J Cancer Res Clin Oncol (2004) 130: 664–670
DOI 10.1007/s00432-004-0594-3

ORIGINAL PAPER

G. Nagel · U. Wedding · H. Hoyer · B. Röhrig
D. Katenkamp

The impact of comorbidity on the survival of postmenopausal women with breast cancer

Received: 8 March 2004 / Accepted: 28 May 2004 / Published online: 6 August 2004

Abstract *Purpose*: The aim was to assess the impact of comorbidity on survival of postmenopausal women with breast cancer diagnosis in the period 1995–1997. *Methods*: The level of comorbidity was described by the methods suggested by Satariano and Charlson. Cox's proportional hazard models were used to explore the impact of comorbidity on all-cause mortality. *Results*: After a median follow-up time of 52 months, an increasing level of comorbidity was associated with a higher all-cause mortality. Compared to patients without comorbid conditions, the hazard ratio of death (HR) was 1.2 (95% CI: 0.8–1.7) for Satariano index 1 and HR 2.3 (95% CI: 1.5–3.5) for Satariano index ≥2, and HR 1.6 and 2.1 for the Charlson comorbidity index, respectively. Independent of comorbidity, the treatment pattern had a strong impact on survival. The level of comorbidity has an influence on the 3-year survival of postmenopausal women with breast cancer. *Conclusions*: Long-term follow-up is required to appraise these findings in relation to treatment strategies.

Keywords Breast cancer · Comorbidity · Survival

G. Nagel · D. Katenkamp
Comprehensive Cancer Center/Field study Breast Cancer,
Friedrich-Schiller-University, Jena, Germany

U. Wedding
Clinic Internal Medicine II, Hematology,
Oncology, Gastroenterology,
Hepatology and Infectious Disease,
Friedrich-Schiller-University, Jena, Germany

H. Hoyer · B. Röhrig
Institute for Medical Statistics,
Computer Sciences and Documentation,
Friedrich-Schiller-University, Jena, Germany

G. Nagel (✉)
Division of Clinical Epidemiology,
Deutsches Krebsforschungszentrum,
Im Neuenheimer Feld 280, 69120 Heidelberg, Germany
E-mail: g.nagel@dkfz-heidelberg.de
Tel.: +49-6221-422352

Introduction

Breast cancer is the most common cancer in women in Europe and North America with 1,000,000 estimated new cases and 373,000 deaths per year worldwide [1]. The prognosis of breast cancer is associated with tumor and sociodemographic characteristics. Tumor-related prognostic factors such as stage, grading, and receptor status are reported in numerous articles. Factors associated with the patient characteristics, such as functional status and comorbid conditions, are rarely considered in prognosis analysis. In Western societies the incidence of breast cancer as well as many non-malignant chronic diseases, such as arterial hypertension, coronary heart disease, diabetes, chronic pulmonary disease, and arthrosis, are increasing with age [2]. In regard to demographic changes and an expected increase in cancer incidence [3], medical decisions on the adequate treatment of elderly cancer patients' gains relevance.

Comorbidity is the presence of one or more health conditions found in people with an index disease, e.g., breast cancer [4]. It is very common that elderly breast cancer patients suffer from concomitant diseases. However, this fact has not received much attention in the past. The comorbid conditions affect medical decision-making, outcomes in terms of treatment complications, recurrence, and survival, as well as the quality of life. In addition, comorbidity effects patterns of care and health service utilization, contributing to health care expenditures [5].

Various attempts have been made to measure comorbidity. Based on different approaches, scores have been suggested by Charlson [6], Kaplan and Feinstein [7], Yancik [8], Linn [9], and Satariano [10]. The most commonly used Charlson comorbidity score was developed based on 1-year age-adjusted risk of death in hospitalized subjects. However, Satariano and Ragland demonstrated that comorbidity is a major prognostic indicator in elderly patients with breast cancer by identifying a subset of seven out of 18 comorbid conditions,

which were independently associated with all-cause mortality. Further studies on breast cancer revealed that the measurement of the comorbidity level explains only a small proportion of variance in treatment patterns in older women [11, 12]. The functional status of a person contributes independently to the health outcome [13]. The balance of benefits and potential harm of treatment becomes more important than the womens' age.

