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Generalisability of survival estimates for patients with breast cancer – A comparison across two population-based series ☆

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ABSTRACT

The purpose of the study was to analyse the generalisability and geographic transportability of survival estimates produced by commonly used prognostic factors. We compared the influence of tumour size, histologic grade, axillary nodal status, oestrogen and progesterone receptor contents, age at diagnosis and two prognostication schemes (the Nottingham Prognostic Index and St. Gallen criteria) in two nationwide cohorts of patients diagnosed with breast cancer in 1991–2, the FinProg ($n = 2923$, Finland) and the SEER series ($n = 43{,}249$, the United States (US)). Eight-year estimates of breast cancer-specific (84% versus 80%), relative (86% versus 83%), and overall (70% versus 69%) survival were slightly more favourable in the SEER than in the FinProg series, respectively. Despite differences in demographic variables and the frequency of use of adjuvant therapies and mammography screening between the series, the prognostic factors examined produced close to overlapping survival curves with similar shapes. The results suggest that quantitative survival estimates based on frequently used prognostic factors and prognostication schemes are generalisable and transportable between large, unselected cohorts of breast cancer patients.

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1. Introduction

Assessment of the risk of recurrence is of prime importance when considering the need and type of adjuvant therapy for women diagnosed with breast cancer, since adjuvant therapy markedly reduces death rates but at the expense of adverse effects and costs.[1] The risk of recurrence is commonly estimated based on a few selected prognostic factors, although

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emerging technologies probably will change the current practice.[2,3] In addition, tools to generate more individualised and quantitative outcome estimates have been developed.[4–8] The Nottingham Prognostic Index (NPI) and St. Gallen consensus criteria are also commonly used in prognostication. The NPI uses the tumour size, nodal stage, and histological grade as prognostic variables, and the St. Gallen criteria include age at diagnosis, tumour size, nodal status, histological grade, peritumoural vascular invasion and HER2 expression or amplification.[6,9]

There are little data available on how the commonly used prognostic factors and prognostication schemes perform in large, unselected patient series, and whether quantitative survival estimates based on these factors can be transported across populations.[10,11] Several potential biases and variability in assessment of prognostic factors exist and may lead to poor reproducibility, and the number of validated factors remains small.[12,13] Positive oestrogen receptor (ER) or progesterone receptor (PgR) status is being defined using variable cut-off levels of receptor protein expression, and assessment of the histological grade of differentiation is subjective and determined according to different protocols. In the present study we examined the efficacy and reproducibility of the factors included in the NPI and the St. Gallen criteria in prediction of survival in two population-based breast cancer series: a series from Finland (the FinProg series) and the Surveillance, Epidemiology, and End Results (SEER) Program series of the United States (US).

2. Materials and methods

2.1. The FinProg series

The FinProg series is based on the Finnish Cancer Registry data, which includes close to 100% of all breast cancers diagnosed in Finland since 1952. According to this registry, a total of 5551 invasive breast cancers were diagnosed in Finland during the two-year period of 1991 to 1992. We selected five well-defined geographical regions comprising approximately 50% of the Finnish population for the present study (the Helsinki and Uusimaa region, Pirkanmaa, Varsinais-Suomi, Northern Savo, and Northern Bothnia and Lapland),[14] where 2930 breast cancer cases were diagnosed between January 1, 1991 and December 31, 1992. Individual clinical data were extracted from the hospital case records, hospital registries, the Finnish Cancer Registry, and Statistics Finland including the histological type and grade of breast cancer, the number of metastatic and non-metastatic nodes, primary tumour size, tumour ER and PgR content (assessed usually using immunohistochemistry), treatment details, and follow-up data. Histological samples of the primary tumours were also collected and assembled into tissue microarrays.[14,15] Histological typing and grading of cancer were done by more than 50 pathologists at the time of the diagnosis according to the World Health Organization guidelines, and scored as well (grade 1), moderately (grade 2), or poorly differentiated (grade 3).[16]

