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ORIGINAL ARTICLE

Excess mortality in postmenopausal high-risk women who only receive adjuvant endocrine therapy for estrogen receptor positive breast cancer

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Abstract

Background. Omission of chemotherapy may affect mortality in postmenopausal high-risk women despite appropriate adjuvant endocrine therapy for estrogen receptor (ER) positive breast cancer. The aim of this study was to determine how all-cause mortality rate in these patients compares to that of the general female population. Furthermore, to identify a subset without excess mortality using clinical and pathological characteristics. *Patients and methods.* From the population-based database of the Danish Breast Cancer Cooperative Group we included 6529 postmenopausal patients with ER positive high-risk breast cancer who in 1996 through 2004 by nationwide guidelines were allocated to five years of tamoxifen, an aromatase inhibitor (AI) or both in sequence. Multivariate categorical and fractional polynomials (MFP) models were used to construct prognostic subsets by clinicopathologic characteristics. *Results.* In a multivariate model excess mortality was inversely ($p < 0.0001$) associated with increasing age at surgery while recurrence-free survival (RFS) was not. Non-adherence to endocrine therapy was associated with excess mortality ($p = 0.0008$) while treatment with an AI was associated with a less pronounced mortality excess ($p = 0.03$). A prognostic standard mortality rate (SMR) index (PSI) was built using the regression coefficients obtained in the MFP model, and the same risk factors were used to construct a flowchart algorithm. Both allocated 75% to a group with increased all-cause mortality as compared to the general female population, but the SMR was significantly increased (SMR 1.38; 95% CI 1.16–1.65) in 462 patients who were allocated to low-risk group by the Flowchart algorithm and to a high-risk group by PSI. *Conclusion.* Only one quarter of postmenopausal ER positive breast cancer patients are free of excess mortality when omitting adjuvant chemotherapy. Patients should be informed about importance of adherence to adjuvant endocrine therapy and inclusion of an AI. A PSI may better guide recommendations regarding adjuvant chemotherapy.

Chemotherapy is well established as adjuvant therapy for early breast cancer and the recent overview from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) suggested that on average, chemotherapy reduces 10-year breast cancer mortality by about a third [1]. Importantly, the proportional benefits were similar in older and younger women and independent of age, nodal status, estrogen receptor (ER) status and type of chemotherapy regimen. The absolute gain in life expectancy corresponding to a given relative reduction in the risk of death from breast cancer is, however, less in older women due to competing causes of death. Patients with a poor prognosis have a larger absolute gain from chemotherapy, and are often more willing to accept the accompanying side effects. Consequently, the use of chemotherapy in postmenopausal patients with ER positive and HER2 negative tumors is highly varying and guided primarily by the clinician's personal evaluation of the tumors endocrine responsiveness and the patient's prognosis. In particular, age and nodal status seem to influence decisions about chemotherapy, but it is unclear exactly how this information is obtained and processed [2].

In order to provide better support about adjuvant therapies multiple clinical and pathological prognostic factors may be incorporated in a prognostic index. The Nottingham Prognosis Index (NPI) is an early

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version and more recently Adjuvant! Online, a web-based application, have provided a prognostic index based on US SEER registry data in combination with estimates derived from reports by EBCTCG of the effect obtained with adjuvant therapies [3–5]. These tools, however, have limitations. Most importantly they use 10-year survival probabilities, which may be adequate for an 80-year-old patient but not for a 50-year-old. Secondly, Adjuvant! Online was derived from the SEER registry using records of 35–59 year old women diagnosed between 1988 and 1992, and results may not be extrapolated to women 60 years or older at diagnosis treated according to more recent standards. Thirdly, the prognostic information added by genomic tests is limited and none of the tests have been developed as a predictive tool for benefit of chemotherapy [6]. Finally, relative mortality might better aid a decision on whether chemotherapy should be added to endocrine therapy in postmenopausal women as compared to summary measures like recurrence-free survival (RFS) and overall survival (OS) [7].

The aim of this population-based study was by clinicopathologic characteristics to develop an algorithm identifying postmenopausal high-risk women who following appropriate local therapy and allocation to five years of endocrine therapy can expect an age-appropriate residual lifespan despite the fact that

