010; 97:671-679.
16. American Joint Committee on Cancer. Manual for staging of cancer, 3rd edition. 1988. New York, NY., J.B. Lippincott Company.
17. 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.
18. Bouchardy C, Rapiti E, Fioretta G et al. Undertreatment strongly decreases prognosis of breast cancer in elderly women. J Clin Oncol 2003; 21:3580-3587.
19. Van Leeuwen BL, Rosenkranz KM, Lei FL et al. The effect of under-treatment of breast cancer in women 80 years of age and older. Crit Rev Oncol Hematol 2010.
20. Fyles AW, McCready DR, Manchul LA et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med 2004; 351:963-970.

21. Hughes KS, Schnaper LA, Berry D et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med 2004; 351:971-977.
22. Engel J, Nagel G, Breuer E et al. Primary breast cancer therapy in six regions of Germany. Eur J Cancer 2002; 38:578-585.
23. Rescigno J, Zampell JC, Axelrod D. Patterns of axillary surgical care for breast cancer in the era of sentinel lymph node biopsy. Ann Surg Oncol 2009; 16:687-696.
24. Gerber B, Heintze K, Stubert J et al. Axillary lymph node dissection in early-stage invasive breast cancer: is it still standard today? Breast Cancer Res Treat 2011.
25. Martelli G, Miceli R, Daidone MG et al. Axillary dissection versus no axillary dissection in elderly patients with breast cancer and no palpable axillary nodes: results after 15 years of follow-up. Ann Surg Oncol 2011; 18:125-133.
26. Chakrabarti J, Kenny FS, Syed BM et al. A randomised trial of mastectomy only versus tamoxifen for treating elderly patients with operable primary breast cancer-Final results at 20-year follow-up. Crit Rev Oncol Hematol 2010.
27. Hind D, Wyld L, Beverley CB et al. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). Cochrane Database Syst Rev 2006;CD004272.
28. Hsiao FY, Mullins CD, Onukwugha E et al. Comparative effectiveness of different chemotherapeutic regimens on survival of people aged 66 and older with stage III colon cancer: a "real world" analysis using Surveillance, Epidemiology, and End Results-Medicare data. J Am Geriatr Soc 2011; 59:1717-1723.

Chapter 3

Treatment strategies and survival of older breast cancer patients - an international comparison between the Netherlands and Ireland

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ABSTRACT

Objectives. Forty percent of breast cancers occur among older patients. Unfortunately, there is a lack of evidence for treatment guidelines for older breast cancer patients. The aim of this study is to compare treatment strategy and relative survival for operable breast cancer in the elderly between The Netherlands and Ireland.

Material and Methods. From the Dutch and Irish national cancer registries, women aged ≥65 years with non-metastatic breast cancer were included (2001-2009). Proportions of patients receiving guideline-adherent locoregional treatment, endocrine therapy, and chemotherapy were calculated and compared between the countries by stage. Secondly, 5-year relative survival was calculated by stage and compared between countries.

Results. Overall, 41,055 patients from The Netherlands and 5,826 patients from Ireland were included. Overall, more patients received guideline-adherent locoregional treatment in The Netherlands, overall (80% vs. 68%, adjusted $p<0.001$), stage I (83% vs. 65%, $p<0.001$), stage II (80% vs. 74%, $p<0.001$) and stage III (74% vs. 57%, $P<0.001$) disease. On the other hand, more systemic treatment was provided in Ireland, where endocrine therapy was prescribed to 92% of hormone receptor-positive patients, compared to 59% in The Netherlands. In The Netherlands, only 6% received chemotherapy, as compared 24% in Ireland. But relative survival was poorer in Ireland (5 years relative survival 89% vs. 83%), especially in stage II (87% vs. 85%) and stage III (61% vs. 58%) patients.

Conclusion. Treatment for older breast cancer patients differed significantly on all treatment modalities between The Netherlands and Ireland. More locoregional treatment was provided in The Netherlands, and more systemic therapy was provided in Ireland. Relative survival for Irish patients was worse than for their Dutch counterparts. This finding should be a strong recommendation to study breast cancer treatment and survival internationally, with the ultimate goal to equalize the survival rates for breast cancer patients across Europe.

INTRODUCTION

Currently, about 40 per cent of all new breast cancer cases in developed countries occur among women aged 65 and older.[1] Life expectancy is increasing, diagnostic tools become more sensitive and screening programs are more widely used and expanded. Consequently, the proportion of elderly breast cancer patients is expected to increase in the near future.[2]

Proper treatment for older breast cancer patients is difficult to define. Older women are frequently excluded from clinical treatment trials because of their age, comorbidity or logistical barriers.[3] Moreover, the elderly who are included in trials are probably not representative for the general older population.[4] Consequently, an evidence-based treatment strategy for older women with breast cancer is lacking. The only guidance for clinicians is from treatment guidelines which have been validated in younger and healthier women.[5] Extrapolation from trials might not be valid since breast cancer biology differs in some respects in older patients, treatment tolerance varies, and there are substantial competing risks of mortality.[2,6] Consequently, clinicians have to decide what is best for their patient: treatment according to the guidelines, or patient-tailored deviation from the guidelines.

In the last decade it has become more accepted to use observational data, preferably population-based , to assess treatment effects in older cancer patients.[7] However, no strong conclusions can be drawn from these studies as bias due to confounding by indication is likely to be present, since specific (unknown) patient and tumor-related factors influence receipt of particular treatments.[8]

A recent observational study comparing locoregional treatment between six European countries and the US found that treatment strategy in The Netherlands and Ireland differed considerably on various items among older women with early stage breast cancer, indicating that older patients with early stage breast cancer in Ireland seemed to be slightly undertreated, compared with The Netherlands. However, relative survival was not demonstrably different.[9]

The aim of the present study is to compare treatment strategy and relative survival for operable (non-metastatic) breast cancer in the elderly between The Netherlands and Ireland in more detail.

MATERIAL AND METHODS

Data

From the Netherlands and Irish cancer registry, all female patients aged 65 years and older diagnosed between 2001 and 2009 with invasive, non-metastasized

breast cancer were selected. Patients with a diagnosis of breast cancer on death certificate or at autopsy only, and other patients with a survival time of zero days, were excluded. If a patient had a second primary tumor during follow-up, only the first primary breast tumor was considered for analyses.

Tumor stage was defined by TNM stage[10], with clinical T and N used when pathological information was lacking. Patients with missing T category were excluded. When nodal and distant metastatic status were unspecified (NX and MX), status was assumed to be N0 and M0, respectively. Stage data were originally coded using 6th-edition TNM rules[10] in the Netherlands and 5th-edition TNM rules[11] in Ireland. Micrometastases (≤0.2 cm) in regional nodes, classified as N1a in 5th-edition TNM were recoded to N0 for 21 Irish cases to conform to 6th-edition TNM rules. For surgical treatment, only the most extensive surgery registered was used for analysis. Axillary surgery was coded as yes or no.

Primary outcome was treatment strategy by stage. Treatments of interest were type of surgery (none, BCS or mastectomy), radiotherapy (RT; yes or no), axillary surgery (yes or no), locoregional guideline adherence (details below), endocrine therapy (yes or no) and chemotherapy (yes or no). Secondary outcome measure was 5-year relative survival in each country.

In both the Dutch and Irish breast cancer guidelines, primary surgical treatment with mastectomy or BCS followed by radiotherapy (RT) is recommended for non-metastasized breast cancer. In addition, it is recommended to assess axillary nodal status by performing a sentinel node procedure or axillary lymph node dissection (Appendix S1).[12-14] Therefore, locoregional treatment was considered guideline-adherent when a patient had BCS and RT or mastectomy with or without RT, in all cases followed by any axillary surgical procedure. In addition the receipt of systemic therapy (adjuvant endocrine therapy and chemotherapy) was analyzed.

Routine cancer registry data on endocrine therapy in Ireland were known to be incomplete (National Cancer Registry of Ireland, unpublished data), because of difficulties associated with outpatient prescription of the drugs involved. Endocrine therapy data for Irish patients were therefore supplemented by linkage to a national database of drug prescription, which covers publicly funded 'medical card' patients including most patients aged 65 years and over. Additional endocrine therapy was identified by this linkage for 21% of patients. Linkage was not possible for about 15% of Irish patients, and for this group, 'missing' endocrine therapy was imputed (4% of all patients). The imputation assumed that the proportion of 'linked' patients receiving endocrine therapy by stage (I, II and III), hormone receptor status (any positive vs. none positive) and broad age-group (65-74 and 75+) also applied to unlinked patients, and these 'extra' treatments were assigned randomly within each stage-by-age group.

Data from both the Netherlands Cancer Registry and the National Cancer Registry of Ireland are fully anonymized prior to being made available to researchers, so data cannot be traced back to the individual patient. Therefore, no informed consent was required from the included patients and there was no need for approval of an ethical committee.

Mortality follow-up was available to December 31st 2011 by linkage of cancer registry with national mortality data.

Statistical analyses

Analyses were performed in IBM SPSS Statistics 20 and Stata SE 12. Treatment strategies were analyzed grouped by tumor stage (I to III). Differences in treatment between countries were tested by a Poisson regression model, adjusted for age (continuous), histological subtype, tumor grade, ER and PR status.

Relative survival was calculated by the Ederer II method[15] as the ratio of the survival observed among the cancer patients to the expected survival based on the corresponding general population (by age, sex, and year of diagnosis), using the 'strs' command in Stata. National life tables for each country were used to estimate expected survival. Results were presented as percentage relative survival after five years, and Relative Excess Risks (RER) derived from relative survival modeling, with The Netherlands as reference category.[16]

RESULTS

Overall, 41,055 patients from The Netherlands and 5,826 patients from Ireland were included. Patient and tumor characteristics are shown in Table 1. Median age for patients in The Netherlands was 74 years (range 65-102), and in Ireland 74.2 (range 65-99). Fewer early stage tumors, and more with advanced stage were observed in Ireland (P<0.001). Recorded grade distribution differed significantly, with a higher proportion of higher grades in Ireland than in The Netherlands (P<0.001).

Table 1 – Patient and tumor characteristics.

		Country				
		The Netherlands (N=41055)		Ireland (N=5826)		P
		N	%	N	%	
Age (years)	65-74	22,036	53.7	3,126	53.7	0.989
	75 or older	19,019	46.3	2,700	46.3	
Year of diagnosis	2001	4,432	10.8	584	10.0	0.333
	2002	4,256	10.4	582	10.0	
	2003	4,339	10.6	601	10.3	
	2004	4,439	10.8	624	10.7	
	2005	4,425	10.8	614	10.5	
	2006	4,519	11.0	664	11.4	
	2007	4,870	11.9	695	11.9	
	2008	4,914	12.0	718	12.3	
	2009	4,861	11.8	744	12.8	
Stage	I	17,790	43.3	1,658	28.5	<0.001
	II	18,023	43.9	3,140	53.9	
	III	5,242	12.8	1,028	17.6	
Grade	1	8,137	19.8	542	9.3	<0.001
	2	16,314	39.7	2,803	48.1	
	3	9,018	22.0	1,720	29.5	
	missing	7,586	18.5	761	13.1	
Morphology	ductal	28,463	69.3	3,861	66.3	<0.001
	lobular	5,488	13.4	789	13.5	
	mixed/other	7,104	17.3	1,176	20.2	
ER	negative	3,209	7.8	930	16.0	<0.001*
	positive	19,785	48.2	4,074	69.9	
	missing	18,061	44.0	822	14.1	
PR	negative	7,350	17.9	1,545	26.5	<0.001*
	positive	14,740	35.9	2,694	46.2	
	missing	18,965	46.2	1,587	27.2	

*missings excluded

Hormone receptor status showed smaller differences, with slightly smaller proportions of estrogen and progesterone receptor positive tumors among Irish patients (81% and 64%, respectively, excluding missing or unknown values) compared with those from the Netherlands (86% and 67%) (P <0.001). The proportion of missing values was much lower in Ireland, mainly because Dutch data were not complete for the years 2001-2005 rather than to differences in proportions of patients tested.

Locoregional treatment

Figure 1A shows the proportions of patients receiving guideline-adherent locoregional treatment by country, grouped by stage. In The Netherlands guideline-adherent treatment was performed in 80%, with little variation between stages, whereas these proportions in Ireland ranged from 57% (stage III) to 74% (stage II). Among patients who did not receive guideline-adherent locoregional treatment, 65% (The Netherlands) and 68% (Ireland), had no locoregional treatment at all, 6% (The Netherlands) and 13% (Ireland) had only BCS (without RT or axillary surgery), and 29% (The Netherlands) and 20% (Ireland) had adequate local treatment, but no axillary surgery. Adjusted RRs for having guideline-adherent locoregional therapy in Ireland relative to The Netherlands were 0.79 (95% CI 0.76-0.81), 0.87 (0.85-0.89) and 0.72 (0.68-0.75) respectively for stage I, II and III (P<0.001 for all stages).

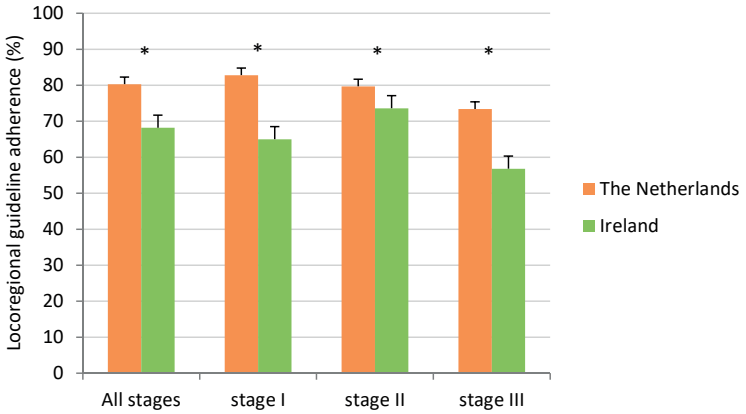

Figure 1a. Locoregional guideline-adherence by stage

Looking more specifically at locoregional treatment (Table 2), overall, more patients in Ireland had no breast surgery at all (19% vs. 12% in The Netherlands), also stratified by stage (P<0.001 in all stages).

In The Netherlands, 82% underwent any axillary surgical procedure, as compared to 74% in Ireland. Also, in all three stage groups, fewer patients in The Netherlands than in Ireland did not undergo axillary surgery (P<0.001).

Regarding radiotherapy (RT), among all patients, more patients received RT in Ireland than in The Netherlands, overall and after mastectomy (P<0.001). For mastectomy patients, the difference was only seen in stage I (18% of patients had post-mastectomy RT in Ireland vs. 3% in The Netherlands) and stage II (42% vs. 14%) (P<0.001). In stage III patients, the difference in the receipt of RT attenuated

and no difference was observed in post-mastectomy RT. However, in all stages significantly fewer patients in Ireland received RT after BCS (79% vs. 94% in The Netherlands, overall, P<0.001). (Table 2).

Table 2. Treatment by stage

	Country				
	The Netherlands		Ireland		
	N	%	N	%	*P*
All stages					
Definitive surgery					
None	4,971	12.1	1,121	19.2	<0.001
BCS	16,079	39.2	2,185	37.5	
Mastectomy	20,008	48.7	2,520	43.3	
Any axillary surgery	33,637	81.9	4323	74.2	<0.001
Radiotherapy					
All	19,407	47.3	2,940	50.5	<0.001
After BCS	15,050	93.6	1,728	79.1	<0.001
After Mastectomy	4,102	20.5	1,092	43.3	<0.001
Chemotherapy	2,638	6.4	138	23.8	<0.001
Endocrine therapy for ER+					
not imputed	11,570	58.5	2,834	88.6	<0.001
imputed (IRL)	11,570	58.5	3,609	92.4	<0.001
Stage I					
Definitive surgery					
None	1,341	7.5	258	15.6	<0.001
BCS	10,244	57.6	928	56.0	
Mastectomy	6,205	34.9	472	28.5	
Any axillary surgery	15,090	84.8	1,212	73.1	<0.001
Radiotherapy					
All	9,928	55.8	832	50.2	<0.001
After BCS	9,693	94.6	733	79.0	<0.001
After Mastectomy	209	3.4	86	18.2	<0.001
Chemotherapy	321	1.8	176	10.6	<0.001
Endocrine therapy for ER+					
not imputed	2,507	27.4	834	87.7	<0.001
imputed (IRL)	2,507	27.4	1,066	91.4	<0.001

Table 2. Treatment by stage (*continued*)

	Country				
	The Netherlands		Ireland		
	N	%	N	%	*P*
Stage II					
Definitive surgery					
None	2,438	13.5	489	15.6	<0.001
BCS	5,226	29.0	1,135	36.1	
Mastectomy	10,359	57.5	1,516	48.3	
Any axillary surgery	14,665	81.4	2,486	79.2	0.004
Radiotherapy					
All	6,287	34.9	1,572	50.1	<0.001
After BCS	4,803	91.9	905	79.7	<0.001
After Mastectomy	1,443	13.9	632	41.7	<0.001
Chemotherapy	1,233	6.8	868	27.6	<0.001
Endocrine therapy for ER+					
not imputed	6,890	83.6	1,573	89.6	<0.001
imputed (IRL)	6,890	83.6	2,000	93.8	<0.001
Stage III					
Definitive surgery					
None	1,192	22.7	374	36.4	<0.001
BCS	606	11.6	122	11.9	
Mastectomy	3,444	65.7	532	51.8	
Any axillary surgery	3,882	74.1	626	60.9	<0.001
Radiotherapy					
All	3,192	60.9	536	52.1	<0.001
After BCS	554	91.4	90	73.8	<0.001
After Mastectomy	2,450	71.1	374	70.3	0.682
Chemotherapy	1,084	20.7	343	33.4	<0.001
Endocrine therapy for ER+					
not imputed	2,173	91.1	427	86.7	0.002
imputed (IRL)	2,173	91.1	543	89.3	0.188

Endocrine therapy

The overall proportion of estrogen receptor positive patients receiving endocrine therapy differed between the countries - 59% in The Netherlands vs. 92% in Ireland (*P*<0.001) for all stages combined. Patients with stage I disease were more than three times as likely to get endocrine therapy in Ireland (91% vs. 27%; *P*<0.001). The difference was smaller in stage II patients, 94% in Ireland vs. 84% in The Netherlands (*P*<0.001), and 89% vs. 91% respectively in stage III patients (P=0.188) (Figure 1B; Table 2). Adjusted RRs for having endocrine therapy in Ireland were 2.91 (95% CI 2.77-3.05), 1.11 (1.09-1.12) and 0.99 (0.96-1.02) respectively for stage I, II and III ER-positive patients. Among patients who did not receive any locoregional treatment at all, the proportions of endocrine monotherapy were 85% in The Netherlands and 86% in Ireland.

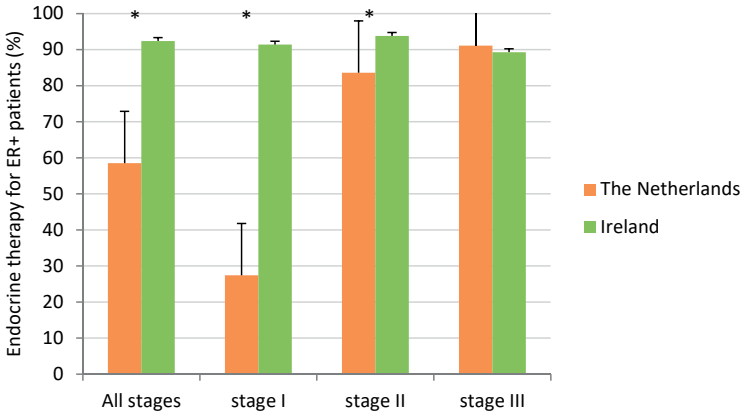

Figure 1b. Endocrine therapy for estrogen receptor positive patients by stage

Chemotherapy

Overall, 6% of patients The Netherlands and 24% of patients in Ireland received chemotherapy, and there was a higher proportion of Irish patients that received chemotherapy in all three stages (*P*<0.001) (Figure 1C; Table 2). Adjusted RRs for having chemotherapy in Ireland were 4.55 (95% CI 3.81-5.43), 3.35 (3.11-3.62) and 1.44 (1.31-1.58), respectively for patients with stage I, II and III.

Relative survival

Median follow-up time was 4.5 years for The Netherlands and 4.3 years for Ireland. During the total follow-up period, 14,771 (36.0%) patients died in The Netherlands, compared to 2,191 patients (37.6%) in Ireland.

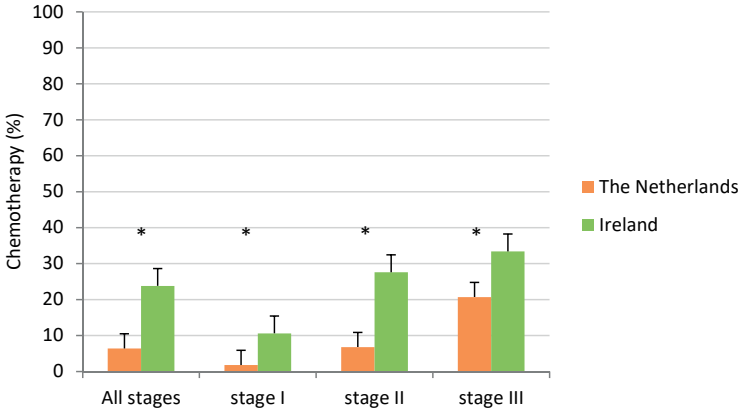

Figure 1c. Chemotherapy by stage

Five-year relative survival was 88.8% in The Netherlands and 82.9% in Ireland, for all stages combined (Figure 2). This survival difference was statistically significant, also after adjustment for age, grade, stage, ER, PR and morphology (relative excess risk [RER] for Ireland, with The Netherlands as reference category: 1.22; 95% confidence interval (CI) 1.10-1.36). Grouped by stage, no survival difference was demonstrated in stage I patients (adjusted RER 1.00, 95% CI 0.59-1.70), but worse survival was confirmed for Irish patients in stage II (adjusted RER 1.20, 95% CI 1.02-1.42) and stage III (1.20, 95% CI 1.04-1.39).

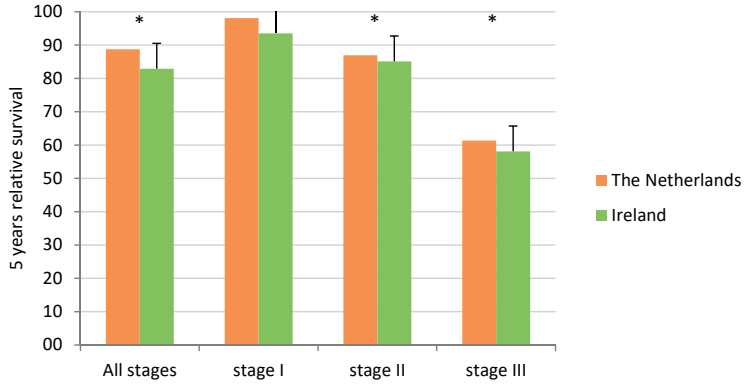

Figure 2. Relative survival by stage

DISCUSSION

The current study, comparing treatment and relative survival of older breast cancer patients between two Western European countries with similar treatment guidelines, showed large differences in treatment approach for older breast cancer patients. A higher proportion of patients in The Netherlands received guideline-adherent locoregional treatment than in Ireland in all stages, but in Ireland the receipt of systemic treatments was higher in all stages of disease. Relative survival of patients in Ireland was significantly poorer than in The Netherlands, but adjusted models suggested the difference most marked for stage II and III patients.

The observed discrepancies in breast cancer treatment are consistent with findings of earlier international comparisons of older and other breast cancer patients across Europe and the US.[9,17–19] However, although international survival and treatment variations among breast cancer patients have recently been assessed on a global scale[20], no clear evidence was published on the potential role of different treatment strategies in influencing survival discrepancies among early-stage cases. However, it is interesting to speculate on reasons for the differences in patterns of care for the specific treatment modalities. Some differences could be explained by discrepancies in guideline recommendations between the two countries. There are differences (Appendix S1) especially for postmastectomy radiotherapy and chemotherapy and for both of these, indications are broader in the Irish guidelines. These differences are reflected in our results, where we observed more patients from Ireland receiving these treatments, as compared to the patients from Netherlands, also stratified by stage of disease. Secondly, physicians from the Netherlands may also be more likely to deviate from the guidelines when treating older breast cancer patients. Unfortunately, in our study it was also not possible to draw any reliable conclusion about the impact of differences in any of the specific treatment modalities, because of a potential bias due to confounding by indication when comparing the outcomes of patients with different treatments directly.

In a large population-based study in The Netherlands, guideline adherence of breast cancer treatment among younger and older breast cancer patients was compared between different regions, and although differences in adherence were observed, there were no significant survival differences between regions.[21] In the current study we found less guideline-adherence on locoregional treatment in Ireland, and this was accompanied by a worse survival in Ireland. On the other hand, patients in Ireland received more systemic therapies (both endocrine therapy and chemotherapy), so no conclusion can be drawn based on the locoregional treatment only, because of a probably counterbalanced effect by adjuvant treatments.

To obtain the highest level of evidence on treatment benefits, the effect of each treatment modality should be investigated based on randomized assignment of treatment. However, randomized clinical trials (RCTs) tend to be slow, expensive, and insensitive to the heterogeneous contexts of the general population.[22] The disadvantages of RCTs are probably even stronger in the older population, because of their limited mobility and large heterogeneity. Observational studies, using population-based registry data, are considered to be a better reflection of the "real world". [5,23] However, although large study populations can be derived from registries, the observational design means that confounding by indication must be considered when studying treatment effects.

A limitation of our study was that the selected populations differed in some respects. Advanced stage and higher grade cases were more frequently observed in Ireland. Although the analyses included patients aged 65 and older, this finding might be explained partly by differences in screening[24,25] and possibly methods of grading between countries. To overcome the difference in stage distribution, we grouped all analyses by stage. Slight under-ascertainment of radiotherapy treatments is known to have occurred among Irish patients who had breast surgery in private hospitals. However, only about 17% of surgical patients in the age 65+ group falls into this category, and we estimate that the percentages of Irish patients reported as having radiotherapy in Ireland may about 2% too low, not enough to affect our conclusions.

To achieve best practice for older breast cancer patients, possibly, attention should be shifted to other outcomes rather than survival to improve quality of care for older breast cancer patients. However, we could draw no conclusions on aspects such as quality of life, risk of recurrence or complications, as we did not have data on these aspects. In addition, because of full anonymization of the datasets used for our analysis, characteristics of hospitals, such as the type (academic/teaching hospital, private/public clinic), but also the presence of radiotherapy facilities were not available. Therefore, we were unfortunately not able to see if guideline-adherence was associated with hospital characteristics.

The retrospective design of the current study, despite the positive arguments mentioned previously, remains a limitation. However, because of the availability of comprehensive cancer registry data, it was possible to create a large database of population-based, generalizable data.

In the future, study designs in which countries are compared on treatment strategy and breast cancer outcome are likely to be applied more frequently. By including many countries in analyses, specific populations that differ on only one treatment modality could be identified. Consequently, more evidence can

be obtained from observational studies, by comparing patient outcomes between countries using an instrumental variable study design.[26]

The European Registration of Cancer Care, or in short European Cancer Audit (EURECCA)[27] aims to create a population-based audit structure that covers all breast cancer patients across Europe: anonymous patient and tumor data, including treatment and outcome information will be registered in a uniform way across countries. The aim is to develop an extensive data source with the ultimate goal to define high-quality care and monitor the quality of care of all European cancer patients and so improving outcome of cancer care. EURECCA aims to investigate best practices and learn from them, as well as perform analysis on patient groups that deviate from guidelines such as the young and elderly. The availability of comprehensive cancer registry data, (like that used in the current study) facilitates the identification of large cohorts of population-based, generalizable data.

In conclusion, in this population-based study comparing patterns of care and survival of older breast cancer patients on a national scale in The Netherlands and Ireland, we found large differences in treatment approach, with more guideline-adherence on locoregional treatment in The Netherlands, and more prescription of systemic therapy in Ireland. Patients in Ireland had a worse relative survival as compared with the Dutch patients, although it was not possible to link this survival difference directly to differences in one or more of the specific treatment modalities. However, our finding should be a strong recommendation to perform more research on an international scale, with the ultimate goal to equalize the survival rates for breast cancer patients across Europe.

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REFERENCES

1. Wildiers H, Kunkler I, Biganzoli L, Fracheboud J, Vlastos G, Bernard-Marty C, Hurria A, Extermann M, Girre V, Brain E, Audisio RA, Bartelink H, Barton M, Giordano SH, Muss H, Aapro M (2007) Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. Lancet Oncol 8: 1101-1115. S1470-2045(07)70378-9
2. Biganzoli L, Wildiers H, Oakman C, Marotti L, Loibl S, Kunkler I, Reed M, Ciatto S, Voogd AC, Brain E, Cutuli B, Terret C, Gosney M, Aapro M, Audisio R (2012) 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 13: e148-e160. S1470-2045(11)70383-7
3. Townsley CA, Selby R, Siu LL (2005) Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. J Clin Oncol 23: 3112-3124. 23/13/3112
4. van de Water W, Kiderlen M, Bastiaannet E, Siesling S, Westendorp RG, van de Velde CJ, Nortier JW, Seynaeve C, de Craen AJ, Liefers GJ (2014) External validity of a trial comprised of elderly patients with hormone receptor-positive breast cancer J Natl Cancer Inst 106: dju051. dju051
5. Al-Refaie WB, Vickers SM, Zhong W, Parsons H, Rothenberger D, Habermann EB (2011) Cancer trials versus the real world in the United States. Ann Surg 254: 438-442.
6. Mieog JS, de Kruijf EM, Bastiaannet E, Kuppen PJ, Sajet A, de Craen AJ, Smit VT, van de Velde CJ, Liefers GJ (2012) Age determines the prognostic role of the cancer stem cell marker aldehyde dehydrogenase-1 in breast cancer. BMC Cancer 12: 42. 1471-2407-12-42
7. Vandenbroucke JP (2004) When are observational studies as credible as randomised trials? Lancet 363: 1728-1731. 10.1016/S0140-6736(04)
8. Altman DG, Bland JM (1999) Statistics notes. Treatment allocation in controlled trials: why randomise? BMJ 318: 1209.
9. Kiderlen M, Bastiaannet E, Walsh PM, Keating NL, Schrodi S, Engel J, van de Water W, Ess SM, van EL, Miranda A, de ML, van de Velde CJ, de Craen AJ, Liefers GJ (2012) Surgical treatment of early stage breast cancer in elderly: an international comparison. Breast Cancer Res Treat 132: 675-682.
10. Greene FL, Page DL Fleming ID et al. (2002) AJCC cancer staging manual, 6th edition. New York: Springer.
11. Fleming I.D., Cooper, J. S., Henson D.E., Hutter, R. V. P., Kennedy B.J., and et al. (1997) AJCC Cancer Staging Manual, fifth edition. Philadelphia, PA: Lippincott-Raven.
12. CBO (2005) Richtlijn Behandeling van het mammacarcinoom 2005.
13. N.O'Higgins, Health Information and Quality Authority (2007) National Quality Assurance Standards for Symptomatic Breast Disease Services - Developing Quality Care for Breast Services in Ireland.
14. T.N.Walsh, N O'Higgins, Royal College of Surgeons in Ireland (2000) Breast Cancer Management Clinical Guidelines.
15. Hakulinen T, Seppa K, Lambert PC (2011) Choosing the relative survival method for cancer survival estimation. Eur J Cancer 47: 2202-2210. S0959-8049(11)00173-0
16. Dickman PW, Sloggett A, Hills M, Hakulinen T (2004) Regression models for relative survival. Stat Med 23: 51-64.

