Regional Differences in Breast Cancer Survival Despite Common Guidelines

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Abstract

Purpose: **Despite a uniform regional breast cancer care program, breast cancer survival differs within regions. We therefore examined breast cancer survival in relation to differences in diagnostic activity, tumor characteristics, and treatment in seven Swedish counties within a single health care region.**
Methods: **We conducted a population-based observational study using a clinical breast cancer register in one Swedish health care region. Eligible women (*n* = 7,656) ages 40 to 69 years diagnosed with primary breast cancer between 1992 and 2002 were followed up until 2003. The 7-year relative survival ratio was used to estimate breast cancer survival. Excess mortality was modeled using Poisson regression to study differences in survival between counties.**
Results: **The 7-year relative survival for breast cancer patients was significantly lower (up to 7% in absolute risk difference) in one county (county A) compared with the others. This difference existed only among women diagnosed before 1998, ages 50 to 59 years, and was strongest among stage II breast cancer patients. Adjustment for amount of diagnostic activity eliminated the survival differences among the counties. The amount of diagnostic activity was also lower in county A during the same time period. After county A, during 1997-1998, began to adhere strictly to the regional breast cancer care program, neither any survival differences nor diagnostic activity differences were observed.**
Interpretations: **Markers of diagnostic activity explained survival differences within our region, and the underlying mechanisms may be several. Low diagnostic activity may entail later diagnosis or inadequate characterization of the tumor and thereby missed treatment opportunities. Strengthening of multidisciplinary management of breast cancer can improve survival.** (Cancer Epidemiol Biomarkers Prev 2005;14(12):2914–8)

Introduction

One of the major goals of a health care program is to ensure high quality and equal care among all residents. It is therefore disturbing that breast cancer survival differs among regions with similar breast cancer etiology and overall health care organization. Within regions, treatment by clinicians with specialist training, a longer practice, or a greater case load and treatment at larger hospitals or units with a larger annual case load consistently improves quality of care for breast cancer (1). Such improvements in quality of care (as measured by, e.g., compliance to guidelines) may affect breast cancer survival (2-4). Although promoting clinical guidelines may change breast cancer management (1), whether such management changes improve survival has not been adequately studied.

Our study investigated breast cancer survival differences across seven counties contained within a single Swedish region with homogenous health care following the same clinical guidelines. For one county within the region, we hypothesized that its lower survival rates resulted from its later adoption of regional treatment guidelines and later establishment of a multidisciplinary team coordinating management for breast cancer patients.

Materials and Methods

Setting. Sweden consists of 21 counties, which are grouped into sex health care regions. Within each region, the county councils should collaborate with respect to highly specialized health care. In this study, we used information from a population-based breast cancer register that captures information on all breast cancers diagnosed in the Uppsala/Örebro health care region. This region consists of seven Swedish counties and had a female population of 743,000 residents ages ≥20 years in the year 2002. The register began in 1992 when formal, written clinical guidelines were issued to ensure that all women with breast cancer in the region had the same opportunity for high quality care; however, each county organizes breast cancer management itself. The register includes 97% of all breast cancer patients in the region based on matches with mandatory reports to the Swedish cancer registry. The register ascertains information on vital status, age and date of diagnosis, detection mode, tumor stage, tumor characteristics, and primary surgical and oncological treatment.

Subjects. The participants were all women with primary breast cancer reported to this register from January 1992 through December 2002 (12,163 women), with follow-up until December 2003. We excluded 105 (0.9%) women for whom we had <1 month of follow-up and 4,542 (37.3%) women

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Note: The work was done at the Regional Oncologic Centre, University Hospital, SE-751 85 Uppsala, Sweden.

Conflict of interest: No one of the authors have any financial or personal relationships with other people or organizations that could inappropriately influence this study. All the authors have had full access to all the data in the study.