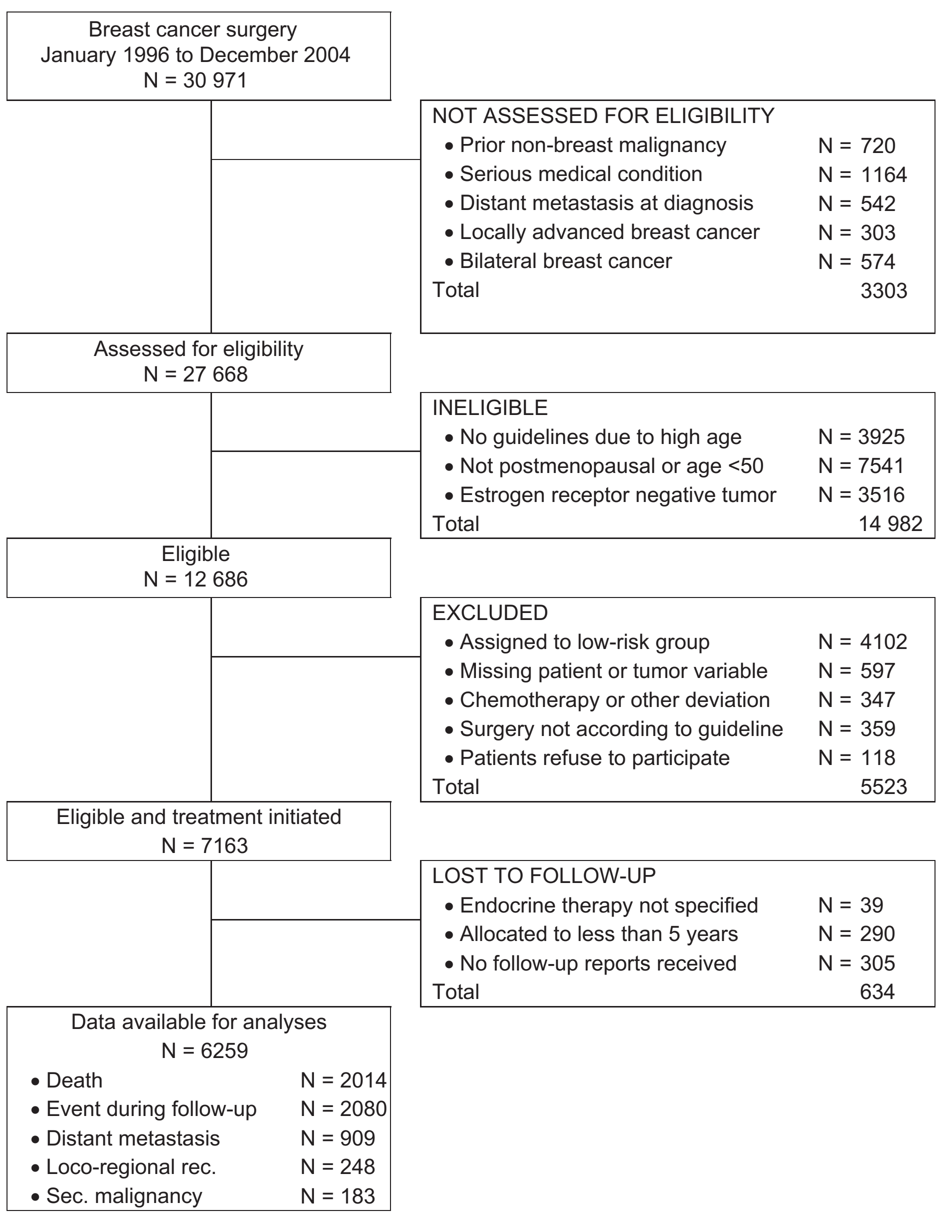

Figure 1. Flow diagram of the population-based cohort study of high-risk postmenopausal Danish breast cancer patients with estrogen receptor positive tumors who in January 1996 through December 2004 were allocated to 5 years of adjuvant endocrine therapy without chemotherapy.

they have been diagnosed with an ER positive breast cancer.

Since these patients have a life expectancy similar to the general population they may not achieve any or very little benefit from chemotherapy. We used complex fractional polynomial (FP) transformations to construct a predictive algorithm for standard mortality ratio (SMR) and to validate categories as used in the multivariate Cox models.

Methods

Since 1977 the Danish Breast Cancer Cooperative Group (DBCG) has provided standard diagnostic and treatment algorithms for early breast cancer [8]. As source population we selected postmenopausal patients operated for ER positive unilateral invasive high-risk breast carcinoma who according to a predetermined treatment algorithm were allocated to five years of endocrine therapy without chemotherapy. This population-based cohort study therefore includes postmenopausal women who from January 2000 through December 2004 were diagnosed with an ER positive breast cancer and had at least one of the following characteristics: 1) node positive disease; 2) a tumor size >2 cm; or 3) malignancy grade II–III. From January 1996 through December 1999 eligible patients had at least one of the following characteristics: 1) node positive disease; 2) a tumor size >5 cm. From 1996 through 2001 eligibility was restricted to patients younger than 75 [8]. Written or witnessed informed consent was required. A patient was classified as postmenopausal if she had undergone oophorectomy, was amenorrhoic for more than 12 months, had amenorrhea for 2–12 months and FSH in the postmenopausal range, or was more than 50 years of age in the case of hysterectomy. Patients were without evidence of distant metastases, as determined by physical examination and chest radiography. Bone scintigraphy (if positive to be confirmed by radiography), or bone radiography was performed in the case of bone pain or bone resorption markers (alkaline phosphatase and ionized calcium) above the reference interval [8].

Tumors were examined in a predetermined manner including tumor size; total number of lymph nodes identified; number of metastatic nodes; histological type; histological grade; lymphovascular invasion; expression of ER by immunohistochemistry and PgR expression if ER staining was negative ($<10\%$ of tumor cells); tumor margin status; and invasion into skin or deep fascia [9]. The required loco-regional treatment was a negative sentinel node biopsy or axillary clearance (level I and part of level II) in combination with breast conserving surgery or mastectomy; in combination with radiotherapy to the residual breast following lumpectomy, and the chest wall following mastectomy in patients younger than 70 if node positive or a tumor larger than 5 cm in diameter, and to regional lymph nodes in node positive disease, all 48 Gy in 2 Gy fractions at five fractions per week. Patients were free of charge supplied with tamoxifen or an aromatase inhibitor (AI) at scheduled follow-up visits and a patient was classified as adherent following continuation of endocrine therapy (tamoxifen or AI) for at least 4.5 years in the absence of a breast cancer event, or otherwise as non-adherent. Treatment adherence, symptoms, adverse events and findings on clinical examination were recorded every three months during the first year after diagnosis, then every six months during the

Table I. Baseline characteristics of 6529 breast cancer patients diagnosed 1996–2004.

	N	(%)
Age at surgery		
50–54 years	818	(13%)
55–59 years	1588	(24%)
60–64 years	1495	(23%)
65–69 years	1316	(20%)
70–74 years	1038	(16%)
>74 years	274	(4%)
Positive lymph nodes		
0	2007	(31%)
1–3 positive	2975	(46%)
4–9 positive	1000	(15%)
>9 positive	547	(8%)
Tumor size		
0–10 mm	573	(9%)
11–20 mm	2515	(39%)
21–30 mm	2193	(34%)
>30 mm	1230	(19%)
Histologic type†		
Infiltrating ductal	5425	(83%)
Infiltrating lobular	899	(14%)
Other or unclassified	205	(3%)
Malignancy grade‡		
Grade 1	1506	(23%)
Grade 2	3333	(51%)
Grade 3	942	(14%)
Not done	748	(11%)
Lymphovascular invasion		
Absent	5345	(82%)
Present	1184	(18%)
Estrogen receptor status§		
10–59% positive	920	(14%)
60–89% positive	1394	(21%)
90–99% positive	1713	(26%)
100% positive	2336	(36%)
Positive, but % not recorded	166	(3%)
Loco-regional therapy		
BCS with radiotherapy	2010	(31%)
Mastectomy with radiotherapy	1782	(27%)
Mastectomy without radiotherapy	2737	(42%)

†Histological type according to World Health Organization criteria [4]; ‡Grade was determined according to Elston and Ellis [5]; §ER status according to DBCG guidelines [6].

second through fifth years, and annually thereafter for a total of 10 years. Additional biochemical tests and imaging were done when indicated by existing symptoms or signs.