The objectives of this study were to investigate the impact of comorbidity on the survival of postmenopausal women with breast cancer adjusted to tumor and treatment factors, and to compare the effects of the Satariano index with the commonly used Charlson index.

Material and methods

Background

The study sample relies on regional cancer registration and relevant additional clinical information [14]. Data were collected in order to evaluate the management of patients with breast cancer, living in Eastern Thuringia, who were diagnosed during the years 1995–1997. The area comprises a population of about 1 million.

Study population

Participants were recruited from the University Hospital in Jena and ten regional hospitals in the area. Patients who attended the hospitals for primary care of breast cancer were informed by the physicians and asked for written consent. During the years 1995–1997, in total 1,324 breast cancer cases were collected. The median follow-up time was 52 months (36–72 months). The study sample was restricted to patients of 50 years and older at diagnosis with histologically confirmed invasive breast cancer [International Classification of Disease (ICD)-9 code 174] [15]. Age over 50 years was used as a proxy variable for postmenopausal state. The sample comprised 946 eligible cases, of which 799 (84.5%) with a complete set of all covariates of interest were considered for a multivariate analysis, including cases with all tumor stages (UICC I–IV). Missing data occurred in the covariates due to histological differentiation grade 87 (9.2%) and hormone receptor status 70 (7.4%).

Data collection

Data regarding age, comorbidity, tumor characteristics, operative and adjuvant therapy were taken from standard cancer registration sheets, where comorbidity was addressed in an open question, or from medical records directly or from copies of relevant reports. Information on vital status was attained by active follow-up by requests from the physicians. This was done annually to check up vital status . In addition, record linkages with the cancer registry in Berlin were conducted, where the death certificates of patients from the study region were centrally registered.

Variables

The Satariano comorbidity index was calculated based on ICD-9 codes. Within a list of 18 comorbid conditions, seven relevant prognostic comorbid conditions [heart disease, myocardial infarction, diabetes, respiratory condition, liver condition, gallbladder condition, and cancer (other than ICD 174)] were identified by survival analysis. The number of the comorbid conditions was added to a score [10]. The Satariano index was categorized as 0, 1, and ≥2 comorbid conditions. Comorbidity conditions, which were present at the time of diagnosis or occurred up to 3 months after diagnosis were considered for the analysis. For comparison, comorbidity burden was also classified according to Charlson [6, 16]. Age at diagnosis was categorized into 50–59 years, 60–69 years, 70–79 years, and ≥ 80 years. Tumor size and nodal and distant metastasis weres classified according to the TNM Classification of Malignant Tumors [15] and summarized as local (T1–4, N0, M0), regional (any T, N1, M0), and distant disease (any T, any N, M1). Histological differentiation grade was coded into G1/G2 versus G3. Tumors were documented as G4 in 0.9% of the cases, which were added to the G3 class. Hormone receptor status was categorized as positive when either estrogen or progesterone or both were positive. The histologic morphology of the tumors was classified as invasive ductal and invasive lobular, and all other morphologies were summarized as other. The treatment was categorized as operation only (OP), operation and adjuvant systemic therapy (hormone and/or chemotherapy) (OP, CT or HT), operation and radiation therapy (OP, RT), and the combination of operation, adjuvant systemic therapy and radiotherapy (OP, CT or HT, RT) in order to adjust for the impact of treatment on survival.

Statistical methods

The associations between the comorbidity score and sample characteristics were examined using chi-square tests. Using the product limit life table method, Kaplan-Meier survival curves were plotted separately for each variable. Based on these procedures and considering clinically relevant factors, Cox's proportional hazards regression models were fitted to identify predictors for survival [17]. The following covariates were included simultaneously in the final models: age, tumor stage, histologic differentiation grade, hormone receptor status, comorbidity, and treatment. Histologic morphology did not improve the fit of the model and was not included in the final model. Interactions were

investigated. The likelihood-ratio test was applied to test for significant effects of one covariate adjusted for the others. The adjusted hazard ratios of death (HR) and the corresponding 95% confidence intervals (95% CI) were estimated. Statistical analysis was performed using the statistical package SPSS (Version 10.0, SPSS). All reported *P*-values are two-sided.