17. Allemani C, Storm H, Voogd AC, Holli K, Izarzugaza I, Torrella-Ramos A, Bielska-Lasota M, Aareleid T, Ardanaz E, Colonna M, Crocetti E, Danzon A, Federico M, Garau I, Grosclaude P, Hedelin G, Martinez-Garcia C, Peignaux K, Plesko I, Primic-Zakelj M, Rachtan J, Tagliabue G, Tumino R, Traina A, Tryggvadottir L, Vercelli M, Sant M (2010) Variation in 'standard care' for breast cancer across Europe: a EUROCARE-3 high resolution study. Eur J Cancer 46: 1528-1536. S0959-8049(10)00119-X
18. Garcia-Etienne CA, Tomatis M, Heil J, Friedrichs K, Kreienberg R, Denk A, Kiechle M, Lorenz-Salehi F, Kimmig R, Emons G, Danaei M, Heyl V, Heindrichs U, Rageth CJ, Janni W, Marotti L, del Turco MR, Ponti A (2012) Mastectomy trends for early-stage breast cancer: a report from the EUSOMA multi-institutional European database. Eur J Cancer 48: 1947-1956. S0959-8049(12)00253-5
19. van Nes JG, Seynaeve C, Jones S, Markopoulos C, Putter H, van de Velde CJ, Hasenburg A, Rea DW, Vannetzel JM, Dirix L, Hozumi Y, Kerin MJ, Kieback DG, Meershoek-Klein Kranenbarg WM, Hille ET, Nortier JW (2010) Variations in locoregional therapy in postmenopausal patients with early breast cancer treated in different countries. Br J Surg 97: 671-679.
20. Allemani C, Sant M, Weir HK, Richardson LC, Baili P, Storm H, Siesling S, Torrella-Ramos A, Voogd AC, Aareleid T, Ardanaz E, Berrino F, Bielska-Lasota M, Bolick S, Cirilli C, Colonna M, Contiero P, Cress R, Crocetti E, Fulton JP, Grosclaude P, Hakulinen T, Izarzugaza MI, Malmstrom P, Peignaux K, Primic-Zakelj M, Rachtan J, Safaei DC, Sanchez MJ, Schymura MJ, Shen T, Traina A, Tryggvadottir L, Tumino R, Velten M, Vercelli M, Wolf HJ, Woronoff AS, Wu X, Coleman MP (2012) Breast cancer survival in the US and Europe: A CONCORD high-resolution study. Int J Cancer .
21. van de Water W, Bastiaannet E, Dekkers OM, de Craen AJ, Westendorp RG, Voogd AC, van de Velde CJ, Liefers GJ (2012) Adherence to treatment guidelines and survival in patients with early-stage breast cancer by age at diagnosis. Br J Surg 99: 813-820.
22. Sullivan P, Goldmann D (2011) The promise of comparative effectiveness research. JAMA 305: 400-401.
23. Dreyer NA, Garner S (2009) Registries for robust evidence. JAMA 302: 790-791.
24. RIVM (2012) Bevolkingsonderzoek Borstkanker.
25. National Cancer Screening Service (2012) The National Breast Screening Program.
26. Rassen JA, Brookhart MA, Glynn RJ, Mittleman MA, Schneeweiss S (2009) Instrumental variables I: instrumental variables exploit natural variation in nonexperimental data to estimate causal relationships. J Clin Epidemiol 62: 1226-1232. S0895-4356(09)00014-6
27. (2014) EURECCA - European Registration of Cancer Care. http://www.essoweb.org/projects/eurecca-cancer-care/

Chapter 4

Variations in compliance to quality indicators by age for 41,871 breast cancer patients across Europe: a European Society of Breast Cancer Specialists database analysis

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ABSTRACT

Objective. The aim of this study is to assess age-specific compliance to quality indicators (QIs) regarding the treatment of breast cancer as defined by the European Society of Breast Cancer Specialists (EUSOMA) for patients across Europe.

Methods. All patients entered into this study were affected by in situ or invasive breast cancer, diagnosed and treated between 2003 and 2012 at 27 Breast Units across Europe, who were entered into the EUSOMA database. Patients were categorized according to age; compliance to thirteen QIs was assessed for each age group and per time period (2003-2007 and 2008-2012). Compliance to QIs was tested by multivariable logistic regression models adjusted for breast unit, incidence year, and tumour characteristics.

Results. Overall, 41,871 patients with a mean age of 59.6 years were available for analysis. The highest compliance was reached for patients aged 55-64 years and in the time period 2008-2012, while the lowest compliance was observed for women aged over 74 or under 40 years and in the earlier time period. In multivariable logistic regression models, a significant difference between age categories was shown for 12 out of 13 QIs ($P<0.001$). Compliance to the QIs for patients aged ≥75 years was significantly lower when compared to patients aged 55-64 years for ten QIs, while for patients in the youngest age group this was true for seven QIs.

Conclusion. In conclusion, we found that among the 27 included breast units across Europe, compliance to QIs for breast cancer treatment is often lower in the youngest and oldest breast cancer patients, with a tendency to *over*treatment in the youngest patients, and to *under*-treatment in the elderly.

INTRODUCTION

Numerous national and international guidelines and recommendations are available to physicians treating breast cancer patients. However, a significant variation in patterns for breast cancer care has been reported throughout Europe.[1,2] This variation in treatment is accompanied by variation in breast cancer survival rates.[3]

The European Society of Breast Cancer Specialists (EUSOMA) aims to improve and standardize the level of patients care throughout Europe. To accomplish this, the measurement of quality indicators in breast cancer care is essential, in order to monitor the effectiveness and to guide improving the healthcare.[4] To identify the appropriate indicators for quality assurance in breast cancer care, EUSOMA organized a workshop in 2008 where 24 experts from different disciplines defined a set of quality indicators (QIs) on the whole process of breast cancer management based on the international literature, which was published in 2010. For each QI, the experts defined minimum and target standards.[4] Breast centres certified in compliance with the standards of the EUSOMA guidelines are required to hold a Breast Unit (BU) database for the purpose of auditing as well as for research purposes.[5]

The QIs are defined without any age-specific comments, and also, the minimum standards are not age-specific. However, probably it is desired to take into account age-specific issues in treatment recommendations for breast cancer treatment.

For instance, it is questionable if deviation from standard treatment has the same impact on patient outcomes across all age groups. Population-based data from Europe and North America have shown that among older women, large differences in *locoregional* treatment between countries have not led to survival differences .[1,6-9] This leads to the question if 'non-inferior' locoregional treatment strategies result in worsened outcomes among elderly. On the other hand, with regards to systemic therapy, a few randomized trials have shown that chemotherapy regimens which are considered inferior (but more patient-friendly, such as oral capecitabine), result in an inferior prognosis for both younger and older patients[10,11], implying no age-specific impact on outcome.

However, when interpreting trial results, it has to be taken into account that in contrast to the growing population of elderly with cancer, older patients are underrepresented in current clinical oncological studies.[12] Moreover, it has been shown that the older subjects who are included in a clinical trial, are not always representative for the general older population.[13] Therefore, the external validity of clinical trial results should be questioned when it concerns older patients.

With regards to younger breast cancer patients, it is opted that these patients probably deserve a different approach and management than older women, taking

into account their longer general life expectancy, but also, their other, more aggressive tumour biology.[14]
In summary, it is understandable to observe differences in treatment approach across age groups, accompanied by varying compliance to QIs by age. To test this hypothesis, the aim of this study is to assess age-specific compliance to the EUSOMA QIs regarding treatment for patients across Europe.

METHODS

The EUSOMA database (db) is a central data warehouse of prospectively collected information which includes individual records on primary breast cancer cases diagnosed and treated at European breast units (BUs) providing patients data in a standardized format. The database was started in 2006 and collects 108 variables for each patient record, including patient and tumour characteristics, information about preoperative work-up, multidisciplinary management, and follow-up data. Different BUs started entering patients in the db on different points in time, but it has been formally checked that the patients that were included in the database are consecutive patients. Records are anonymous but BUs can identify their own patients by the use of an ID code. The data transfer from each Unit database to the EUSOMA db occurs yearly through an online application and represents a requirement to obtain and to continue holding certification. BUs can access the EUSOMA db to check data quality, calculate QIs, perform data analysis and benchmarking and agree to use it for certification purposes and for co-operative clinical research.[15] For research purposes, the data are fully anonymized, as well on case record level, as on BU level. To assure the data quality, there have been several consistency checks built into the database, as is a report on missing values. In order to maintain EUSOMA certification, BUs are required to minimize inconsistencies an incompleteness and may send several data transfers in order to achieve this.

Patients

All patients with a diagnosis of in situ or invasive breast cancer diagnosed between 2003 and 2012 from 27 certified BUs from Austria, Belgium, Germany, Italy, and Switzerland who provided their data to the EUSOMA db before August 2013 were included into this analysis. Patients with missing data on age or with non-epithelial tumours or other neoplasms were excluded. Age was categorized as <40 years, 40-54 years, 55-64 years, 65-74 years, and ≥75 years.

Outcome measures

Primary outcome measure was the compliance to EUSOMA QIs by age.[4] We selected the thirteen QIs considering treatment (rather than diagnosis, staging, follow-up or counselling). QIs were divided into five groups: appropriate surgical approach, post-operative radiotherapy (RT), avoidance of overtreatment, appropriate hormonal therapy, appropriate chemotherapy, and other medical therapy. Data on trastuzumab were incomplete; therefore, QIs regarding this treatment modality were disregarded from the present investigation.

Statistical analyses

All analyses were performed using IBM SPSS Statistics 20 or R (v.3.0.0). All tests of significance were two-sided and *P*-values smaller than 0.05 were considered statistically significant.

For each QI, the appropriate selection of patients was used (based on tumour stage or type of treatment). Patients with missing data on the treatment of interest for a specific QI, were excluded from the analyses (per QI). The EUSOMA db datacentre considers outcomes of QIs with more than 25% missing values as highly unstable and therefore, QI compliance is not calculated when the proportion of missing values exceeds 25%.

Proportions of compliance to each QI were stratified by age group and time period (2003-2007 and 2008-2012).

Primary outcome measure was the proportion of compliance to each QI. Multivariable logistic regression analyses were performed to calculate adjusted odd's ratios (ORs) and 95% confidence intervals (CIs) by age group, with the middle age group (55-64 years) as reference category. The results were adjusted for BU, incident year, and, when appropriate, tumour characteristics (stage, grade, morphology, and hormone receptor expression). In case of missing data in one of the adjustment variables, these patients were not excluded from the multivariable models, but the missing data were taken into account as a separate value of the variable.

With the purpose of presenting the results into a more intuitive way, adjusted ORs were converted to risks using the formula: adjusted OR/ 1 - adjusted OR.[16]

RESULTS

In total, 41,871 patients from the EUSOMA db were included into this study. The mean age was 59.6 years (Standard Deviation (SD) 13.0). The majority of patients were categorized into the middle three age groups, 5% were <40 years, and 13% were ≥75 years. There was an increasing trend in the number of patients per year, from

2.6% in the year of initiation of the database (2003), to 18.8% in 2011. Most patients had stage I or II breast cancer (39.5% and 31.4%, respectively). Most cancers were hormone receptor positive (81.5%) and invasive ductal carcinoma (72.2%) (Table 1).

Table 1. Patient and tumour characteristics.

	Age categories											
	< 40		**40-54**		**55-64**		**65-74**		**75+**		**All ages**	
	N=2,260		N=13,701		N=10,706		N=10,323		N=5,475		N=41,871	
	N	%	N	%	N	%	N	%	N	%	N	%
Incidence year												
2003	69	3.1	380	2.9	335	3.1	205	2.0	97	1.8	1,086	2.6
2004	127	5.6	565	4.3	519	4.8	370	3.6	190	3.5	1,771	4.2
2005	157	6.9	779	5.9	713	6.7	531	5.1	281	5.1	2,461	5.9
2006	179	7.9	904	6.9	820	7.7	727	7.0	329	6.0	2,959	7.1
2007	210	9.3	1113	8.5	902	8.4	916	8.9	372	6.8	3,513	8.4
2008	238	10.5	1,471	11.2	1,227	11.5	1,266	12.3	570	10.4	4,772	11.4
2009	334	14.8	2,027	15.5	1,674	15.6	1,801	17.4	831	15.2	6,667	15.9
2010	360	15.9	2,221	16.9	1,827	17.1	1,870	18.1	1,023	18.7	7,301	17.4
2011	386	17.1	2,552	19.5	1,868	17.4	1,849	17.9	1,212	22.1	7,867	18.8
2012	200	8.8	1,095	8.4	821	7.7	788	7.6	570	10.4	3,474	8.3
Stage												
in situ	205	9.1	1,767	13.5	1,366	12.8	1,083	10.5	358	6.5	4,779	11.4
I	802	35.5	5,064	38.6	4,584	42.8	4,428	42.9	1,677	30.6	16,555	39.5
II	780	34.5	4,077	31.1	3,110	29.0	3,127	30.3	2,055	37.5	13,149	31.4
III	289	12.8	1,371	10.5	1,033	9.6	1,057	10.2	758	13.8	4,508	10.8
IV	40	1.8	216	1.6	184	1.7	202	2.0	132	2.4	774	1.8
missing	144	6.4	612	4.7	429	4.0	426	4.1	495	9.0	2,106	5.0
Grade												
1	139	6.2	2,058	15.7	1,727	16.1	1,646	15.9	757	13.8	6,327	15.1
2	901	39.9	6,433	49.1	5,619	52.5	5,766	55.9	3,138	57.3	21,857	52.2
3	1054	46.6	3,902	29.8	2,897	27.1	2,538	24.6	1,447	26.4	11,838	28.3
missing	166	7.3	714	5.4	463	4.3	373	3.6	133	2.4	1,849	4.4
Hormone receptor (ER and/or PR)												
negative	680	30.1	2,108	16.1	1,617	15.1	1,372	13.3	721	13.2	6,498	15.5
positive	1,483	65.6	1,0523	80.3	8,774	82.0	8,708	84.4	4,633	84.6	34,121	81.5
missing	97	4.3	476	3.6	315	2.9	243	2.4	121	2.2	1,252	3.0
Morphology												
Ductal	1,851	81.9	9,422	71.9	7,611	71.1	7,294	70.7	4,043	73.8	30,221	72.2
Lobular	99	4.4	1,495	11.4	1,350	12.6	1,545	15.0	742	13.6	5,231	12.5
Combined/other	91	4.0	492	3.8	403	3.8	410	4.0	329	6.0	1,725	4.1
missing	219	9.7	1,698	13.0	1,342	12.5	1,074	10.4	361	6.6	4,694	11.2

Percentages indicate the proportion of patients within an age-group. ER=estrogen receptor. PR=progesterone receptor.

The thirteen scrutinized QIs with definitions are listed in Table 2, which also displays the minimum standards as defined by EUSOMA[4] and the absolute numbers of QI compliance by time period, including the number and proportion of missing values. The proportions of QI compliance by age and time-period are shown in Webtable 1. The highest compliance to QIs was reached in patients aged 55-64 years, where the minimum standard was reached for ten QIs during 2008-2012 and for six during 2003-2007. In patients aged ≥75 years, the minimum standard was reached in the two time periods for three and seven QIs respectively, while in women <40 for four and six QIs.

In multivariable logistic regression models (Webtable 2), a significant difference between age categories was shown for 12 of 13 QIs (P<0.001). No difference between age groups was shown for QI 13e (p=0.07). The adjusted proportions of guideline adherence per age group are shown in Figure 1. Compliance to QIs for patients aged ≥75 years differed significantly from patients in the middle age group (55-64 years) for almost all QIs, except QI 11b. For two indicators, 9a and 9b, the compliance was higher among the oldest patients. However, for the remaining ten QIs, compliance of patients aged ≥75 years was significantly lower, when compared to patients aged 55-64 years.

Table 2. Definition of QIs and compliance by time period.

Definition		Minimum standard	Time period	Compliance		Missing	
				N	%	*N*	%
Surgery and locoregional treatment							
Appropriate surgical approach	9a. % of patients with invasive cancer who received a single operation (excluding reconstruction)	80%	2003-2007	10254	75.0%	19	0.2%
			2008-2012	25432	**82.0%**	45	0.2%
			Total	35686	**80.0%**	64	0.2%
	9b. % of patients with DCIS who received only one operation	70%	2003-2007	1218	53.9%	3	0.2%
			2008-2012	3300	64.8%	1	0.0%
			Total	4518	61.8%	4	0.1%
	9c. % of patients with cN0 who had a SNB.	90%	2003-2007	9590	44.9%	173	1.8%
			2008-2012	23376	81.1%	171	0.7%
			Total	32966	70.5%	344	1.0%
	9d. % if patients with ALND performed, with at least 10 LNs examined	95%	2003-2007	5896	84.7%	261	4.2%
			2008-2012	8476	90.3%	333	3.8%
			Total	14372	88.0%	594	4.0%
Post-operative RT	10a. % of patients with RT after BCS for M0 invasive cancer.	90%	2003-2007	4982	**95.8%**	1418	22.2%
			2008-2012	15714	**94.2%**	1227	7.2%
			Total	20696	**94.6%**	2645	11.3%
	10b. % of patients with pN2a or more who received postmastectomy RT	90%	2003-2007	589	**91.9%**	190	24.4%
			2008-2012	1225	85.2%	128	9.5%
			Total	1814	87.4%	318	14.9%

Table 2. Definition of QIs and compliance by time period. (*continued*)

Definition		Minimum standard	Time period	Compliance		Missing	
				N	%	*N*	%
Avoidance of overtreatment	11a. % of patients with invasive cancer not greater than 3 cm who underwent BCT	70%	2003-2007	7398	**75.0%**	158	2.1%
			2008-2012	16967	**82.3%**	658	3.7%
			Total	24365	**80.1%**	816	3.2%
	11b. % of patients with non-invasive cancer not greater than 2 cm who underwent BCS	70%	2003-2007	801	**77.8%**	36	4.3%
			2008-2012	1882	**87.0%**	149	7.3%
			Total	2683	**84.3%**	185	6.5%
	11c. % of patients with DCIS who do not undergo ALND	95%	2003-2007	1130	86.4%	18	1.6%
			2008-2012	3236	**96.0%**	8	0.2%
			Total	4366	93.5%	26	0.6%
	11d. % of invasive breast cancer patients with pN0 who do not undergo ALND	80%	2003-2007	5818	48.7%	2	0.0%
			2008-2012	15824	**86.4%**	4	0.0%
			Total	21642	76.3%	6	0.0%
Systemic treatment							
Appropriate hormonotherapy	12a. % of patients with HR+ invasive cancer who received hormonotherapy	80%	2003-2007	5403	**96.5%**	3116	36.6%
			2008-2012	18994	**93.8%**	3385	15.1%
			Total	24397	**94.4%**	6501	21.0%
Appropriate chemotherapy and other medical therapy	13a. % of patients with HR- (T>1 or N+) invasive cancer who received adjuvant chemotherapy	80%	2003-2007	1266	**91.7%**	324	20.4%
			2008-2012	2806	**90.6%**	178	6.0%
			Total	4072	**90.9%**	502	11.0%
	13e. % of patients with inflammatory cancer or locally advanced irresectable cancer who had neoadjuvant chemotherapy	90%	2003-2007	27	11.1%	15	35.7%
			2008-2012	111	78.4%	21	15.9%
			Total	138	65.2%	36	20.7%

Numbers shown in bold type indicate that the minimum standard is reached. Patients with missing values were excluded for calculating the proportion of compliance per QI. The proportion of missing values indicate the missing values of the treatment of interest in the selection that was made for the specific QI.

DCIS=ductal carcinoma in situ. cN0=clinically node negative. SNB=sentinel node biopsy. ALND=axillary lymph node dissection. LN=lymph node. RT=radiotherapy. BCS=breast conserving surgery. M0=non-metastatic. HR=hormone receptor

Furthermore, for eight QIs, compliance for the patients in the youngest age group differed significantly compared to those aged 55-64 years (Webtable 2). The compliance was lower, with the exception of QI 13a.

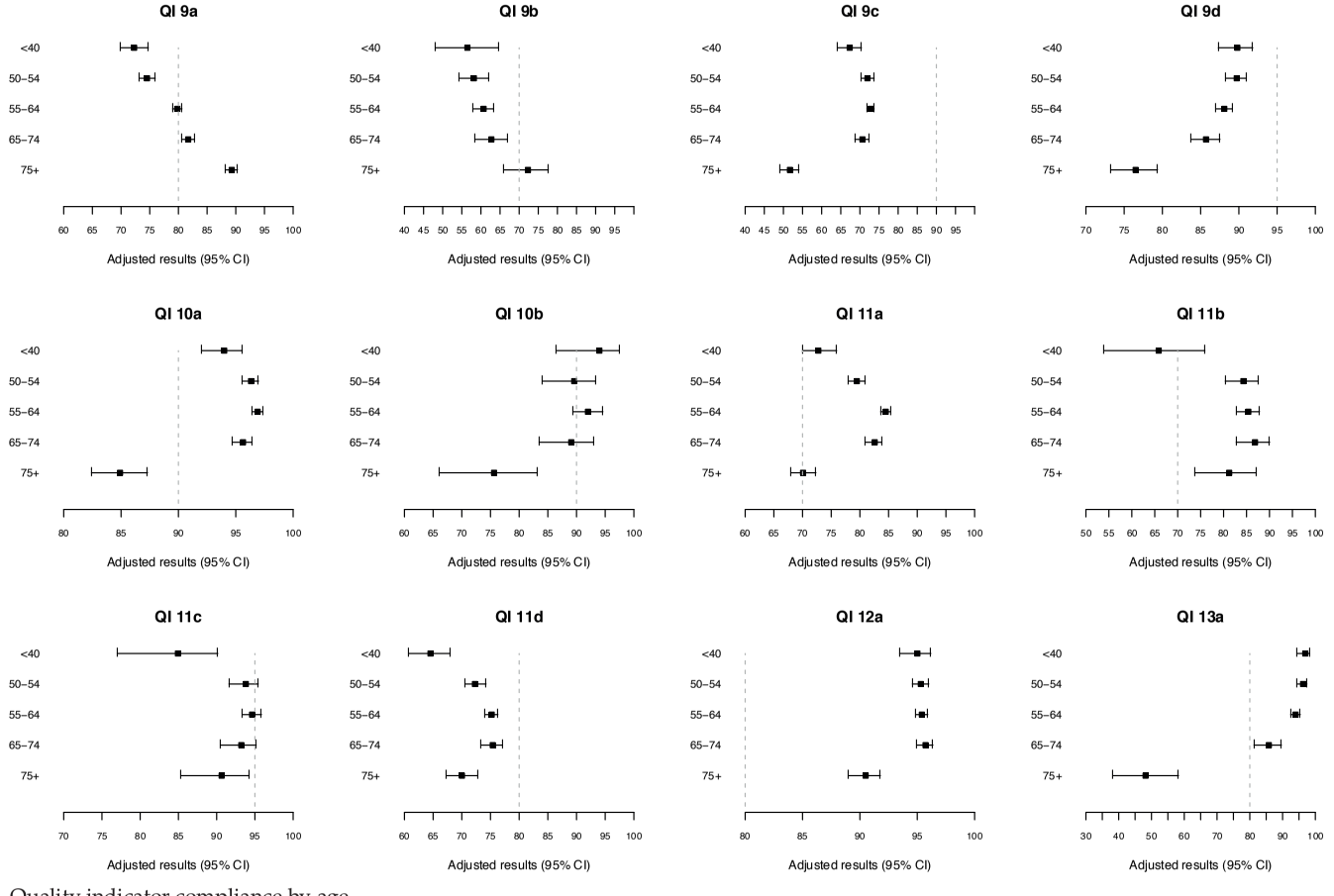

Figure 1. Quality indicator compliance by age

DISCUSSION

This observational study conducted on the largest European breast cancer database demonstrates a low compliance to quality indicators among the youngest (<40 years) and the oldest (≥75 years) patients. Below we will discuss compliance to the specific QIs per treatment category.

The category "Appropriate surgical approach" includes four QIs. Firstly, we observed that the proportion of patients receiving only one operation for invasive cancer (9a) increases with age. A possible explanation is that there is a more reluctant approach to older patients with positive margins, whereas in younger breast cancer patients, positive margins are considered unacceptable, with regards to a higher risk on local recurrence.[17] The same applies for QI 9b: the proportion of patients with ductal carcinoma in situ (DCIS) receiving only one operation; only patients aged ≥75 years met the minimum standard. For QI 9c; the proportion of clinically node negative patients receiving sentinel node biopsy was lower in the youngest and the oldest age group. Again, this is probably reflecting a more aggressive treatment approach in the youngest patients (axillary lymph node dissection), and a more reluctant approach to elderly. The time-period analyses showed almost twice as much compliance in the period 2008-2012 as compared to 2003-2007, reflecting the increasing use of sentinel node procedures.[18] For QI 9d; the proportion of patients with axillary clearance with at least ten lymph nodes examined, the compliance declined with increasing age. This is in keeping with previous studies.[19,20]

QIs for "Post-operative radiotherapy" are separated for radiotherapy after breast conserving surgery (BCS) for non-metastatic invasive cancer (10a), and after mastectomy for pN2a or more (10b). The minimum standard for QI 10a was reached, except in the oldest group (≥75 years). Our observation is a confirmation of many population-based studies showing a decrease in the receipt of RT after BCS in older breast cancer patients, but still a proportion of 82% in the EUSOMA db is higher than previous observations.[1,21,22] The compliance to QI10b was lower in patients aged ≥75 years, which again reflects a more reluctant treatment approach towards older patients.[23] Interestingly, the compliance to QI 10b was higher in the time period 2003-2007. The decrease over time might be explained by the increasing use of aromatase inhibitors, which are considered more tolerable than other (chemotherapeutic) systemic therapies, and moreover probably more effective than tamoxifen for advanced hormone receptor positive breast cancer.[24]

The category "Avoidance of overtreatment" comprises four QIs. QI 11a and 11b consider the proportion of patients with small invasive and non-invasive breast cancers receiving BCS, respectively. We have found that compliance decreases with

increasing age, in line with previous studies which showed an increase in mastectomies with increasing age.[21,25] In contrast, for non-invasive cancer the compliance was lowest for the youngest age group, indicating more extensive surgery. For QIs 11c and 11d, considering the avoidance of axillary lymph node dissection (ALND) for patients with non-invasive lesions or for pathologically confirmed N0 disease (pN0), the minimum standards were not reached in any of the age categories before 2008, which can be explained by the limited use of sentinel node procedures at that time.[26] From 2008 onwards, this QI compliance increased dramatically, and the minimum standard for both QIs was reached in all age groups, except for patients aged <40 years. This indicates a possible overtreatment of the young patients, because there is no hard evidence and no guidelines that justify the use of ALND in non-invasive cancers.[4]

The relatively greater overtreatment in the youngest patients group is probably due to the attempt to assure the lowest risk of recurrence, although this practice should be challenged by considering the balance between benefits and harms.

The category "Appropriate hormonal therapy" comprises one QI (12a), which describes the proportion of patients with hormone receptor (HR) positive invasive breast cancer who received endocrine therapy. This is the only QI for which the minimum standard was achieved in all age categories, indicating good consensus on the provision of hormonal therapy for hormone receptor positive breast cancer.

The last category is "Appropriate chemotherapy and other medical therapy". The standard for QI 13e (chemotherapy for HR-, T>1 or N+) was reached for all patients, except for the oldest patients, where the compliance dropped to 53%. Reluctance to administer chemotherapy in the elderly has been described in previous studies. Reluctance is probably related to the expectation of as well physicians and patients that older patients have a lower treatment tolerability, but also to patient preferences.[4,21,27]

For QI 13e (the proportion of patients with inflammatory cancer or locally advanced irresectable cancer who had neoadjuvant chemotherapy) we showed the same trend in reluctance with chemotherapy with increasing age; although the minimum standard was not reached in any age category, the compliance was by far the lowest in patients aged ≥75 years (44%).

Summarizing our results, we found that treatment of breast cancer patients <40 years and ≥75 years was most often not compliant to the quality indicators as defined by EUSOMA. In the youngest age group, this non-compliance can most probably be explained by *over*-treatment rather than *under*-treatment. In 2012, EUSOMA published recommendations for the treatment of young women (<40 years) with breast cancer.[14] In 2007, the first recommendations for treatment of older patients with breast cancer were published by SIOG (International Society of

Geriatric Oncology), which were updated in 2012 in collaboration with EUSOMA (a summary of treatment recommendations is provided in Webtable 3).[28,29]

The largest difference between these recommendations regards the use of systemic therapy: EUSOMA advises to offer chemotherapy to all young patients with stage I-III breast cancers while EUSOMA/SIOG advises to restrict the provision of chemotherapy to older patients for node-positive, ER negative disease.