Statistical analysis

Follow-up time was quantified in terms of a Kaplan-Meier estimate of potential follow-up [10]. OS was calculated as the time elapsed from the date of definitive surgery until death from any cause, and were estimated using the Kaplan-Meier method. RFS was as defined as the time from surgery to invasive loco-regional recurrence or distant metastases, with censoring in the event of new contralateral breast cancer, another malignancy or death without prior recurrence. Cumulative incidence of recurrence in the presence of competing risk was estimated. Univariate and multivariate Cox regression analysis for RFS were performed. The number of deaths observed was compared with the number of deaths expected, calculated by applying age and calendar year specific female mortality figures of the general Danish population and the corresponding person years of the respective cohort members. We used the Danish Civil Personal Registration number to link datasets. Time at risk was defined as time from definitive surgery until date of death from any cause, emigration or end of follow-up (December 1, 2010). The SMR, computed as the ratio of the observed to the expected number of deaths, served as an estimate of relative risk of death, and 95% confidence intervals (CI) were computed based on the assumption that the observed number of deaths followed a Poisson distribution. The SMR were analyzed using univariate and multivariate Poisson regression models.

Table II. Multivariate analyses of recurrence-free survival and standard mortality ratio.

	Recurrence-free survival (RFS)			Standard mortality ratio (SMR)		
	HR	(95% CI)	p-value	RR	(95% CI)	p-value
Age at surgery			0.22			< 0.0001
< 55 vs. > 74 years	1.08	(0.74–1.56)		4.31	(3.33–5.58)	
55–59 vs. > 74 years	1.19	(0.83–1.70)		3.80	(3.01–4.79)	
60–64 vs. > 74 years	1.02	(0.71–1.47)		2.56	(2.03–3.23)	
65–69 vs. > 74 years	0.99	(0.69–1.43)		1.87	(1.48–2.36)	
70–74 vs. > 74 years	0.96	(0.67–1.37)		1.51	(1.20–1.88)	
Tumor size			< 0.0001			< 0.0001
11–20 vs. 0–10 mm	1.23	(0.91–1.67)		1.21	(0.98–1.50)	
21–30 vs. 0–10 mm	1.71	(1.27–2.33)		1.48	(1.19–1.83)	
> 30 vs. 0–10 mm	2.27	(1.67–3.09)		2.04	(1.64–2.54)	
Lymph node status			< 0.0001			< 0.0001
1–3 positive vs. 0	1.92	(1.59–2.33)		1.35	(1.18–1.55)	
4–9 positive vs. 0	3.52	(2.87–4.33)		2.15	(1.85–2.50)	
> 9 positive vs. 0	7.14	(5.76–8.84)		3.39	(2.87–4.00)	
Histological type			0.003			0.56
Lobular vs. ductal	1.33	(1.34–1.91)		1.08	(0.94–1.24)	
Other types vs. ductal	0.75	(0.45–1.25)		1.01	(1.64–2.19)	
Malignancy grade†			< 0.0001			< 0.0001
Grade 2 vs. 1	1.53	(1.30–1.79)		1.19	(1.06–1.33)	
Grade 3 vs. 1	2.77	(2.30–3.34)		1.90	(1.64–2.19)	
Lymphovascular Invasion‡			< 0.0001			< 0.0001
Present vs. absent	1.93	(1.56–2.39)		1.26	(1.13–1.40)	
ER expression level§			< 0.0001			0.0001
10–59% vs. 100%	1.82	(1.49–2.21)		1.54	(1.28–1.85)	
60–89% vs. 100%	1.27	(1.04–1.54)		1.31	(1.10–1.55)	
90–99% vs. 100%	1.33	(1.10–1.60)		1.23	(1.04–1.46)	
Positive but % unknown vs. 100%	1.43	(0.95–2.14)		1.33	(0.90–1.95)	
Treatment adherence			0.002			0.0008
Discontinued vs. continuing	1.45	(1.14–1.85)		1.26	(1.11–1.44)	
Local and regional therapy			< 0.0001			< 0.0001
BCS + RT vs. Mastectomy	0.69	(0.60–0.80)		0.72	(0.63–0.83)	
Mastectomy + RT vs. Mastectomy				0.93	(0.82–1.06)	

†Grade was determined in ductal and lobular carcinomas according to Elston and Ellis; ‡An interaction was in the multivariate analysis of RFS observed between presence of LVI and time since surgery and the figures shown represent years 0 to 2; §An interaction was in the multivariate analysis of RFS and SMR observed between ER and time since surgery and the figures shown represent years 0–5.

The sliding window approach of Subpopulation Treatment Effect Pattern Plots (STEPP) were used to explore the pattern of effect from tumor size and nodal status with respect to age at surgery and the magnitude of ER expression [11]. Multivariable fractional polynomials (MFP) were used to assess the functional form of continuous prognostic variables and to assist building the multivariate Cox and Poisson regression models in addition to cut-points previously used by the Statistical Office of the DBCG [9,12–14]. A MFP regression analysis with age, tumor size, number of positive lymph nodes, and percent ER positive cancer cells kept as continuous and expressed with FP was performed, using the Cox proportional hazards model for RFS and the Poisson regression model for SMR. In addition a regression model was used to assess the hazard ratios within subgroups. Factors included in the multivariable analyses were age (50–54, 55–59, 60–64, 65–69, 70–74, >74 years), tumor size (0–10, 11–20, 21–30, >30 mm in diameter), number of positive lymph nodes (0, 1–3, 4–9, >9), histological type (ductal, lobular, other histological types), lymphovascular invasion (yes, no), grade (1, 2, 3) and percent ER tumor cells (<60%, 60–89%, 90–99%, 100%), local therapy (mastectomy without radiotherapy, mastectomy with radiotherapy, BCS with radiotherapy), and systemic therapy (tamoxifen, tamoxifen and AI in sequence, AI as monotherapy). The assumption of proportional hazards was assessed by Schoenfeld residuals. The hazard rates of lymphovascular invasion as well as ER status were not proportional, and a time-dependent component was included in the model. Interactions between covariates were investigated in separate models by applying the Wald test in the multivariate categorical models and by using MFP Interaction models (MFPI). The Kaplan-Meier method was used to estimate the proportion of patients who continued endocrine therapy [15]. Patients adherent to therapy were censored at the date of recurrence, death or other reason for off-study. Also, discontinuation was included in the multivariate analyses as a time dependent variable. All p-values are two-sided. Central review, monitoring, and statistical analyses were done by the DBCG Statistical Office using SAS v9.2 (SAS Institute, Inc., Cary, USA), R v2.13.0 and the STATA v11.0 (StataCorp, Texas, USA).