Male patients, and women diagnosed with bilateral cancer, carcinoma *in situ*, or other invasive cancer than breast cancer were excluded, as well as women who had overt distant metastases at the time of the diagnosis or who did not undergo breast surgery, leaving 2036 women in the final data set (accessible at http://www.finprog.org/seer). The median follow-up time of the individuals alive at the end of the study period was 9.5 years. Thirteen percent received chemotherapy, 23% hormone therapy, and 0.5% received both. In the subset of patients with node negative disease 8.8% received adjuvant therapy; 6.2% received chemotherapy, 2.4% hormone therapy, and 0.2% data on the type of adjuvant treatment was not available to us. Adjuvant therapy was given to 92.3% of the women with node-positive disease; 52.0% received chemotherapy, 36.1% hormone therapy, 1.1% received both, and in 3.1% the type of adjuvant treatment administered was not available.

A nationwide mammography screening program has been active in Finland since 1987. Because of legislation, 460 municipalities in Finland had to screen women aged 50 to 59 years during 1991 and 1992 and the overall compliance was 89%.[17] However, a few of the municipalities decided also to screen other age cohorts (40–49 years, or $\geqslant$60 years). Twenty-two percent of the patients in the entire FinProg series were diagnosed based on tumours detected by mammography screening; 9% of those younger than 50 years at the time of the diagnosis, 49% of those aged 50 to 64, and 6% of those who were 65 or older.[15]

2.2. The SEER series

The SEER Program is a set of geographically defined, population-based, central cancer registries in the US, operated by local nonprofit organisations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research. From the SEER 1973–2001 Public-Use Data a subset of 43,238 women diagnosed with breast cancer in 1991 or 1992 was extracted,[18] and after applying the same exclusion criteria as for the FinProg series (see above) 25,753 women with operable, unilateral invasive breast cancer were left in the analysis. The median follow-up for the patients alive at the cut-off date of the April 2004 release, based on the November 2003 submission, was 9.7 years.

In the SEER data, histological grading was coded either using a three-grade system from grade 1 (well differentiated) to grade 3 (poorly differentiated), or a four-grade scale from grade 1 (well differentiated) to grade 4 (undifferentated). Information on adjuvant treatment has not been made available in the SEER Public-Use data due to underreporting of data on treatment given outside of the hospital setting. Approximate figures on the percentages of the women who received adjuvant therapy in 1991 to 1992 by age and tumour stage within the regions that participate in SEER data collection are found in reports that combine the SEER data with the data produced by the Patterns of Care (POC) studies.[19,20] According to these sources, approximately 66% of the breast cancer patients received adjuvant therapy in 1991 to 1992; 18% received chemotherapy, 35% hormone therapy, and 9% received both.

The SEER data does not contain information on the use of mammography screening or the method of tumour detection. Approximations for these can be derived from a study based on the National Health Interview Survey (NHIS), a multipur-

pose health survey conducted by the National Center for Health Statistics.[21] According to this source 56% of women aged under 50 years, 61% of those aged 50 to 64, and 48% of those aged 65 or older reported recent (during the past 2 years) use of screening mammography in 1992.

2.3. *The St. Gallen consensus criteria and the Nottingham Prognostic Index*

According to the St. Gallen criteria, node negative patients older than 35 at diagnosis with a well-differentiated (grade1) tumour smaller or equal to 2 cm in diameter, with neither peritumoural vascular invasion nor HER2 overexpression or amplification, have a low risk for breast cancer recurrence. Patients who do not fulfill these criteria are classified as having an intermediate-high risk for recurrence.[9] In the present study we adopted slightly modified St. Gallen criteria, not taking peritumoral vascular invasion or HER2 status into account, since these data were not available in the SEER dataset. The Nottingham Prognostic Index was calculated using the following formula: tumour size in cm $\times$ 0.2 + lymph-node stage (node negative = 1, 1–3 positive nodes = 2, and >3 positive nodes = 3) + histologic grade (1, 2 or 3). The Nottingham 'excellent or good prognosis', 'moderate prognosis' and 'poor prognosis' groups were defined as those patients with an index value of $\leqslant$3.40, 3.41–5.40, and >5.40, respectively.[6]