Results

In Table 1 the sample characteristics for 799 postmenopausal women with breast cancer regarding the Satariano comorbidity score are shown. Associations were observed between the level of comorbidity and age ($P < 0.001$), treatment ($P = 0.003$), and vital status ($P < 0.001$) , whereas no statistical significant relationship was found for histologic differentiation grade ($P = 0.147$), localization ($P = 0.106$), and hormone receptor status ($P = 0.326$). In Table 2 the frequency of the comorbidities are shown. The most common comorbid conditions in our sample were hypertension, heart disease, diabetes, thyroid, circulatory and gallbladder conditions. In Table 3 the cause of death regarding the comorbidity level is summarized. In 156 out of 190 cases information on the cause of death was available. In 112 cases breast cancer was identified as the cause of death and in 44 cases other causes of death were identified. Figure 1 shows the Kaplan-Meier estimates for three levels of comorbidity for a follow-up time of 60 months. With an increasing number of comorbid conditions the survival time decreased.

In the multivariate analysis (Table 4) the number of comorbid conditions as classified with the Satariano index was strongly associated with survival. The hazard ratio of death increased from 1.2 (95% CI: 0.8–1.7) when one comorbid condition was present to 2.3 (95% CI: 1.5–3.5) when at least two comorbidities were present. Furthermore, a strong association was observed between stage and survival. For regional disease the relative risk was 2.4 (95% CI: 1.8–3.3) and for remote disease the hazard ratio increased to 8.4 (95% CI: 5.2–13.5).

The treatment of breast cancer patients was associated with survival ($P < 0.001$). Compared to the combination of surgical treatment, adjuvant systemic treatment, and radiation therapy, the other treatment options were associated with a higher risk of dying within 3 years after diagnosis. For the surgical and adjuvant systemic therapy as well as for surgical and radiation therapy the hazard ratio was 1.5 (95% CI%: 1, 1–2.1, and 0.8–2.8, respectively). Compared to other treatment options, for patients who underwent surgical treatment only, the highest relative risk estimates were observed (HR: 4.3, 95% CI: 2.7–7.0).

Age was associated with survival ($P = 0.029$). Compared to the age group 50–59 years, the hazard ratio increased with increasing age from 1.4 (95% CI: 0.9 – 2.5) for the age group 60–69 years, and 1.4 (95% CI: 1.2–2.1) in the age group 70–79 years, to 2.7 (95% CI:

Table 1 Level of comorbidity according to Satariano (SCI) for women aged > 50 years with invasive breast cancer diagnosed 1995–1997 ($n = 799$)

Variable	Total number of cases	Level of co-morbidity (SCI)			*P*-value
		0	1	≥2	
	n (%)	*n* (%)	*n* (%)	*n* (%)	χ^2-test
Age/years					< 0.001
50–59	263 (32.9)	224 (40.1)	34 (20.2)	5 (6.9)	
60–69	244 (30.5)	189 (33.8)	44 (26.2)	11 (15.3)	
70–79	209 (26.2)	112 (20.0)	61 (36.3)	36 (50.0)	
≥80	83 (10.4)	34 (6.1)	29 (17,3)	20 (27.8)	
Survival					< 0.001
Alive	609 (76.2)	447 (80.0)	122 (72.6)	40 (55.6)	
Dead	190 (23.8)	112 (20.0)	46 (27.4)	32 (44.4)	
Treatment					0.003
OP, CT or HT, RT	358 (44.8)	275 (49.2)	62 (36.9)	21 (29.2)	
OP, CT or HT	354 (44.3)	224 (40.1)	87 (51.8)	43 (59.7)	
OP, RT	46 (5.8)	33 (5.9)	11 (6.5)	2 (2.8)	
OP	41 (5.1)	27 (4.8)	8 (4.8)	6 (8.3)	
Histologic differentiation grade					0.147
G1/G2	528 (66.1)	359 (64.2)	115 (68.5)	54 (75.0)	
G3	271 (33.9)	200 (35.8)	53 (31.5)	18 (25.0)	
Tumor stage					0.106
Local	446 (55.8)	303 (54.2)	97 (57.7)	46 (63.9)	
Regional	321 (40.2)	238 (42.6)	60 (35.7)	23 (31.9)	
Distant	32 (4.0)	18 (3.2)	11 (6.6)	3 (4.2)	
Hormone receptor status					0.326
Positive	655 (82.0)	461 (82.5)	132 (78.6)	62 (86.1)	
Negative	144 (18.0)	98 (17.5)	36 (21.4)	10 (13.9)	
Sum	799	559	168	72	