Results

From January 1996 to December 2004 a total of 30 971 women underwent breast cancer surgery at a

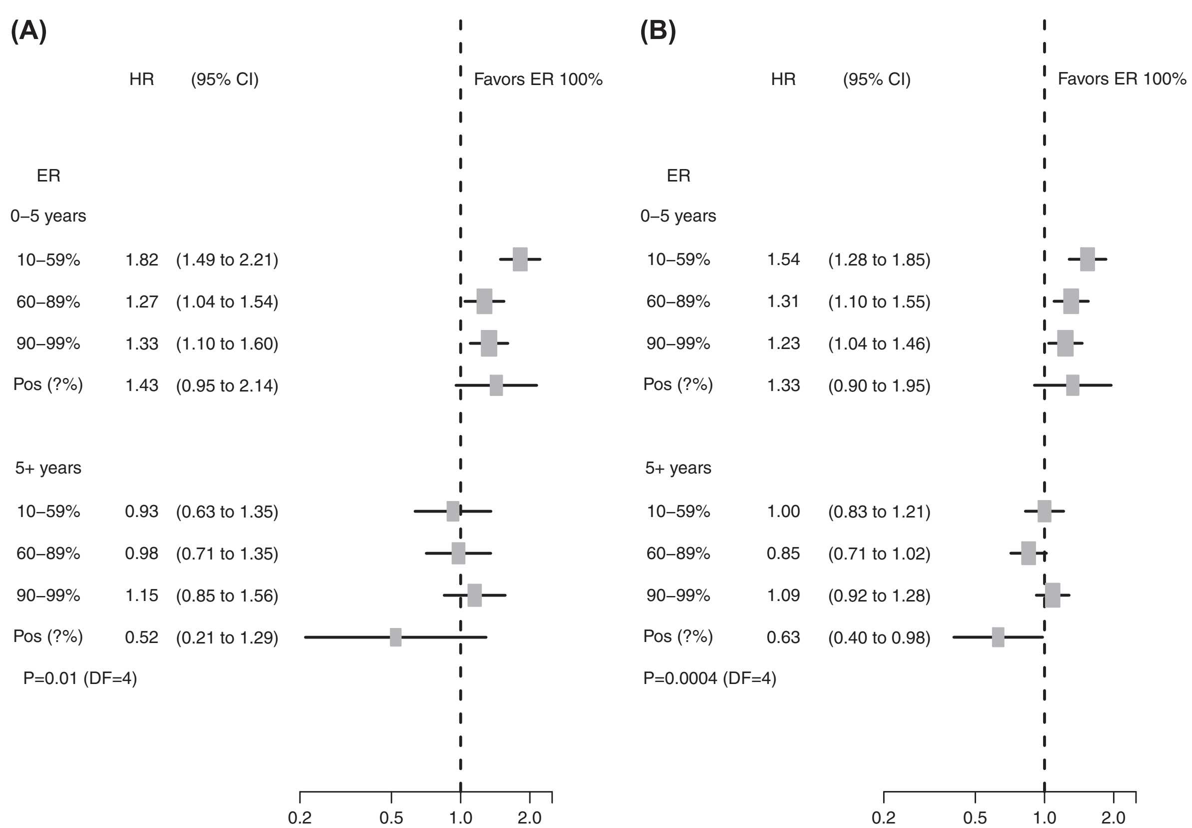

Figure 2. Adjusted hazard ratios for recurrence-free survival (RFS) (Panel A) and standardized mortality ratio (SMR) (Panel B) by time since surgery for patients with 10–59%, 60–89% and 90–99% estrogen receptor positive tumors compared to patients with 100% positive tumors.

Danish breast center and among these we identified 7163 postmenopausal patients who initiated therapy and who were eligible for this cohort study (Figure 1). Detailed treatment information was available from 6529 (91.1%) patients and complete follow-up for survival was achieved for 6515 patients (91.0%) while 14 patients emigrated 18–122 months after surgery. The estimated median potential follow-up for RFS and overall survival was 7.8 and 8.9 years, respectively. Mean age at BCS or mastectomy was 62.8 years, and Table I summarizes patient and tumor characteristics.

Analyses of recurrence-free survival (RFS)

At 10 years 1157 patients (21.0%) had a breast cancer recurrence as first event, and 18.2% had another first event (contralateral breast cancer, second malignancy or death without recurrence). Factors significantly associated with prognosis in univariate RFS analyses ($p < 0.0001$) were tumor size, nodal status, histological type, grade, ER expression levels, lymphovascular invasion, and loco-regional therapy, while age was not ($p = 0.36$). These results were confirmed by a multivariate analysis using previously defined categories (Table II) [9,14]. The RFS benefits observed by high levels of ER expression were obtained primarily during the first five years after surgery (Figure 2A) and the detrimental effects of lymphovascular invasion were accomplished the first two years. A second multivariate Cox regression model using MFPs broadly confirmed the prognostic value of tumor