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younger than 40 years old or older than 69 years old who are not recommended for the breast cancer screening program or who receive more individualized, less uniform breast cancer care. This left us with 7,516 women ages 40 to 69 years (61.8%).

Study Design and Statistical Methods. To investigate potential differences in breast cancer survival in the seven counties, we took the following steps:

First, we compared the 7-year relative survival ratio (RSR), i.e. the ratio of the observed survival in the population of interest to the survival expected had the patients experienced only the age- and period-specific mortality rates of each county's general population (5). Relative survival is the survival complement of excess mortality. We then estimated the county-specific RSRs by stage (Unio Internationale Contra Cancrum stages I, II, III-IV, and undefined), age at diagnosis, and calendar period of diagnosis to study whether the differences in survival between counties were consistent across these strata. We also estimated excess mortality and the number of excess deaths during follow-up.

Second, to reduce the number of comparison counties for the county with the worst survival (county A), we selected three of the counties in the region as comparison counties [i.e., the county containing the university hospital (county B), the county where the mammography screening program excluded women ages 40-49 years (county C), and the county with the longest duration screening program (county D)]. To adjust for potential determinants and confounding factors, we modeled excess mortality using Poisson regression (6). The potential determinants included detection mode (mammography screening and clinical), diagnostic activities [proliferation status checked (yes, no, missing), estrogen receptor status checked (yes, no, missing), number of lymph nodes examined (1-4, 5-9, ≥10, missing)], tumor characteristics [number of positive lymph nodes (0, 1-3, ≥4, unknown, missing) and tumor size (≤20, ≥21 mm, unknown)] and treatment measures [primary surgical treatment (mastectomy, breast conserving, none) and oncological treatment (radiotherapy, hormonal, chemotherapy, none)], and treating clinic (main county hospital, local hospital). The potential confounders were period of diagnosis (1992-1993, 1994-1995, 1996-1997, 1998-1999, 2000-2002), age at diagnosis (40-49, 50-59, and 60-69 years), and menstrual status at diagnosis (premenopausal/postmenopausal). Information about a variable was ''missing'' if the case record did not mention the variable and was ''unknown'' if the case record mentioned that the variable was not tested for.

Finally, we used binomial regression analysis (7) to study whether the level of diagnostic activity, various tumor characteristics, and treatment (in dichotomized form) for stage II breast cancer patients differed among the counties. The effect estimates are ratios of proportions for each of counties B, C, and D compared with county A.

Ethics and Role of the Funding Source. Study data came from a register legally required for quality assurance of Swedish health care and inspected by the Swedish Data Inspection Board. The Swedish Cancer Society supported this study with grants but had no other involvement.

Results

Distribution of Year, Age, and Stage. Period of diagnosis, age at diagnosis, and breast cancer stage were similar in the counties, except that fewer women were diagnosed during 1992 to 1995 in county A, and fewer older women were diagnosed with breast cancer in county B (data not shown).

Overall Prognosis. The unadjusted 7-year RSR was significantly lower in county A than in several of the other counties (Table 1). The RSR ranged between 82% in county A and 89% in county D. Of the 1,031 women diagnosed in county A, 137 excess deaths occurred during the first 7 years of follow-up, a 50% higher excess mortality rate than that in county D (95 excess deaths among 1,097 women; data not shown). The difference in relative excess mortality between county A and the other counties increased when we adjusted for year of and age at detection (Table 1), mainly because survival was worse during 1992 to 1997 in county A (data not shown).

Prognosis by Stage. The difference in the 7-year RSR between county A and the other counties varied by stage and was particularly large in stage II, where patients in county A had a significantly worse survival than those in five of the other counties after adjusting for year of and age at diagnosis (Table 2). The 7-year RSR ranged from 73% in county A to 82% in counties C and D.

The RSR of stage II breast cancer patients varied by year and age of diagnosis but not menstrual status (data not shown). Only patients diagnosed from 1992 through 1997 (using 3- and 5-year survival) and patients 50 to 59 years old in county A had worse survival than their counterparts in the other counties (data not shown).