Table 2 Comorbid conditions present in women with breast cancer in the cancer registry up to 3 months after diagnosis ($n = 799$). The diseases in bold letters are summarized in the Satariano score. Prevalence = (count/799)×100

Category	Count	Prevalence %
Hypertension	485	60.7
Heart disease	149	18.6
Arthritis	2	0.3
Gallbladder condition	31	3.9
Thyroid condition	40	5.0
Diabetes	100	12.5
Gastrointestinal condition	8	1.0
Broken bones/skeletal disease	16	2.0
Eye condition	20	2.5
Respiratory condition	21	2.6
Urinary condition	9	1.1
Circulatory condition	53	6.6
Cancer (other than ICD 174)	18	2.3
Ear condition	8	1.0
Myocardial infarction	7	0.9
Stroke	14	1.8
Kidney condition	3	3.8
Liver condition	9	1.1

1.7 –4,3) in women aged 80 years or older. Furthermore, survival was influenced by the histologic differentiation grade (HR: 1.4, 95% CI: 1.1–1.9). Negative hormone receptor status was associated with higher mortality (HR: 1.4, 95% CI: 1.0–1.9) compared to positive hormone receptor status but no statistical significant association was observed ($P = 0.074$).

The estimates for the Charlson comorbidity index was calculated by replacing the Satariano index in the model with the same set of adjustment variables. For the Charlson comorbidity index (Table 5) HR increased from 1.6 (95% CI: 1.2–2.3) for one or two comorbidities, to 2.1 (95% CI: 1.1–4.1) when a score of three or more was present.

The hypothesized interaction between the Satariano comorbidity index and stage of disease in relation to survival was not statistical significant ($P = 0.078$). This observation was affected by the inclusion of tumor stage ($P = 0.061$), but failed to reach statistical significance. In Fig. 2 the relative risks and 3-year mortality rate of 799 patients are presented by the number of comorbid conditions and stage of disease. Survival was influenced by stage independently of the comorbidity level.

Table 3 Causes of death by Satariano comorbidity level in women with breast cancer (not known 34)

Satariano comorbidity level	Cause of death		Total
	Breast cancer	Other	
0	80 (82.5%)	17 (17.5%)	97
1	23 (63.9%)	13 (36.1%)	36
≥2	9 (39.1%)	14 (60.9%)	23
Total	112	44	156

Discussion

In our study sample, comorbidities influence the survival of postmenopausal women with breast cancer, confirming the observations made by Satariano and Ragland [10]. The mortality risk increases with the number of comorbid conditions independent of the disease stage. In a recent study among patients with lung cancer, the total number of all comorbid conditions was associated with the all-cause mortality [18]. In line with former research, the Charlson Comorbidity index, a weighted score, revealed similar effects on survival.

When using the Charlson comorbidity index, the greatest impact was observed for the group with local disease independent of whether there was an adjustment for stage and initial treatment [19]. Aging is a complex process, which is associated on molecular level with promoting and inhibiting changes in carcinogenesis [20]. In older patients with breast cancer, increasing age is associated with more favorable tumor characteristics [21]. In contrast, the prevalence of chronic diseases increases with age [22]. Both conditions may be influenced by common risk factors such as body weight [23], smoking habits [24], and physical activity [25].