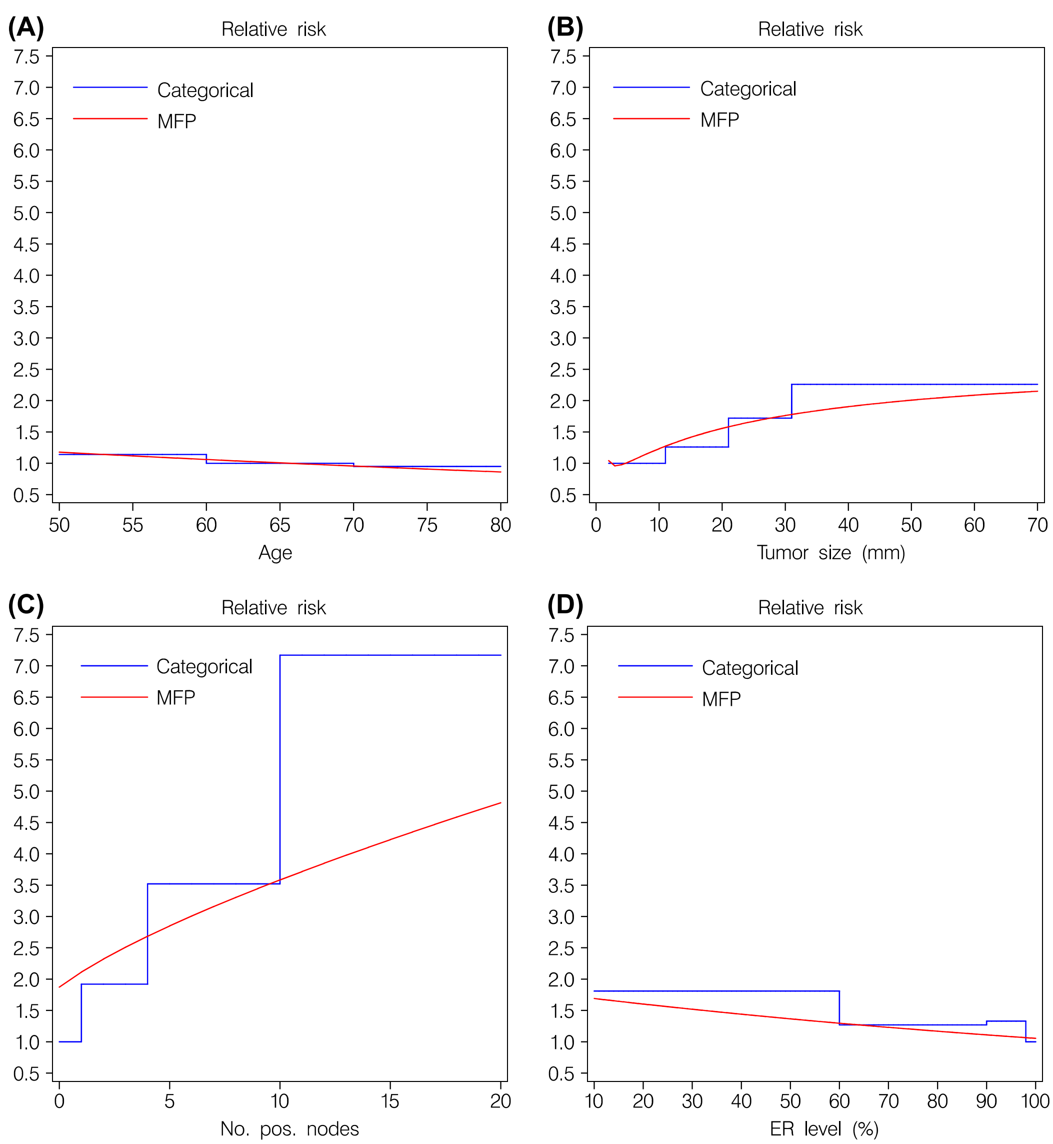

Figure 3. Functional influence of age (Panel A), tumor size (Panel B), number of positive lymph nodes (Panel C), and ER levels (Panel D) on time to recurrence using continuous factors based on multiple fractional polynomials (red line) or pre-defined cut-points for each factor (blue line).

size, positive lymph nodes, and ER expression when used as continuous factors in combination with the categorical variables (lymphovascular invasion, grade, histological type and loco-regional treatment). The estimates of the functional relationship between the four continuous factors and RFS were similar in the multivariate models using categorized and continuous variables (Figure 3).

STEPP analyses demonstrated an increasing 10-year RFS with increasing ER expression in node positive but not in node negative patients (Figure 4A), with $p = 0.01$ for interaction. A similar pattern was not seen according to increasing age at surgery (Figure 4B). When comparing patients with larger (> 20 mm) tumors to patients with smaller (0–20 mm) tumors with ER level (Figure 4C) or according to age at surgery (Figure 4D), no significant interactions were found.

Analysis of OS and SMR

Of the 6529 women in the study cohort 2014 died (10-year OS 67.3%; 95% CI 65.9–68.6) while 949 deaths were expected (SMR 2.12; 95% CI 2.03–2.22:

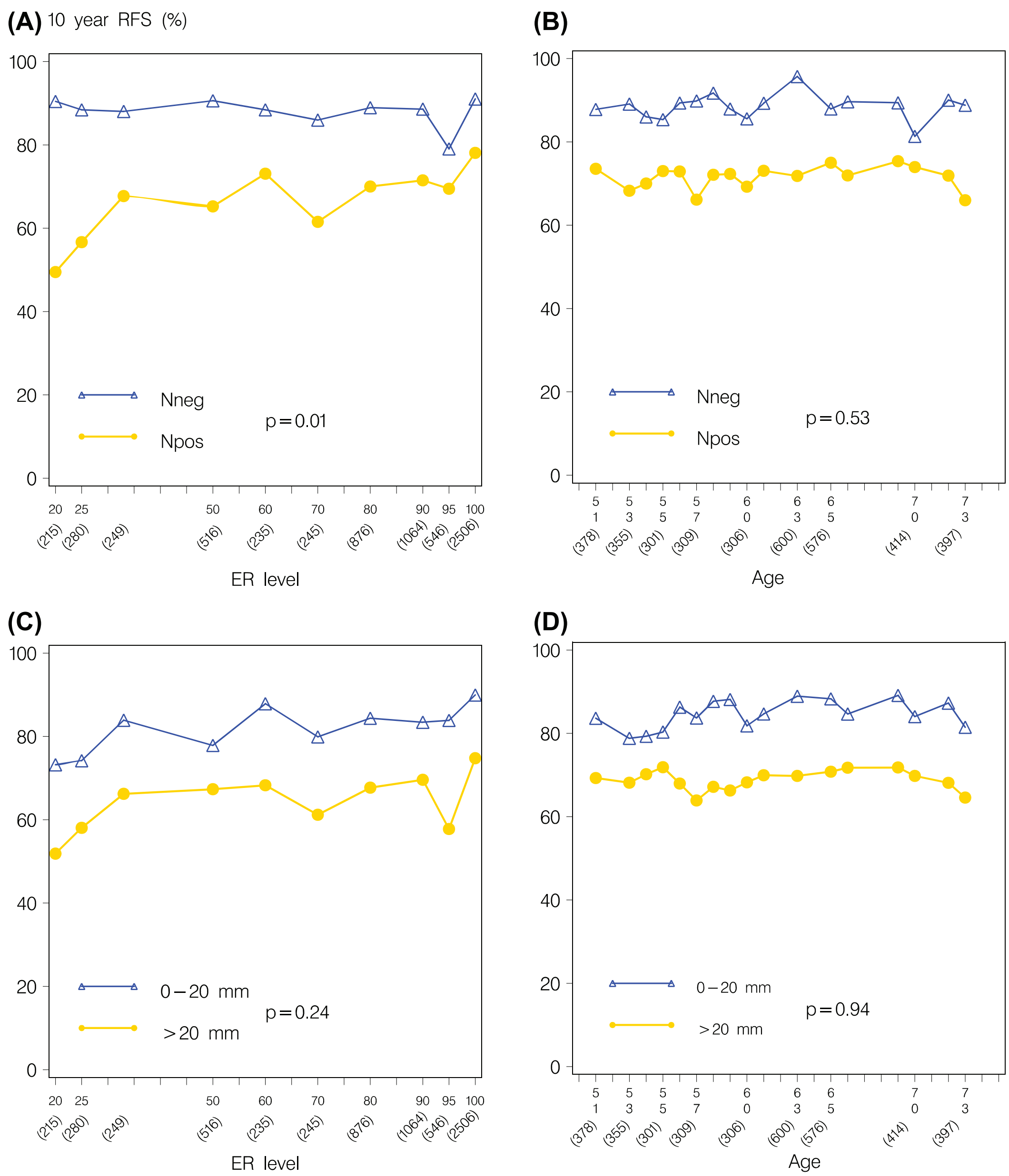

Figure 4. Subpopulation treatment effect pattern plots (STEPP) of 10-year recurrence-free survival (RFS) percents for node positive versus node negative for overlapping subpopulations defined according ER levels (Panel A) and age at surgery (Panel B), for larger (> 20 mm) versus smaller (≤ 20 mm) tumors according to ER levels (Panel C) and age at surgery (Panel D). The values on the x-axis show median values of ER and age for patients in each subpopulation with the number of patients given in brackets. The p-values, based on simulations, are for tests of interaction.

$p < 0.0001$) [16]. Age at surgery, nodal status, tumor size, histological type, grade, ER expression levels, lymphovascular invasion, and loco-regional therapy were all significantly ($p < 0.0001$) associated with excess mortality in univariate analyses. A multivariate analysis of SMR, using categories as specified in the analysis of RFS, confirmed that excess mortality declined with increasing age at diagnosis ($p < 0.0001$). Furthermore, a highly significant association ($p < 0.0001$) regarding nodal status, tumor size, grade, lymphovascular invasion, ER, and loco-regional therapy was confirmed in the multivariate analysis of SMR (Table II) while histological type not was significantly associated with SMR ($p = 0.56$). Again, the benefits of high ER expression were mainly achieved the first five years (Figure 2B). The prognostic value of age, tumor size, positive lymph nodes, and ER expression was confirmed when they were included as continuous factors in a second multivariate regression model based on MFP analyses (Figure 5).

Adherence to treatment and treatment type

Overall 879 event-free patients discontinued endocrine therapy equivalent to a 84.6% (95% CI 83.8–85.5) treatment adherence at five years, and 140 of the 879 patients resumed endocrine therapy. Discontinuation of endocrine therapy was associated with a significantly higher risk of recurrence (adjusted HR 1.45; 95% CI 1.14–1.85; $p = 0.002$) and mortality excess (adjusted RR 1.26; 95% CI 1.11–1.44; $p = 0.0008$). The proportion of patients who received

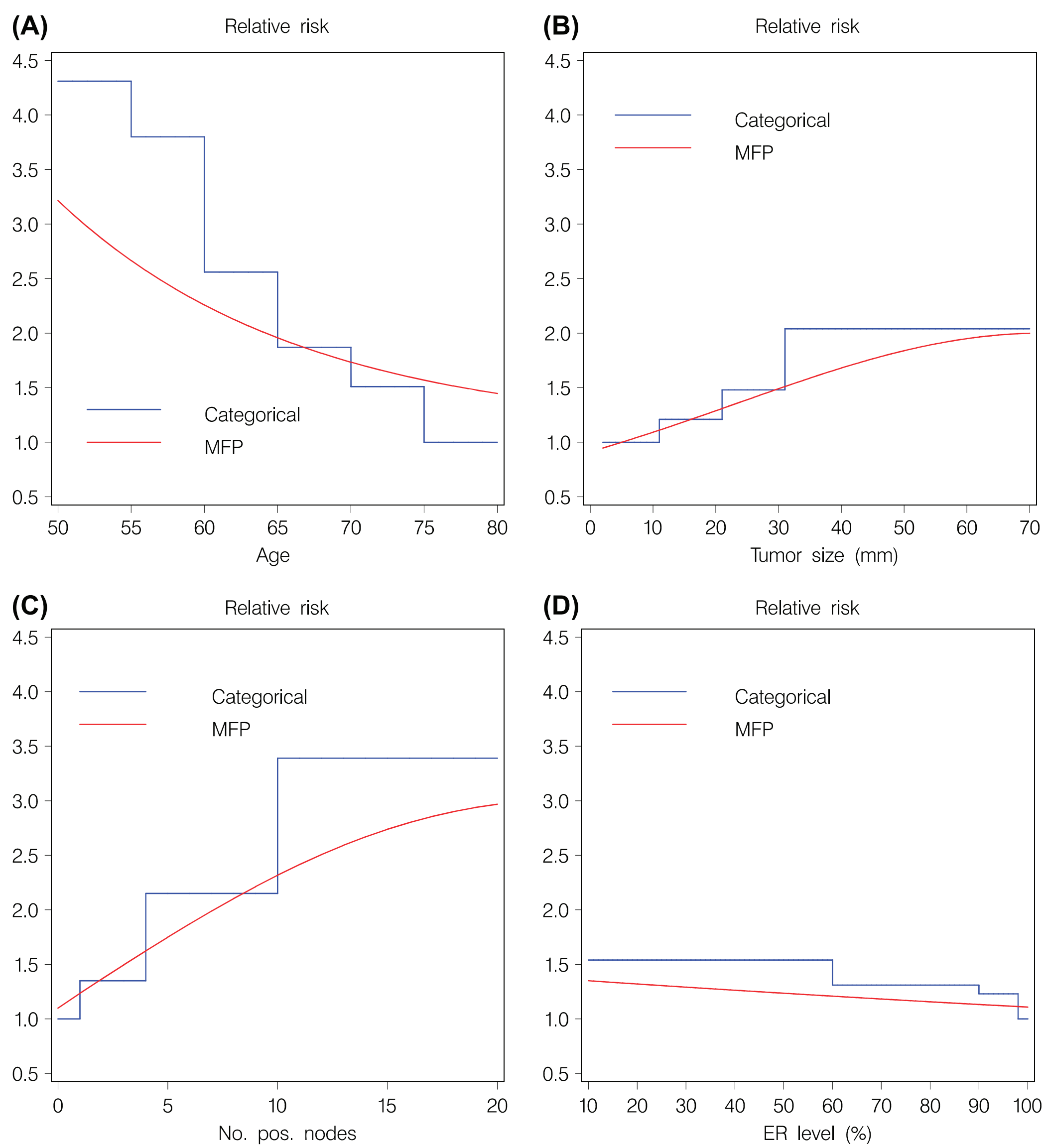

Figure 5. Functional influence of age (Panel A), tumor size (Panel B), number of positive lymph nodes (Panel C), and ER levels (Panel D) on standardized mortality ratio (SMR) in multivariate models using continuous factors based on multiple fractional polynomials (red line) or pre-defined cut-points for each factor (blue line).

an AI increased substantially during the study period. As we were unable to adjust for time period separately the significantly lower risk of recurrence (adjusted HR 0.72; 95% CI 0.62–0.83; $p < 0.0001$) and less pronounced mortality excess (adjusted RR 0.88; 95% CI 0.78–0.98; $p = 0.03$) holds a risk of a considerable bias in favor of AI when compared to tamoxifen.