With regards to the older patients, our findings raise the question whether a minimalistic attitude results into poorer outcomes. In the last decade, several studies have documented the omission of certain treatments. A small number of clinical trials omitting radiotherapy for selected groups of older, HR positive patients, have been performed[30] none of them showing a deterred survival. However, the risk of locoregional recurrence was higher, as was also shown in the EBCTCG overview.[31] In addition, Martelli et al. published a two-armed trial in which axillary dissection versus no axillary dissection in elderly patients without clinically suspicious nodes.[32] After a median follow-up of 15 years, no significant difference in breast cancer mortality was shown. More on, only a restricted number of randomized studies takes into account the omission of local surgery for older breast cancer patients. A meta-analysis of these trials showed that primary endocrine therapy with tamoxifen associates with inferior local disease control but non-inferior cancer specific survival after surgery.[33] On the other hand, a few trials that studied the effectiveness of more tolerable chemotherapy regimens have shown that these regimens are, less effective in older patients, similar to the younger breast cancer population.[10,11] However, the question is if the older patients that were included in these trials are comparable to the general older cancer patients in terms of, for example, tumour characteristics and comorbidity. Therefore, the generalizability of these trial results should be further explored.[13] From these studies, among others, it is clear that the treatment of breast cancer for older women should not be always the same as the treatment for their younger counterparts, at least not for all treatment modalities. Therefore, in quality of care research regarding breast cancer treatment, it is probably worth considering to define age-specific QIs in the future, or at least to re-define the minimum standards by age category.

One limitation of our study rests on the voluntary certification of contributing breast centres, implying that enrolled patients are likely to be subjected to a selection of top performing breast units.[5] A further limitation of the data is that hospitals did not start recruiting patients' information at the same point in time. Furthermore, the QIs have been prepared in 2008 and published in 2010, whilst the patients in the database are included from 2003 onwards.[4] The expected increasing trend in QI compliance due to the increasing awareness of these quality measurements has indeed been observed in our stratified analyses. Another limitation of our study

is one that often arises in observational studies, namely the existence of missing data. For the majority of treatment modalities, patients with missing values were limited to a proportion of lower than 10%, with the exception of data on systemic treatments, where the proportion was somewhat higher, but still not exceeding the preliminary defined limit of 25%. For our analyses regarding QI compliance, we excluded patients with missing data per QI. It is unknown if the missing data are 'missing at random', therefore, it was not justified to use imputation techniques to fill in the missing data. Theoretically, in the case of 'non-missing at random' data, it is possible that our results slightly over- or underestimate the real compliance. However, we have no reason to believe that the missing data are related to the level of QI compliance, and therefore, we believe that the low proportion of missing data will not impact our results.

Further insight in patterns of care is mandatory to improve the quality of care and outcomes of cancer patients across Europe. The inclusion of follow up information in the EUSOMA db is on-going but not yet available, therefore we were not able to analyse the impact of QI compliance on patient outcome in our current study.

The European Registration of Cancer Care, or in short European Cancer Audit (EURECCA) aims at improving outcome of cancer care through registration and auditing.[34] The aim of EURECCA is to create a population-based audit structure that covers all breast cancer patients across Europe: anonymous patient and tumour data, including treatment and outcome information will be registered in an uniform way across countries. The aim is to develop an extensive data source with the ultimate goal to define high-quality care and monitor the quality of care of all European cancer patients. EURECCA aims to investigate best practices and learn from them, as well as perform analysis on patient groups that deviate from guidelines such as the young and elderly.

In conclusion, we found that among twenty-seven BUs across Europe, compliance to quality indicators for breast cancer treatment is often lower for the youngest and oldest breast cancer patients, with a tendency to *over*treatment in the youngest patients, and to *under*-treatment in the elderly. In the near future EURECCA, in close collaboration with EUSOMA, will map patterns of care and the clinical outcome of European breast cancer patients and will develop an international audit structure to improve quality of care.

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REFERENCES

1. Kiderlen M, Bastiaannet E, Walsh PM, et al: Surgical treatment of early stage breast cancer in elderly: an international comparison. Breast Cancer Res Treat 132:675-682, 2012
2. Allemani C, Storm H, Voogd AC, et al: Variation in 'standard care' for breast cancer across Europe: a EUROCARE-3 high resolution study. Eur. J. Cancer 46:1528-1536, 2010
3. De AR, Sant M, Coleman MP, et al: Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE-5-a population-based study. Lancet Oncol 15:23-34, 2014
4. del Turco MR, Ponti A, Bick U, et al: Quality indicators in breast cancer care. Eur. J. Cancer 46:2344-2356, 2010
5. Wilson AR, Marotti L, Bianchi S, et al: The requirements of a specialist Breast Centre. Eur. J. Cancer 49:3579-3587, 2013
6. Ess S, Joerger M, Frick H, et al: Predictors of state-of-the-art management of early breast cancer in Switzerland. Ann. Oncol 22:618-624, 2011
7. van de Water W, Bastiaannet E, Dekkers OM, et al: Adherence to treatment guidelines and survival in patients with early-stage breast cancer by age at diagnosis. Br. J. Surg 99:813-820, 2012
8. Showalter SL, Grover S, Sharma S, et al: Factors influencing surgical and adjuvant therapy in stage I breast cancer: a SEER 18 database analysis. Ann. Surg. Oncol 20:1287-1294, 2013
9. Giordano SH, Duan Z, Kuo YF, et al: Use and outcomes of adjuvant chemotherapy in older women with breast cancer. J. Clin. Oncol 24:2750-2756, 2006
10. Muss HB, Berry DA, Cirrincione CT, et al: Adjuvant chemotherapy in older women with early-stage breast cancer. N. Engl. J. Med 360:2055-2065, 2009
11. Jones S, Holmes FA, O'Shaughnessy J, et al: Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. J. Clin. Oncol 27:1177-1183, 2009
12. Hurria A, Dale W, Mooney M, et al: Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. J. Clin. Oncol 32:2587-2594, 2014
13. 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 106:dju051, 2014
14. Cardoso F, Loibl S, Pagani O, et al: The European Society of Breast Cancer Specialists recommendations for the management of young women with breast cancer. Eur. J. Cancer 48:3355-3377, 2012
15. Garcia-Etienne CA, Tomatis M, Heil J, et al: Mastectomy trends for early-stage breast cancer: a report from the EUSOMA multi-institutional European database. Eur. J. Cancer 48:1947-1956, 2012
16. Grant RL: Converting an odds ratio to a range of plausible relative risks for better communication of research findings. BMJ 348:f7450, 2014
17. Elkhuizen PH, van Slooten HJ, Clahsen PC, et al: High local recurrence risk after breast-conserving therapy in node-negative premenopausal breast cancer patients is greatly reduced by one course of perioperative chemotherapy: A European Organization for Research and Treatment of Cancer Breast Cancer Cooperative Group Study. J. Clin. Oncol 18:1075-1083, 2000

18. Rescigno J, Zampell JC, Axelrod D: Patterns of axillary surgical care for breast cancer in the era of sentinel lymph node biopsy. Ann. Surg. Oncol 16:687-696, 2009
19. Olaya W, Wong J, Wong J, et al: When is a lymph node dissection a lymph node dissection? The number of lymph nodes resected in sentinel and axillary lymph node dissections. Ann. Surg. Oncol 20:627-632, 2013
20. Schaapveld M, de Vries EG, van der Graaf WT, et al: The prognostic effect of the number of histologically examined axillary lymph nodes in breast cancer: stage migration or age association? Ann. Surg. Oncol 13:465-474, 2006
21. 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 124:801-807, 2010
22. Lavelle K, Downing A, Thomas J, et al: Are lower rates of surgery amongst older women with breast cancer in the UK explained by co-morbidity? Br. J. Cancer, 2012
23. Jagsi R, Abrahamse P, Morrow M, et al: Patterns and correlates of adjuvant radiotherapy receipt after lumpectomy and after mastectomy for breast cancer. J. Clin. Oncol 28:2396-2403, 2010
24. Milla-Santos A, Milla L, Portella J, et al: Anastrozole versus tamoxifen as first-line therapy in postmenopausal patients with hormone-dependent advanced breast cancer: a prospective, randomized, phase III study. Am. J. Clin. Oncol 26:317-322, 2003
25. Louwman WJ, Vulto JC, Verhoeven RH, et al: Clinical epidemiology of breast cancer in the elderly. Eur. J. Cancer 43:2242-2252, 2007
26. van Steenbergen LN, Voogd AC, Roukema JA, et al: Time trends and inter-hospital variation in treatment and axillary staging of patients with ductal carcinoma in situ of the breast in the era of screening in Southern Netherlands. Breast 23:63-68, 2014
27. Schonberg MA, Marcantonio ER, Li D, et al: Breast cancer among the oldest old: tumor characteristics, treatment choices, and survival. J. Clin. Oncol 28:2038-2045, 2010
28. 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 13:e148-e160, 2012
29. Wildiers H, Kunkler I, Biganzoli L, et al: Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. Lancet Oncol 8:1101-1115, 2007
30. van de Water W, Bastiaannet E, Scholten AN, et al: Breast-Conserving Surgery With or Without Radiotherapy in Older Breast Patients With Early Stage Breast Cancer: A Systematic Review and Meta-analysis. Ann. Surg. Oncol, 2013
31. Darby S, McGale P, Correa C, et al: Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 378:1707-1716, 2011
32. Martelli G, Miceli R, Daidone MG, et al: Axillary dissection versus no axillary dissection in elderly patients with breast cancer and no palpable axillary nodes: results after 15 years of follow-up. Ann. Surg. Oncol 18:125-133, 2011
33. Hind D, Wyld L, Reed MW: Surgery, with or without tamoxifen, vs tamoxifen alone for older women with operable breast cancer: cochrane review. Br. J. Cancer 96:1025-1029, 2007
34. EURECCA - European Registration of Cancer Care, 2014. http://www.essoweb.org/projects/eurecca-cancer-care/

APPENDIX A

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Webtable 1 QI compliance by age and time period

Webtable 2 QI compliance by age, multivariable logistic regression analyses

Webtable 3 EUSOMA and SIOG recommendation for the treatment of young and older breast cancer patients

Chapter 5

Impact of comorbidity on outcome of older breast cancer patients: a FOCUS cohort study

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ABSTRACT

Purpose. Older breast cancer patients often suffer from comorbid diseases, which may influence life expectancy. The aim of this study was to assess the impact of specific comorbidities on overall survival and distant recurrence free period (DRFP) of older breast cancer patients.

Methods. Patients were included from the population-based FOCUS cohort, which contains 3,672 breast cancer patients aged 65 years or older. The impact of comorbidity on overall survival and DRFP were analyzed using multivariable Cox proportional hazard models and Poisson regression models.

Results. Median follow-up time was 6.8 years (range 0-14.0). Irrespective of age, the number of comorbid diseases was significantly associated with worse overall survival (hazard ratio (HR) per increasing number of comorbid diseases: 1.20, 95% confidence interval (CI) 1.13-1.27 and HR 1.09, 95% CI 1.05-1.13 for age <75 and age ≥75 respectively). Median follow-up time for DRFP was 5.7 years (range 0-14.0). An increasing number of comorbid diseases was associated with a decreasing risk of metastases among patients aged ≥75 (HR 0.94, 95% CI 0.87-1.02), whereas an increasing risk was shown for patients aged <75 (HR 1.09, 95% CI 1.01-1.19).

Conclusions. This study shows that in older breast cancer patients overall survival and DRFP are influenced by comorbidity. This reiterates that patient outcome is not only influenced by breast cancer, and non-cancer related factors should be taken into account.

INTRODUCTION

Breast cancer among the elderly comprises 40% of all breast cancer cases in the Western society.[1] Due to age and other restrictions to inclusion of older patients in clinical trials, there is a lack of evidence for the treatment of this specific and growing patient category.[2]

One of the most important differences between older and younger patients is the heterogeneity of the former in terms of general fitness. Furthermore, older patients have a high competing risk of mortality, which is the risk of dying from another cause than cancer before developing a cancer-specific event, such as a recurrence or cancer-related death.[3] This competing risk of death unsurprisingly increases with age, but is also affected by the presence and severity of comorbid diseases.[4] With increasing age, the proportion of breast cancer deaths among all-cause mortality has been shown to decrease.[5-7]. In contrast, recently a higher cumulative incidence of distant recurrences and breast cancer mortality has been reported among the oldest patients (≥75 years).[5-8]

With the knowledge that competing risk of mortality increases with age and comorbidity[4], and the number of prevalent comorbid diseases increase with age in general[9], the competing risk of other cause-mortality should always be taken into account when studying breast cancer specific endpoints among older patients. When studying older patients included in clinical trials (with or without age restrictions), one should constantly be aware of the effect of selection, as only the fittest and most motivated patients will be included in trials.[10,11] Therefore, to be able to get a reliable impression of the 'real world' patient, observational cohorts with detailed information on patient, disease, treatment and follow up, are pivotal when studying the older cancer patient.

The aim of the present study is to assess the impact of the extent of comorbidity and specific comorbid diseases on overall survival and distant recurrence free period in two age strata of a large population-based cohort of older breast cancer patients in The Netherlands.

METHODS

Patients

The FOCUS cohort study (Female breast cancer in the elderly; Optimizing Clinical guidelines USing clinico-pathologocial & molecular data) is based on the National Cancer Registry in The Netherlands, which contains data of all newly diagnosed malignancies. The FOCUS database contains information on all consecutive female

patients aged 65 years and older with invasive and in situ breast cancer who were diagnosed between 1997 and 2004 in the South-West part of the Netherlands. Trained personnel reviewed the charts of these patients, and collected information on tumor characteristics, specific treatments, comorbidity, adverse events, geriatric parameters, and recurrence.

All comorbidity, as present at the time of diagnosis, was recorded according to the categories in the ICD-10 classification[12], on the basis of the case record forms and extracted from the medical charts by an experienced research nurse.

Follow up on survival status was available until January 1st 2011 through linkage of cancer registry data with municipal population registries. For this study, all patients with breast cancer stage I–IV and in situ of all histological subtypes were included. Stage was described using the tumor-node-metastasis (TNM) classification, as valid in the year of diagnosis. If the data on T- or N- stage from pathological reports were missing (pT or pN), data from clinical reports (cT or cN) were used to complete the combined TNM stage. Hormone receptor status was analyzed in a combined dichotomized variable for estrogen receptor status and/or progesterone receptor status. If patients received breast-conserving surgery followed by mastectomy, the most extensive surgery was used for analyses. Axillary surgery was defined as a sentinel node procedure or an axillary lymph node dissection, and dichotomized for analyses. Again, the most extensive surgery was used for the analyses. To compare different age groups, patients were categorized into two groups: 65–74 years and 75 years or older, as discussed at the meeting of the International Society of Geriatric Oncology (SIOG) in 2009[13] and in line with other publications.[5,7] The number of comorbid diseases was categorized in three groups: 0 or 1 concomitant diseases, 2-4 concomitant diseases, and 5 or more concomitant diseases. Specific groups of comorbid disease were defined according to the ICD-10 classification.[12] Endocrine diseases, psychiatric diseases, neurologic diseases, cardiovascular diseases, respiratory diseases, digestive diseases and musculoskeletal diseases were considered as the clinically most important subgroups defined in the ICD-10 and were analyzed separately. The remaining comorbidities were defined as a category “other comorbidity”.

Statistical analyses

The primary study endpoints were overall survival and distant recurrence free period (DRFP), defined as time from breast cancer diagnosis to death of any cause and time to first distant recurrence respectively.

Overall survival and DRFP were calculated using univariable and multivariable Cox Regression models. All multivariable analyses were adjusted for age (continuous), tumor stage (in situ, I, II, III, IV or missing), tumor grade (1, 2, 3 or missing),

hormone receptor status (negative, positive or missing), morphology (ductal, lobular or other/unknown), local surgical treatment (none, breast conserving surgery or mastectomy), axillary surgery (dichotomous), radiation therapy (dichotomous), endocrine therapy (dichotomous) and chemotherapy (dichotomous). Analyses of specific comorbid disease categories according to the ICD-10 were additionally adjusted for the number of additional comorbidities. In case of missing data, patients were not excluded from the analyses, but analyzed in a separate group. For DRFP analyses, patients with primary metastatic disease (stage IV) were excluded. Also for DRFP analyses, sensitivity analyses using Poisson regression models were performed, comparing incidence rates of distant recurrences per 1000 person years, taking account of the actual follow-up time of each patient, to rule out the impact of short life expectancy of the oldest patients with more comorbidity.

In all statistical analyses, a p-value smaller than 0.05 was considered statistically significant. All statistical tests were performed two-sided. All statistical analyses were performed in IBM SPSS Statistics 20, except for Poisson regression analyses, which were performed in STATA SE 12.0.

RESULTS

Characteristics of patients

All 3,672 patients in the FOCUS cohort were included for the analyses. Of all patients, 1747 (48%) were aged 65-74 years at diagnosis, and 1925 (52%) patients were 75 years or older. Patient, tumor and treatment characteristics per age group are shown in Table 1A. Patients in the older age group (≥75) more frequently had advanced (stage III or IV) tumors, more missing data on grade and morphology, reflecting the fewer surgeries (and consequently less histology) performed among the ≥75 (no surgery: 6.1% among patients aged <75, 20.1% among patients aged ≥75). Also, patients aged ≥75 years received radiotherapy and chemotherapy less often, and received endocrine monotherapy more often.

Comorbidity

Table 1B shows the distribution of comorbidity. The mean number of comorbidities was higher in the group aged ≥75 years (2.2 vs. 1.6 among the patients aged <75 years; p<0.001). The larger proportion of comorbidity in the older group can be explained by a significantly higher burden of psychiatric diseases, neurologic diseases, cardiovascular diseases, digestive diseases and musculoskeletal diseases.

Table 1 - patient, tumor and treatment characteristics

	all patients (N=3,672)		<75 (N=1747)		≥75 (N=1925)		
Mean age in years (SD)	76.5 (7.4)		70.0 (2.9)		82.3 (4.9)		
	N	%	N	%	N	%	P*
Stage							**<0.001**
In situ	208	5.7	142	8.1	66	3.4	
I	1,130	30.8	704	40.3	426	22.1	
II	1,532	41.7	639	36.6	893	46.4	
III	368	10	121	6.9	247	12.8	
IV	212	5.8	72	4.1	140	7.3	
missing	222	6	69	3.9	153	7.9	
Tumor grade							**<0.001**
1	437	11.9	233	13.3	204	10.6	
2	1,005	27.4	507	29.0	498	25.9	
3	784	21.4	403	23.1	381	19.8	
missing	1,446	39.4	604	34.6	842	43.7	
HR status							0.215
ER and PR negative	540	14.7	274	15.7	266	13.8	
ER or PR positive	2,290	62.4	1,068	61.1	1,222	63.5	
missing	842	22.9	405	23.2	437	22.7	
Morphology							**<0.001**
Ductal	2,560	69.7	1,294	74.1	1,266	65.8	
Lobular	400	10.9	175	10	225	11.7	
other/unknown	712	19.4	278	15.9	434	22.5	
Surgery							**<0.001**
None	493	13.4	107	6.1	386	20.1	
BCS	1,194	32.5	839	48	355	18.4	
Mastectomy	1,985	54.1	801	45.9	1,184	61.5	
Axillary surgery	2,614	71.2	1,385	79.3	1,229	63.8	**<0.001**
Adjuvant radiotherapy	1,532	41.7	981	56.2	551	28.6	**<0.001**
Endocrine therapy	1,661	45.2	638	36.5	1023	53.1	**<0.001**
Endocrine monotherapy	371	10.1	74	4.2	297	15.4	
Adjuvant endocrine therapy	1,290	35.1	564	32.3	726	37.7	
Chemotherapy	306	8.3	184	10.5	122	6.3	

*p for difference between age categories (Chi square)

Overall survival

As shown in Figure 1, in multivariable Cox regression models, overall survival was worse for patients with an increasing number of comorbidities in both age groups (multivariable Hazard Ratio (HR) for patients with 5 or more comorbidities compared to 0-1 comorbidities: 2.61 (95% Confidence Interval (CI) 1.92-3.56) and HR 1.51 (95% CI 1.24-1.83) respectively for the <75 and ≥75 group. In patients aged <75, specific categories of comorbidity that were associated with a worse overall survival were psychiatric diseases (HR 1.41, 95% CI 1.07-1.85), neurologic diseases (HR 1.94, 95% CI 1.50-2.52), cardiovascular diseases (HR 1.52, 95% CI 1.28-1.81) and other comorbidity (HR 1.47, 95% CI 1.03-1.30). Among the highest age group, only psychiatric diseases (HR 1.62, 95% CI 1.12-1.93) and cardiovascular diseases (HR 1.16, 95% CI 1.03-1.30) were associated with a worse overall survival.

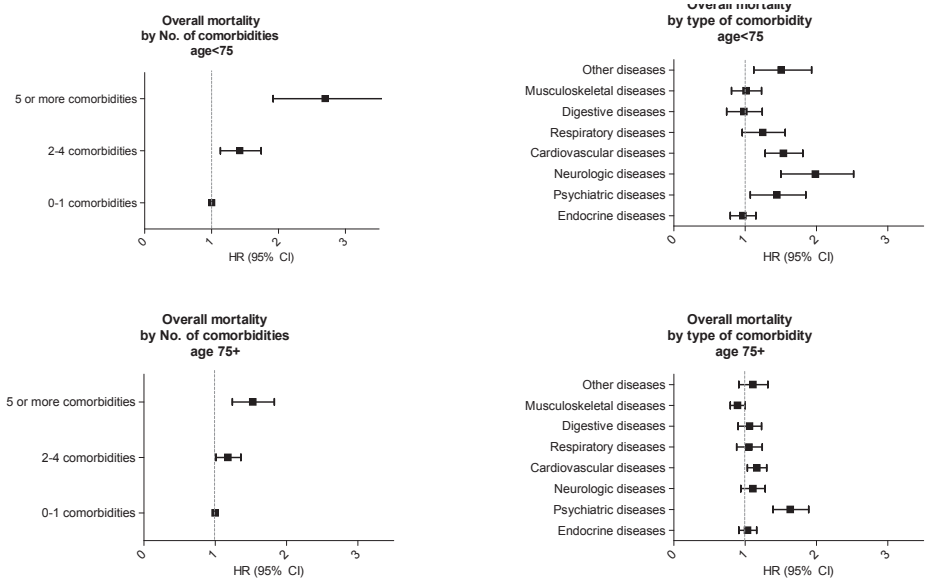

Figure 1. All-cause mortality, multivariable Cox regression analyses.

Distant recurrence free period

Overall, the proportion of patients who developed distant metastases among stage 0 to III patients did not differ between the age categories (11% in both categories). Among the patients aged ≥75, the majority of breast cancer patients died without registered distant metastases (62%), in other words: they died due to a "competing event", This proportion was almost three times smaller in the younger elderly (22%) (Figure 2).

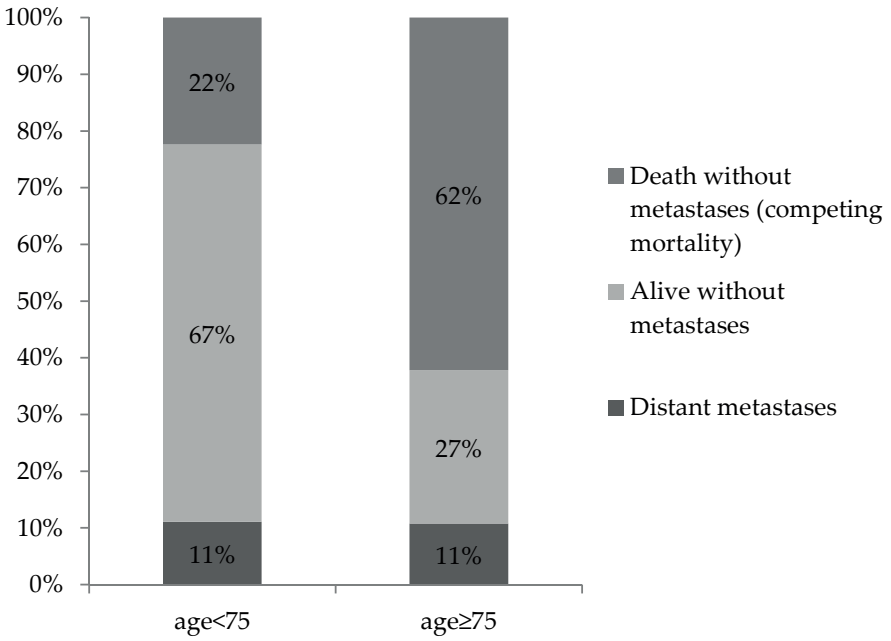

Figure 2. Distant recurrences and competing mortality.

Results of the multivariable Cox regression analysis on Distant recurrence free period (DRFP) are shown in Figure 3. In the patients aged <75, an association between the number of comorbidities and a higher risk of distant recurrences was found, the HR for each increase in number of comorbidities was 1.09 (95% CI 1.01-1.19). With the exception of neurologic diseases (HR 1.82, 95% CI 1.10-3.01, p=0.02) and cardiovascular diseases (HR 1.34, 95% CI 0.98-1.82), no association was observed between any of the specific comorbidities and DRFP. Among the patients aged ≥75, there was also an association between the number of comorbidities and DRFP, multivariable Cox regression analyses showed a trend to decreased risk of distant metastases among the oldest group (HR per unit increase in number of comorbidities: 0.94, 95% CI 0.0.87-1.02, p=0.12). The finding that the number of comorbidities is associated with fewer distant metastases in older patients is endorsed by categorizing the number of comorbidities, showing that patients aged 75 or older having 5 or more comorbid diseases have a significantly lower HR for DRFP (HR 0.54, 95% CI 0.30-0.96, p=0.036). In addition, a lower risk on distant metastases was shown for patients with psychiatric comorbidity (HR 0.42, 95% CI 0.20-0.90, p=0.026).

Poisson regression analyses, adjusted for the same factors as the Cox regression analyses, and taking account with the actual time a patient was followed in the study, showed an increasing trend for the incidence rate of distant recurrences in

the <75 group with increasing number of comorbidities (Webtable 1) (multivariable Incidence Rate Ratio (IRR) 1.09 (95%CI 1.00-1.18; p=0.046); whereas a decreasing trend was shown in the patients aged ≥75 (IRR 0.93 (95% CI 0.86-1.01; p=0.094).

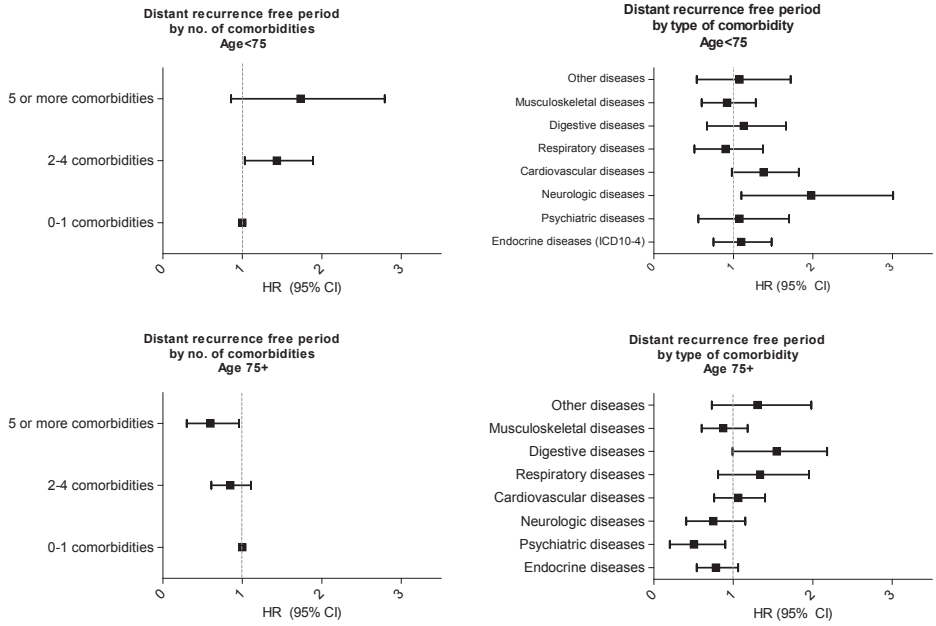

Figure 3. Distant recurrence free period, multivariable Cox regression analyses.