Adjusted Analyses

Diagnostic Activity. The differences in excess mortality between county A and the comparison counties decreased after adjusting for the degree of diagnostic activity (model 1; Table 3). The proportion of women not having examined proliferation status and estrogen receptor status, or having <10 nodes examined was higher in county A than in counties B and C (Table 4). Because the survival difference between

Table 1. Cumulative 7-year survival ratio (RSR) of female breast cancer patients ages 40 to 69 years diagnosed between 1992 and 2002 (7,516 women), and the estimated relative excess mortality (RR) and 95% CI

	Total no.	7-year RSR (95% CI)	Crude RER (95% CI)	Adjusted* RER (95% CI)
County A	1,031	82.2 (78.7-85.2)	1.00 (reference)	1.00 (reference)
County B	1,088	88.7 (85.8-91.20)	0.65 (0.48-0.88)	0.60 (0.45-0.82)
County C	1,225	86.0 (83.2-88.4)	0.88 (0.68-1.15)	0.84 (0.65-1.10)
County D	1,079	89.2 (86.3-91.6)	0.66 (0.49-0.90)	0.66 (0.49-0.88)
County E	1,061	85.9 (82.8-88.7)	0.80 (0.60-1.07)	0.79 (0.60-1.050
County F	1,028	86.4 (83.3-89.0)	0.80 (0.60-1.07)	0.75 (0.57-1.00)
County G	1,004	87.4 (84.4-90.1)	0.74 (0.55-1.00)	0.70 (0.52-0.94)
Deviance†			42	757
Residual *df*			36	632

Abbreviation: *df*, degree of freedom.

*Model adjusted for year of diagnosis (1992-1993, 1994-1995, 1996-1997, 1998-1999, 2000-2002) and age at diagnosis (40-49, 50-59, 60-69 years). Likelihood ratio test of the effect of county in the model: $df = 6$, $\chi^2 = 15.15$, $P = 0.0192$.

†Goodness-of-fit: under the hypothesis that the model fits, the deviance should follow a χ^2 distribution with the specified degrees of freedom.

Table 2. Cumulative 7-year survival ratio (RSR) by stage and the estimated relative excess mortality (RR) and 95% CI

Stage	County	No.	7-year RSR (95% CI)	Adjusted* RR (95% CI)
Stage I	A	446	95.3 (90.7-98.5)	1.00 (reference)
	B	522	97.7 (94.3-100.0)	0.57 (0.22-1.47)
	C	514	97.2 (93.7-99.7)	0.53 (0.19-1.49)
	D	439	100.2 (97.0-102.3)	0.19 (0.04-1.03)
	E	457	96.7 (92.7-99.5)	0.70 (0.25-1.95)
	F	452	97.2 (93.7-99.7)	0.50 (0.15-1.70)
	G	415	97.6 (93.7-100.2)	0.47 (0.15-1.51)
Stage II	A	396	73.1 (67.2-78.2)	1.00 (reference)
	B	394	81.9 (76.4-86.40)	0.61 (0.41-0.89)
	C	469	82.0 (77.2-86.1)	0.65 (0.46-0.92)
	D	417	81.9 (76.5-86.4)	0.68 (0.47-0.97)
	E	432	78.8 (74.3-84.4)	0.74 (0.52-1.04)
	F	413	79.4 (73.5-84.4)	0.65 (0.45-0.94)
	G	395	81.4 (75.7-86.10)	0.67 (0.46-0.97)
Stage III-IV	A	66	55.4 (38.7-69.8)	1.00 (reference)
	B	60	50.3 (34.0-65.0)	0.93 (0.51-1.69)
	C	83	49.6 (36.1-61.9)	1.22 (0.71-2.11)
	D	70	55.2 (40.1-68.5)	0.97 (0.54-1.74)
	E	55	30.5 (11.1-53.2)	1.28 (0.70-2.35)
	F	46	38.5 (23.1-53.8)	1.53 (0.85-2.76)
	G	74	51.9 (36.7-65.50)	0.95 (0.54-1.68)
Not definable †	A	123	80.6 (68.8-89.1)	1.00 (reference)
	B	112	90.8 (80.3-97.1)	0.67 (0.27-1.64)
	C	159	78.7 (69.1-86.2)	1.09 (0.54-2.19)
	D	153	90.3 (80.4-96.6)	0.44 (0.17-1.13)
	E	117	84.9 (73.4-92.7)	0.51 (0.20-1.26)
	F	117	84.0 (72.6-91.8)	0.95 (0.42-2.14)
	G	120	90.8 (81.7-96.50)	0.64 (0.27-1.52)