Identifying patients free of excess mortality

By summing the significant risk factors weighted by the estimated regression coefficients (β) in the MFP model (Table III) we constructed a prognostic SMR index (PSI). When patients were divided into quartiles according to PSI, those with the lowest risk (Q1) had a mortality similar to the background population, and excess mortality progressively increasing for each subsequent quartile. The PSI allocated less than 1% of patients younger than 54 to the quartile with the lowest risk compared to 74% of patients 75 or older (Table IV).

We proceeded to construct a SMR low-risk subset by a flowchart algorithm based on the risk factors previously used to construct the PSI (Table II). Under the guidance of Figure 3 and previously used cut-points [9,14], we identified the following node negative subsets who were free of excess mortality 1) age ≥ 50, tumor size ≤ 10 mm, and malignancy grade I–II; 2) age ≥ 60, tumor size 11–20 mm, malignancy grade I–II; and 3) age ≥ 65 and either tumor size ≤ 20 mm or malignancy grade I–II. Similarly among patients with 1–3 positive nodes two subsets were free of excess mortality; 1) age ≥ 65, tumor size ≤ 20 mm, and malignancy grade I–II; and 2) age ≥ 75, and either tumor size ≤ 20 mm or malignancy grade I–II. None of the remaining subsets were free from excess mortality. When dividing patients into a low- and high-risk group by the flowchart algorithm we were unable to identify a subset without excess mortality among patients with four or more positive nodes, while 37 were assigned to the SMR low-risk group by the PSI (Table IV). A total of 1665 patients were by the flowchart approach classified as being free of excess mortality. SMR was 1.14 (95% CI 0.91–1.43) among the 383 patients assigned to be free of excess mortality by PSI but discordantly assigned by the flowchart algorithm to an increased SMR (Figure 6). In contrast SMR was significantly increased (1.38; 95% CI 1.16–1.65) in the 462 patients who by the flowchart algorithm were allocated to a group without excess mortality but discordantly classified to a group with increased SMR by the PSI. Furthermore ER expression levels did not influence boundaries of the SMR low-risk subset obtained by the flowchart algorithm, not even in patients with 1–3 positive nodes where the STEPP analysis showed a significant relationship.

Discussion

The present population-based study on postmenopausal patients with ER positive breast cancer clearly illustrates that even if given adequate local and endocrine therapy, only one quarter of these women will be free of excess mortality when compared to the general population.

Non-adherence to endocrine therapy was associated with a significantly increased risk of a RFS event and excess SMR. Treatment compliance in our cohort was high, as only 879 patients (16%) discontinued treatment without a disease event. Others have reported a compliance of 49–89% at five years [15, 17–21]. Possible reasons for the high compliance in our cohort include nationwide implemented practice guidelines, use of a centralized treatment assignment algorithm, continued follow-up at a Department of Oncology within a multidisciplinary breast cancer

Table III. Prognostic Index; β coefficients according to MFP regression model of SMR.

Characteristics		β coefficient
Age	Continuous	−0.0602
Tumor size	(Tumor size mm/100)	2.9910
	(Tumor size mm/100)^2	−2.0650
Nodal status	(No. pos. nodes + 1)/10	1.2837
	(No. pos. nodes + 1)/10 × log(no. pos. nodes + 1)/10	−0.6777
Histological type	Lobular	0.1191
	Other than ductal or lobular	0.0897
Malignancy grade	Continuous	0.3212
Lymphovascular invasion	Present	0.2215
ER status	Continuous	−0.0025
Treatment adherence	Discontinuing	0.2557
Local and regional therapy	BCS and radiotherapy	−0.3389
	Mastectomy & radiotherapy	−0.0825
AI cohort	Yes	−0.1717

Table IV. Characteristics of patient's subsets according to risk classification.

	Low risk		Intermediate low risk		Intermediate high risk		High risk	
Standard mortality ratio (SMR)	0.96		1.58		2.43		5.86	
95% CI	0.86–1.06		1.43–1.75		2.21–2.61		5.46–6.29	
	N	(%)	N	(%)	N	(%)	N	(%)
Age at surgery								
50–54 years	4	< 1%	83	5%	276	17%	421	27%
55–59 years	95	6%	388	24%	532	34%	531	33%
60–64 years	265	17%	432	27%	385	24%	368	29%
65–69 years	492	31%	390	25%	230	15%	175	11%
70–74 years	529	33%	252	16%	144	9%	85	5%
> 74 years	201	13%	42	3%	20	1%	7	< 1%
Tumor size								
≤ 10 mm	302	19%	151	10%	85	5%	23	1%
11–20 mm	759	48%	756	48%	632	40%	310	20%
21–30 mm	450	28%	506	32%	58	37%	597	38%
> 30 mm	75	5%	174	11%	290	18%	657	41%
Lymph nodes								
Negative	842	53%	590	37%	419	26%	100	6%
1–3 positive	707	45%	870	55%	841	53%	470	30%
4–9 positive	34	2%	115	7%	275	17%	551	35%
> 9 positive	3	< 1%	12	1%	52	3%	466	29%
Histological type								
Ductal carcinoma	1356	86%	1307	82%	1308	82%	1307	81%
Lobular carcinoma	148	9%	230	15%	229	16%	259	18%
Other or unclassified	82	5%	50	3%	50	1%	21	1%
Malignancy grade								
Grade 1	547	34%	441	28%	328	21%	158	10%
Grade 2	807	51%	822	52%	818	52%	789	50%
Grade 3	79	5%	142	9%	252	16%	444	28%
Not done*	153	10%	182	11%	189	12%	196	12%
Lymphovascular invasion								
Absent	1521	96%	1457	92%	1312	83%	914	58%
Present	65	4%	130	8%	275	17%	673	42%
ER expression								
10–59%	101	6%	167	11%	272	17%	378	24%
60–89%	275	17%	326	21%	378	24%	410	26%
90–99%	401	25%	460	29%	436	27%	412	26%
100%	809	51%	634	40%	501	32%	387	24%
Total	1586		1587		1587		1587	

*Malignancy grading was not performed systematically in non-ductal carcinomas.

center, provision of drugs free of charge, written information about treatment to the patients from the DBCG, and quality assurance founded on continuous follow-up and prospective registration of treatment and disease events in a nationwide clinical database.