Table 2 - Comorbidity

	all patients		<75		≥75		
	N	%	N	%	N	%	p*
Number of comorbidities - mean (SD)	1.9 (1.8)		1.6 (1.7)		2.2 (1.9)		<0.001**
Endocrine diseases (ICD10-4)	983	26.8	447	25.6	536	27.8	0.13
hypercholesterolaemia	90	2.5	51	2.9	39	2.0	0.09
obesity	147	4.0	92	5.3	55	2.9	<0.001
diabetes	576	15.7	266	15.2	310	16.1	0.5
thyroid diseases	342	9.3	146	8.4	196	10.2	0.06
other endocrine diseases	13	0.4	4	0.2	9	0.5	0.3
Psychiatric diseases (ICD10-5)	354	9.6	127	7.3	230	11.9	<0.001
depression	109	3.0	49	2.8	60	3.1	0.6
severe psychiatric diseases	69	1.9	36	2.1	33	1.7	0.5
dementia/Alzheimer's	170	4.6	27	1.5	143	7.4	<0.001
other psychiatric diseases	48	1.3	27	1.5	21	1.1	0.2

Table 2 - Comorbidity (*continued*)

	all patients		<75		≥75		
	N	%	N	%	N	%	p*
Neurologic diseases (ICD10-6)	414	11.3	138	7.9	276	14.3	<0.001
Parkinson's disease	51	1.4	18	1.0	33	1.7	0.1
other neurologic diseases	366	10.0	120	6.9	246	12.8	<0.001
Cardiovascular diseases (ICD10-9)	1849	50.4	794	45.4	1055	54.8	<0.001
myocardial infarction	245	6.7	95	5.4	150	7.8	0.004
heart failure	190	5.2	37	2.1	153	7.9	<0.001
valve problems	159	4.3	52	3.0	107	5.6	<0.001
arrhythmia	426	11.6	137	7.8	289	15.0	<0.001
conduction disorder	60	1.6	13	0.7	47	2.4	<0.001
peripheral arterial occlusive disease	86	2.3	34	1.9	52	2.7	0.2
deep venous thrombosis	110	3.0	46	2.6	64	3.3	0.2
stroke	284	7.7	86	4.9	198	10.3	<0.001
hypertension	1177	32.1	561	32.1	616	32.0	0.9
other venous diseases	17	0.5	8	0.5	9	0.5	1.0
other cardiovascular diseases	79	2.2	33	1.9	46	2.4	0.6
Respiratory diseases (ICD10-10)	392	10.7	184	10.5	208	10.8	0.8
asthma	49	1.3	28	1.6	21	1.1	0.2
COPD	328	8.9	149	8.5	179	9.3	0.4
other respiratory diseases	23	0.6	11	0.6	12	0.6	1.0
Digestive diseases (ICD10-11)	469	12.8	194	11.1	275	14.3	0.004
ulcerative disease	142	3.9	50	2.9	92	4.8	0.003
diverticulosis	178	4.8	75	4.3	103	5.4	0.1
other digestive diseases	171	4.7	76	4.4	95	4.9	0.4
Musculoskeletal diseases (ICD10-13)	849	23.1	325	18.6	524	27.2	<0.001
arthrosis	564	15.4	206	11.8	358	18.6	<0.001
Sjogren's disease	6	0.2	3	0.2	3	0.2	1.0
rheumatoid arthritis	126	3.4	60	3.4	66	3.4	1.0
osteoporosis	175	4.8	65	3.7	110	5.7	0.005
other musculoskeletal diseases	101	2.8	44	2.5	57	3.0	0.4
Other diseases	306	8.3	133	7.6	173	9.0	0.1
blood/immune disease (ICD10-3)	37	1.0	20	1.1	17	0.9	0.5
ear/mastoid disease (ICD10-8)	18	0.5	9	0.5	9	0.5	1.0
genitourinary disease (ICD10-14)	226	6.2	95	5.4	131	6.8	0.06
other diseases not otherwise specified (ICD10-18)	30	0.8	13	0.7	17	0.9	0.7

*P for difference between age categories (Chi-square test). **unpaired T-test

DISCUSSION

The main finding of our present study is that comorbidity in older breast cancer patients has a major impact on all-cause mortality. This association is most pronounced among patients aged <75 years, but is also present in patients aged 75 years or older. Regarding breast cancer specific outcome, the risk to be diagnosed with distant breast cancer metastases decreases with an increasing number of comorbidities among patients aged ≥75, whereas comorbidity in patients <75 years is associated with a higher incidence of distant recurrences.

Several previous studies have shown that both younger and older breast cancer patients with comorbidity have increased all-cause mortality.[14-16] With the knowledge that there is a significant increase in the number and severity of comorbidities with increasing age[7,9,16], several studies reported on age-specific effects of comorbidity on outcome of older breast cancer patients.[7,14,17-24] But those results were not consistent across studies.

In the present study we found that although the presence and number of comorbidity is predictive for mortality irrespective of age, the impact of comorbidity on overall mortality decreases among the oldest old, although total mortality rates are almost three times higher in this oldest age group. A recent large population-based study performed in the US showed that the presence of comorbid conditions among older breast cancer patients is substantially associated with more all-cause mortality. Moreover, they showed that the impact of the investigated specific comorbidities decreased with increasing age.[14] Hence, our findings are fully consistent with these previous results, showing that the majority of specific comorbidities did not have a significant impact on all-cause mortality among the patients aged ≥75.[14] This finding indicates that there is an additional role of age (or age related factors) in the life expectancy, irrespective of the number or type of comorbidity. Probably, this can be explained by other factors that are associated with ageing, such as decreased physiologic reserves, functional status and cognition. The combination of these factors makes a patient more vulnerable to institutionalization and mortality.[25]

A remarkable outcome of our study that supports our hypothesis about the vulnerability of the oldest breast cancer patients, is the impact of psychiatric comorbidity on all-cause mortality. This probably reflects the effect of cognitive disorders, that are usually included in tools used in measuring frailty scores.[26] Unlike other specific comorbidities, psychiatric comorbidity is associated with higher hazards of all-cause mortality in the oldest group compared to their younger counterparts. In previous studies, dementia was shown to be associated with an increased risk of all-cause mortality in breast cancer patients[14,24,27-29], although the higher impact

among the oldest old found in our study was not previously described. Additionally, psychiatric diseases were associated with a lower risk on distant recurrences among the patients aged ≥75 in our study. This finding might reflect underreporting of recurrent disease in the oldest and most vulnerable patients rather than a true decrease in the incidence of distant recurrences. A recent study by Hamaker et al., showed that a substantial part of elderly care physicians working in nursing homes, do not refer patients with suspected (recurrent) breast cancer. The most important reason (accounting for 57% of all non-referrals) was end-stage dementia. By non-referral the patients will remain unregistered and will not be included in the cancer registry.[30] Nonetheless, our finding warrants further exploration.

In addition, we showed that an increasing number of comorbidities is associated with a lower risk on distant recurrences among patients aged ≥75, irrespective of tumor or treatment factors. To our knowledge, there are no previous studies assessing age-specific impact of comorbidity on breast cancer recurrence risk. The few studies assessing the impact of comorbidity on cancer-specific outcome use combined outcome measures like disease free survival or progression free survival, endpoints that in addition to recurrent disease, also include all-cause mortality in the endpoint.[31] This results in worse outcomes for patients with more comorbidity, but for the oldest patients, this is probably due to a higher risk on mortality and not on cancer recurrence. However, in the patients aged <75, after adjusting for breast cancer treatment, we found an increasing trend for distant recurrence incidence with an increasing number of comorbidities.

To our knowledge, the FOCUS cohort is the largest available cohort comprising detailed information about almost 3,700 older breast cancer patients. Additionally, the registration of all specific comorbidities, instead of the use of a comorbidity index or a predefined selection of specific comorbidities is a major strength of this paper. The volume of the cohort and the detailed registration of comorbidities makes this a robust analysis. A limitation of our study is the retrospective design, which only allowed us to assess qualitative comorbidity diagnoses and their predictive value on outcome. Future prospective studies should also assess other age-related factors that can influence patient related outcomes such as functional status and cognition. Furthermore, future prospective studies are needed in order to register the severity and treatment of comorbidity, and to study interactions of breast cancer itself and the cancer treatment with (the treatment of) comorbidity.

In conclusion, in our present study we showed an important negative impact of an increasing number of comorbid diseases and several specific comorbidities on the overall survival of older breast cancer patients, that cannot be explained by worse breast cancer specific outcome. However, the relative impact of the number of comorbidities on survival decreases with increasing age, indicating that clini-

cians should be aware of other factors that influence prognosis when treating older breast cancer patients.

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REFERENCE LIST

1. Wildiers H, Kunkler I, Biganzoli L et al. Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. Lancet Oncol 2007; 8: 1101-15.
2. 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). The Lancet Oncology 2012; 13: e148-e160.
3. Wildiers H, Mauer M, Pallis A et al. End points and trial design in geriatric oncology research: a joint European organisation for research and treatment of cancer--Alliance for Clinical Trials in Oncology--International Society Of Geriatric Oncology position article. J Clin Oncol 2013; 31: 3711-8.
4. Mell LK, Jeong JH, Nichols MA et al. Predictors of competing mortality in early breast cancer. Cancer 2010; 116: 5365-73.
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: 590-7.
6. Schairer C, Mink PJ, Carroll L et al. Probabilities of death from breast cancer and other causes among female breast cancer patients. J Natl Cancer Inst 2004; 96: 1311-21.
7. 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: 885-92.
8. 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. Oncologist 2013; 18: 8-13.
9. Barnett K, Mercer SW, Norbury M et al. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet 2012; 380: 37-43.
10. Al-Refaie WB, Vickers SM, Zhong W et al. Cancer trials versus the real world in the United States. Ann Surg 2011; 254: 438-42.
11. Hutchins LF, Unger JM, Crowley JJ et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999; 341: 2061-7.
12. World Health Organization. The International Statistical Classification of Diseases and Related Health Problems ICD-10, 2012.
13. Conference communication: age categorization proposed at oral session, accessible for members only. Discussed at: International Society of Geriatric Oncology Annual Meeting; October 15-17, 2009; Berlin, Germany.
14. Patnaik JL, Byers T, Diguiseppi C et al. The influence of comorbidities on overall survival among older women diagnosed with breast cancer. J Natl Cancer Inst 2011; 103: 1101-11.
15. 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: 1013-20.
16. Ording AG, Cronin-Fenton DP, Jacobsen JB et al. Comorbidity and survival of Danish breast cancer patients from 2000-2011: a population-based cohort study. Clin Epidemiol 2013; 5: 39-46.

17. Patnaik JL, Byers T, Diguiseppi C et al. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Res 2011; 13: R64.
18. Siegelmann-Danieli N, Khandelwal V, Wood GC et al. Breast cancer in elderly women: outcome as affected by age, tumor features, comorbidities, and treatment approach. Clin Breast Cancer 2006; 7: 59-66.
19. Janssen-Heijnen ML, Houterman S, Lemmens VE et al. Prognostic impact of increasing age and co-morbidity in cancer patients: a population-based approach. Crit Rev Oncol Hematol 2005; 55: 231-40.
20. Janssen-Heijnen MLG, Szerencsi K, van de Schans SAM et al. Cancer patients with cardiovascular disease have survival rates comparable to cancer patients within the age-cohort of 10 years older without cardiovascular morbidity. Critical Reviews in Oncology/Hematology 2010; 76: 196-207.
21. Houterman S, Janssen-Heijnen ML, Verheij CD et al. Comorbidity has negligible impact on treatment and complications but influences survival in breast cancer patients. Br J Cancer 2004; 90: 2332-7.
22. Ring A, Sestak I, Baum M et al. Influence of comorbidities and age on risk of death without recurrence: a retrospective analysis of the Arimidex, Tamoxifen Alone or in Combination trial. J Clin Oncol 2011; 29: 4266-72.
23. Harris EE, Hwang WT, Urtishak SL et al. The impact of comorbidities on outcomes for elderly women treated with breast-conservation treatment for early-stage breast cancer. Int J Radiat Oncol Biol Phys 2008; 70: 1453-9.
24. Louwman WJ, Janssen-Heijnen ML, Houterman S et al. Less extensive treatment and inferior prognosis for breast cancer patient with comorbidity: a population-based study. Eur J Cancer 2005; 41: 779-85.
25. Pal SK, Katheria V, Hurria A. Evaluating the older patient with cancer: understanding frailty and the geriatric assessment. CA Cancer J Clin 2010; 60: 120-32.
26. Hamaker ME, Jonker JM, de Rooij SE et al. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. Lancet Oncol 2012; 13: e437-e444.
27. Raji MA, Kuo Y-F, Freeman JL et al. Effect of a dementia diagnosis on survival of older patients after a diagnosis of breast, colon, or prostate cancer: Implications for cancer care. Archives of Internal Medicine 2008; 168: 2033-40.
28. Robb C, Boulware D, Overcash J et al. Patterns of care and survival in cancer patients with cognitive impairment. Critical Reviews in Oncology/Hematology 2010; 74: 218-24.
29. Ording AG, Garne JP, Nystrom PM et al. Comorbid diseases interact with breast cancer to affect mortality in the first year after diagnosis--a Danish nationwide matched cohort study. PLoS One 2013; 8: e76013.
30. 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: 464-9.
31. Lin TL, Kuo MC, Shih LY et al. The impact of age, Charlson comorbidity index, and performance status on treatment of elderly patients with diffuse large B cell lymphoma. Ann Hematol 2012; 91: 1383-91.

Chapter 6

Diabetes in relation to breast cancer relapse and all-cause mortality in elderly breast cancer patients: a FOCUS study analysis

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ABSTRACT

Background. In developed countries, 40% of breast cancer patients is older than 65 years of age at diagnosis, of whom 16% additionally suffer from diabetes. The aim of this study was to assess the impact of diabetes on relapse free period and overall mortality in elderly breast cancer patients.

Patients and Methods. Patients were selected from the retrospective FOCUS cohort, which contains detailed information of elderly breast cancer patients. Relapse free period was calculated using Fine & Gray competing risk regression models for patients with diabetes versus patients without diabetes. Overall survival was calculated by Cox regression models, in which patients were divided into four groups: no comorbidity, diabetes only, diabetes and other comorbidity or other comorbidity without diabetes.

Results. Overall, 3,124 patients with non-metastasized breast cancer were included. Relapse free period was better for patients with diabetes compared to patients without diabetes (multivariable HR 0.77, 95% CI 0.59-1.01), irrespective of other comorbidity and most evident in patients aged 75 years and older (HR 0.67, 95% CI 0.45-0.98). In overall survival analyses, patients with diabetes only had a similar outcomes patients without comorbidity (HR 0.86, 95% CI 0.55-1.33), while patients with diabetes and other comorbidity had the worst overall survival (HR 1.70, 95% CI 1.44-2.01).

Conclusion. When taking competing mortality into account, relapse free period was better in elderly breast cancer patients with diabetes compared to patients without diabetes. Moreover, patients with diabetes without other comorbidity had a similar overall survival as patients without any comorbidity. Possibly, unfavourable effects of (complications of) diabetes on overall survival are counterbalanced by beneficial effects of metformin on the occurrence of breast cancer recurrences.

INTRODUCTION

With the aging of Western Societies, elderly will account for an increasing percentage of breast cancer patients in developed countries.[1] High age is predictive for comorbidity and decreased functioning[2,3] both associated with decreased overall survival in elderly breast cancer patients.[4] The incidence of diabetes is increasing worldwide. Importantly, diabetes mellitus type 2 has been shown to increase breast cancer risk in postmenopausal women.[5] High levels of insulin may have a direct effect on breast tissue, or indirect effects through increase in sex steroids due to inhibition of sex hormone-binding globulin (SHBG), disruption of adipokines and increased insulin-like growth factor-I (IGF-I) production.[6] Additionally, diabetes is associated with obesity and excess body weight is related to increased cancer risk in postmenopausal women.[7]

At present, up to 16% of elderly breast cancer patients additionally suffer from diabetes.[8] In several cohort studies, it has been shown that diabetes increases both overall and cancer-specific mortality in the general population and in cancer patients.[9-12] Also, the presence of diabetes and its complications can influence the allocation of treatment, leading to possible negative effects on patient outcome.[8] Furthermore, diabetes may accentuate side-effects and complications of chemotherapy.[8] Few studies have studied diabetes in combination with other comorbid diseases on the prognosis of elderly breast cancer patients, even though the incidence of both diabetes mellitus type 2 and breast cancer increases with age.

The aim of this study was to assess the impact of diabetes on relapse free period, and the impact of diabetes in combination with other comorbidities on overall survival in elderly breast cancer patients.

MATERIALS AND METHODS

Patients

Patients were selected from the FOCUS cohort study (Female breast cancer in the elderly; Optimizing Clinical guidelines USing clinico-pathologocial & molecular data). The FOCUS-database contains information of all consecutive female patients aged 65 years and older with invasive and in situ breast cancer who were diagnosed between 1997 and 2004 in the South-West part of the Netherlands. Trained personnel reviewed the medical charts of these patients between 2009 and 2011, and collected information on treatment characteristics, specific treatments, comorbidity, adverse events, geriatric parameters and recurrences. Follow-up on survival status

was available until January 1st 2011 through linkage of cancer registry data with municipal population registries.

Comorbidity was registered according to the ICD-10 classification, and analysed in subgroups. Respectively, endocrine diseases (ICD10-4), psychiatric disorders (ICD10-5), neurologic diseases (ICD10-6), cardiovascular diseases (ICD10-9), respiratory diseases (ICD10-10), digestive diseases (ICD10-11) and musculoskeletal diseases (ICD10-13) were used for analyses. Due to a low incidence in the studied population, diseases of the blood/immune diseases (ICD10-3), ear and mastoid (ICD10-8), the genitourinary system (ICD10-14) and other symptomatic diseases (ICD-10-18) were grouped together in one category "other". The remaining disease groups in the ICD10 were not considered of importance and were not registered. Additionally, a category was created for patients who had no comorbid disease registered at the time of breast cancer diagnosis.

Recurrences were defined as any first registered relapse of breast cancer, this could either be a local recurrence (in the ipsilateral breast), regional recurrence (in the ipsilateral axilla or supraclavicular) or distant recurrence.

For this study, patients with *in situ* and stage I-III breast cancer who were treated with any breast surgery were selected. Stage was described using the pathological tumor-node-metastasis (TNM) classification, as valid in the year of diagnosis. Receptor positive disease was defined as either estrogen receptor positive disease, progesterone receptor positive disease, or both. Adequate locoregional treatment was defined as breast conserving surgery followed by radiotherapy or mastectomy, both followed by any axillary surgery.[13]

Statistical analyses

All analyses were performed in IBM SPSS Statistics version 20.0 and STATA SE 12.0.

The primary outcome measure was relapse free period (RFP), defined as time of diagnosis to any first locoregional or distant recurrence. Uni- and multivariable competing risk regression analyses according to the method of Fine & Gray were performed for RFP, taking the risk of competing mortality into account. Under the assumption that additional comorbidity next to diabetes does not affect breast cancer relapse risk, patients with diabetes were compared to patients without diabetes. Multivariable analyses were adjusted for clinically relevant patient (age), tumour, (stage, grade, histological subtype, hormone receptor) and treatment characteristics (breast and axillary surgery, radiotherapy, endocrine therapy and chemotherapy). We also adjusted for the number of comorbidities next to diabetes to assure negligibility of other comorbidity than diabetes.

Secondary outcome was overall survival, defined as the time of diagnosis to death of any cause. Because additional comorbidity next to diabetes is assumed to play a major role in overall prognosis, patients were analysed in 4 groups no comorbidity, diabetes only, diabetes and other comorbidity, and other comorbidity without diabetes, and overall survival was compared between groups by the Log rank test and uni- and multivariable Cox regression models (adjusted for the same factors as RFP analyses).

Patient and tumour characteristics, even as the provision of adequate locoregional treatment, endocrine therapy and chemotherapy, were compared between the groups using Chi-square tests.

In case of missing data, patients were not excluded from the analyses, except for patients with missing stage in multivariable models. Missing data were analysed as separate groups in the analyses. Additionally, stratified sensitivity analyses were performed in two age groups, based on the median age of the cohort.

RESULTS

Patient characteristics

Overall, 3,124 patients were included. Median age was 74.6 years (range 65.0-98.3). Of all patients, 505 (16.2%) were diagnosed with diabetes mellitus, of whom 444 patients (87.9%) also had other comorbidity (Table 1). Tumour stage, histological grade, morphology and hormone receptor status did not significantly differ between groups. Patients with other and additional comorbidity besides diabetes were generally older than patients without comorbidity or diabetes only ($P<0.001$). In the groups with other or additional comorbidity, patients with diabetes also had more endocrine diseases (obesity) and neurologic diseases (TIA), but the largest difference was observed in the coexistence of cardiovascular diseases; 85.6% of patients with diabetes and other comorbidity suffered from additional cardiovascular diseases, compared to 67% in the group with other comorbidity without diabetes ($P<0.001$).

Treatment

Similar proportions of adequate locoregional treatment, endocrine therapy and chemotherapy were allocated to the four groups ($P=0.7$, $P=0.1$ and $P=0.9$, respectively; Supplementary Table 1).

Table 1. Patient and tumour characteristics

		No comorbidity (N= 786)		Diabetes, no other comorbidity (N=61)		Diabetes + other comorbidity (N=444)		Other comorbidity, no diabetes (N=1833)		*P*
		N	%	N	%	N	%	N	%	
Age (years)	<74,6	472	60,1	37	60,7	199	44,8	853	46,5	
	≥74,6	314	39,9	24	39,3	245	55,2	980	53,5	<0.001
Stage	0	52	6,6	2	3,3	27	6,1	117	6,4	
	I	272	34,6	20	32,8	131	29,5	635	34,6	0,202
	II	347	44,1	28	45,9	219	49,3	836	45,6	
	III	75	9,5	9	14,8	56	12,6	177	9,7	
	Missing	40	5,1	2	3,3	11	2,5	68	3,7	
Grade	1	104	13,2	7	11,5	57	12,8	253	13,8	
	2	220	28,0	23	37,7	146	32,9	571	31,2	0,637
	3	203	25,8	12	19,7	108	24,3	426	23,2	
	missing	259	33,0	19	31,1	133	30,0	583	31,8	
Morphology	ductal	567	72,1	46	75,4	337	75,9	1366	74,5	
	lobular	108	13,7	4	6,6	40	9,0	192	10,5	0,128
	other	111	14,1	11	18,0	67	15,1	275	15,0	
HR status	ER/PR-	135	17,2	12	19,7	52	11,7	289	15,8	
	ER/PR+	510	64,9	44	72,1	306	68,9	1203	65,6	0,084
	Missing	141	17,9	5	8,2	86	19,4	341	18,6	
Type of comorbidity (ICD-10)	Endocrine diseases*					127	28,6	364	19,9	<0.001**
	Psychiatric diseases					48	10,8	235	12,8	0.3**
	Neurologic disesaes					88	19,8	253	13,8	0.002**
	Cardiovascular diseases					380	85,6	1228	67,0	<0.001**
	Respiratory diseases					57	12,8	280	15,3	0.2**
	Digestive diseases					88	19,8	327	17,8	0.3**
	Muscoloskeletal diseases					145	32,7	605	33,0	0.9**
	Other					55	12,4	208	11,3	0.6**

*excluding diabetes

** Patients without additional comorbidity were excluded for this analysis

Relapse free period

Median follow-up time for RFP was 6.0 years. Overall, 474 patients developed a recurrence during the total follow up, 66 (13.1%) among patients with diabetes, 408 (15.6%) among patients without diabetes (Table 2). Multivariable hazard ratio (HR) was 0.77 (95% confidence interval (CI) 0.59-1.01) for patients with diabetes compared to patients without diabetes. This effect was even stronger in patients in the oldest age group (HR 0.67, 95% CI 0.45-0.98). The cumulative incidence of recurrences and competing mortality for patients with and without diabetes in different age groups are shown in Figure 1.

Table 2. RFP analyses, stratified for age

	Recurrences	Competing Mortality		95% CI		
	N (%)	N (%)	HR	Lower	Upper	*P*
All patients						
Fine and Gray						
No diabetes	408 (15.6)	916 (35.0)	1 (ref)			
Diabetes	66 (13.1)	227 (45.0)	0.82	0.63	1.07	0.14
Fine and Gray-adjusted[a]						
No diabetes	408 (15.6)	916 (35.0)	1 (ref)			
Diabetes	66 (13.1)	227 (45.0)	0.77	0.59	1.01	0.06
Age < 74,6 (years)						
Fine and Gray						
No diabetes	194 (14.6)	233 (17.6)	1 (ref)			
Diabetes	34 (14.4)	68 (28.8)	0.96	0.67	1.37	0.8
Fine and Gray-adjusted[a]						
No diabetes	194 (14.6)	233 (17.6)	1 (ref)			
Diabetes	34 (14.4)	68 (28.8)	0.88	0.61	1.27	0.5
Age ≥ 74,6 (years)						
Fine and Gray						
No diabetes	214 (16.5)	683 (52.8)	1 (ref)			
Diabetes	32 (11.9)	159 (59.1)	0.71	0.49	1.03	0.07
Fine and Gray-adjusted[a]						
No diabetes	214 (16.5)	683 (52.8)	1 (ref)			
Diabetes	32 (11.9)	159 (59.1)	0.67	0.45	0.98	0.04

[a]Adjusted for age, stage, grade, histology, hormone receptor, breast and axillary surgery, radiotherapy, endocrine therapy, chemotherapy, number of comorbidities excluding diabetes

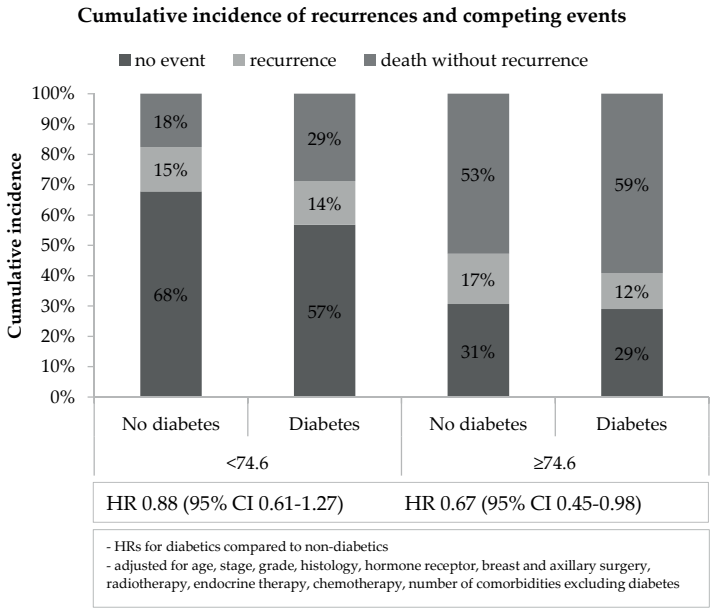

Figure 1. Cumulative incidence of recurrences and competing mortality.

Overall survival

Median follow-up time was 7.3 years (interquartile range (IQR) 4.2-9.7). In log rank analyses, there was a significant overall survival difference between the four groups (P<0.001), patients without comorbidity or diabetes only had the most favourable prognosis (Figure 2). This effect was even more evident in patients in the oldest age group (Supplementary Figure 1a and 1b). In uni- and multivariable Cox regression analysis, patients with diabetes only had a similar overall survival compared to patients without comorbidity (multivariable HR 0.85, 95% CI 0.55-1.33). Contrary, patients with diabetes and other comorbidity (HR 1.70, 95% CI 1.44-2.01), and patients without diabetes but with other comorbidity (HR 1.37, 95% CI 1.20-1.56) had a significantly worse overall survival compared to patients without comorbidity.

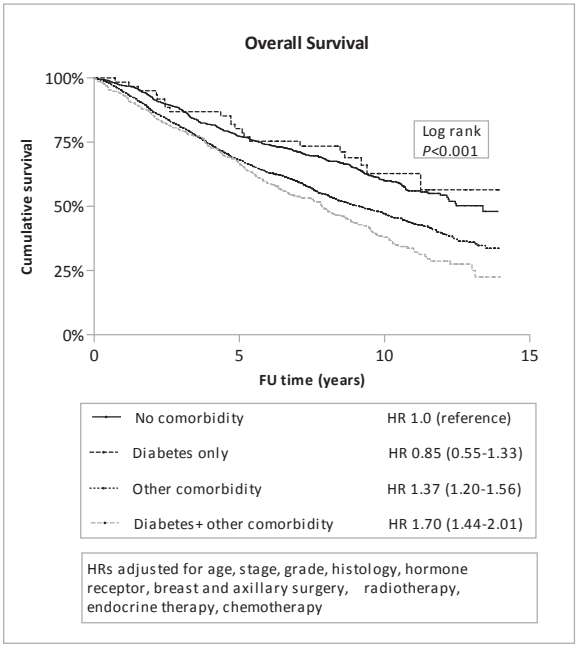

Figure 2. Overall survival.

DISCUSSION

The main finding of our study is that elderly breast cancer patients with diabetes, irrespective of other comorbidity, had a better relapse free period than patients without diabetes. In addition, overall survival of elderly breast cancer patients with diabetes without other comorbidity was similar to overall survival in patients without comorbidity. These differences were most evident in patients aged 75 years and older.

In contrast to our present study, a recently published review and meta-analysis about diabetes mellitus and breast cancer outcomes concluded that patients with diabetes and breast cancer had a greater risk of all-cause mortality compared to patients without diabetes.[14] In addition, a large cohort study in the US general population showed a multivariable adjusted relative risk of death of 1.90 (95% CI 1.87-1.93) among breast cancer patients with diabetes, compared to their counterparts without diabetes.[9] However, none of the reported studies investigated the effect of diabetes on mortality in combination with other comorbidities. Based on the literature, we expected to find a worse prognosis for all patients with diabetes in our study as well. By separating the patients with diabetes only, we discovered a novelty in the breast cancer and diabetes research field.

In elderly breast cancer patients, the risk of death due to causes other than cancer is high, and this increases with age.[15] Obviously, patients with multiple comorbidity are at higher risk of competing death than patients without comorbidity.[4,16] In our study, the majority of patients with diabetes and other comorbidity suffered from additional cardiovascular disease, most likely as a coexisting disease caused by shared risk factors, or as a diabetic complication. We found that overall mortality of this group was higher than patients suffering from comorbidity without diabetes, independent of the type of comorbidity. This suggests that the additional comorbidity in patients with diabetes has a larger impact on survival than in patients with the same comorbidity without diabetes. Since patients with the worst overall survival are more likely to die before experiencing a breast cancer recurrence, it is very important to take this risk into account when studying breast cancer outcomes in this population. Therefore, we used Fine & Gray competing risk analysis to analyse the relapse free period.[17]

Interestingly, our data suggest that patients with diabetes in our cohort are at lower risk to develop a breast cancer relapse. The relation between diabetes and RFP appeared to be even stronger in the oldest patients in the cohort. Unfortunately, we were not able to compare these findings with previous studies, since the association between diabetes and recurrence risk has not been described before.