NOTE: Cumulative 7-year RR for stage II breast cancer patients adjusted for year and age of diagnosis.
*Model adjusted for year of (1992-1995, 1996-1999, 2000-2002) and age at diagnosis (40-49, 50-59, 60-69 years).
†Stage not definable because lymph nodal involvement was not noted (92%) or information on tumor size was missing.

county A and the comparison counties disappeared after 1997, we compared the level of diagnostic activity during 1992 to 1997 with that during 1998 to 2002. Almost all of the differences in diagnostic activity between the counties occurred during 1992 to 1997. The proportions of women with known proliferation status in 1998 to 2002 were 93.6%, 98.5%, 99.0%, and 97.2% for counties A, B, C, and D, respectively, and those for known estrogen receptor status were 94.1%, 97.0%, 98.5%, and 98.2%, respectively. The proportion of ≥10 nodes examined increased in county A from 37.9% during 1992 to 1997 to 59.4% during 1998 to 2002 (data not shown).

Tumor Characteristics. Adjusting for lymph nodal involvement, the number of positive nodes, and tumor size did not diminish the differences in excess mortality between county A and the comparison groups. If anything, the differences increased somewhat compared with the crude excess mortality (model 2; Table 3). However, women in county D were less likely to have lymph nodal involvement and tumor sizes >20 mm D [risk ratio (RR), 0.90; 95% confidence interval (95% CI), 0.81-0.99 and RR, 1.14; 95% CI, 1.03-1.27, respectively] than in county A (Table 4).

Detection Mode. The difference in excess mortality between county A and county D disappeared after adjustment for detection mode (model 3; Table 3). Women in county D were more likely to have had their cancer detected by mammography screening (RR, 1.25; 95% CI, 1.05-1.48) than in county A (Table 4). Although we did not find any great difference in the proportion of women with stage II whose breast cancer was detected by screening during the years 1992 to 1997 (screening detected 33.5%, 38.1%, 33.3%, and 48.8%, respectively, in counties A, B, C, and D), the overall proportion of women who had had their cancer detected by screening was lower in county A during the first period (screening detected cancers 42.9%, 52.6%, 50.0%, and 62.2%, respectively; data not shown).

Treatment. The difference in excess mortality between county A and counties B and D disappeared after adjustment for type of treatment (model 4; Table 3), specifically type of surgery (which decreased the difference between counties A and B) and treating clinic (which decreased the difference between counties A and D; data not shown). Compared with women in county A, women in county B were less likely to receive mastectomy B (RR, 0.58; 95% CI, 0.49-0.69), and women in county D were more likely to be treated in the main county hospital (RR, 2.63; 95% CI, 2.04-3.45). Differences in treatment by radiotherapy and chemotherapy between county A and the other counties (Table 4) did not the affect differences in excess mortality.