Tamoxifen was gradually exchanged with letrozole during the study period and patients who received an AI (primarily letrozole) either as monotherapy or in sequence with tamoxifen had a significant 28% reduction in the risk of a RFS event and a 12% reduction in SMR as compared to those treated with tamoxifen alone. The gradual introduction of AI may have introduced a bias although the results from this observational cohort are in line with trials of AI's demonstrating a 15–20% reduction in the risk of a RFS event when compared to tamoxifen alone [17,18].

Unfortunately, excess mortality was revealed among groups comprising three quarters of postmenopausal patients with ER positive tumors. There is growing awareness of endocrine resistance (primary or acquired) through the PI3K-AKT-mTOR signaling pathway, and in advanced breast cancer the addition of everolimus to endocrine therapies have improved clinical outcome [22]. However, the addition of chemotherapy is currently the only option further to reduce mortality in postmenopausal patients with early ER positive and HER2 negative breast cancer [1].

The frequency of RFS events was similar across age groups, but excess mortality inflicted by breast

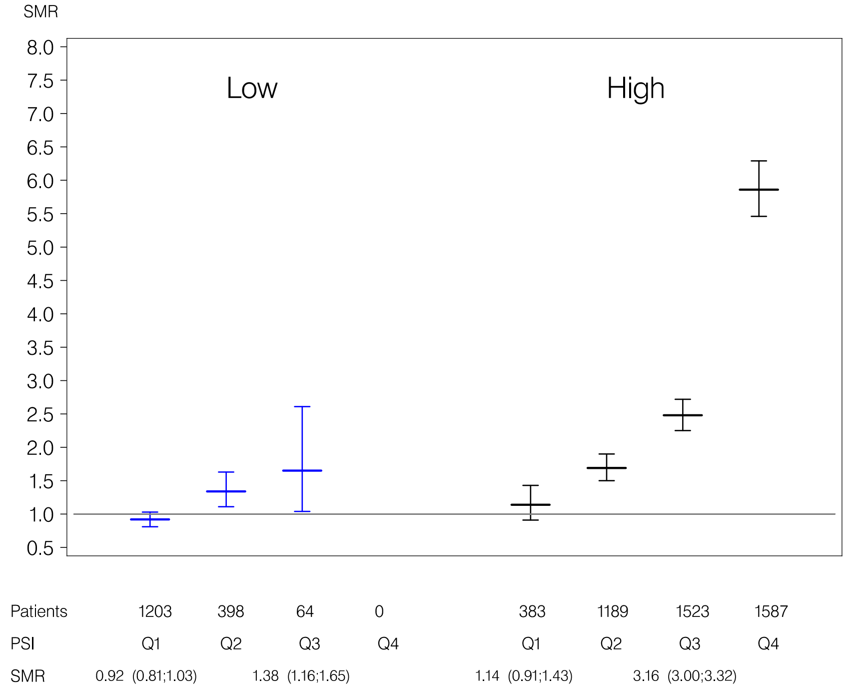

Figure 6. Standard mortality ratio (SMR) grouped as low risk or high risk according to the flowchart algorithm, and for each category sub-grouped as low (Q1), intermediate low (Q2), intermediate high (Q3), and a high risk (Q4) according to the prognostic SMR index (PSI). SMR is shown with 95% confidence interval.

cancer recurrences gradually decreased as the risk of mortality from co-morbidity increased with older age. The importance of classical prognostic factors including nodal status; tumor size; malignancy grade; lymphovascular invasion; and ER expression level was confirmed in the categorical and the MFP model, and for RFS as well as SMR.

Noteworthy, ER expression levels and lymphovascular invasion lost their impact on SMR when subsets were constructed by a flowchart algorithm but were preserved in the PSI constructed using the MFP model. In the PSI low risk quartile, lymphovascular invasion was however rare as shown previously [9]. All significant factors identified in the multivariate models are involved in the calculation of a patients PSI and the PSI is therefore expected to more accurately reflect the individual patients risk of excess mortality. Nevertheless, the number of patients classified as being free of excess mortality does not change substantially as a result of a more precise identification and the same may prove to be the case by the introduction of multigene assays.

The strengths of our study include a study cohort prospectively identified by a standardized treatment algorithm, use of standardized breast cancer management guidelines including diagnostic procedures, surgical treatment, radiotherapy, medical therapy, and follow-up. For example, omission of radiotherapy has in the systematic EBCTCG overview been associated with an increase in the risk of recurrence and deaths while conflicting results have been reported from population-based observational studies [23]. Finally, the use of registries complementing the DBCG database allowed us to estimate SMR that in contrast to OS allow to separate breast cancer specific events from non-breast cancer deaths events. The noise inflicted by competing mortality will increase with increasing age, and use of composite endpoints will increasingly confuse the possibility to separate biological aggressiveness from deaths from other causes, e.g. ischemic heart disease, stroke and non-breast cancer [24].

Our study also had some limitations. First, despite a large initial study population certain subsets were small following stratification according to age, nodal status, tumor size and other variables yielding limited statistical power for the affiliated questions. Adjustment according to specific co-morbidities may in some situations be more accurate than relative mortality. Furthermore, no attempt was made to adjust for multiple comparisons based subgroup analyses, and these results consequently should be regarded as explorative in nature. Incorporation of information on intrinsic biological subtypes using gene expression arrays or even a simplified clinocopathological approximation could possibly have enabled us more precisely to identify a subset with a good prognosis [25]. Although the DBCG database provides extensive information on tumor characteristics and treatment, some important tumor characteristics including HER2 status and Ki67 is currently not available. The results of the current study, however, urge caution when the impact of newer potential prognostic factors or multigene assays is judged against risk assessments based on simplified clinicopathological models.

In conclusion, excess mortality affects the majority (75%) of postmenopausal high-risk patients who only receive endocrine therapy adjuvant for ER positive early breast cancer. Non-adherence to endocrine therapy increases mortality while receiving an AI reduces SMR as compared to tamoxifen alone. A PSI more precisely identified patients without excess mortality but did not identify a substantial larger proportion as having mortality similar to the general population when compared to categories constructed by individual risk factors.

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