How is it possible that patients with diabetes had a better relapse free period than patients without diabetes (when taking competing mortality into account)? A possible explanation might be the frequent use of metformin in patients with diabetes. In the Dutch diabetes guidelines, metformin is the primary advised drug treatment in type 2 diabetes.[18] Consequently, we can assume that the majority of patients with diabetes used metformin. Previous observational studies showed that the daily use of metformin in cancer patients is related to a survival benefit[10] and a higher pathologic complete response after neoadjuvant chemotherapy.[19]

The mechanism behind these findings has been thoroughly debated. Metformin, an insulin sensitizer from the family of the biguanides is widely used in the treatment of diabetes but potentially also has modulator effects on the enhancement of cell cycle arrest, induced apoptosis, reduced growth factor signalling, the inflammatory response and on sex-steroid production.[20-22] The suggested positive effect of metformin on the clinical course of breast cancer could be through its insulin-independent stimulation of the adenosine monophosphate-activated protein kinase (AMPK) and the subsequent inhibition of the mTOR pathway.[22] In most cancer entities, increased mTOR signalling is associated with malignant tumour progression and resistance to chemotherapy. Inhibition of the mTOR pathway has a cellular growth inhibitory effect resulting in inhibited pathologic cell cycle progression, cell growth and angiogenesis.[22] Currently, a large multicentre ran-

domized placebo-controlled trial in Canada is recruiting early stage breast cancer patients to assess the impact of the addition of metformin to standard therapy on disease-free survival; results are expected not earlier than 2016.[23] Unfortunately, this trial has an upper age limit of 74 years, which means that the findings cannot be extrapolated to the oldest patients. Especially in the elderly breast cancer patient, metformin might be a good adjuvant therapy, since our study showed that relapse free survival was best in the eldest breast cancer patients with diabetes. Additionally, metformin is relatively well-tolerated and new treatment strategies for the elderly population are highly desired. Therefore, we propose that future studies should focus on the benefit of metformin in the elderly breast cancer population.

Strengths and limitations

To our knowledge, this is the largest and most detailed cohort of elderly breast cancer patients. Elderly patients are rarely included in clinical trials because of age restrictions, comorbidity or poor physical function.[24] Therefore, observational studies can be considered an appropriate alternative for studying patient outcome in this patient group, since data are not conflicted by selective inclusion in clinical trials, and studies generally contain more patients.[25]

However, there are some limitations in our study. First, medication was not registered. Therefore, our hypothesis about the effect of metformin on breast cancer outcome could not be confirmed. Second, one could state that the absence of data about causes of death in the cohort is a limitation. However, patients with non-metastasized breast cancer who are primary surgically treated are unlikely to die of breast cancer without developing distant metastases. Additionally, causes of death extracted from death certificates of cancer patients have been shown not always to be accurate and can be overestimated.[26,27] This issue is of large importance in elderly patients, as the risk of competing mortality strongly increases with age[28], which can lead to an even larger overestimation of breast cancer mortality in elderly when death certificates are used. Therefore, in our opinion relapse free period is a more reliable breast cancer specific endpoint than breast cancer specific survival in elderly breast cancer patients. A possible drawback of relapse free period is that it does not include breast cancer therapy related deaths due to cancer therapies.

In conclusion, this study shows that diabetes in itself does not lead to a worse overall survival in elderly breast cancer patients. Diabetes might even lead to a lower relapse risk, especially in the oldest elderly, possibly through the effect of the use of metformin. Future studies should evaluate the effect of new adjuvant therapies such as metformin especially in elderly breast cancer patients, in order to improve the treatment for this vulnerable patient group.

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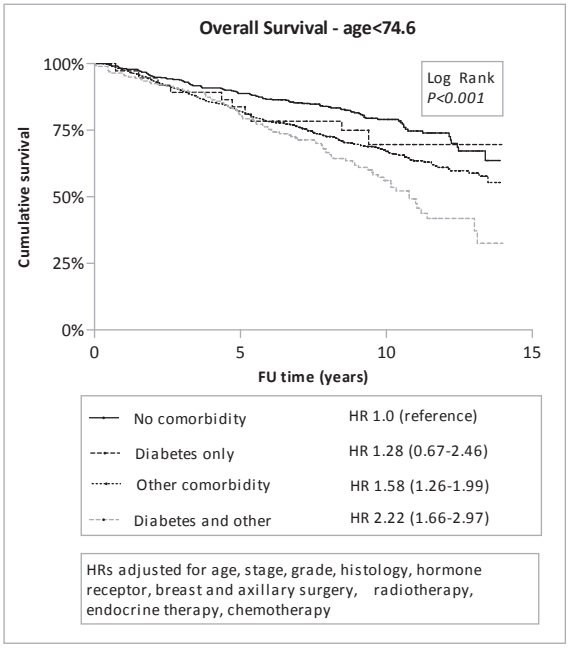
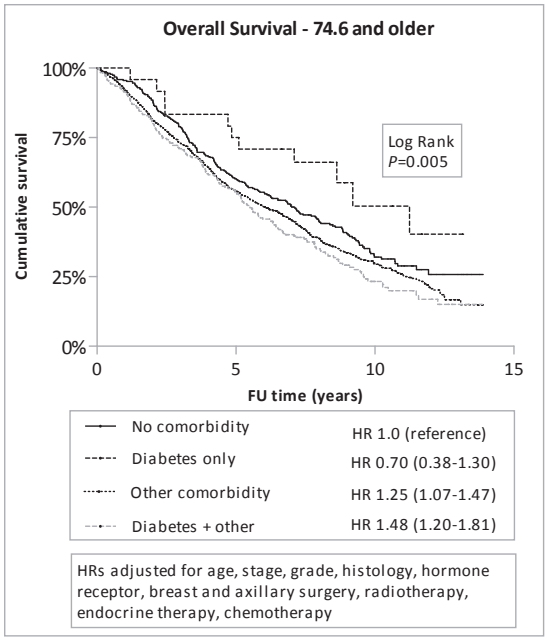
REFERENCES

1. Wildiers H, Kunkler I, Biganzoli L et al. Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. Lancet Oncol 2007; 8: 1101-15.
2. Guralnik JM. Assessing the impact of comorbidity in the older population. Ann Epidemiol 1996; 6: 376-80.
3. Braithwaite D, Satariano WA, Sternfeld B et al. Long-term prognostic role of functional limitations among women with breast cancer. J Natl Cancer Inst 2010; 102: 1468-77.
4. Patnaik JL, Byers T, Diguiseppi C et al. The influence of comorbidities on overall survival among older women diagnosed with breast cancer. J Natl Cancer Inst 2011; 103: 1101-11.
5. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer 2007; 121: 856-62.
6. Vona-Davis L, Howard-McNatt M, Rose DP. Adiposity, type 2 diabetes and the metabolic syndrome in breast cancer. Obes Rev 2007; 8: 395-408.
7. Bianchini F, Kaaks R, Vainio H. Overweight, obesity, and cancer risk. Lancet Oncol 2002; 3: 565-74.
8. Wolf I, Sadetzki S, Catane R et al. Diabetes mellitus and breast cancer. Lancet Oncol 2005; 6: 103-11.
9. Campbell PT, Newton CC, Patel AV et al. Diabetes and cause-specific mortality in a prospective cohort of one million U.S. adults. Diabetes Care 2012; 35: 1835-44.
10. Currie CJ, Poole CD, Jenkins-Jones S et al. Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. Diabetes Care 2012; 35: 299-304.
11. Cleveland RJ, North KE, Stevens J et al. The association of diabetes with breast cancer incidence and mortality in the Long Island Breast Cancer Study Project. Cancer Causes Control 2012; 23: 1193-203.
12. Barone BB, Yeh HC, Snyder CF et al. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA 2008; 300: 2754-64.
13. Nationaal Borstkanker Overleg Nederland . Richtlijn Mammacarcinoom. 2008.
14. Peairs KS, Barone BB, Snyder CF et al. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. J Clin Oncol 2011; 29: 40-6.
15. van de Water W, Markopoulos C, van de Velde CJ et al. Association between age at diagnosis and disease-specific mortality among postmenopausal women with hormone receptor-positive breast cancer. JAMA 2012; 307: 590-7.
16. Mell LK, Jeong JH, Nichols MA et al. Predictors of competing mortality in early breast cancer. Cancer 2010; 116: 5365-73.
17. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007; 26: 2389-430.
18. Bouma M, Rutten GE, de Grauw WJ et al. [Summary of the practice guideline 'Diabetes mellitus type 2' (second revision) from the Dutch College of General Practitioners]. Ned Tijdschr Geneeskd 2006; 150: 2251-6.
19. Jiralerspong S, Palla SL, Giordano SH et al. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J Clin Oncol 2009; 27: 3297-302.

20. Soares SR, Martinez-Varea A, Hidalgo-Mora JJ et al. Pharmacologic therapies in endometriosis: a systematic review. Fertil Steril 2012; 98: 529-55.
21. Takemura Y, Osuga Y, Yoshino O et al. Metformin suppresses interleukin (IL)-1beta-induced IL-8 production, aromatase activation, and proliferation of endometriotic stromal cells. J Clin Endocrinol Metab 2007; 92: 3213-8.
22. Schott S, Bierhaus A, Schuetz F et al. Therapeutic effects of metformin in breast cancer: involvement of the immune system? Cancer Immunol Immunother 2011; 60: 1221-5.
23. Goodwin P. ClinicalTrials.gov - A Phase III Randomized Trial of Metformin vs Placebo in Early Stage Breast Cancer - NCT 01101438. 23-1-2013.
24. Zulman DM, Sussman JB, Chen X et al. Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. J Gen Intern Med 2011; 26: 783-90.
25. Vandenbroucke JP. When are observational studies as credible as randomised trials? Lancet 2004; 363: 1728-31.
26. Hu CY, Xing Y, Cormier JN et al. Assessing the utility of cancer-registry-processed cause of death in calculating cancer-specific survival. Cancer 2013.
27. Goldoni CA, Bonora K, Ciatto S et al. Misclassification of breast cancer as cause of death in a service screening area. Cancer Causes Control 2009; 20: 533-8.
28. 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: 590-7.



Webfigure 1a. Overall survival, patients aged <74.6 years.



Webfigure 1b. Overall survival, patients aged ≥74.6 years.

Chapter 7

Impact of co-medication on breast cancer prognosis – a Tamoxifen Exemestane Adjuvant Multinational (TEAM) side study

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Submitted

ABSTRACT

Background. It has been suggested that the use of non-cancer drugs may improve breast cancer specific prognosis. Due to the low risk of toxicity, this may be especially of interest for older patients who potentially cannot tolerate all conventional systemic therapies. The objective of the current analysis was to assess the impact of three commonly used non-cancer medications on breast cancer prognosis of women participating in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) study.

Patients and Methods. Patients were selected from the TEAM study, enrolling postmenopausal, hormone receptor positive, early breast cancer patients. The primary endpoint was distant metastasis free period (DMFP). Secondary endpoint was breast cancer specific survival (BCSS). Medications of interest comprised metformin, statins and beta blockers. These co-medications were incorporated in Cox regression analyses as time-varying covariates. All analyses were repeated in three age strata (<65, 65-74 and ≥ 75 years).

Results. Overall, 8,137 patients were included. Among them, 470 (5.8%) patients used metformin, 1,361 (16.7%) a statin, and 1,481 (18.2%) a beta blocker during the study period. No significantly beneficial effect of either of the three co-medications on DMFP was observed. Among the youngest patients, statin use was associated with a small but significantly better DMFP (HR 0.64, 95% CI 0.45-0.91). Regarding BCSS, there was a significant benefit for statin (HR 0.80, 95% CI 0.66-0.98) and beta blocker users (HR 0.80, 95% CI 0.67-0.96). No significant effect was observed for metformin users. No effect of age was observed.

Conclusion. In postmenopausal breast cancer patients, we found no significant impact of the use of metformin, statins and/or beta blockers on DMFP. A small but significant association was observed between the use of statins and beta blockers and better BCSS.

INTRODUCTION

In recent years, interest about the potential anti-cancer effect of commonly used drugs that are not primarily registered as anti-cancer medication has been increasing due to reports from several studies suggesting a beneficial effect of different non-cancer medications on cancer prognosis. However, the results of studies hereon for breast cancer are scarce and inconsistent. The most described non-cancer medications in association with breast cancer (BC) prognosis include metformin, statins, beta blockers, and aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs).[1]

Breast cancer patients with type 2 diabetes using metformin were observed to have an improved overall survival compared to patients using other or no anti-diabetic medications.[1] Also, for older breast cancer patients with diabetes, without other comorbidities, a lower risk of breast cancer recurrence has been reported.[2] Both observations are suggestive for an improved breast cancer prognosis in diabetic patients, potentially due to the use of metformin. It has been hypothesized that this possible beneficial effect may be caused by a combination of various potential anti-cancer mechanisms. Metformin inhibits cancer cell growth by the activation of AMP activated protein kinase (AMPK), which results in reduced levels of insulin and insulin like growth factor 1 (IGF-1). Activation of AMPK also results in blockage of the mammalian target of rapamycin (mTOR) pathway, which has shown to be an important player in tumor growth of most common human cancers. Furthermore, metformin can suppress HER-2 protein expression. Also, metformin lowers levels of VEGF, which inhibits angiogenesis, and it can induce apoptosis and block cell cycle arrest via reduced cyclin D1 expression[3]. All these mechanisms potentially impact tumor growth.

The use of statins has similarly been associated with an improved cancer-specific survival in several types of cancer. This effect is possibly due to the lower availability of free cholesterol, which can lead to a decreased proliferation and migration of cancer cells.[4] Previous studies demonstrated that statins induce apoptosis, but also reduce cell invasiveness in various tumor types, including breast cancer.[5]

Regarding aspirin or NSAIDs, it is thought that these drugs may improve cancer survival due to the inhibition of prostaglandins and cyclooxygenase (COX-1 and COX-2). Herewith, NSAIDs can inhibit tumor growth and decrease invasiveness of cancer cells. Through blockage of COX-2, which has shown to be increased in patients with metastatic breast cancer, aspirin can reduce the risk of metastases.[1,6]

Finally, a small number of observational studies indicate a positive effect of beta blockers on the breast cancer specific prognosis, potentially due to the blockage of the beta-adrenergic receptor, which mediates the stress response by binding

catecholamines.[1] A preclinical study in mice showed that chronic stress increased the risk of breast cancer metastases.[7]

These types of medications (without relevant toxicity) and their potential anti-cancer effect are especially of interest for older cancer patients, as the risk of adverse events due to chemotherapy, which is an option for breast cancer therapy especially in some subtypes and in case of metastatic disease, strongly increases with age. Improving outcome as of diagnosis might be welcomed in the older patient group in order to avoid the necessity of chemotherapy.

The international Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial provides a unique opportunity to study the effect of non-cancer medication on breast cancer prognosis, as the use of co-medication was well registered. Furthermore, a relatively large number of older patients were included, enabling to study this effect in older patients specifically.

Hence, the objectives of this study were to assess the impact of commonly used non-cancer medications on breast cancer prognosis in terms of distant metastasis free period (DMFP) and breast cancer specific survival (BCSS) in a large cohort of postmenopausal women with hormone receptor positive early breast cancer, and stratified by age (<65, 65-75 and >75 years).

METHODS

Participants

The TEAM trial is an international randomized controlled trial in postmenopausal patients with hormone-receptor positive early breast cancer. A detailed description of inclusion criteria and the study design and results, has been previously published.[8] In short, patients were randomized to 5 years of exemestane versus 2,5 years of tamoxifen followed by 2,5 years of exemestane. Patients were assessed every 3 months during the first year of endocrine treatment and at least once every year in the years thereafter. Patients with a survival time of zero (or less), probably indicating withdrawal before the study started, were excluded from all analyses (N=9). For the current analyses, all participants of the original TEAM trial from countries that registered co-medications were included (all countries, except for Japan, Greece and France).

Statistical analysis

Data from the original TEAM database were completed with co-medication data as was registered on the Case Report Forms (CRFs) at baseline and during follow-up, including name, start- and end dates of drug use. The database was locked for

follow-up at July 14th, 2015. The primary endpoint of the current analyses was distant metastasis free period (DMFP), defined as the time from randomization to the diagnosis of distant metastasi(e)s. A secondary endpoint was breast cancer specific survival (BCSS), defined as the time from randomization to death due to breast cancer.

Cumulative incidences of distant metastases and breast cancer specific deaths were calculated for patients using metformin, statins and/or beta blockers (users), respectively, and compared to non-users. Both DMFP and BCSS were analyzed using Cox regression analysis using the medicine of interest as a time dependent covariate, to take the actual time that patients were using the medicine of interest into account. For the time dependent analyses, only the medication use during the study follow-up period (since date of randomization) was taken into consideration. Patients who were non users throughout the whole study period, but started the medicine of interest after randomization, were split in two episodes: one for the period they were non-user, and one for the period they were user. We handled the co-medication data according to the 'intention to treat' principle. When a patient had started metformin, a statin or beta blocker, she was considered a user since the recorded start date until the end of the study period. The NSAIDs were not taken into account in the analyses, because, due to different indications (i.e. shorter pain medication prescriptions) for the use of NSAIDs, the intention to treat assumption does not hold for this medication group.

Analyses were performed both univariable and multivariable. According to the method of Hernan, a list of possible confounders was assessed, including patient, tumor and treatment characteristics, which resulted in a multivariable model including age at diagnosis only.[9] The proportional hazards assumptions were tested using Schoenfeld residuals.

All survival analyses were additionally stratified by age at diagnosis (<65, 65-74 and ≥75), similar to the age-group categorization previously used for other analyses within the TEAM trial.[10]

All analyses were performed using IBM SPSS Statistics 20.0, or STATA SE 12.0. All P values are two-sided and a *P* value <0.05 was considered as statistically significant.

RESULTS

Overall, 8,137 TEAM patients were included in our present study (*Webfigure 1 – flowchart*). Patients had a mean age of 64.6 years (Standard Deviation (SD) 9.1). Patient and tumor characteristics, and cancer treatment types are summarized in Table 1.

Table 1. Patient characteristics and treatment.

Age	in years (mean-SD)	64.6	9.1
		N	%
Country of origin			
	Netherlands	2,752	33.8%
	Germany	1,467	18.0%
	UK/Ireland	1,275	15.7%
	US	2,230	27.4%
	Belgium/Luxembourg	413	5.1%
T stage			
	Tis	4	0.0%
	T1	4,585	56.3%
	T2	3,124	38.4%
	T3	288	3.5%
	T4	120	1.5%
	TX	16	0.2%
N stage			
	N0	4,169	51.2%
	N1	3,529	43.4%
	N2	325	4.0%
	N3	88	1.1%
	NX	26	0.3%
Histological grade			
	well	1,205	14.8%
	moderate	4,049	49.8%
	poor	2,126	26.1%
	Unknown	757	9.3%
Most extensive breast surgery			
	Mastectomy	3,910	48.1%
	Wide local excision	4,218	51.8%
	None	3	0.0%
	Unknown	6	0.1%
Axillary dissection			
	No	1,232	15.1%
	Yes	5,436	66.8%
	Unknown	1,469	18.1%
Radiotherapy			
	No	2,793	34.3%
	Yes	5,262	64.7%
	Unknown	82	1.0%
Endocrine therapy (randomisation scheme)			
	Exemestane	4,082	50.2%
	Tamoxifen -> Exemestane	4,055	49.8%
Chemotherapy			
	No	5,237	64.4%
	Yes	2,900	35.6%
Total number of patients		8,137	100.0%

Among all patients, 470 (5.8%) used metformin, 1,361 (16.7%) a statin, and 1,481 (18.2%) a beta blocker during any point of the study follow-up period. For all three co-medications, the proportional hazard assumptions were not violated, according to the Schoenfeld residuals (*P*=0.42, *P*=0.92 and *P*=0.96 for the multivariable analyses).

Median time to distant metastasi(e)s or end of study follow up was 6.1 years (interquartile range (IQR) 5.0-9.6). Among metformin users, 42 (8.9%) patients developed distant metastases during follow-up, as compared to 818 (12.7%) among non-users. Cox proportional hazard models did not show a statistically significant benefit for metformin users (adjusted Hazard Ratio (HR) (users/non-users) 0.77, 95% Confidence Interval (CI) 0.57-1.05). Statin users had a lower proportion of distant metastases during follow-up than non-users (9.4% versus 13.1%), which was not statistically significant (adjusted HR 0.84, 95% CI 0.70-1.01). Among patients using a beta blocker, 165 (11.1%) developed distant metastasi(e)s, compared to 850 (12.8%) in the non-user group, which was not statistically significant (HR 0.93, 95% CI 0.78-1.10) (Table 2).

Table 2. Distant metastasis free period - Cox regression with time-varying covariate

	N of events user group (%)	*N* of events in non-using group (%)	HR*	95% CI lower	95% CI upper	Adjusted HR*	95% CI lower	95% CI upper
Metformin	42 (8.9)	973 (12.7)	0.78	0.57	1.06	0.77	0.57	1.05
Statin	128 (9.4)	887 (13.1)	0.86	0.71	1.04	0.84	0.70	1.01
Beta blocker	165 (11.1)	850 (12.8)	0.94	0.80	1.12	0.93	0.78	1.10

*reference category is patients not using the specific drug. **adjusted for age.

Age-stratified analyses yielded no significant benefit in terms of DMFP in all three age strata, except for statin users in the youngest age group (HR 0.64, 95% CI 0.45-0.91) (Appendix A1-A3).

For the analyses regarding BCSS, the median time to breast cancer death or end of follow up was 6.5 years (IQR 5.0-9.8). Among metformin users, statin and beta blocker users, 39 (8.3%), 117 (8.6%) and 136 (9.2%) patients, respectively, died due to breast cancer. Among non-users, this concerned 801 (10.5%), 723 (10.7%) and 704 (10.6%) patients, respectively. Age-adjusted Cox models, with the medicine of interest as time varying covariate, showed a significant benefit for statin (HR 0.80, 95% CI 0.66-0.98) and beta blocker users (HR 0.80, 95% CI 0.67-0.96). In contrast, there was no significant BCSS benefit for metformin users (HR 0.73, 95% CI

0.53-1.01) (Table 3). For the analyses regarding metformin and beta blockers, the proportional hazard assumption was not violated (Schoenfeld p=0.59 and 0.72). For the analysis regarding statins, there was a violation of the proportional hazard assumption (Schoenfeld *P*=0.04).

Table 3. Breast cancer specific survival - Cox regression with time-varying covariate

	N of events user group (%)	*N* of events in non-using group (%)	HR*	95% CI lower	95% CI upper	Adjusted HR*	95% CI lower	95% CI upper
Metformin	39 (8.3)	801 (10.5)	0.75	0.55	1.04	0.73	0.53	1.01
Statin	117 (8.6)	723 (10.7)	0.84	0.69	1.02	**0.80**	**0.66**	**0.98**
Beta blocker	136 (9.2)	704 (10.6)	0.83	0.69	1.00	**0.80**	**0.67**	**0.96**

*reference category is patients not using the specific drug. **adjusted for age.

Age-stratified analyses of BCSS yielded no significant benefit for any of the co-medications in all three age strata (Appendix B1-B3).

DISCUSSION

The current analyses in postmenopausal hormone receptor positive early breast cancer patients, enrolled in the TEAM study, found less distant metastasi(e)s in metformin, statin or beta blocker users, although not statistically significant. However, we found a statistically significant association between the use of statins and beta blockers and an improved breast cancer specific survival. No differences were observed between age groups.

Our results could not confirm the positive results of observational studies reporting a positive impact of metformin on breast cancer recurrence or BCSS,[11,12] although a trend toward a beneficial effect was observed. It should be noted that all positive studies on this topic analyzed metformin use as a time-fixed variable, based on the use of metformin at the time of diagnosis. It has been shown, however, that the use of co-medications in association with cancer prognosis always should be analyzed as a time-varying covariate, to avoid overestimation of the effect due to various biases.[13] Therefore, we consider the results of our present analysis as more reliable. On the other hand, in view of the heterogeneity of breast cancer (different molecular subtypes) it is possible that the impact of metformin on cancer outcome might be different for the various subtypes, and prospectively planned sub analyses are warranted therefore. The impact of metformin on breast cancer prognosis is currently studied in a Canadian phase III randomized trial

of metformin vs. placebo in early stage non-diabetic breast cancer patients.[14] This study is expected to close in 2017, and results are not to be expected before 2023, because the primary endpoint is invasive disease free survival at 6 years.

In our analyses, we found a trend for a positive effect of statins on the development of distant metastases, but only in patients aged younger than 65 years. This may be due to the lower number of statin users and events in the older age group. Moreover, the significantly BCSS benefit we observed for statin users should be interpreted with caution, because the proportional hazard assumption was violated. Still, our results are in line with the findings of two observational studies showing a positive impact of statins on breast cancer specific prognosis, also analyzing the medication data as time-varying covariate.[15,16]

With regards to the use of beta blockers, we found no impact on DMFP, but a significant BCSS benefit for users. This finding is partly in concordance with previous studies showing a beneficial impact on different breast cancer specific endpoints.[17-19] It should be taken into account that, at least part of the previous studies reporting on the association between beta blockers and breast cancer prognosis, did not analyze the usage as a time-varying covariate[17,18]. Furthermore, a number of recently published observational studies, including one very large (N=18.733) Danish population-based study, and a very recent study that pooled data from eight European countries, resulting in a sample size of 55.252 patients, did not show an association between the use of beta-blockers and BCSS.[20-23] Considering these findings, combined with the data of our present study, it is questionable whether it is worthwhile to initiate a clinical trial on this issue.

We did not find a beneficial effect of either one of the medications in older patients specifically. This may be due to the lower number of events in these groups, since the risk estimates did not strongly differ between the three age-groups.

Strengths & Limitations

A major strength of our study is that we used a very large cohort of postmenopausal early BC patients enrolled in the TEAM study including patients from the U.S. and Europe, with robust and well-registered data.

We chose distant metastasis free period as the primary endpoint of our current study to avoid that the endpoint might be contaminated with non-breast cancer specific events, as would be the case if we considered all-cause mortality. As secondary endpoint, we considered BCSS. This endpoint should be interpreted with caution, because it has been shown that the cause of death of breast cancer patients is often misclassified.[24,25]

Ideally, we would have preferred to adjust our analyses for comorbidity, as this can act as a possible confounder influencing both the determinant (co-medication

use) and the endpoint. However, data on comorbidity were not completely available for all countries. Most probably, additionally adjusting the data for comorbidity would have nuanced the Hazard Ratio's even more towards one.

Another limitation is that we only had one start date, and one stop date for a specific co-medication per patient available in the database. Therefore, we chose to use the recorded start date in our intention-to-treat analyses. This should not be a major problem regarding the co-medications which normally are prescribed for chronic conditions, which is the case for metformin, statins and/or beta blockers. However, several studies report about the association of NSAIDs and (breast) cancer prognosis, but due to unreliable data, we were not able to analyze the effect of NSAIDs in our study. NSAIDs are generally prescribed on an "as need" base for pain. We chose to not use the NSAIDs as intention-to-treat data.

Although we were not able to use the full cohort of TEAM study participants (N=9,766), because of lack of data on co-medication from three countries, we were able to use the great majority of the patients (>80%) from six full countries. Therefore, we consider the chance of inducing selection bias small.

Finally, we have previously shown that the TEAM trial comprises a selected population. It was shown that the trial included patients with fewer comorbidity, more favorable tumor characteristics and a better prognosis than the general population of the same age, which limits external validity, especially in older patients.[26]

Conclusion

Among 8,137 patients from the TEAM study, we found no statistically significant impact of the use of metformin, statins and/or beta blockers on the development of distant metastasis, although all risk estimates were all below one. However, we did find a small but significant association between the use of statins and beta blockers, and breast cancer specific survival. No differences in age-groups were found. Eventually, the results of randomized clinical trials investigating these medications have to be awaited before to conclude on the real value of metformin, statins and beta blockers as adjuvant therapies for breast cancer.

REFERENCES

1. Holmes MD, Chen WY: Hiding in plain view: the potential for commonly used drugs to reduce breast cancer mortality. Breast Cancer Res 14:216, 2012
2. Kiderlen M, de Glas NA, Bastiaannet E, et al: Diabetes in relation to breast cancer relapse and all-cause mortality in elderly breast cancer patients: a FOCUS study analysis. Ann. Oncol 24:3011-3016, 2013
3. Jalving M, Gietema JA, Lefrandt JD, et al: Metformin: taking away the candy for cancer? Eur. J. Cancer 46:2369-2380, 2010
4. Nielsen SF, Nordestgaard BG, Bojesen SE: Statin use and reduced cancer-related mortality. N. Engl. J. Med 367:1792-1802, 2012
5. Bonovas S, Filioussi K, Tsavaris N, et al: Use of statins and breast cancer: a meta-analysis of seven randomized clinical trials and nine observational studies. J. Clin. Oncol 23:8606-8612, 2005
6. Holmes MD, Chen WY, Li L, et al: Aspirin intake and survival after breast cancer. J. Clin. Oncol 28:1467-1472, 2010
7. Sloan EK, Priceman SJ, Cox BF, et al: The sympathetic nervous system induces a metastatic switch in primary breast cancer. Cancer Res 70:7042-7052, 2010
8. van de Velde CJ, Rea D, Seynaeve C, et al: Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. Lancet 377:321-331, 2011
9. M.A.Hernan, J.M.Robins: Causal Inference, Chapman & Hall, 2011
10. 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 307:590-597, 2012
11. He X, Esteva FJ, Ensor J, et al: Metformin and thiazolidinediones are associated with improved breast cancer-specific survival of diabetic women with HER2+ breast cancer. Ann. Oncol 23:1771-1780, 2012
12. Currie CJ, Poole CD, Jenkins-Jones S, et al: Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin on survival. Diabetes Care 35:299-304, 2012
13. Suissa S, Azoulay L: Metformin and the risk of cancer: time-related biases in observational studies. Diabetes Care 35:2665-2673, 2012
14. Goodwin P: ClinicalTrials.gov - A Phase III Randomized Trial of Metformin vs Placebo in Early Stage Breast Cancer - NCT 01101438, 2013
15. Ahern TP, Pedersen L, Tarp M, et al: Statin prescriptions and breast cancer recurrence risk: a Danish nationwide prospective cohort study. J. Natl. Cancer Inst 103:1461-1468, 2011
16. Murtola TJ, Visvanathan K, Artama M, et al: Statin use and breast cancer survival: a nationwide cohort study from Finland. PLoS. One 9:e110231, 2014
17. Barron TI, Connolly RM, Sharp L, et al: Beta blockers and breast cancer mortality: a population- based study. J. Clin. Oncol 29:2635-2644, 2011
18. Botteri E, Munzone E, Rotmensz N, et al: Therapeutic effect of beta-blockers in triple-negative breast cancer postmenopausal women. Breast Cancer Res. Treat 140:567-575, 2013
19. Ganz PA, Habel LA, Weltzien EK, et al: Examining the influence of beta blockers and ACE inhibitors on the risk for breast cancer recurrence: results from the LACE cohort. Breast Cancer Res. Treat 129:549-556, 2011

20. Cardwell CR, Coleman HG, Murray LJ, et al: Beta-blocker usage and breast cancer survival: a nested case-control study within a UK clinical practice research datalink cohort. Int. J. Epidemiol 42:1852-1861, 2013
21. Sakellakis M, Kostaki A, Starakis I, et al: beta-Blocker Use and Risk of Recurrence in Patients with Early Breast Cancer. Chemotherapy 60:288-289, 2015
22. Sorensen GV, Ganz PA, Cole SW, et al: Use of beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and risk of breast cancer recurrence: a Danish nationwide prospective cohort study. J. Clin. Oncol 31:2265-2272, 2013
23. Cardwell CR, Pottegard A, Vaes E, et al: Propranolol and survival from breast cancer: a pooled analysis of European breast cancer cohorts. Breast Cancer Res 18:119, 2016
24. Hu CY, Xing Y, Cormier JN, et al: Assessing the utility of cancer-registry-processed cause of death in calculating cancer-specific survival. Cancer, 2013
25. Goldoni CA, Bonora K, Ciatto S, et al: Misclassification of breast cancer as cause of death in a service screening area. Cancer Causes Control 20:533-538, 2009
26. 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 106:dju051, 2014

APPENDIX

Appendix A1. Distant metastasis free period - Cox regression with time-varying covariate. Age<65

	N of events user group (%)	*N* of events in non-using group (%)	HR*	95% CI lower	95% CI upper	Adjusted HR**	95% CI lower	95% CI upper
Metformin	17 (7.7)	525 (12.2)	0.72	0.44	1.16	0.81	0.61	1.09
Statin	50 (8.1)	492 (12.0)	0.81	0.60	1.08	0.64	0.45	0.91
Beta blocker	67 (10.1)	475 (12.0)	0.85	0.66	1.10	0.85	0.66	1.10

*reference category is patients not using the specific drug. **adjusted for age.