Comorbidity is defined as one or more other diseases in relation to an index-disease [4]. In most etiological and mortality analyses the assumption of independent competing risks is applied. Former work suggested that cancer and comorbid conditions interact regarding survival. [20] Little is known about the causes and effects of comorbidity on diagnosis and the course of the disease of interest [5, 26]. However, the presence of comorbid conditions is not necessarily associated with advanced stage breast cancer [27]. The prevalence of comorbid conditions depends on age and tumor localization. Coebergh et al. reported that the prevalence was highest for patients with lung, kidney, stomach, bladder, and prostate cancer [28]. Furthermore, the outcome may influence the tumor stage through different levels of health awareness or different access to the health care system [29], and the treatment strategy [30, 11]. By comparing non-breast-cancer cohorts and non-comorbidities cohorts, estimates of statistical interaction between comorbidities and breast cancer were found. For women with breast cancer and comorbid conditions the observed excess mortality rate was greater than expected [19].

There is evidence that treatment patterns influence survival independently of the level of comorbidities observed. Various studies have found that older patients are more likely to receive less aggressive treatment [31, 32]. Hébert-Croteau and et al. concluded that older patients received less aggressive locoregional and adjuvant treatment, independent of comorbidity [33]. Mandelblatt et al. observed that patients aged 80 years or older were likely to receive no adjuvant chemotherapy, independent of other clinical and sociodemographic factors [34]. The evaluation of predictors in order to facilitate the utilization of appropriate therapy in older

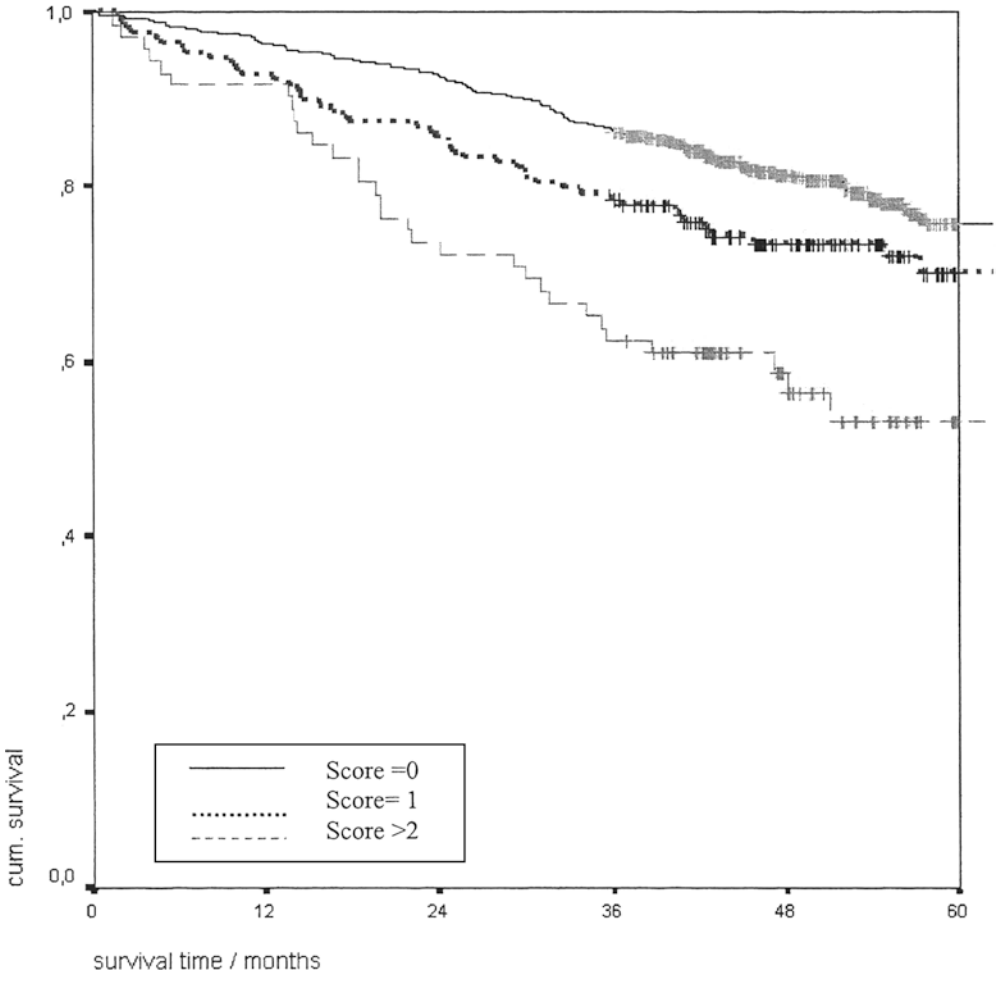

Fig. 1 Kaplan-Meier overall survival curve for level of comorbidities (Satariano comorbidity index) of breast cancer patients aged > 50 years ($n = 799$)

age at the individual and group level remains an important issue in clinical oncology.