2.4. *Statistical analysis*

Frequency tables were analysed using the χ^2 test. Life-tables were calculated according to the Kaplan–Meier method. Overall survival (OS) was calculated from the date of the diagnosis to the date of death of any cause, and breast cancer-specific survival (BCSS) from the date of diagnosis to the date of death from breast cancer, censoring deaths from intercurrent causes. Survival curves were compared with the logrank test.

Table 1 – Distribution of clinicopathologic variables

Variables	FinProg *n*(%)	SEER *n* (%)	χ^2	*P*
Age at diagnosis				
<35	46 (2)	739 (3)	56.3	<0.0001
35–49	521 (26)	6245 (24)		
50–64	734 (36)	7618 (30)		
>=65	735 (36)	11120 (43)		
Tumour size				
0.1–0.5 cm	55 (3)	1452 (6)	44.4	<0.0001
0.6–1.0 cm	334 (17)	4379 (18)		
1.1–2.0 cm	819 (42)	9170 (39)		
2.1–5.0 cm	666 (34)	7382 (31)		
>5 cm	71 (4)	1361 (6)		
0.1–2.0 cm	1208 (62)	15001 (63)	0.84	0.36
>2 cm	737 (38)	8743 (37)		
Nodal status				
0	1239 (66)	14706 (66)	46.7	<0.0001
1–3	452 (24)	4454 (20)		
4–9	154 (8)	1920 (9)		
>=10	37 (2)	1102 (5)		
negative	1239 (66)	14706 (66)	0.15	0.70
positive	643 (34)	7476 (34)		
No. of nodes examined				
<5	424 (25)	3932 (16)	1733.8	<0.0001
5–10	928 (55)	4385 (17)		
>10	348 (20)	16840 (67)		
Histological grade[a]				
1	394 (26)	2068 (12)	321.3	<0.0001
2	716 (47)	6991 (42)		
3–4	403 (27)	7713 (46)		
ER				
positive	1082 (70)	15359 (76)	29.3	<0.0001
negative	466 (30)	4835 (24)		
PgR				
positive	940 (61)	12955 (66)	16.0	<0.0001
negative	607 (39)	6729 (34)		

a Histological grade score 4 was not used in the FinProg series. Tumour size was missing in 4% and 8%, nodal status in 8% and 14%, number of examined nodes in 17% and 2%, histologic grade in 26% and 35%, ER in 24% and 21% and PgR in 24% and 23% of the patients in the FinProg and SEER series, respectively.

Relative survival was calculated according to the Ederer II method.[22] The relative survival ratio is defined as the observed survival in the patient group divided by the expected survival of a comparable group from the general population. Expected survival for the Finnish series was calculated based on population mortality data for the entire female population in Finland during the period from 1991 to 1996 published by Statistics Finland. For the SEER cohort the expected survival was based on the Decennial Life table for females in the US for the 1989–91 period published by the National Center for Health Statistics.[23] Multivariate survival analyses were performed with the Cox proportional hazards model, entering the following covariates: tumour size in centimetres, the number of metastatic lymph nodes, the number of examined lymph nodes, histological grade, ER expression, PgR expression, age at diagnosis, and series (FinProg or SEER). A *P* value of 0.05 was adopted as the limit for inclusion of a covariate. The assumption of proportional hazards was ascertained by assessment of log minus log survival plots. All *P* values are two-tailed.