Appendix A2. Distant metastasis free period - Cox regression with time-varying covariate. Age 65-74

	N of events user group (%)	*N* of events in non-using group (%)	HR*	95% CI lower	95% CI upper	Adjusted HR**	95% CI lower	95% CI upper
Metformin	20 (10.8)	301 (12.5)	0.88	0.56	1.38	0.87	0.55	1.37
Statin	53 (10.2)	268 (12.4)	0.83	0.62	1.12	0.82	0.61	1.11
Beta blocker	61 (11.3)	260 (12.1)	0.93	0.70	1.23	0.91	0.69	1.21

*reference category is patients not using the specific drug. **adjusted for age.

Appendix A3. Distant metastasis free period - Cox regression with time-varying covariate. Age ≥ 75

	N of events in exposed group (%)	*N* of events in unexposed group (%)	HR*	95% CI lower	95% CI upper	Adjusted HR**	95% CI lower	95% CI upper
Metformin	5 (8.1)	147 (12.6)	0.62	0.26	1.52	0.61	0.25	1.48
Statin	25 (11.4)	127 (12.2)	0.84	0.52	1.35	0.96	0.62	1.46
Beta blocker	37 (13.5)	115 (11.6)	1.13	0.78	1.64	1.14	0.79	1.66

*reference category is patients not using the specific drug. **adjusted for age.

Appendix B1. Breast cancer specific survival - Cox regression with time-varying covariate. Age<65

	N of events user group (%)	*N* of events in non-using group (%)	HR**	95% CI lower	95% CI upper	Adjusted HR**	95% CI lower	95% CI upper
Metformin	16 (7.2)	407 (9.7)	0.74	0.45	1.21	0.74	0.45	1.22
Statin	45 (7.3)	378 (10.0)	0.79	0.58	1.08	0.80	0.58	1.09
Beta blocker	52 (7.8)	371 (9.9)	0.75	0.56	1.00	0.75	0.56	1.00

*reference category is patients not using the specific drug. **adjusted for age.

Appendix B2. Breast cancer specific survival - Cox regression with time-varying covariate. Age 65-74

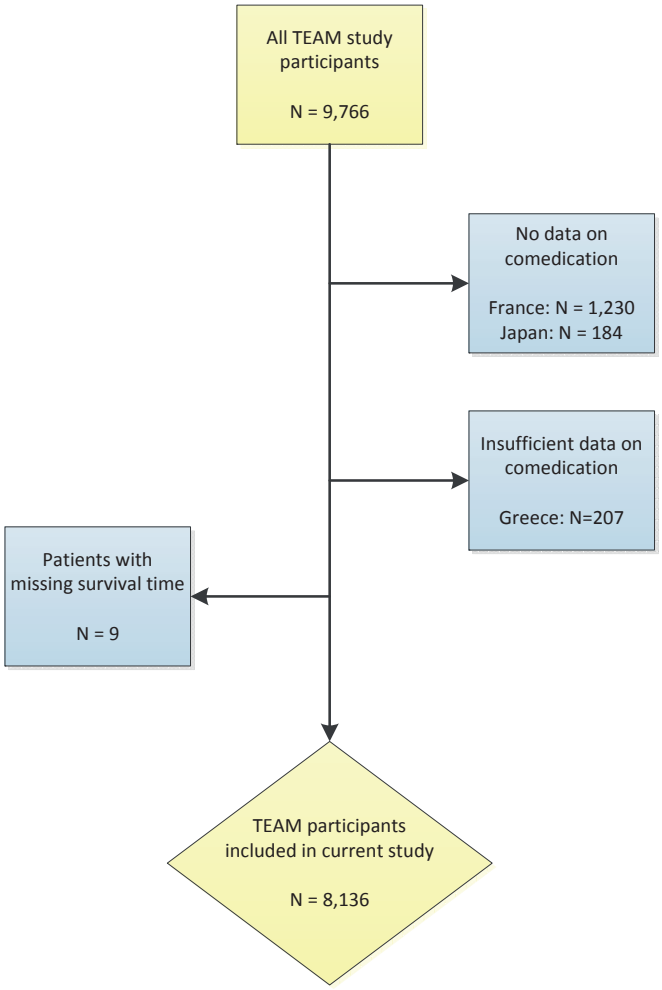
	N of events user group (%)	*N* of events in non-using group (%)	HR**	95% CI lower	95% CI upper	Adjusted HR**	95% CI lower	95% CI upper
Metformin	18 (9.7)	250 (10.7)	0.81	0.50	1.30	0.80	0.50	1.29
Statin	44 (8.5)	224 (11.2)	0.73	0.53	1.01	0.72	0.52	1.00
Beta blocker	50 (9.2)	218 (11.0)	0.80	0.58	1.08	0.78	0.57	1.06

*reference category is patients not using the specific drug. **adjusted for age.

Appendix B3. Breast cancer specific survival - Cox regression with time-varying covariate. Age ≥ 75

	N of events user group (%)	*N* of events in non-using group (%)	HR**	95% CI lower	95% CI upper	Adjusted HR**	95% CI lower	95% CI upper
Metformin	5 (8.1)	144 (12.6)	0.58	0.23	1.41	0.57	0.23	1.39
Statin	28 (12.8)	121 (28)	1.03	0.68	1.55	1.02	0.68	1.54
Beta blocker	34 (12.4)	115 (12.3)	0.94	0.64	1.38	0.95	0.65	1.39

*reference category is patients not using the specific drug. **adjusted for age.



Webfigure 1. Consort diagram

Chapter 8

External validity of a trial comprised of elderly patients with hormone receptor-positive breast cancer

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ABSTRACT

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

Methods. We compared characteristics and outcome of breast cancer patients (n = 1325) who participated in a randomized clinical trial (Tamoxifen Exemestane Adjuvant Multinational trial) with unselected breast cancer patients of corresponding age from the general population (n = 1056). Dutch patients aged ≥65 years 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; ≥75 years). Primary outcome was overall mortality. Multivariable Cox proportional hazards models were used to assess the association between covariates and overall mortality. All statistical tests were two-sided.

Results. Irrespective of age, patients who participated in the trial had fewer comorbid diseases, a higher 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 to patients from the general population (multivariable hazard ratio (HR) = 1.08 (95%CI 0.73-1.60)). Alternatively, in patients aged ≥75y, those who participated in the trial had a lower overall mortality (multivariable HR = 0.72 (95%CI 0.55-0.95)) than patients in the general population.

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

INTRODUCTION

In developed countries, over 40% of all newly diagnosed breast cancer patients are 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 patients suffer from a higher risk of competing mortality[3] and have a lower remaining life expectancy. Consequently, the absolute benefit of anticancer therapy may be smaller, 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 obtained in younger patients.

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

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

METHODS

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

Patients who participated in a trial

Patients who participated in the Tamoxifen Exemestane Adjuvant Multinational trial[9,10] were eligible for inclusion in the current study. Because five-year results of the TEAM trial showed no statistically significant differences in efficacy endpoints between the two treatment arms[9], we were able to conduct 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 for 5 years or to a sequential regimen consisting of tamoxifen followed by exemestane for a total of 5 years. Inclusion for patients

in The Netherlands was restricted to those who either had nodal involvement, a tumor >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 >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, pre-specified 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). For the patients included in the TEAM trial, appropriate approvals from the ethical committee were obtained. All patients provided written informed consent.

Statistical analyses

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

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 $1 - \hat{S}(t)$ where $\hat{S}(t)$ is the Kaplan–Meier estimator for the probability of survival at time (t), based on the life tables.[16] Corresponding 95% confidence intervals 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 particularly present in older populations.[3] Therefore, distant breast cancer recurrence was estimated by regression analyses according to Fine and Gray.[21,22] A Fine and Gray analysis is used to assess the risk of a distant breast cancer recurrence while taking into account the risks of reaching other, competing endpoints. Competing endpoints were a locoregional recurrence (recurrence in the ipsilateral breast or chest wall, ipsilateral axillary or supraclavicular lymph node(s)), contralateral breast cancer, and death due to any cause.

Covariates were included in the multivariable model if they were judged to be clinically relevant, regardless of statistical significance. The fully adjusted multivariable model included tumor characteristics (histological grade [Bloom

Richardson grade I, II, III, unknown], T stage [T1/T2, T3/T4, unknown], nodal stage [negative, positive, unknown]), treatment characteristics (most extensive surgery [breast conserving surgery, mastectomy], radiotherapy [yes, no, unknown], endocrine therapy [yes, no], and chemotherapy [yes, no, unknown]), and patient characteristics (age [continuous], year of diagnosis [continuous], 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 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

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				
Patient and tumor characteristics	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**

fewer comorbid diseases and more often had a high socio-economic status. Moreover, patients who participated in a trial had smaller tumors (all p <.001).

Second, we investigated whether treatment of patients who participated in a clinical trial differs from treatment of patients from the general population (Table 2). Needless to say, all patients who participated in the trial received endocrine therapy, whereas in both age groups 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 (p<.001).

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.

Treatment characteristics	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. To test for statistical differences in proportions, the Pearson χ^2 test was used. All statistical tests were two-sided; p values <.05 were considered to be statistically significant.

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 year 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.

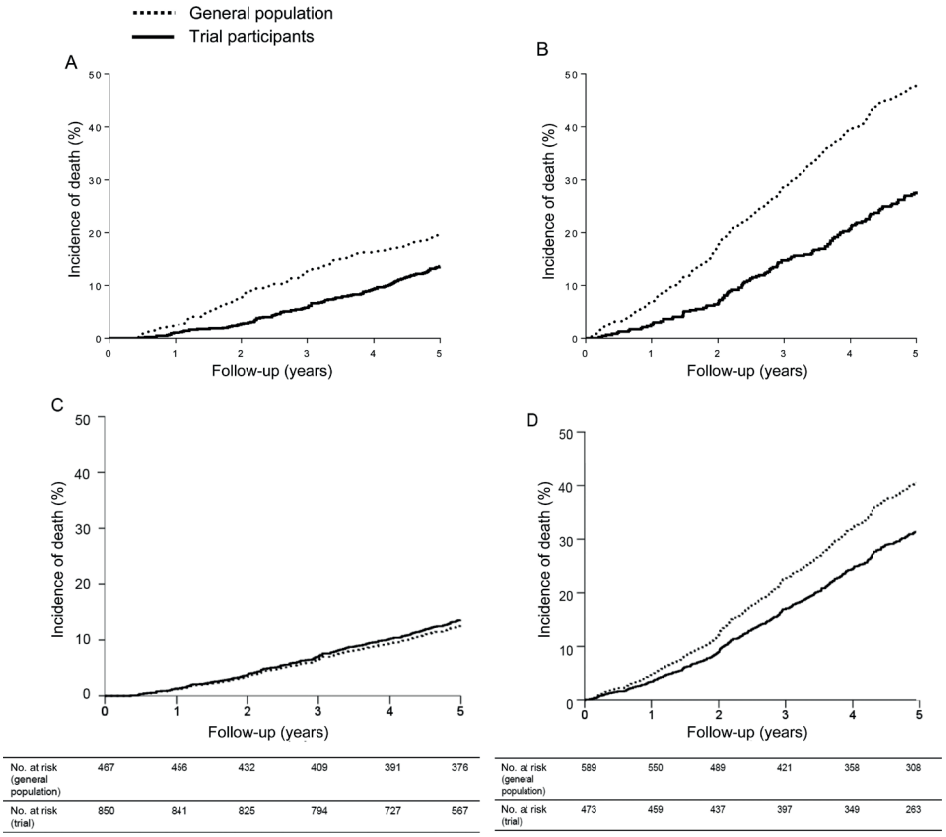

Figure 1. Univariate and multivariable cumulative incidence of death in elderly patients who participated in the TEAM trial compared with those in the general population.

A. Unadjusted cumulative incidence of death of elderly breast cancer patients aged 65-75 years who participated in a trial, as compared to elderly breast cancer patient from the general population. Cumulative incidence of death was estimated by $1 - \hat{S}(t)$ where $\hat{S}(t)$ is the Kaplan–Meier estimator for the probability of survival at time (t), *based on the life tables.*

B. Unadjusted cumulative incidence of death of elderly breast cancer patients aged 75 years or older who participated in a trial, as compared to elderly breast cancer patient from the general population. Cumulative incidence of death was estimated by $1 - \hat{S}(t)$ where $\hat{S}(t)$ is the Kaplan–Meier estimator for the probability of survival at time (t), *based on the life tables.*

C. Adjusted cumulative incidence of death of elderly breast cancer patients aged 65-75 years participated in a trial, as compared to elderly breast cancer patient from the general population, based on multivariable Cox regression analysis.

D. Adjusted cumulative incidence of death of elderly breast cancer patients aged 75 years or older who participated in a trial, as compared to elderly breast cancer patient from the general population, based on multivariable Cox regression analysis. All statistical tests were two-sided. TEAM = Tamoxifen Exemestane Adjuvant Multinational trial.

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)). The adjusted cumulative incidence of death is depicted in Figure 1C.

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 and covariates	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)	

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. (*continued*)

Patients and covariates	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
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.

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 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; p = .019). The adjusted cumulative incidence of death is depicted in Figure 1D.

To explore whether differences in overall mortality could be explained by differences in breast cancer outcome, we evaluated the risk of a distant recurrence (Table 4). Irrespective of age, multivariable analyses did not reveal any differences. Of note, in both age groups, the absolute number of patients who developed a distant recurrence was exceeded by the number of patients who died. Among patients aged 75 years or older, the number of patients who died during 5 years of follow up was 124 for trial participants and 281 for the general population. Alternatively, the number of patients who developed a distant recurrence was 54 and 74, respectively, for the two groups. 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.

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.

Age group	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		0.514
General population (n=467)	61	59	1 (reference)		1 (reference)	
Trial participants (n=852)	84	62	0.72 (0.52-1.00)		1.17 (0.73-1.87)	
≥75 years				0.447		0.277
General population (n=589)	74	228	1 (reference)		1 (reference)	
Trial participants (n=473)	54	95	0.87 (0.66-1.24)		1.33 (0.79-2.34)	

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.

DISCUSSION

To warrant the internal validity of a clinical trial, inclusion of patients into a trial is often selective, 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 the trial had a similar overall mortality as patients from the general population after adjustment. Thus, selective inclusion can be overcome by taking into account patient, tumor and treatment characteristics. Selection of patients into a trial may be more pronounced with increasing age, given the larger heterogeneity of patients with increasing age. This hypothesis was confirmed in 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.

A selective inclusion of patients into a trial is multifactorial. First, eligibility criteria may hamper inclusion of elderly patients in general and inclusion of certain elderly in particular. Patients were ineligible for the TEAM trial if they had a malignancy within 5 years preceding breast cancer diagnosis, an Eastern Cooperative Oncology Group performance status of >2, substantial cardiac disease, or other illness interfering with study participation and follow-up.[10] Others have published about the impact of eligibility criteria on the inclusion in trials.[24] Of all clinical trials published in 2008 in five major medical journals, 20% excluded patients based on age.[7] In the remaining trials, almost half of the studies excluded patients with age-related diseases, which could disproportionally impact inclusion of certain elderly patients. Next to eligibility criteria hampering inclusion of elderly patients, physician factors[25-27], patient factors[25], and factors related to trial logistics may affect participation.[25]. From a patient point of view, age has not been shown to be a statistically significant predictor as 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 other characteristics, fewer comorbid diseases. Additionally, participation in a trial in itself may *result in* lower overall mortality. One may argue that more attention is being paid to treatment of comorbid disease of elderly patients who participate in a trial, as compared 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 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, by misclassification of baseline characteristics and follow-up data. 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 of overall mortality is unlikely; vital status was established through linkage with the municipal population registries for all patients. Regarding the secondary endpoint, the method of detection of a breast cancer recurrence was similar for all patients. Of note, those who participated in the trial had strict follow-up schemes, whereas this may not always be

accomplished in general practice. Therefore, we cannot exclude the possibility of underdiagnosis of breast cancer recurrence among patients from the general population. Regarding overall mortality, sample size was sufficient to detect a difference among patients aged 75 years or older. Among patients aged 65-75 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

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

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 unlikely that clinical trials are sufficient to fill this 'evidence gap'. Even in the absence of eligibility criteria it is expected that elderly included in a trial will be selected.[26;27;29] Moreover, the large heterogeneity in the elderly population makes it difficult to conduct clinical trials 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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REFERENCES

1. Surveillance Epidemiology and End Results. 2011. 18-2-2011.
2. DeSantis C, Siegel R, Bandi P, Jemal A. Breast cancer statistics, 2011. CA Cancer J Clin 2011;61(6):409-18.
3. Mell LK, Jeong JH, Nichols MA, Polite BN, Weichselbaum RR, Chmura SJ. Predictors of competing mortality in early breast cancer. Cancer 2010;116(23):5365-73.
4. Aapro M, Bernard-Marty C, Brain EG, Batist G, Erdkamp F, Krzemieniecki Ket al. Anthracycline cardiotoxicity in the elderly cancer patient: a SIOG expert position paper. Ann Oncol 2011;22(2):257-67.
5. Sokol KC, Knudsen JF, Li MM. Polypharmacy in older oncology patients and the need for an interdisciplinary approach to side-effect management. J Clin Pharm Ther 2007;32(2):169-75.
6. Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJet al. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol 2003;21(7):1383-9.
7. Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA. Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. J Gen Intern Med 2011;26(7):783-90.
8. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Jr., Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 1999;341(27):2061-7.
9. van de Velde CJ, Rea D, Seynaeve C, Putter H, Hasenburg A, Vannetzel JMet al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. Lancet 2011;377(9762):321-31.
10. van Nes JG, Seynaeve C, Jones S, Markopoulos C, Putter H, van de Velde CJet al. Variations in locoregional therapy in postmenopausal patients with early breast cancer treated in different countries. Br J Surg 2010;97(5):671-9.
11. de Glas NA, Kiderlen M, Bastiaannet E, de Craen AJ, van de Water W, van de Velde CJet al. Postoperative complications and survival of elderly breast cancer patients: a FOCUS study analysis. Breast Cancer Res Treat 2013;138(2):561-9.
12. The International Classification of Diseases and Related Health Problems ICD-10. 10th ed. 2013.
13. Tesser P, Van Praag C, Van Dugteren F, Herweijer L, Van der Wouden H. Rapportage minderheden 1995. Sociaal en Cultureel Planbureau/VUGA, Rijswijk/Den Haag. 2013.
14. International Society of Geriatric Oncology. 2011.
15. van de Water W, Markopoulos C, van de Velde CJ, Seynaeve C, Hasenburg A, Rea Det al. Association between age at diagnosis and disease-specific mortality among postmenopausal women with hormone receptor-positive breast cancer. JAMA 2012;307(6):590-7.
16. Andersen PK, Geskus RB, de WT, Putter H. Competing risks in epidemiology: possibilities and pitfalls. Int J Epidemiol 2012;41(3):861-70.
17. Schoenfeld D. Partial residuals for the proportional hazards regression model. Biometrika 1982;69:239-41.
18. Lu TH, Shih TP, Lee MC, Chou MC, Lin CK. Diversity in death certification: a case vignette approach. J Clin Epidemiol 2001;54(11):1086-93.
19. Harteloh P, de BK, Kardaun J. The reliability of cause-of-death coding in The Netherlands. Eur J Epidemiol 2010;25(8):531-8.

20. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365(9472):1687-717.
21. Fine JP GRJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association 1999;(94):496-509.
22. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007;26(11):2389-430.
23. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". Lancet 2005;365(9453):82-93.
24. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA 2007;297(11):1233-40.
25. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. J Clin Oncol 2005;23(13):3112-24.
26. Kemeny MM, Peterson BL, Kornblith AB, Muss HB, Wheeler J, Levine Eet al. Barriers to clinical trial participation by older women with breast cancer. J Clin Oncol 2003;21(12):2268-75.
27. Kornblith AB, Kemeny M, Peterson BL, Wheeler J, Crawford J, Bartlett Net al. Survey of oncologists' perceptions of barriers to accrual of older patients with breast carcinoma to clinical trials. Cancer 2002;95(5):989-96.
28. Townsley CA, Chan KK, Pond GR, Marquez C, Siu LL, Straus SE. Understanding the attitudes of the elderly towards enrolment into cancer clinical trials. BMC Cancer 2006;6:34.
29. Hamaker ME, Seynaeve C, Nortier JW, Wymenga M, Maartense E, Boven Eet al. Slow accrual of elderly patients with metastatic breast cancer in the Dutch multicentre OMEGA study. Breast 2013.
30. Vandenbroucke JP. When are observational studies as credible as randomised trials? Lancet 2004;363(9422):1728-31.

Chapter 9

Performing survival analyses in the presence of competing risks: a clinical example in older breast cancer patients

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ABSTRACT

An important consideration in studies that use cause-specific endpoints such as cancer-specific survival or disease recurrence is that risk of dying from another cause before experiencing the event of interest is generally much higher in older patients. Such competing events are of major importance in the design and analysis of studies with older patients, as a patient who dies from another cause before the event of interest cannot reach the endpoint. In this Commentary, we present several clinical examples of research questions in a population-based cohort of older breast cancer patients with a high frequency of competing events and discuss implications of choosing models that deal with competing risks in different ways. We show that in populations with high frequency of competing events, it is important to consider which method is most appropriate to estimate cause-specific endpoints. We demonstrate that when calculating absolute cause-specific risks the Kaplan-Meier method overestimates risk of the event of interest and that the cumulative incidence competing risks (CICR) method, which takes competing risks into account, should be used instead. Two approaches are commonly used to model the association between prognostic factors and cause-specific survival: the Cox proportional hazards model and the Fine and Gray model. We discuss both models and show that in etiologic research the Cox Proportional Hazards model is recommended, while in predictive research the Fine and Gray model is often more appropriate. In conclusion, in studies with cause-specific endpoints in populations with a high frequency of competing events, researchers should carefully choose the most appropriate statistical method to prevent incorrect interpretation of results.

INTRODUCTION

In order to study treatment efficacy or other outcomes in clinical research, large cohorts of patients are often followed during a certain period of time. Frequently, cause-specific endpoints are used in these studies, such as recurrence, cancer-specific mortality, or cardiovascular mortality.[1] For these endpoints, statistical methods that assess the time to an event such as the Kaplan-Meier method or the Cox Proportional Hazards model are frequently used.[2,3]

An important consideration in studies that use these cause-specific endpoints is that the risk of dying from a cause other than reaching the endpoint of interest is generally much higher in older patients than in younger patients.[4,5] These so-called competing events are of major importance in the design and analyses of studies with older patients[5] because a patient who dies from another cause can obviously not reach the endpoint of interest anymore. This topic is especially important in geriatric oncology research as a large proportion of older cancer patients will die from non-cancer-related causes before reaching the endpoint of interest.[5] For example, around 70% of breast cancer patients age 75 years or older who die do not die from breast cancer but from another cause.[6] There are several statistical methods that are frequently used for time-to-event analyses such as the Cox Proportional Hazards Model and the Fine and Gray model. These methods deal with competing events in different ways.[2] It is likely that the choice of model can strongly influence the interpretation of the outcome, especially in populations with a high frequency of competing events.[3,4] Several studies have described the methodology of dealing with competing risks in detail, but these methodological papers may be difficult to interpret in clinical research. Therefore, the aim of this study is to present clinical examples of research questions in a population-based cohort of older breast cancer patients with a high frequency of competing events and to discuss the implications of choosing different methods for the interpretation of the results. In addition, this paper will give recommendations for choosing specific statistical methods for specific research questions.

THEORETICAL FRAMEWORK

First, we will provide some background information on methods that can be used to calculate absolute risks (ie, cumulative incidences), and models that can be used to model the effect of variables on the outcome.

Estimating Absolute Risks

The Kaplan-Meier method is a commonly used method to estimate survival probabilities over time. It can deal with censored follow-up times; ie, it can handle situations where the exact time of death is not known because patients drop out of the study or are still alive at the end of follow-up. One important assumption of the Kaplan-Meier method is independent censoring: at any time patients with censored survival times have the same survival prognosis as patients who are still in the study.[7] Kaplan-Meier curves are often used to calculate survival probabilities for a specific cause of death. Patients who die of other causes are censored. Clearly, the assumption that censored patients have the same prognosis as those who are still followed is invalid because patients who die of other causes have a probability of zero to reach the cause of interest. This means that estimated survival probabilities of the Kaplan-Meier method are no longer correct. Hence, the Kaplan-Meier method does not estimate the actual survival probability but estimates what would have been observed if dying from other causes would not have been possible.

Alternatively, the Cumulative Incidence Competing Risks (CICR) method[2,3] assumes that patients who experienced a competing event are no longer at risk for the endpoint of interest.[8] This approach estimates the actual probabilities of reaching different endpoints (cumulative incidences). At each time point, the sum of all the cumulative incidences will be equal to the total probability to reach an endpoint before that time.

To illustrate the difference between the two methods, consider a very simple example in which three women with breast cancer are followed. One woman dies after one month of a myocardial infarct (MI), the second woman dies after two months of breast cancer, and the third woman is still alive after three months. The Kaplan-Meier method will estimate the probability to die of a MI within three months as 1/3. However, when considering death because of breast cancer, the Kaplan-Meier method treats the women who died in the first month of MI as censored after month 1, meaning that there are only two women at risk at month 2. The risk of dying of breast cancer in month 2 is therefore estimated as being 1/2. The three-month probability to die of breast cancer is then estimated as being 1/2, the probability to die of MI as 1/3, and the probability to be alive after three months as only 1/6. This clearly shows that the Kaplan-Meier method yields incorrect results. The CICR method accounts for the woman with the competing event by adding her to the denominator of the probability to die of breast cancer. This yields a three-month probability to die of breast cancer of 1/3, the probability to die of MI is 1/3, and the probability to be alive is 1/3.

Hazard Functions

There are different ways to assess the association between certain variables and the outcome with the possibility to adjust for confounding factors. The most commonly used methods are Cox proportional hazards models and Fine and Gray models. In order to understand the difference between these two models, we first have to introduce the concept of the hazard function. Roughly speaking, hazard functions are event rates that vary over time. An intuitive explanation of the hazard can be given in the situation when time is discrete. In this instance, the hazard at a certain time is the probability to die at that time point in those patients who are still alive.[2] In absence of competing risk, there is a 1:1 mathematical relation between the hazard function and the survival function.

Cox Proportional Hazards Model

The Cox proportional hazards model assesses the effects of variables on the hazard function. In the Cox proportional hazards model, hazard functions for different values of the prognostic variable are assumed to be proportional over time, and the parameters of the models can be interpreted as hazard ratios (HRs). In absence of competing risk, a hazard ratio above 1 implies smaller survival probabilities for the exposed group compared with the unexposed group.

In a similar way, cause-specific hazard functions can be defined. Cause-specific hazards are similar to cause-specific mortality rates over small time periods. Effects of prognostic factors on cause-specific hazards can be assessed using the Cox proportional hazards model, where subjects who die of other causes are censored. However, a hazard ratio above 1 no longer implies that subjects with the risk factor are truly more likely to experience the specific event because subjects can die of other causes before they are able to reach this event. If the hazards for dying from other causes are much larger and the prognostic factor also affects these hazards, it could happen that actually fewer people reach the cause of interest. For example, smoking increases the hazard to develop dementia, but only few smokers will actually develop dementia because of the competing effects of death because of cancer or cardiovascular diseases. As a result, it could happen that actually fewer smokers than nonsmokers will experience dementia (ie, the cumulative incidence of dementia is lower in the smoking group), even though the cause-specific hazard ratio for the effect of smoking on dementia may actually be larger than 1. Assuming that there is a biological relation between smoking and dementia, this relation can be found by the Cox regression model (ie, the HR is higher than 1 for smokers) while the cumulative incidence of dementia is in fact lower in smokers because of competing causes of death.

