Patterns of care and prognosis of older women with breast cancer

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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

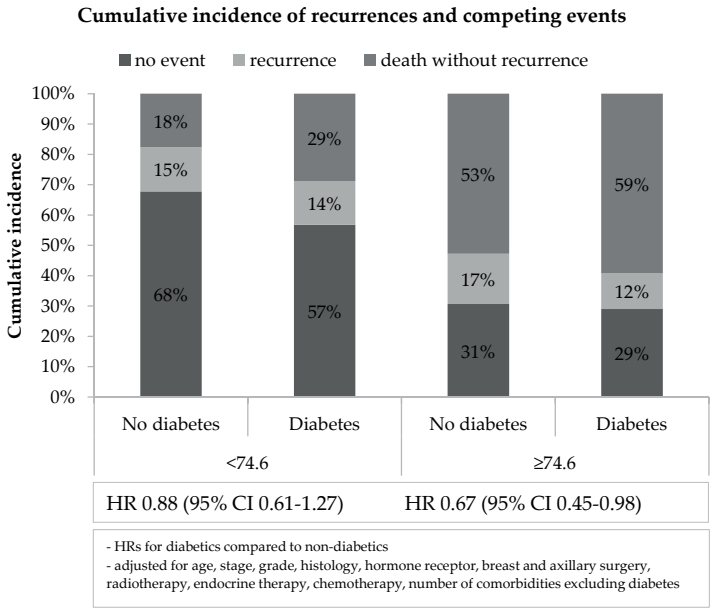

Figure 1. Cumulative incidence of recurrences and competing mortality.

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.

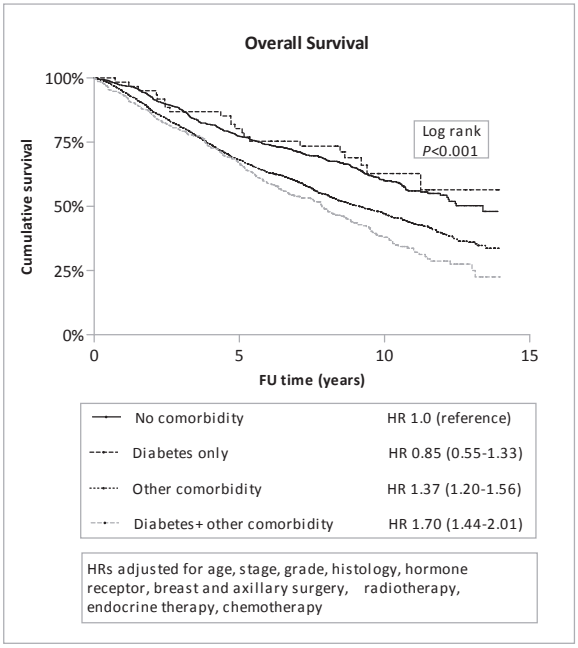

Figure 2. Overall survival.

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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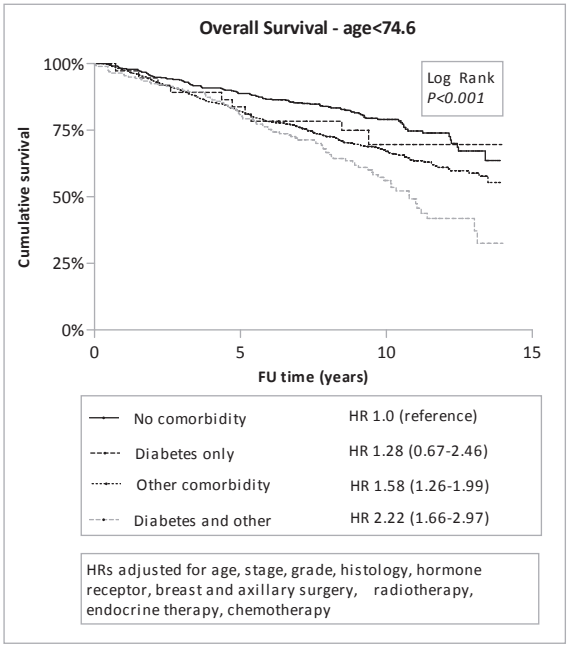
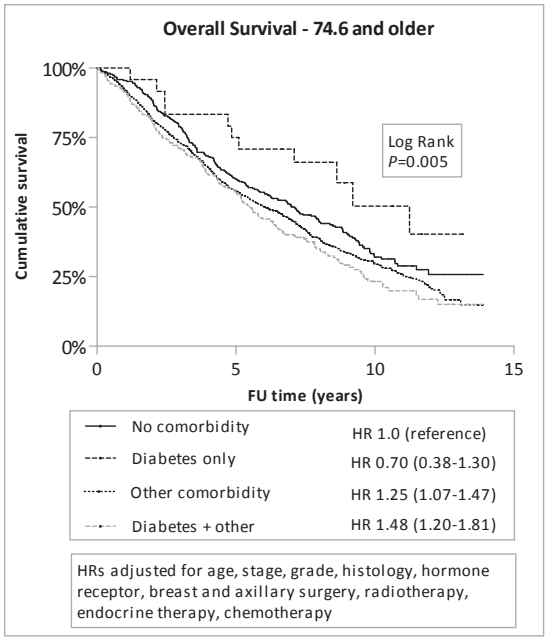


Webfigure 1a. Overall survival, patients aged <74.6 years.



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