Tumor stage is a strong predictor of survival in women with breast cancer. In our data a trend towards an interaction between comorbidity and stage of disease was observed, which did not reach statistical significance. Satariano and Ragland found an interaction between comorbidity level and stage of disease [10]. This may be related to the differences of the age bounds. Satariano and Ragland included women aged from 40 years while we included only women 50 years or older as a proxy variable for postmenopausal state. Risk factors of breast cancer may be different among pre- and postmenopausal women [35]. However, in the group with local disease the presence of two or more comorbid conditions increased the mortality rate. Similar findings were reported by Newschaffer et al. who detected a statistical significant interaction between comorbidity and stage [19]. Satariano and Ragland observed an increased mortality risk for patients with local disease, whereas among patients with remote disease no effects on mortality were found [10].

Differences might be related to the ascertainment of the comorbid conditions. Compared with the prevalence of comorbid conditions reported by Satariano, in our sample a different pattern was found. Some comorbid conditions, such as arthritis, gallbladder conditions, and gastrointestinal conditions, were less frequent in our sample. Other authors reported that different patterns of comorbid conditions were less prevalent [28]. Differences in prevalence may depend on the health care system, the ascertainment of comorbid conditions, and the index applied [36, 37, 38]. Our study is based on routine clinical data. Since the data on comorbid conditions were collected during the treatment, it is likely that specific comorbidities were reported. However, Newschaffer et al. compared data on comorbidities in medical records and physicians' claims data and observed similar associations between comorbidity indices and mortality [11]. Lash et al. suggested that the use of a multiple informants' method might be an alternative when no single index is considered to be ideal [39]. The comorbidity indices consider the number of diseases and impact on life expectancy. Functional status, which was not available for our cohort, may independently influence the outcome [13].

Conclusion

Multiple comorbid conditions have impact on the 3-year all-cause mortality of postmenopausal women with

Table 4 Hazard ratio estimates of death and 95% confidence intervals (95% CI) from Cox's Proportional Hazards model on 799 breast cancer patients age > 50 years diagnosed in the years 1995–1997 for the Satariano comorbidity index

Variable	Total number of cases	Hazard ratio (95% confidence interval)			Likelihood-ratio test
	n = 799	HR	95% CI		P-value
Age/years					0.001
50–59	263	1.0			
60–69	244	1.4	0.9	2.0	
70–79	209	1.4	0.9	2.1	
≥80	83	2.7	1.7	4.3	
Satariano comorbidity index					0.001
0	559	1.0			
1	168	1.2	0.8	1.7	
≥2	72	2.3	1.5	3.5	
Treatment					< 0.001
OP,CT or HT, RT	358	1.0			
OP, CT or HT	354	1.5	1.1	2.1	
OP, RT	46	1.5	0.8	2.8	
OP	41	4.3	2.7	7.0	
Tumor stage					< 0.001
Local	446	1.0			
Regional	321	2.4	1.8	3.3	
Distant	32	8.4	5.2	13.5	
Histologic differentiation grade					0.024
G1/G2	528	1.0			
G3	271	1.4	1.1	1.9	
Hormone receptor status					0.074
Positive	655	1.0			
Negative	144	1.4	1.0	1.9	

Table 5 Hazard ratio estimates of death and 95% confidence intervals from Cox's Proportional Hazards model on 799 breast cancer patients age > 50 years diagnosed in the years 1995–1997 for the Charlson comorbidity index

	Number of cases	Hazard ratio (95% confidence interval)	Likelihood-ratio test
Charlson Comorbidity Index[a]			0.004
0	634	1.0	
1–2	140	1.6 1.2 2.3	
≥3	25	2.1 1.1 4.1	