Fine and Gray Model

The Fine and Gray model[9] links the effect of risk factors directly to the cause-specific cumulative incidences of death. In our smoking/dementia example, the Fine and Gray model considers the direct effect of smoking on the cumulative incidence of dementia (which was lower for smokers because of the competing risks). The effects of risk factors are expressed in subdistribution hazard ratios (SHR), where the subdistribution hazard function has a 1:1 relation with the cause-specific cumulative distribution function. An intuitive interpretation of this SHR is difficult, but readers should be reminded that an SHR above 1 corresponds to higher cause-specific event probabilities. In our dementia example, the Fine and Gray model will yield an SHR below 1 as it directly models the cumulative incidence of developing dementia in both subgroups, resulting in a lower risk of dementia for smokers. For a more detailed theoretical background of these models, we refer to Putter et al.[3]

CLINICAL EXAMPLES

For the examples in this Commentary, we used data from the population-based Female breast cancer in the elderly; Optimizing Clinical guidelines USing clinico-pathological & molecular data (FOCUS) cohort. This cohort comprises all incident breast cancer patients age 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 (n = 3672). Trained personnel reviewed the charts of these patients and collected information on specific treatments, comorbidity according to the ICD-10 classification[10], adverse events, recurrences, and geriatric parameters including polypharmacy, difficulties walking, poor vision and hearing, and living in a nursing home.[11]

For the examples that are used below, only patients with nonmetastatic invasive breast cancer who received primary surgery were included. The endpoint of interest was breast cancer recurrence, defined as any local recurrence (skin or in-breast), regional recurrence (axillary or supraclavicular lymph nodes), or distant metastasis. The competing event was defined as death because of any cause without breast cancer recurrence. Censoring only occurred because of end of follow-up or emigration, the latter being very rare in our cohort.

Overall, 2805 patients were included in the analyses. Patient and tumor characteristics are briefly described in Table 1. Median follow-up time was 5.6 years, ranging from 0 to 14.2 years. Overall, 478 (17%) developed a breast cancer recurrence. The prevalence of competing events (death without recurrence) was 36%

(n = 1015). The risk of competing events increased with age, from 19% in patients younger than age 75 years to 54% in patients age 75 years or older.

Table 1. Patient and tumor charachteristic of patients in the FOCUS cohort

Characteristics	N (%)
Age, y	
65-74	1425 (50.8)
≥75	1380 (49.2)
Stage	
I	1058 (37.7)
II	1430 (51.0)
III	317 (11.3)
Grade	
1	385 (13.7)
2	906 (32.3)
3	670 (23.9)
Missing	844 (30.1)
Morphology	
Ductal	2074 (73.9)
Lobular	328 (11.7)
Mixed/other	403 (14.4)
Number of comorbid diseases	
0	694 (24.7)
1	656 (23.4)
2 or more	1455 (51.9)
Total	2805 (100)

Example 1: Psychiatric Disorders in Association With Breast Cancer Recurrence

Recently, we assessed the association between concomitant disease and breast cancer recurrence[11] as it has been suggested that concomitant diseases can interact with tumor growth and treatment.[12] Hence, the research question that we aimed to study was of an etiological nature. One of the concomitant diseases that we assessed was psychiatric disorders, defined according to the ICD10-classification.[10] We will now discuss several models that can be used to study the association between psychiatric disease and breast cancer recurrence. For simplicity, we will present univariate analyses only.

Overall, 256 patients in the FOCUS cohort had a psychiatric disorder. Of all patients with a psychiatric disorder, 29 (11%) developed a breast cancer recur-

rence during follow-up. Among the 2549 patients without psychiatric disorders, 449 (18%) developed a recurrence. Among patients with psychiatric disorders, 150 (59%) competing events occurred, as compared with 865 (34%) among patients without psychiatric disorders.

First, we assessed the association of psychiatric disease with breast cancer recurrence using the Kaplan-Meier method. The 10-year cumulative incidence of breast cancer recurrence as calculated by the Kaplan-Meier method in patients without a psychiatric disorder was 24%, compared with 18% among patients with a psychiatric disorder (Table 2). Second, we used the CICR method to assess cumulative incidence of recurrence, which resulted in a 10-year cumulative incidence of recurrence of 20% and 12%, respectively, for patients without and with a psychiatric disorder. This shows that the Kaplan-Meier method overestimates the cumulative incidences.

As shown in Table 2, the hazard ratio for having a recurrence for patients with a psychiatric disorder was 0.78 (95% confidence interval [CI] = 0.53 to 1.13) compared with patients without a psychiatric disorder, calculated by unadjusted Cox regression analysis. This implies that there is no statistical difference in the hazard on recurrences between patients with and without psychiatric disorders. The hazards were proportional over time (tested using Schoenfeld residuals, $P = .27$). Patients with a psychiatric disorder had a higher probability to die of any cause (HR = 1.6, 95% CI = 1.4 to 1.8, $P < .001$, compared with patients without psychiatric diseases). In Fine and Gray regression analysis, the SHR was 0.61 (95% CI = 0.42 to 0.90) for patients with a psychiatric disorder, as compared with patients without psychiatric disorders. This implies that the probability of recurrence was estimated to be lower for patients with psychiatric disease when the Fine and Gray model was used compared with the Cox Regression Model. In this example, the Fine and Gray model, in contrast with the Cox model, even yielded a statistically significant result.

Table 2. 10-year cumulative incidence of recurrence for patients with and without psychiatric disorders

			Cox regression		Fine and Gray Competing risks regression	
Psychiatric disorder	KM	CICR	HR (95% CI)	*P*	SHR (95% CI)	*P*
No	24%	20%	1 (referent)		1 (referent)	
Yes	18%	12%	0.78 (0.53 -1.13)	0.188	0.61 (0.42-0.90)	0.012

*CI = confidence interval; CICR = cumulative incidence competing risks; HR = Hazard ratio; KM = Kaplan Meier; SHR = subdistribution hazard ratio

Example 2: Prediction of Breast Cancer Recurrence in Older Patients

Currently, interest is in the prediction of the risk of breast cancer recurrence and breast cancer mortality in order to estimate which patients are at high risk and should receive additional treatments. Most currently available models were developed in generally young populations and were not validated in older populations.[13] We recently showed that the online Adjuvant! program, which is widely implemented in daily clinical practice, does not accurately predict breast cancer recurrence in older patients.[13] Therefore, one of the aims of the FOCUS study was to develop a new prediction tool that can be used to estimate breast cancer recurrence in older patients. Hence, for this study, we were interested in predictors of breast cancer recurrence and in calculating the absolute risk of recurrence.

Ten-year cumulative incidences of recurrence and competing events, calculated by the Kaplan-Meier method and the CICR function, are presented in Figure 1, A and B, respectively. As shown in Figure 1A, towards the end of follow-up the probability of dying without breast cancer recurrence and the cumulative incidence of recurrence as calculated by the Kaplan-Meier method added up to an estimate higher than the cumulative incidence of death or recurrence combined. In contrast, the sum of the estimates of mortality and recurrence was equal to the cumulative incidence of death or recurrence combined when the CICR method was used (Figure 1B). Clearly, the Kaplan-Meier method overestimated the cumulative incidence of recurrence and the cumulative incidence of competing events.

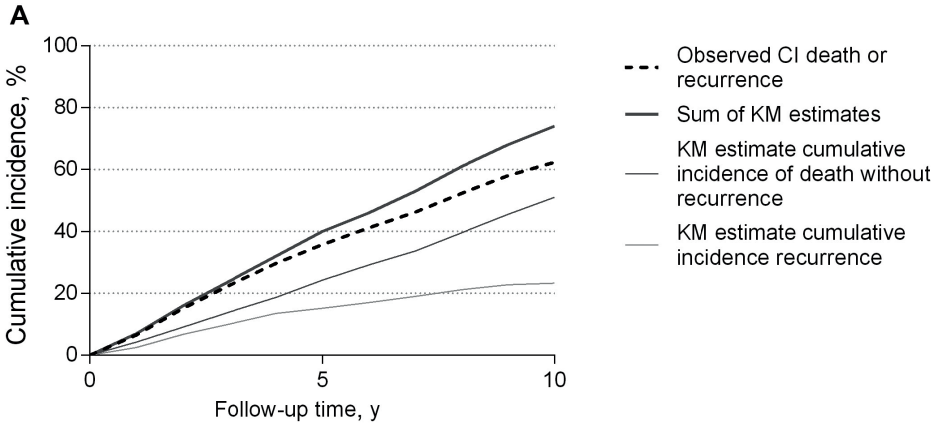

Figure 1a. Cumulative incidences based on Kaplan-Meier estimates

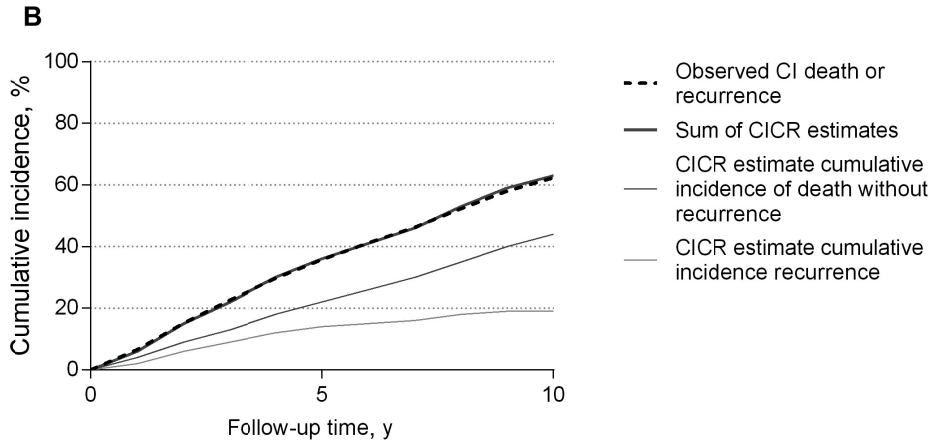

Figure 1b. Cumulative incidences based on cumulative incidence competing risk estimates.

In a recent review, it was shown that both tumor size and nodal status are the most incorporated variables in prediction models for breast cancer prognosis.[13] Therefore, for this example we assessed the predictive value of tumor stage according to the Tumor-Node-Metastasis (TNM) classification.[15] In order to further demonstrate the impact of competing events, we stratified patients into two age groups: younger than age 75 years and age 75 years or older (Table 3). In both age groups, tumor stage was predictive for breast cancer recurrence, as can be expected. However, in patients younger than age 75 years, the prevalence of competing events was 19% during follow-up, which is much lower than in patients age 75 years or older, of whom 54% of all patients died without a recurrence. Among patients younger than age 75 years, the lower incidence of competing events, as compared with patients age 75 years or older, resulted in relatively small differences in outcomes between the Kaplan-Meier method and the CICR method, while in the patients age 75 years or older the Kaplan-Meier method more strongly overestimated the risk of recurrence. Cox Regression analyses resulted in a strongly increased risk of recurrence with increasing tumor stage (HR = 5.42, 95% CI = 4.08 to 7.21 for stage III vs stage I) (Table 3). Although the difference between the tumor stages remained statistically significant in the Fine and Gray analysis, the Fine and Gray analysis attenuated the effect estimates. For predictive research, we are interested in the direct effect on the cumulative incidence, and therefore Fine and Gray analyses provide more valid effect estimates. As shown in Table 3, the differences between estimates that are calculated in Cox Regression analyses and Fine and Gray analyses become larger when the frequency of competing events increases.

Table 3. 10-year cumulative incidence of recurrence by stage

Stage	KM	CICR	HR* (95% CI)	SHR† (95% CI)
Overall				
Stage I	12%	10%	1 (referent)	1 (referent)
Stage II	28%	22%	2.72 (2.15-3.44)	2.43 (1.93-3.07)
Stage III	45%	33%	5.42 (4.08-7.21)	4.10 (3.08-5.46)
Patients age <75 y				
Stage I	12%	11%	1 (referent)	1 (referent)
Stage II	27%	24%	2.68 (1.98-3.63)	2.59 (1.91-3.50)
Stage III	55%	46%	6.62 (4.51-9.72)	5.72 (3.89-8.41)
Patients age ≥ 75 y				
Stage I	12%	9%	1 (referent)	1 (referent)
Stage II	29%	20%	2.56 (1.75-3.75)	2.32 (1.59-3.40)
Stage III	35%	26%	4.31 (2.77-6.71)	3.35 (2.15-5.23)

*Derived from univariate Cox regression analysis. †Derived from Fine and Gray analyses. CI = confidence interval; CICR = cumulative incidence competing risks; HR = hazard ratio; KM = Kaplan Meier; SHR = subdistribution hazard ratio.

DISCUSSION

Our results show that in populations with a high frequency of competing events, it is important to consider which methods are the most appropriate to deal with cause-specific endpoints. The Kaplan-Meier method should never be used to estimate cause-specific survival curves because it overestimates the absolute risk of the event of interest. The CICR method appropriately deals with competing risks. When assessing relative effect sizes in etiologic research, the Cox proportional hazards model is most appropriate. In contrast, to estimate effects on the absolute risk in predictive research, the Fine & Gray Model should be used in populations with a high frequency of competing events.

The main strength of this Commentary is that the examples were performed using a real cohort of patients with a high prevalence of competing risk. By presenting the results of several methods in different research questions, we were able to demonstrate the effects of the choice of a certain method in different settings. Of course, this study also has its limitations. First, it must be noted that the recurrence rate that was registered in the cohort may have been underestimated as older patients may be less adherent to follow-up schemes. This may have influenced our analyses, especially if there was selective nonadherence to follow-up schemes. In addition, 10-year follow-up for recurrence was not complete for the whole cohort, but this mostly applied to the most recent years of the cohort, and it is unlikely that

this has influenced our results as it has been shown that outcome of older patients has not changed in recent years.[16]

With the results of our current study, we want to highlight the difference between etiological and predictive research questions in the comparison between the Cox proportional hazards model and the Fine and Gray model. In Example 1, the Fine and Gray model yielded rather strange results from an etiologic point of view as it suggests that psychiatric disorders are protective for recurrence. It is very unlikely that there is some biological mechanism in which psychiatric disorders are protective for breast cancer recurrence. More likely, our finding can be explained by the fact that the Fine and Gray analysis incorporates the competing risk of death, which influences the cumulative incidences of recurrence. This makes sense because patients with psychiatric disorders (especially dementia) have an increased risk of dying compared with patients without psychiatric disorders and patients who have died cannot get a breast cancer recurrence anymore. In contrast, the Cox regression model considers the effect on the cause-specific hazards, ie, on the instantaneous risk of recurrence for patients who are still at risk for the event at a certain time point, which is what interested us in this research question.

Therefore, in etiologic research questions, the Cox regression model is often the most appropriate method. In contrast, for predictive studies, methods that incorporate competing events such as Fine and Gray competing risk regression are more appealing because they provide a single summary value for the association between a risk variable and the cumulative cause-specific risk. In this case, it is important to consider that patients with a large risk of experiencing a competing event are unlikely to develop a breast cancer recurrence. Note that in this Commentary we focused on the choice of the appropriate measures for the effect of risk factors on breast cancer recurrence. Estimates of absolute mortality probabilities for specific causes as functions of risk variables can be obtained from either of the two models. For the Cox model approach, this implies estimating the causespecific hazard ratios and using the Aalen-Johansen estimator to get the cumulative incidences, a direct extension of the CICR method, which can be carried out in, for example, the R packages mstate and survival[3,17,18]. A major advantage of this Cox model approach is that it ensures that the sum of the cause-specific cumulative incidence equals the total cumulative incidence of experiencing any of the endpoints. This is not guaranteed when calculating cumulative incidences using Fine and Gray models. Another statistical argument in favor of modeling the cause-specific hazards using Cox models is that the proportional hazard assumption is often not unreasonable and can straightforwardly be checked. The proportional sub distribution hazard assumption in the Fine and Gray model is unlikely to hold over longer time periods. Moreover, the proportional subdistribution hazard assumptions of the Fine

and Gray model will generally not hold for each of the different endpoints, and using Fine and Gray models to calculate absolute mortality probabilities could therefore yield impossible results .[19,20] Hence, the Fine and Gray model does have some major limitations that should be taken into account.

These issues that we highlight are especially important for studies in older patients with indolent cancer types such as prostate cancer or hormone receptor–positive breast cancer as the risk of competing mortality is generally large in these studies, especially in studies that require a long period of follow-up (eg, adjuvant studies). In addition, the issue of competing mortality should be considered in other populations with a large frequency of competing events as well, such as populations with many concomitant diseases or a limited performance status, even if these are not limited to older patients. In contrast, the issue of competing mortality does not play a major role in studies that investigate older populations with highly aggressive tumors such as pancreas cancer or lung cancer as the risk of dying from the cancer itself is high in these populations, such that cancer-specific mortality will be almost similar to overall survival. This also applies to studies in the metastatic setting as patients with metastatic disease have a large risk of dying from cancer and follow-up is generally short.

In conclusion, in studies with cause-specific endpoints in populations with a high frequency of competing events, researchers should carefully choose the most appropriate statistical method in order to prevent incorrect interpretation of study results.

REFERENCES

1. de Glas NA, Hamaker ME, Kiderlen M, et al. Choosing relevant endpoints for older breast cancer patients in clinical trials: an overview of all current clinical trials on breast cancer treatment. Breast Cancer Res Treat. 2014;146(3):591–597.
2. Andersen PK, Geskus RB, de WT, Putter H. Competing risks in epidemiology: possibilities and pitfalls. Int J Epidemiol. 2012;41:861–870.
3. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007;26:2389–2430.
4. Berry SD, Ngo L, Samelson EJ, Kiel DP. Competing risk of death: an important consideration in studies of older adults. J Am Geriatr Soc. 2010;58:783–787.
5. Pallis AG, Ring A, Fortpied C, et al. EORTC workshop on clinical trial methodology in older individuals with a diagnosis of solid tumors. Ann Oncol. 2011;22:1922–1926.
6. van de Water W, Markopoulos C, van de Velde CJ, et al. Association between age at diagnosis and disease-specific mortality among postmenopausal women with hormone receptor-positive breast cancer. JAMA. 2012;307(6):579–597.
7. Bland JM, Altman DG. Survival probabilities (the Kaplan-Meier method). BMJ. 1998;317:1572.
8. Verduijn M, Grootendorst DC, Dekker FW, Jager KJ, le Cessie S. The analysis of competing events like cause-specific mortality--beware of the Kaplan-Meier method. Nephrol Dial Transplant. 2011;26:56–61.
9. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94:496–509.
10. World Health Organisation. The ICD-10 Classification of Mental and Behavioural Disorders. 1992;10(5):1–267.
11. Kiderlen M, de Glas NA, Bastiaannet E, et al. Impact of comorbidity on outcome of older breast cancer patients: a FOCUS cohort study. Breast Cancer Res Treat. 2014;145(1):185–192.
12. Patnaik JL, Byers T, Diguiseppi C, Denberg TD, Dabelea D. The influence of comorbidities on overall survival among older women diagnosed with breast cancer. J Natl Cancer Inst. 2011;103:1101–1111.
13. Engelhardt EG, Garvelink MM, de Haes JH, et al. Predicting and Communicating the Risk of Recurrence and Death in Women With Early-Stage Breast Cancer: A Systematic Review of Risk Prediction Models. J Clin Oncol. 2014;32:238–250.
14. de Glas NA, van de Water W, Engelhardt EG, et al. Validity of Adjuvant! Online program in older patients with breast cancer: a population-based study. Lancet Oncol. 2014;15:722–729.
15. Fleming ID, Cooper JS, Henson DE, et al. AJCC Cancer Staging Manual, fifth edition. 5th ed. Philadelphia, PA: Lippincott-Raven, 1997.
16. de Glas NA, Jonker JM, Bastiaannet E, et al. Impact of omission of surgery on survival of older patients with breast cancer. Br J Surg. 2014;101(11):1397–1404.
17. de Wreede LC, Fiocco M, Putter H. The mstate package for estimation and prediction in non- and semi-parametric multi-state and competing risks models. Comput Methods Programs Biomed. 2010;99:261–274.
18. Therneau. A Package for Survival analysis in R version 2.38; 2015.
19. Grambauer N, Schumacher M, Beyersmann J. Proportional subdistribution hazards modeling offers a summary analysis, even if misspecified. Stat Med. 2010;29:875–884.

20. Beyersmann J, Allignol A, Schumacher M. Competing Risks and Multistate Models with R. Springer Science+Business Media, LLC; 2012

Chapter 10

Summary and general discussion

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Eur J Surg Oncol. 2017 May;43(5):944-948

This thesis has three main conclusions:

1. There are large international differences in the treatment strategy of breast cancer among older women. These differences are not associated with a significant difference in prognosis.
2. The presence of comorbidity has an important impact on the general prognosis of older women with breast cancer. We did not show an important association between specific comorbidities or the use of co-medications and the breast cancer specific prognosis.
3. Concerning older women with breast cancer for research, there are very important methodological issues to take into account, including to avoidance of selection bias and the proper methodologies to take in to account the chance of dying from another cause of cancer: the competing risk of mortality.

THE FOCUS STUDY

A large part of this thesis is established using data from the FOCUS study. With the aim to develop guidelines for the treatment of older women with breast cancer, the FOCUS study was initiated in 2007: "Female breast cancer in the elderly: Optimizing Clinical guidelines USing clinico-pathological and molecular data". The FOCUS database is the largest, most detailed population-based database of older women with breast cancer. Worldwide, no other database of this size included only older women, and gathered this detailed data about the patients, tumour characteristics, treatment and follow up. In addition to clinical data, tumour tissues of a very large part of the included patients, was collected. The database consists of 3,672 consecutive breast cancer patients, aged 65 years or older at the time of diagnosis, diagnosed between 1997 and 2004 in the South West region of The Netherlands. In addition to the standard data included in the cancer registry, detailed information was gathered on the tumours' treatment and the occurrence of a recurrence during follow-up. Also, patient-related information was registered, including comorbidity and social economic status.

Within the FOCUS project, also large datasets from (national) cancer registries were shared for research projects. In addition, data from the TEAM trial were used. The Tamoxifen Exemestane Adjuvant Multinational was a large multicentre phase III trial on endocrine therapy. This is one of the few trials without an upper age limit, which results in a relative large number of older participants.

TREATMENT OF OLDER WOMEN WITH BREAST CANCER

The FOCUS study group has been conducting a number of studies in the available observational data and the relevant literature was reviewed. Important to note is that, due to the observational nature of the data that were used, it was impossible to directly link the observed treatment strategies in our cohorts to survival outcomes. This is due to the likelihood of introducing bias due to confounding by indication. In observational studies, treatment allocation is not controlled. Therefore, there can be several other factors related to treatment allocation, which interfere with the prognosis of a patient. This is one of the most important reasons why observational data should be interpreted with caution, especially when the intention of the study is to answer a prognostic question. One of the suggested methodologies to study treatment effects in observational studies, is using an Instrumental Variable.[1] This is a variable that is not directly related to the outcome, but which is related to the 'determinant'. In this thesis, two studies are included using country as an instrumental variable.

In **Chapter 2**, a large population-based study is discussed, using data from cancer registries from five European countries and the US (SEER database). In this study, local treatment as provided to older women with early breast cancer was compared between the countries. Large international differences were observed in the provision of *any* surgery, the type of surgery (breast conserving or mastectomy) and radiotherapy after breast conserving surgery. Despite these large differences, a rough comparison of survival data, showed no large international differences in survival. **Chapter 3** describes a follow-up study, in which all treatment modalities were assessed and compared between older women with breast cancer treated in Ireland and The Netherlands. This study also showed very large differences, in which the reluctance in local therapy seems to be compensated by providing more systemic (endocrine) therapy. Again, in this study, large treatment differences did not affect the outcome of the patients. These studies, in which treatment strategies are compared between countries, will be followed up by larger studies from the EURECCA group (EUropean REgistry of Cancer Care). In our opinion, these large population-based studies can provide us with a lot of knowledge. Especially for older patients, as stated before, there is a large gap in the literature, resulting in a lack of evidence for treatment. Probably, the answer to the questions that are still open for the treatment of older patients will not only come from randomized clinical trials, but also from observational studies, using proper methodology.

In **Chapter 4,** guideline adherence was shown to decline with increasing age at an international level. For this study, EUSOMA (European Society of Breast cancer specialists) provided their database, comprising data from 27 breast cancer units

across Europe associated to the society. In this study, the objective was to assess compliance to quality indicators, as defined by EUSOMA. The EUSOMA database consisted of 41.871 breast cancer patients across Europe. It was shown that among the oldest patients, aged 75 years and older, compliance to the indicators was significantly lowest, as compared to the younger age groups, with a tendency to *under* treatment. Interestingly, patients from the youngest age category (<40 years), were also observed to have a low compliance to the quality indicators. However, in this age group, there was an intention to *over* treatment.

COMORBIDITY AND CO-MEDICATIONS

An important early finding from the FOCUS studies is that cancer-specific prognosis of women with breast cancer declines with age, independent of tumour and treatment characteristics. This was studied both in the national cancer registry, as well as in the FOCUS cohort and the TEAM trial.[2-5] One of the possible explanations of the worse prognosis of older women with breast cancer is the impact of other diseases on prognosis, or the interaction of other diseases with breast cancer treatment. Therefore, in **Chapter 5** of this thesis, the FOCUS database was used to study if the existence of comorbidity during diagnosis was associated with the breast cancer specific prognosis. It was demonstrated that the number of comorbidities, but also a number of specific diseases by itself were associated with a higher overall mortality, which we considered as an expected result. More interestingly, it was found that more comorbidity was associated with a higher recurrence risk among younger elderly (<75 years), but with a *lower* recurrence risk among the oldest elderly (75 years and older). Also, the co-existence of psychiatric comorbidity (mostly reflecting dementia), was associated with a lower recurrence risk. New insights, which are discussed in **Chapter 9**, suggest this is the case of *competing mortality*: these women probably died from another cause than cancer, before experiencing a breast cancer recurrence. In **Chapter 6**, the association of the coexistence of diabetes during diagnosis and breast cancer prognosis among elderly was studied. In this study, a trend towards a more favourable cancer prognosis for diabetic women was observed, which was also most pronounced in the oldest patients. These findings are not thoroughly understood yet, but may **also** be explained by competing mortality: patients with more or severe comorbidity are at higher risk to die from another reason, before they can develop a cancer recurrence. Another possible explanation for the finding that breast cancer patients, with co-existing diabetes at the time of diagnosis, had a more favourable prognosis is the potential anti-cancer effect of metformin.[6] This hypothesis has been studied

in several observational studies; a clinical trial has also been designed to assess the association between the use of metformin and prognosis of breast cancer[7]. Results of this trial are not to be expected before 2023.

In **Chapter 7**, we present an observational study investigating the association of three different co-medications (including metformin, statins and beta blockers) and breast cancer specific prognosis. These analyses in postmenopausal hormone receptor positive early breast cancer patients, enrolled in the TEAM study, found less distant metastases in metformin, statin or beta blocker users, although not statistically significant. However, a statistically significant association between the use of statins and beta blockers and an improved breast cancer specific survival were demonstrated. These analyses are specifically important for the older patients. Conventional systemic adjuvant therapies, have shown to be associated with more adverse events and toxicity with increasing age. However, in our analyses no differences were observed between age groups, indicating that these drugs cannot serve as a specific new treatment option for breast cancer, neither in the elderly.

PROGNOSIS

One of the problems to face in the lack of evidence for treatment for older women with breast cancer, is the underrepresentation of elderly in clinical cancer trials.[8,9] Furthermore, in **Chapter 8,** we describe a study showing that older patients who are included in a large breast cancer trial, are not representative for the patients in de general population. In this study, patients from the population-based FOCUS cohort, who met the inclusion criteria for the TEAM study, were compared with the participants from the TEAM study aged 65 years and older. This study showed first, regarding patient characteristics, that women included in the trial had fewer comorbid diseases and a higher socioeconomic status. Moreover, although the same inclusion criteria were applied, tumours from women in the trial appeared to be smaller. Finally, the oldest patients (≥75 years) who participated in the trial, had a lower overall mortality than women from the population based cohort. The results of this study show that results from a clinical trial, can often not be extrapolated to the general population. The question is, if the current lack of evidence on the treatment of breast cancer among older women, can be filled with clinical trial results. Therefore, we suggest to use more observational study designs to fill the gap. Using the appropriate study designs, data obtained from observational studies can be of equivalent value as clinical trial results.[1] Probably, considering the older patients and their heterogeneity, which is an almost unsolvable issue in clinical trials, observational studies can be even more valuable.

In **Chapter 9**, we address one important issue to take into account using observational studies for prognostic research. In geriatric oncology, there are more goals to achieve than curing cancer, for instance, to preserve functional capabilities. Moreover, in older patients, the risk of competing mortality, i.e. dying of another cause than breast cancer, is a very important matter to take into account. The competing risk of mortality should be taken into account when making a treatment plan, but also in research. In this chapter, we show with an example study, using data from the FOCUS cohort, that not using the appropriate model in risk prediction in a population with a high risk on competing mortality, can result in an overestimation of the real risk on cancer-specific events. Therefore, when predicting the prognosis in a population with a high risk of competing mortality, we advise to use specific models taking into account this risk of competing mortality, to make a more adequate estimation of the risk of interest. This risk of competing mortality should also be taken into account when making decisions about treatment. In clinical practice, this is a process taking place in the physician's room, or in the multidisciplinary team, when the treatment plan is being discussed. Currently, physicians are forced to determine this risk by their 'gut feeling', to decide how aggressive or reluctant the patient sitting in front of them will be treated.

FUTURE PERSPECTIVES

Recently it was shown, that the most frequently used and recommended tool, 'Adjuvant! Online' is not able to accurately predict the prognosis of breast cancer patients aged 65 years or older. Using data from the FOCUS cohort, the actual prognosis was compared with the predicted prognosis by Adjuvant! Online. Using the tool, overall survival appeared to be *over*-estimated by 9.8%. This overestimation was even larger in patients aged 75-79 and 80-84, compared to younger elderly. Also, the degree of overestimation increased with increasing numbers of comorbidities. These findings can probably be explained by the fact that the Adjuvant! Online model is created using a cohort from which elderly patients were excluded: there was an upper age limit of 69 years.[10] Therefore, this study implies that results derived from younger (and obviously healthier) patients, cannot be extrapolated directly to an older population of patients with the same disease.

Another, increasingly used prediction tool is the PREDICT tool. This tool was also subject to a validation study, using the FOCUS data. In this validation study, the PREDICT tool was shown to be more accurate in the prediction of the prognosis of older patients, compared to the previously described Adjuvant! Online tool.[11] The most reasonable explanation for the more accurate prediction is that de PREDICT

tool was designed in a cohort including a relatively large number of older women. Also, PREDICT added two extra markers to the model: HER-2 and Ki-67.