3. Results

The two series differed in some respects (Table 1). The Finnish patients were Caucasian, and a higher proportion of them was diagnosed at the age of 50 to 59 probably due to the mammography screening program carried out by legislation in this age cohort in Finland, and relatively fewer were in their sixties or seventies. Although similar proportions of the US and Finnish patients had a primary tumour size 2 cm or smaller in diameter at diagnosis (63% and 62%, respectively), tumours smaller than 6 mm were less commonly detected in Finland (3% versus 6%). In both countries 66% of cancers were node-negative, but a substantially smaller proportion of the Finnish women had ten or more axillary lymph nodes examined histologically (20% versus 67%). Less well differentiated (grade 1) cancers and more grade 3 or 4 cancers were diagnosed in the US compared to Finland, but in Finland the grade category 4 was not used. ER or PgR positive cancers were somewhat more frequently diagnosed in the US than in Finland.

Overall survival was similar in the two series; 69% (95% confidence interval (CI), 67 to 71%) of the Finnish and 70% (95% CI, 70 to 71%) of the US patients were alive 8 years after the diagnosis (Fig. 1A). The 8-year breast cancer-specific survival was slightly better in the US than in Finland (84%, 95% CI 83% to 84%; versus 80%, 95% CI 78% to 82%; $P < 0.0001$), as was also the relative survival rate (86% versus 83%, respectively) (Fig. 1B and C). These differences were due to the better outcome of American women aged 65 or older. In a univariate Cox model stratified by age, the overall survival was significantly better for the US patients $\geqslant$65 years at diagnosis (SEER versus FinProg hazard ratio (HR) 1.34, 95% CI 1.21–1.48), whereas the opposite was found in patients aged 50–64 years (HR 0.80, 95% CI 0.67–0.95). Among patients aged 50 or less at the time of the diagnosis, there was no significant difference in survival between the two series (HR 1.09, 95% CI 0.92–1.29).

Despite differences between the two series, all prognostic factors investigated had remarkably similar association with survival, and produced close to overlapping survival curves with roughly similar shapes (Fig. 2). The only statistically significant differences between the series were found in the subset of women aged 65 or older at diagnosis ($P < 0.0001$), and between grade 2 or 3 cancers ($P = 0.003$). Subgroups created using either the NPI or the St. Gallen criteria had markedly different outcome within the series, but fairly similar outcome between the series (Fig. 2).

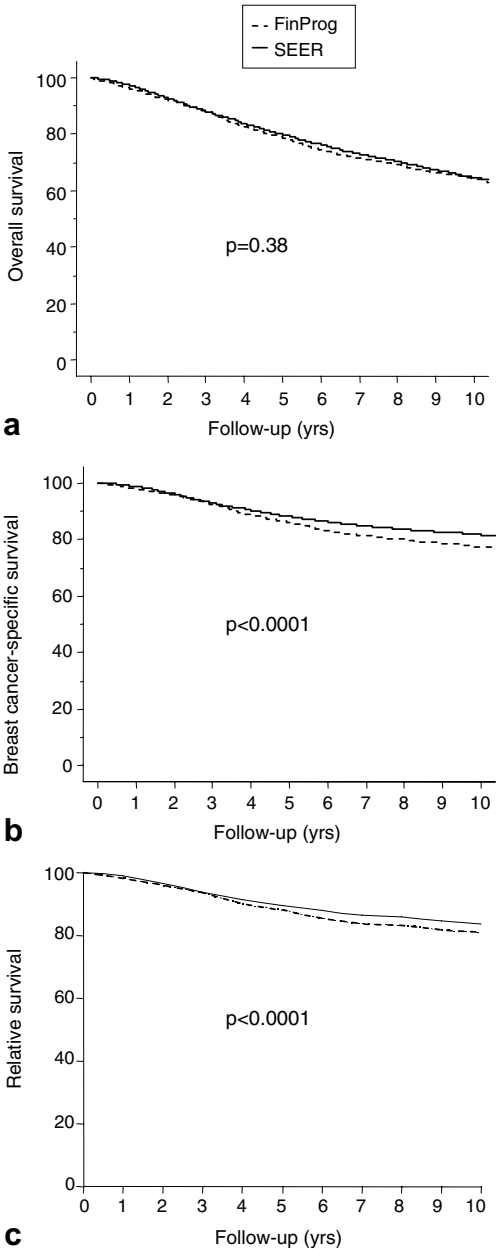

Fig. 1 – Overall, breast cancer specific, and relative survival in the SEER (n = 25,722; —) and FinProg series (n = 2036; - - -).