[a]In the model the Satariano comorbidity index was replaced in the model by the Charlson comorbidity index while the adjustment variables remained

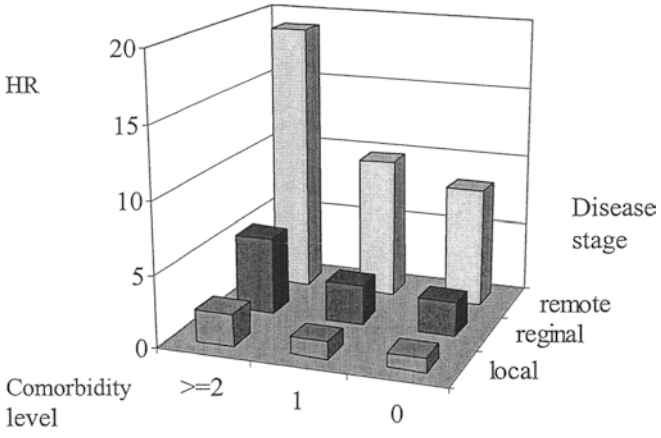

Fig. 2 Bar chart for the hazard rate estimates of the Satariano comorbidity index by disease stage in 799 breast cancer patients aged > 50 years

breast cancer. The Charlson index revealed similar risk estimates to the Satoriano index. Independent of comorbidity, treatment pattern had strong impact on survival. Comorbid conditions should be considered in medical decision-making. The measurement of other outcome factors, such as quality of life and adverse effects of treatment, may add further guidance in medical decision-making in elderly patients with breast cancer, in order to provide the appropriate treatment for older women with breast cancer.

Acknowledgements This study was supported by grants from the German Ministry of Health (FB2–43332–70/1). We are grateful to our documentation team and give thanks to S. Berg, I. Köhler, B. Osten and K. Polte.

References

1. International Agency for Research on Cancer Globocan 2000 (2001) Cancer incidence, mortality and prevalence wordwide. IARC, Lyon, 2001
2. Van den Akker M, Buntinx F, Matsemakers JF, et al (1988) Multimorbidity in general practice: prevalence, incidence and determinants of co-occurring chronic and recurrent diseases. J Clin Epidemiol 51:367–375