The available tools, have one thing in common: they predict the prognosis in terms of recurrence free survival or overall survival. Currently, the FOCUS study group is working on new studies among older women with breast cancer. In this novel study, a prediction model will be created using the data from the FOCUS cohort. In this model more patient characteristics will be added to the formerly used, conventional predictors. Suggested endpoints are: overall survival, treatment toxicity, quality of life and functional decline.

The studies described in this thesis, along with the other studies performed by the FOCUS study group, have highlighted the urgent need for a new type of investigation to create a tool which might assist in identifying the individualised treatment strategy for older women with breast cancer. This will have to take into consideration patient's *and* the tumour's information as well as the endpoints for each individual patient.

REFERENCES

1. Vandenbroucke JP. When are observational studies as credible as randomised trials? Lancet. 2004;363(9422):1728-1731.
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(3):801-807.
3. 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(1):42-47.
4. van de Water W, Markopoulos C, van de Velde CJ, et al. Association between age at diagnosis and disease-specific mortality among postmenopausal women with hormone receptor-positive breast cancer. JAMA. 2012;307(6):590-597.
5. 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. Oncologist. 2013;18(1):8-13.
6. Jalving M, Gietema JA, Lefrandt JD, et al. Metformin: taking away the candy for cancer? Eur J Cancer. 2010;46(13):2369-2380.
7. Goodwin P. ClinicalTrials.gov - A Phase III Randomized Trial of Metformin vs Placebo in Early Stage Breast Cancer - NCT 01101438. 2013.
8. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Jr., Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med. 1999;341(27):2061-2067.
9. Hurria A, Dale W, Mooney M, et al. Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. J Clin Oncol. 2014;32(24):2587-2594.
10. de Glas NA, van de Water W, Engelhardt EG, et al. Validity of Adjuvant! Online program in older patients with breast cancer: a population-based study. Lancet Oncol. 2014;15(7):722-729.
11. de Glas NA, Bastiaannet E, Engels CC, et al. Validity of the online PREDICT tool in older patients with breast cancer: a population-based study. Br J Cancer. 2016;114(4):395-400.

Appendices

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NEDERLANDSE SAMENVATTING

De drie belangrijkste conclusies van dit proefschrift zijn:

1. Er zijn grote internationale verschillen in de behandelstrategie van oudere vrouwen met borstkanker. Deze verschillen zijn echter niet geassocieerd met een verschil in prognose.
2. De aanwezigheid van comorbiditeit heeft een belangrijke invloed op de algemene prognose van oudere vrouwen met borstkanker. We hebben geen significante associatie aangetoond tussen specifieke comborbiditeiten óf van het gebruik van comedicatie en de borstkanker-specifieke prognose.
3. Bij onderzoek naar oudere vrouwen met borstkanker, zijn er verschillende belangrijke methodologische zaken die in acht zouden moeten worden genomen. Ten eerste het vermijden van selectieve inclusie, wat kan leiden tot "selection bias". Ten tweede moet een adequate methodologie gebruikt worden om de kans om rekening te houden met de kans om te overlijden door een andere oorzaak dan borstkanker: "competing risk of mortality".

DE FOCUS STUDIE

Een groot deel van dit proefschrift is tot stand gekomen met data uit de FOCUS studie: "Female breast cancer in the elderly: Optimizing Clinical guidelines USing clinico-pathological and molecular data". Deze studie werd in 2007 opgezet, met initieel als doel om specifieke richtlijnen te formuleren voor de behandeling van oudere vrouwen met borstkanker. De FOCUS database is de grootste en meest gedetailleerde population-based database van oudere vrouwen met borstkanker. Wereldwijd bestaat er geen andere database van deze grootte die alleen oudere vrouwen met borstkanker bevat, of die zodanig gedetailleerde data verzamelde over de patiënten, tumor karakteristieken, behandeling en follow-up. Bovendien zijn in de FOCUS database de klinische data aangevuld met data van een groot deel van de tumorweefsels van de patiënten, welke ook werden verzameld en geanalyseerd. De database bestaat uit 3672 opeenvolgende vrouwen met borstkanker, met de leeftijd van 65 jaar of ouder ten tijde van de diagnose, gediagnosticeerd tussen 1997 en 2004 in de Zuid-West Nederland (Integraal Kanker Centrum Nederland (IKNL), regio Leiden). In aanvulling op de standaard data uit de kankerregistratie, werd gedetailleerde informatie verzameld over de behandeling en het optreden van een recidief tijdens de follow-up. Bovendien werden patient-gerelateerde variabelen toegevoegd, inclusief comorbiditeit en sociaal economische status.

Binnen het FOCUS project werden ook grote datasets van nationale en internationale kankerregistraties gedeeld voor onderzoeksprojecten. Daarnaast werden data van de Tamoxifen Exemestane Adjuvant Multination (TEAM) trial gebruikt. De TEAM studie was een grote multicentre fase 3 trial naar endocriene therapie bij postmenopauzale vrouwen met borstkanker. Dit is één van de weinige borstkanker trials zonder een leeftijdsgrens. Dit resulteert in een relatief groot aantal oudere deelnemers.

BEHANDELING VAN OUDERE VROUWEN MET BORSTKANKER

De FOCUS studiegroep heeft een aantal ruim aantal studies verricht met beschikbare observationele data en waar nodig werd de relevante literatuur gereviewd. Belangrijk om op te merken is dat door de observationele aard van de data die werden gebruikt, het onmogelijk was om causale verbanden te leggen tussen de geobserveerde behandelstrategieën in de cohorten en de uitkomsten in termen van overleving. Dit komt door de grote kans op het introduceren van een bias door 'confounding by indication'. In observationele studies is de toewijzing van behandeling ongecontroleerd (anders dan in gerandomiseerd onderzoek). Daarom kunnen er verschillende factoren aanwezig zijn die gerelateerd zijn aan de toewijzing van een bepaalde behandeling, die interfereren met de prognose van de patiënt. Dit is een van de belangrijkste redenen waarom de uitkomsten van observationele studies voorzichtig moeten worden geïnterpreteerd, in het bijzonder als er sprake is van een prognostische vraagstelling. Eén van de gesuggereerde methodologieën om te gebruiken wanneer men het effect van een behandeling wil onderzoeken in observationele data, is een 'Instrumentele Variabele'.[1] Dit is een variabele die niet direct gerelateerd is aan de uitkomst, maar welke wel gerelateerd is aan de 'determinant' van interesse. In dit proefschrift zijn twee studies opgenomen die een land als instrumentele variabele gebruiken.

In **Hoofstuk 2** is een grote observationele, "population-based" studie beschreven. In deze studie werd gebruik gemaakt van data van kankerregistraties uit vijf verschillende Europese landen en de Verenigde Staten (SEER database). Dit onderzoek vergelijkt lokale behandeling van borstkanker bij oudere vrouwen tussen de landen. Er werden grote internationale verschillen geobserveerd, met name in het wel of niet toepassen van chirurgie, maar ook in het type chirurgie (borstsparend of ablatief), en radiotherapie na borstsparende chirurgie. Ondanks deze grote verschillen in behandeling, leverde een grove vergelijking van overlevingsdata geen grote internationale verschillen in overleving op.

Hoofdstuk 3 beschrijft een vervolgstudie, waarin alle modaliteiten van de behandeling werden beschreven en vergeleken tussen oudere vrouwen met borstkanker in Ierland en Nederland. Deze studie liet eveneens grote internationale verschillen zien, waarbij terughoudendheid op het gebied van lokale therapie werd gecompenseerd door meer systemische (endocriene) therapie. Ook in deze studie leken grote verschillen in behandelstrategie geen effect op de overleving van de patiënten te hebben.

Bovengenoemde studies, waarin behandelstrategieën internationaal werden vergeleken, zullen worden opgevolgd door grotere studies door de EURECCA groep (EUropean REgistry of Cancer CAre). Deze grote observationele, 'population-based' studies kunnen volgens ons een grote hoeveelheid aan kennis verschaffen. In het bijzonder voor oudere patiënten met kanker is er een grote lacune in de literatuur, wat resulteert in een gebrek aan bewijs, 'evidence', voor behandeling. Meest waarschijnlijk zullen de antwoorden van openstaande vraagstukken voor oudere vrouwen met borstkanker niet komen vanuit gerandomiseerd onderzoek, maar mogelijk wel uit observationele onderzoeken, gebruik makend van de juiste methodologie.

In **Hoofdstuk 4** wordt aangetoond dat onder Europese vrouwen met borstkanker, het naleven van behandelrichtlijnen afneemt met het toenemen van de leeftijd. Voor deze studie heeft The European Society of Breast cancer specialists (EUSOMA) hun database gedeeld. Deze database bestond uit data uit 27 'breast cancer units' verspreid door Europa, welke gelieerd zijn aan de society. Het doel van deze studie was het evalueren van het naleven van kwaliteitsindicatoren, die gedefinieerd zijn door EUSOMA. De EUSOMA database bevatte data van 41.871 vrouwen met borstkanker in Europa. Aangetoond werd dat bij de oudste patiënten, 75 jaar en ouder, naleving van de indicatoren proportioneel het laagst was. Er werd onder de oudste patiënten een neiging tot *onder*-behandeling geobserveerd. Interessant genoeg, werd ook aangetoond dat in de jongste patiënten categorie, jonger dan 40 jaar, een lage proportie aan naleving van de indicatoren werd geobserveerd. In deze leeftijdscategorie was echter sprake van een neiging tot *over*-behandeling.

COMORBIDITEIT EN COMEDICATIE

Een belangrijke bevinding uit een van de eerste FOCUS studies is dat de kankerspecifieke prognose van vrouwen met borstkanker afneemt met toenemende leeftijd, onafhankelijk van tumorkarakteristieken en behandeling. Dit is onderzocht in zowel de nationale kankerregistratie, als in het FOCUS cohort en de TEAM trial.[2-5] Eén van de mogelijke verklaringen voor de slechtere prognose van oudere

vrouwen met borstkanker is de invloed van ander ziekten op de prognose, óf de interactie van andere ziekten (comorbiditeit) met de behandeling van borstkanker. Daarom werd in **Hoofdstuk 5** van dit proefschrift in het FOCUS cohort onderzocht of de aanwezigheid van comorbiditeit ten tijde van de diagnose, geassocieerd was met de borstkankerspecifieke prognose. Aangetoond werd dat het aantal comorbiditeiten, maar ook een aantal specifieke ziekten waren geassocieerd met de borstkankerspecifieke prognose. Dit resultaat werd beschouwd als een verwachte uitkomst. Een interessanter bevinding was dat meer comorbiditeit geassocieerd was met een hogere kans op een recidief onder jongere ouderen (<75 jaar), maar met een *lagere* kans op een recidief onder de oudste ouderen (75 jaar en ouder). Bovendien was de aanwezigheid van een psychiatrische ziekte (waarschijnlijk dementie) geassocieerd met een *lager*e kans op een recidief. Nieuwe inzichten, welke beschreven worden in **Hoofdstuk 9**, suggereren dat dit is een geval van *competing mortality*: deze vrouwen zijn waarschijnlijk overladen door een andere oorzaak dan kanker, voordat zij überhaupt blootgesteld konden worden aan een recidief borstkanker.

In **Hoofstuk 6** werd de associatie tussen de aanwezigheid van diabetes ten tijde van de diagnose en borstkankerspecifieke prognose onderzocht onder oudere vrouwen met borstkanker, eveneens in het FOCUS cohort. In deze studie werd een iets betere kankerspecifieke prognose geobserveerd voor vrouwen met borstkanker mét diabetes, dit was het meest uitgesproken onder de oudste vrouwen. Deze bevindingen worden nog niet volledig begrepen, maar zouden eveneens verklaard kunnen worden door het concept van *competing mortality*: patienten met meer of ernstiger comorbiditeit hebben een hoger risico om te sterven door een andere oorzaak dan kanker, voordat zij een borstkankerrecidief kunnen krijgen. Een andere mogelijke verklaring voor de bevinding dat vrouwen met borstkanker en daarnaast diabetes een betere prognose hadden is het potentiele anti-kanker effect van metformine.[6] Deze hypothese is eerder onderzocht in observationele studies, en ook loopt er een gerandomiseerde trial om de associatie tussen het gebruik van metformine en de borstkankerspecifieke prognose te onderzoeken.[7] De resultaten van deze trial worden niet voor 2023 verwacht.

In **Hoofdstuk 7** wordt een onderzoek beschreven dat kijkt naar de associatie tussen drie verschillende types comedicatie (metformine, statines en bètablokkers) en de borstkankerspecifieke prognose. De analyses werden gedaan in data van de TEAM studie, waar in alleen postmenopauzale vrouwen met hormoonreceptor positieve borstkanker in een vroeg stadium geïncludeerd zijn. De analyses toonden absoluut minder afstandsmetastasen onder gebruiksters van metformine, statines en bètablokkers, echter dit was niet statistisch significant. Er werd wel een statisch

significante associatie gevonden tussen het gebruik van statines en bètablokkers en een betere borstkankerspecifieke overleving. Dit resultaat is wel moeilijk te verklaren gezien het ontbreken van een verband tussen het medicatiegebruik en het optreden van metastasen. Dit onderzoek is belangrijk voor oudere patiënten in het bijzonder. De conventionele systemische adjuvante behandelingen zijn geassocieerd met meer bijwerkingen en toxiciteit bij ouderen. Echter in onze analyses werden geen verschillen geobserveerd tussen leeftijdscategorieën. Deze studie geeft onvoldoende aanleiding om de onderzochte medicamenten in te zetten als een nieuwe behandelingsoptie voor borstkanker, ook niet bij ouderen.

PROGNOSE

Eén van de problemen waarmee men geconfronteerd wordt bij het gebrek aan bewijs (evidence) voor de behandeling van oudere vrouwen met borstkanker, is de *onder-representatie* van ouderen in klinische trials.[8,9] Bovendien, wordt in **Hoofstuk 8** van dit proefschrift een onderzoek beschreven dat aantoont dat oudere patiënten die wel geïncludeerd zijn in een grote borstkanker trial, niet representatief zijn voor de patiënten uit de algemene bevolking. In deze studie werden de patiënten uit het population-based FOCUS cohort, die voldeden aan de inclusiecriteria voor de TEAM studie, vergeleken met de deelneemsters van de TEAM studie, die 65 jaar en ouder waren. Dit onderzoek toonde, bij het vergelijk van patiëntkarakteristieken, dat de vrouwen uit de trial minder comorbiditeit hadden en een hogere sociaal economische status. Verder, ondanks dezelfde inclusiecriteria, waren de tumoren van de vrouwen in de trial toch kleiner dan in het FOCUS cohort. Tot slot werd aangetoond dat de oudste vrouwen uit de trial (75 jaar of ouder) een lagere mortaliteit (dus betere overleving) dan de vrouwen uit het FOCUS cohort. De resultaten van dit onderzoek impliceren dat de resultaten van een klinische trial niet altijd geëxtrapoleerd kunnen worden naar patiënten in de algemene bevolking. De vraag is of het huidige gebrek aan evidence voor de behandeling van borstkanker bij ouderen aangevuld kan worden met data van gerandomiseerde klinische trials. Mits adequate studie methodiek wordt gebruikt, kunnen data uit observationele studies wellicht van gelijkwaardige waarde zijn als resultaten van gerandomiseerd onderzoek.[1] Mogelijk, gezien de heterogeniteit van oudere patiënten, wat een onoplosbaar probleem is in klinische trials, zijn observationele studies misschien zelfs waardevoller in deze populatie.

In **Hoofdstuk 9** wordt een belangrijke kwestie aangehaald waar rekening mee gehouden moet worden bij prognostisch onderzoek met observationele data. Bij onderzoek naar ouderen met kanker zijn er meer doelen te bereiken dan alleen het

genezen van kanker. Een voorbeeld is het behouden van het functioneel vermogen. Bovendien, bij oudere patienten is het risico van het sterven ten gevolge van een andere oorzaak dan borstkanker, "competing mortality", zeer belangrijk om rekening mee te houden. Dit risico zou in acht moeten worden genomen op het moment dat een behandelplan gemaakt wordt, maar ook bij het doen van wetenschappelijk onderzoek. In dit hoofdstuk wordt een voorbeeldstudie beschreven, waarin gebruik gemaakt werd van data uit het FOCUS cohort. Hiermee wordt aangetoond dat gebruik van het *on*juiste model bij het voorspellen van risico's in een populatie met een hoog risico op 'competing mortality', kan resulteren in een overschatting van het echte risico op kanker-specifieke events. Daarom, bij analyses met als doel het voorspellen van de prognose in een populatie met een hoog risico op 'competing mortality', wordt geadviseerd om gebruik te maken van specifieke modellen die rekening houden met dit risico, om zo een adequatere voorspelling te maken van het risico (bijvoorbeeld risico op recidief) waarin men daadwerkelijk geïnteresseerd is.

Het risico op 'competing mortality' zou ook altijd in acht moeten worden genomen bij het maken van beslissingen over behandeling in de kliniek. In de praktijk is dit een proces dat plaatsvindt in de spreekkamer, of in het multidisciplair onverleg, waar het behandelplan wordt besproken. In de huidige situatie wordt van artsen verwacht om dit risico te bepalen op basis van een gevoel, om daarmee te bepalen hoe agressief, of juist terughoudend, de patiënte die voor hen zit behandeld zou moeten worden.

TOEKOMSTPERSPECTIEVEN

Uit recent onderzoek van onze groep blijkt dat het meest gebruikte en aangeraden hulpprogramma in het voorspellen van prognose van vrouwen met borstkanker, 'Adjuvant! Online', niet in staat is om een accurate voorspelling van de prognose te geven van vrouwen met borstkanker die 65 jaar of ouder zijn. Met data uit het FOCUS cohort werd de werkelijke prognose van patienten vergeleken met de prognose zoals voorspeld door het programma 'Adjuvant! Online'. Het programma maakte een overschatting van de algemene overleving van 9.8%. Deze overschatting was zelfs groter onder nog oudere patiënten (75-79 jaar en 80-84 jaar). Daarnaast nam de mate van overschatting ook toe met een toenemend aantal comorbiditeiten. Deze bevindingen kunnen waarschijnlijk worden verklaard door het feit dat 'Adjuvant! Online' is gecreëerd op basis van een cohort waar oudere patiënten warden geëxcludeerd: er was een leeftijdsgrens van maximaal 69 jaar.[10] Deze studie toont aan dat resultaten van studies onder jongere (en waarschijnlijk

gezondere) patiënten, niet zo maar kan worden geëxtrapoleerd naar een populatie van oudere patiënten met dezelfde ziekte.

Een ander hulpprogramma dat de prognose van patienten met borstkanker voorspelt is PREDICT. Dit programma werd eveneens gevalideerd in het FOCUS cohort. Uit deze studie blijkt dat PREDICT beter in staat is om de prognose van oudere patienten te bepalen, in vergelijking met 'Adjuvant! Online'.[11] De meest waarschijnlijke verklaring voor het de meer accurate voorspelling is dat het PREDICT programma ontwikkeld werd in een cohort waar een relatief groot aantal ouderen in zat. Daarnaast heeft PREDICT twee extra markers toegevoegd aan het model: HER-2 en Ki-67.

De nu beschikbare digitale hulpprogramma's hebben één ding gemeen: ze voorspellen de prognose in termen van recidief vrije overleving of overleving. De FOCUS groep is op dit moment bezig met nieuwe studies onder oudere vrouwen met borstkanker. Het doel van deze nieuwe studies is om een predictiemodel te creëren met data van alleen oudere vrouwen (het FOCUS cohort). In dit model worden meer voorspellende factoren onderzocht, met name patiënt-gerelateerde factoren zoals comorbiditeit. Ook zullen andere eindpunten worden onderzocht zoals bijvoorbeeld: toxiciteit van behandeling, kwaliteit van leven en functionele capaciteit.

De onderzoeken zoals beschreven in dit proefschrift, samen met de andere studies die verricht zijn door de FOCUS studiegroep, hebben het belang van een nieuw type onderzoek aangetoond. Dit onderzoek moet een model creëren dat kan helpen om een geïndividualiseerde behandelstrategie voor oudere vrouwen met borstkanker. Dit model zal rekening houden met zowel de patiënt- als de tumorkarakteristieken, maar ook met de eindpunten die belangrijk zijn voor iedere individuele patiënte.

REFERENTIES

1. Vandenbroucke JP. When are observational studies as credible as randomised trials? *Lancet.* 2004;363(9422):1728-1731.
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(3):801-807.
3. 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(1):42-47.
4. van de Water W, Markopoulos C, van de Velde CJ, et al. Association between age at diagnosis and disease-specific mortality among postmenopausal women with hormone receptor-positive breast cancer. *JAMA.* 2012;307(6):590-597.
5. 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. *Oncologist.* 2013;18(1):8-13.
6. Jalving M, Gietema JA, Lefrandt JD, et al. Metformin: taking away the candy for cancer? *Eur J Cancer.* 2010;46(13):2369-2380.
7. Goodwin P. ClinicalTrials.gov - A Phase III Randomized Trial of Metformin vs Placebo in Early Stage Breast Cancer - NCT 01101438. 2013.
8. Hutchins LF, Unger JM, Crowley JJ, Coltman CA, Jr., Albain KS. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med.* 1999;341(27):2061-2067.
9. Hurria A, Dale W, Mooney M, et al. Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. *J Clin Oncol.* 2014;32(24):2587-2594.
10. de Glas NA, van de Water W, Engelhardt EG, et al. Validity of Adjuvant! Online program in older patients with breast cancer: a population-based study. *Lancet Oncol.* 2014;15(7):722-729.
11. de Glas NA, Bastiaannet E, Engels CC, et al. Validity of the online PREDICT tool in older patients with breast cancer: a population-based study. *Br J Cancer.* 2016;114(4):395-400.

LIST OF PUBLICATIONS

Kiderlen M, van de Velde CJ, Liefers GJ. "Targeted therapy in older women with breast cancer – what's the target?". Eur J Surg Oncol. 2017 May;43(5):944-948.

Engels CC, Kiderlen M, Bastiaannet E, Mooyaart AL, van Vlierberghe R, Smit VT, Kuppen PJ, van de Velde CJ, Liefers GJ. The clinical prognostic value of molecular intrinsic tumor subtypes in older breast cancer patients: A FOCUS study analysis. Mol Oncol. 2016 Apr;10(4):594-600

Engels CC, Kiderlen M*, Bastiaannet E, van Eijk R, Mooyaart A, Smit VT, de Craen AJ, Kuppen PJ, Kroep JR, van de Velde CJ, Liefers GJ. The clinical value of HER-2 overexpression and PIK3CA mutations in the older breast cancer population: a FOCUS study analysis. Breast Cancer Res Treat. 2016 ;156(2):361-70.

Derks M, Kiderlen M, de Glas N,Bastiaannet E,van de Velde C,Liefers G,Portielje J Borstkanker bij ouderen: balanceren tussen overbehandeling en onderbehandeling . Nederlands Tijdschrift voor Oncologie, 2016;1:5-14.

de Glas NA, Kiderlen M*, Vandenbroucke JP, de Craen AJ, Portielje JE, van de Velde CJ, Liefers GJ, Bastiaannet E, Le Cessie S. Performing Survival Analyses in the Presence of Competing Risks: A Clinical Example in Older Breast Cancer Patients. J Natl Cancer Inst. 2015 Nov 26;108(5)

Kiderlen M, Ponti A, Tomatis M, Boelens PG, Bastiaannet E, Wilson R, van de Velde CJ, Audisio RA; eusomaDB Working Group. Variations in compliance to quality indicators by age for 41,871 breast cancer patients across Europe: a European Society of Breast Cancer Specialists database analysis. Eur J Cancer. 2015 Jul;51(10):1221-30

Kiderlen M, Walsh PM, Bastiaannet E, Kelly MB, Audisio RA, Boelens PG, Brown C, Dekkers OM, de Craen AJ, van de Velde CJ, Liefers GJ. Treatment strategies and survival of older breast cancer patients - an international comparison between the Netherlands and Ireland. PLoS One. 2015 Feb 3;10(2):e0118074

de Glas NA, Kiderlen M*, de Craen AJ, Hamaker ME, Portielje JE, van de Velde CJ, Liefers GJ, Bastiaannet E. Assessing treatment effects in older breast cancer patients: systematic review of observational research methods. Cancer Treat Rev. 2015 Mar;41(3):254-61

Kiderlen M, van de Water W, Bastiaannet E, de Craen AJ, Westendorp RG, van de Velde CJ, Liefers GJ. Survival and relapse free period of 2926 unselected older breast cancer patients: a FOCUS cohort study. Cancer Epidemiol. 2015 Feb;39(1):42-7. doi: 10.1016/j.canep.2014.11.007

de Glas NA, de Craen AJ, Bastiaannet E, Op 't Land EG, Kiderlen M, van de Water W, Siesling S, Portielje JE, Schuttevaer HM, de Bock GT, van de Velde CJ, Liefers GJ. Effect of implementation of the mass breast cancer screening programme in older women in the Netherlands: population based study. BMJ. 2014 Sep 14;349:g5410

de Glas NA, Hamaker ME, Kiderlen M, de Craen AJ, Mooijaart SP, van de Velde CJ, van Munster BC, Portielje JE, Liefers GJ, Bastiaannet E. Choosing relevant endpoints for older breast cancer patients in clinical trials: an overview of all current clinical trials on breast cancer treatment. Breast Cancer Res Treat. 2014 Aug;146(3):591-7

Kiderlen M, de Glas NA, Bastiaannet E, van de Water W, de Craen AJ, Guicherit OR, Merkus JW, Extermann M, van de Velde CJ, Liefers GJ. Impact of comorbidity on outcome of older breast cancer patients: a FOCUS cohort study. Breast Cancer Res Treat. 2014 May;145(1):185-92

van de Water W, Kiderlen M*, Bastiaannet E, Siesling S, Westendorp RG, van de Velde CJ, Nortier JW, Seynaeve C, de Craen AJ, Liefers GJ. External validity of a trial comprised of elderly patients with hormone receptor-positive breast cancer.J Natl Cancer Inst. 2014 Apr;106(4):dju051

de Glas NA, Kiderlen M, Bastiaannet E, de Craen AJ, Portielje JE, Liefers GJ. Chirurgische complicaties bij ouderen met borstkanker. Ned Tijdschr Geneeskd., 2013;157(38):A6525

van de Water W, Bastiaannet E, Scholten AN, Kiderlen M, de Craen AJ, Westendorp RG, van de Velde CJ, Liefers GJ. Breast-conserving surgery with or without radiotherapy in older breast patients with early stage breast cancer: a systematic review and meta-analysis. Ann Surg Oncol. 2014 Mar;21(3):786-94

Kiderlen M, de Glas NA, Bastiaannet E, Engels CC, van de Water W, de Craen AJ, Portielje JE, van de Velde CJ, Liefers GJ. Diabetes in relation to breast cancer relapse and all-cause mortality in elderly breast cancer patients: a FOCUS study analysis. Ann Oncol. 2013 Dec;24(12):3011-6

de Glas NA, Kiderlen M, Liefers GJ. Survival after lumpectomy and mastectomy for early stage invasive breast cancer: the effect of age and hormone receptor status. Cancer. 2013 Sep 1;119(17):3253-4

de Glas NA, Kiderlen M, Bastiaannet E, de Craen AJ, van de Water W, van de Velde CJ, Liefers GJ. Postoperative complications and survival of elderly breast cancer patients: a FOCUS study analysis. Breast Cancer Res Treat. 2013 Apr;138(2):561-9

Kiderlen M, Bastiaannet E, Walsh PM, Keating NL, Schrodi S, Engel J, van de Water W, Ess SM, van Eycken L, Miranda A, de Munck L, van de Velde CJ, de Craen AJ, Liefers GJ. Surgical treatment of early stage breast cancer in elderly: an international comparison. Breast Cancer Res Treat. 2012 Apr;132(2):675-82

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CURRICULUM VITAE

Mandy Kiderlen was born on January 12th, 1986 in Voorburg, as the oldest child in her family. She grew up with her parents and sister Debby and brother Colin. In 2003 she graduated from the Erasmus College in Zoetermeer.

In 2005 she started medical school at the University of Leiden. During the course of her study she did an scientific internship at the department of surgical oncology of the Leiden University Medical Center under supervision of Esther Bastiaannet and Gerrit-Jan Liefers. She collected data to complete the FOCUS database (Female breast cancer in the elderly; Optimizing Clinical guidelines using clinicopathological and molecular data), and also performed the first analyses on this database. After her clinical rotations, she decided to do a second internship on the department of surgical oncology. She gathered data from older women with breast cancer from six European countries and the US. The analysis of comparing these data led to her first publication at the end of 2011.

After obtaining her medical degree in 2011, she started working at the department of surgery of the Rijnland Hospital in Leiderdorp. In 2012, she started her PhD project at the department of surgical oncology of the Leiden University Medical Center, under supervision of Prof. C.J.H. van de Velde, dr. G.J. Liefers and dr. E. Bastiaannet. This resulted in the current thesis. During her PhD research period she followed a post-master educational program at the department of Clinical Epidemiology, from which she graduates as clinical epidemiologist simultaneously with her PhD defense. In 2013 she was one of the initiators of "Young SIOG", an interest group from the International Society for Geriatric Oncology (SIOG), which has grown to have an important role in the organization. In 2015-2016 she worked at the department of surgery of Medisch Centrum Haaglanden-Bronovo.

During her PhD research period, she received a fellowship grant from the European Society of Surgical Oncology to participate in the ECCO-AACR-EORTC-ESMO workshop 'Methods in Clinical Cancer Research' in Flims, Switzerland. Furthermore she received, together with her FOCUS team members Willemien van de Water and Nienke de Glas, the 'Marie Parijs prijs' for outstanding research in the Leiden University Medical Center.

In September 2017 she started her residency in Radiation Oncology at the Erasmus MC Cancer Institute in Rotterdam, under supervision of dr. M.J.J. Olofsen-van Acht and drs. M. van de Pol.

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