We entered the tumour size, the number of examined axillary lymph nodes, the number of positive axillary lymph nodes, the histologic grade, the ER and PgR status, age at diagnosis into a Cox multivariate hazard model that was based on the FinProg series and into another model that was based on the SEER series (Table 2). We also fitted a third Cox regression model using the pooled data from both series, and entered the series (SEER versus FinProg; n = 12,356) as a covariate to this model to examine the influence of the series on survival. Except for the series ($P = 0.61$; HR 0.97, 95% CI 0.86–1.10), all

other covariates that were entered into the model that was based on the pooled data had independent influence on survival ($P < 0.0001$ for each covariate, Table 2). Similarly, the series did not have an independent influence on survival in multivariate Cox models, based on the pooled data from the FinProg and the SEER series, that were fitted for age at diagnosis (age strata <50, 50–64, and ⩾65 were analysed separately; $P = 0.22$, 0.34, and 0.73, respectively).

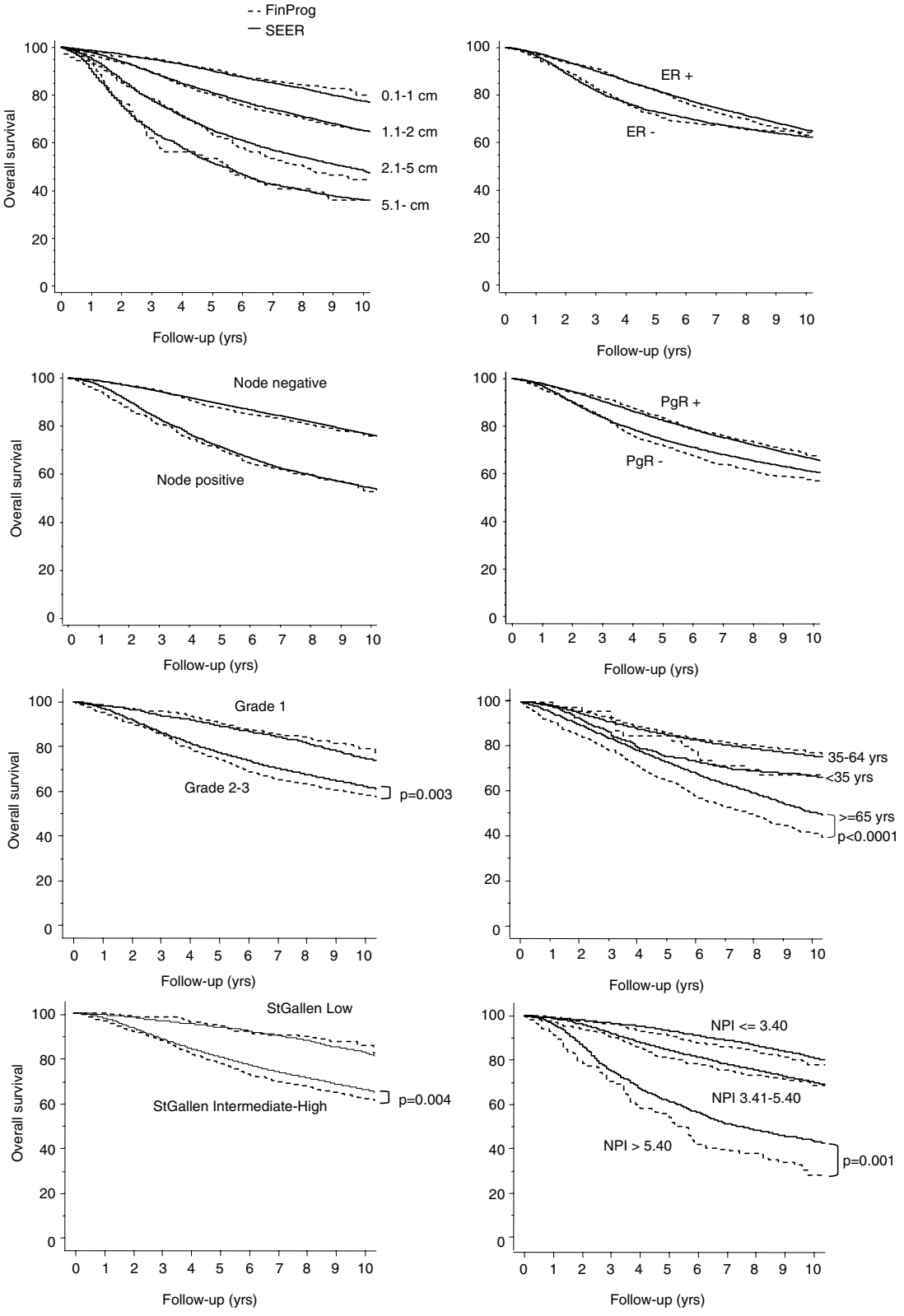

Fig. 2 – Overall survival according to prognostic factors and prognostication schemes in two nationwide series of breast cancer (- - - FinProg; — SEER).

4. Discussion

The main finding of the study is that commonly used prognostic factors and prognostication schemes have surprisingly similar influence on survival in nationwide series of breast cancer. The result also suggests that the St. Gallen criteria and the NPI work in a similar fashion between large, unselected patient populations, and that quantitative outcome estimates based on prognostic factors and classification schemes can be considered transportable across populations.