3. Yancik R, Wesley MN, Ries LA, et al (2001) Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 285:885–892
4. Feinstein AR (1970) The pre-therapeutic classification of co-morbidity in chronic disease. J Chron Dis 23:455–469
5. Gijsen R, Hoeymans N, Schellevis FG, et al (2001) Causes and consequences of comorbidity, a review. J Clin Epidemiol 54:661–674
6. Charlson ME, Pompei P, Ales KL, et al (1987) A new method of classification prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 40:373–383
7. Kaplan MH, Feinstein AR (1974) The importance of classifying initial comorbidity I elevating the outcome of diabetes mellitus. J Chron Dis 242:291–298
8. Yancik R, Wesley MN, Ries LA, et al (1998) Comorbidity and age as predictors of risk for early mortality of male and female colon cancer patients. Cancer 82:2123–2134
9. Linn BS, Linn MW, Gurel L (1968) Cumulative illness rating scale. J Am Geriatr Soc 16:622–666
10. Satariano WA, Ragland DR (1994) The effect of co-morbidity on 3 year survival of women with primary breast cancer. Ann Intern Med 120:104–110
11. Newschaffer CJ, Penberthy L, Desch CE, et al (1996) The effect of age and comorbidity in the treatment of elderly women with nonmetastatic breast cancer. Arch Intern Med 156:85–90
12. Silliman RA, Troyan SL, Guadagnoli E, et al (1997) The impact of age, material status and physician-patient interactions on the care of older women with breast carcinoma. Cancer 20:1326–1334
13. Extermann M, Overcash J, Lyman GH, et al (1998) Comorbidity and functional status are independent in older cancer patient. J Clin Oncol 16:1582–1587
14. Engel J, Nagel G, Breuer E, et al (2002) Primary breast cancer therapy in six regions of Germany. Eur J Cancer 38:578–585
15. International Union against Cancer (UICC) (1997) TNM classification of malignant tumours, 5th edn. Wiley, New York
16. D'Hoore W, Bouckaert A, Tilquin C (1996) Practical considerations on the use of the Charlson index with administrative data bases. J Clin Epidemiol 49:1429–1433
17. Cox DR (1972) Regression models and life-tables. J R Stat Soc 34:187–220
18. Tammemagi CM, Neslund-Dudas C, Simoff M, et al (2003) Impact of comorbidity on lung cancer survival. Int J Cancer 103:792–802
19. Newschaffer CJ, Bush TL, Penberthy LE, et al (1998) Does comorbidity diseases interact with cancer? An epidemiologic analysis of mortality in a cohort of elderly breast cancer patients. J Gerontol A Biol Sci Med Sci 53A:372–378
20. Repetto L, Balducci L (2002) A case for geriatric oncology. Lancet Oncol 3:289–297
21. Diab SG, Elledge RM, Cark RM (2000) Tumor characteristics and clinical outcome of elderly women with breast cancer. J Natl Cancer Inst 92:550–556
22. Olge KS, Swanson GM, Woods N, Azzouz F (2000) Cancer and comorbidity-redefining chronic diseases. Cancer 88:653–663
23. Rossner S (2002) Obesity: the disease of the twenty-first century. Int J Obes Relat Metab Disord 26 [Suppl 4]:S2–4
24. Terry PD, Rohan TE (2002) Cigarette smoking and the risk of breast cancer in women: a review of the literature. Cancer Epidemiol Biomarkers Prev 11:953–971
25. Hamerman D (1999) Toward an understanding of frailty. Ann Intern Med 130:945–950
26. Yancik R, Havlik RJ, Wesley MN, et al (1996) Cancer and comorbidity in older patients: a descriptive profile. Ann Epidemiol 6:399–412
27. Vaeth PA, Satariano WA, Ragland DR (2000) Limiting comorbid conditions and breast cancer at diagnosis. J Gerontol 55:M593–600
28. Coebergh JW, Janssen-Heijnen ML, Post PN, et al (1999) Serious co-morbidity among unselected cancer patients newly diagnosed in the southeastern part of The Netherlands in 1993–1996. J Clin Epidemiol 52:1131–1136
29. Taplin SH, Barlow W, Urban N, et al (1995) Stage, age comorbidity, and direct costs of colon, prostate, and breast cancer. Care J Natl Cancer Inst 87:417–426
30. Nicolucci A, Mainini F, Penna A, et al (1993) The influence of patients characteristics on the appropriateness of surgical treatment for breast cancer patients. Ann Oncol 4:133–140
31. Guadagnoli E, Shapiro C, Gurwitz JH, et al (1997) Age-related patterns of care: evidence against ageism in the treatment of early stage breast cancer. J Clin Oncol 15:2338–2344
32. Nagel G, Röhrig B, Hoyer H, et al (2003) A population-based study on variations in the use of adjuvant systemic therapy on postmenopausal patients with early stage breast cancer. J Cancer Res Clin Oncol 129:183–191
33. Hébert-Croteau N, Brisson J, Latreille J, et al (1999) Compliance with consensus recommendations for the treatment of early stage breast carcinoma in elderly women. Cancer 85:1104–1113
34. Mandelblatt JS, Hadley J, Kerner JF, et al (2000) Patterns of breast carcinoma treatment in older women. Cancer 89:561–573
35. Key TJ, Verkasalo PK, Banks E (2001) Epidemiology of breast cancer. Lancet Oncol 2:133–140
36. Newschaffer CJ, Bush TL, Penberthy LT (1997) Comorbidity measurement in elderly females breast cancer patients with administrative and medical record data. J Clin Epidemiol 50:725–733
37. Klabunde CN, Potosky AL, Legler JM, et al (2000) Development of a comorbidity index using physician claims data. J Clin Epidemiol 53:1258–1267
38. Extermann M (2000) Measurement and impact of comorbidity in older cancer patients. Crit Rev Oncol Hematol 35:181–200
39. Lash TL, Thwin SS, Horton NJ, et al (2003) Multiple informants: a new method to assess breast cancer patients' comorbidity. Am J Epidemiol 153:249–257