A limitation of the analysis is that the effect of adjuvant systemic therapies could not be accounted for due to lack of data. In the subset of node-negative disease a larger proportion of patients likely received adjuvant therapy in the US than in Finland in 1991 to 1992. According to prior studies 40 to 50% of women with node negative disease received chemotherapy or hormonal therapy in the US,[19,20] as compared to only 9% in the FinProg series. Yet, only small survival differences were observed between the two series also in this subset of patients.

The largest survival difference between the series was found among patients older than 65 years at diagnosis, which is in accordance with a previous report comparing outcome between European and US breast cancer patients.[24] Much of this difference in survival may be explained by the somewhat less advanced stage of cancer at diagnosis in the US as compared to Europe.[24] As in the FinProg series, elderly (75 years or over) breast cancer patients had lower breast cancer-specific survival in a Canadian population-based series as compared to the SEER-based prognostic estimates.[10] The generally lower stage of breast cancer in the SEER series might partly be explained by more frequent use of mammography by older women in the US. Approximately 48% of women older than 65 reported recent use of mammography in the US in 1992,[21] whereas less than 10% of the corresponding Finnish patients aged 65 or older had participated in a screening program.[25]

Among women 65 or younger the only significant differences between the SEER and the FinProg series were found in the subsets of women diagnosed with node-negative, well differentiated (grade 1) cancer and among those with node-positive, poorly differentiated (grade 3–4) cancer. These

Table 2 – Results of Cox proportional hazards model on overall survival

Covariates	FinProg $n = 988$			SEER $n = 11,368$			Pooled $n = 12,356$		
	P-Value	HR	CI 95%	*P*-Value	HR	CI 95%	*P*-Value	HR	CI 95%
Tumour size									
0.1–1.0		1			1			1	
1.1–2.0	0.39	1.20	(0.79–1.82)	<0.0001	1.45	(1.29–1.63)	<0.0001	1.44	(1.29–1.6)
2.1–3.0	0.007	1.81	(1.17–2.8)	<0.0001	2.09	(1.85–2.36)	<0.0001	2.08	(1.85–2.34)
3.1–5.0	0.004	1.96	(1.24–3.12)	<0.0001	2.58	(2.26–2.94)	<0.0001	2.53	(2.23–2.86)
>5	0.0007	2.88	(1.56–5.31)	<0.0001	3.07	(2.64–3.58)	<0.0001	3.09	(2.67–3.57)
Positive lymph nodes									
0		1			1			1	
1–3	0.04	1.30	(1.01–1.69)	<0.0001	1.56	(1.44–1.7)	<0.0001	1.54	(1.42–1.66)
4–9	<0.0001	2.44	(1.77–3.35)	<0.0001	2.63	(2.39–2.9)	<0.0001	2.61	(2.37–2.86)
> = 10	<0.0001	3.98	(2.29–6.92)	<0.0001	3.99	(3.55–4.48)	<0.0001	3.97	(3.54–4.44)
Examined lymph nodes									
> 10		1			1			1	
5–10	0.03	1.47	(1.04–2.1)	<0.0001	1.98	(1.68–2.34)	<0.0001	1.84	(1.6–2.12)
<5	0.36	1.15	(0.85–1.57)	<0.0001	1.25	(1.15–1.35)	<0.0001	1.25	(1.15–1.35)
Histologic grade									
1		1			1			1	
2	0.0017	1.74	(1.23–2.47)	0.02	1.18	(1.03–1.35)	0.001	1.24	(1.09–1.41)
3–4	0.0014	1.87	(1.28–2.74)	<0.0001	1.43	(1.24–1.64)	<0.0001	1.49	(1.31–1.69)
ER status									
Pos		1			1			1	
Neg	0.63	0.93	(0.7–1.24)	<0.0001	1.23	(1.13–1.35)	<0.0001	1.20	(1.1–1.31)
PgR status									
Pos		1						1	
Neg	0.046	1.30	(1.01–1.69)	<0.0001	1.18	(1.09–1.28)	<0.0001	1.19	(1.1–1.28)
Age at diagnosis									
35–69 yrs		1			1			1	
< 35 yrs	0.12	1.59	(0.89–2.84)	0.90	0.99	(0.81–1.21)	0.77	1.03	(0.85–1.24)
> = 65 yrs	<0.0001	2.56	(2.04–3.2)	<0.0001	2.44	(2.28–2.61)	<0.0001	2.44	(2.29–2.6)
Series									
SEER								1	
FinProg							0.6127	0.97	(0.86–1.1)

differences may be true survival differences and due to therapy effects, but they may also be explained by different grading scales; in the SEER series a smaller proportion of the tumours was assigned to grade 1 and a larger proportion to grade 3 or 4 than in the FinProg series, where grading was scored from 1 to 3 and the grade category of 4 was not applied. Although histological grading is known to be subjective, the present and other data indicate that histologic grading has independent prognostic value in multivariate models that include the primary tumour size and the axillary nodal status.[11]

The high similarity of the survival estimates across the two population-based breast cancer patient series suggests that sharing and combining of breast cancer databases may be feasible for generating quantitative estimates of survival.[7] The prognostic impact of cancer stage and biology related factors, such as tumour size, lymph node involvement, and hormone receptor status clearly regressed towards a mean in these population-based datasets. The survival differences associated with these factors within each one of the series (intra-series analysis) were consistently larger than the differences produced by the same factors between the two series (inter-series analysis).

These findings suggest that despite some ambiguity in their definition and application, frequently used prognostic factors reproduce similar outcome data in unselected populations. The results of the present study indicate that a reasonable generalisability can be reached by using large, population-based data as the source for the survival estimates. Further studies are needed to explore the potential utility of pooled and shared databases. Preferably, these studies should also include patients from recent time periods and with detailed treatment data.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2006.06.028.

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