Discussion

Women diagnosed with breast cancer in one (county A) of seven counties within a health care region with uniform health care organization had a lower survival than those in the other six counties. County A was the county we hypothesized a priori would have a worse survival. This clinically highly relevant difference in survival, despite common accepted guidelines, occurred mostly in patients diagnosed from 1992 through 1997, ages 50 to 59 years, and in stage II. Differences in the level of diagnostic activity was the factor most clearly associated with this difference in survival, and the reorganization of the breast cancer team during1996 to 1997 in county A decreased both differences in diagnostic activity and differences in survival. The reorganization entailed recruitment of new staff members to the multidisciplinary breast team, active quality assurance of the mammography screening and other diagnostic activities, stricter adherence to guidelines, and multidisciplinary conferences via telephone between the central hospital and the second largest hospital in the county.

Table 3. Estimated 7-year relative excess mortality (RR) and 95% CI for women living in counties A, B, C, and D, adjusted for year of diagnosis, age at diagnosis, diagnostic activity, tumor characteristics, and treatments

	RSR	Model 1, RR (95% CI)	Model 2, RR (95% CI)	Model 3, RR (95% CI)	Model 4, RR (95% CI)
County A	73.1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
County B	81.9	0.66 (0.43-1.01)	0.60 (0.41-0.88)	0.66 (0.45-0.96)	0.71 (0.47-1.08)
County C	82.0	0.71 (0.47-1.05)	0.62 (0.44-0.89)	0.65 (0.46-0.93)	0.64 (0.44-0.93)
County D	81.9	0.69 (0.48-1.01)	0.66 (0.46-0.95)	0.73 (0.51-1.05)	0.73 (0.50-1.08)

NOTE: Model 1: adjusted for year, age, examined proliferation status, examined estrogen receptive status, and number of nodes examined (likelihood ratio test of the effect of county in the model: $df = 3$, $\chi^2 = 5.44$, $P = 0.1425$).
Model 2: adjusted for year, age, number of positive nodes, and tumor size (likelihood ratio test of the effect of county in the model: $df = 3$, $\chi^2 = 9.66$, $P = 0.0217$).
Model 3: adjusted for year, age, and screening (likelihood ratio test of the effect of county in the model: $df = 3$, $\chi^2 = 7.25$, $P = 0.0642$).
Model 4: adjusted for year, age, treating clinic, surgery, radiotherapy, hormonal therapy, and chemotherapy (likelihood ratio test of the effect of county in the model: $df = 3$, $\chi^2 = 5.99$, $P = 0.1123$).
Abbreviation: *df*, degree of freedom.

Table 4. Percentages of women with stage II breast cancer (1,676 women) receiving diagnostic activity, having certain tumor characteristics, and receiving treatment by county

	County A, *n* (%)	County B, *n* (%)	*P**	County C, *n* (%)	*P**	County D, *n* (%)	*P**
Diagnostic activity							
Proliferation status checked	251 (63.4)	345 (87.6)	<0.001	401 (85.5)	<0.001	296 (71.0)	<0.05
Estrogen receptor status checked	297 (75.0)	375 (95.2)	<0.001	430 (91.7)	<0.001	325 (77.9)	NS
No. examined nodes† (≥10)	184 (46.5)	228 (57.9)	<0.01	343 (73.1)	<0.001	186 (44.6)	NS
Tumor characteristics							
Positive lymph nodal involvement	277 (70.0)	287 (72.8)	NS	320 (68.2)	NS	261 (62.6)	<0.05
Tumor size† (21-50)	236 (59.6)	221 (56.1)	NS	290 (61.8)	NS	284 (68.1)	<0.05
Detection mode†							
Screening	142 (35.9)	142 (36.0)	NS	169 (36.0)	NS	185 (44.4)	<0.05
Treatment							
Clinic, main hospital	235 (59.3)	270 (68.5)	<0.01	314 (67.0)	<0.05	353 (84.7)	<0.001
Surgery†							
Mastectomy	219 (55.3)	127 (32.2)	<0.001	292 (62.3)	<0.05	207 (49.6)	NS
Breast-conserving	174 (43.9)	265 (67.3)	172 (36.7)	207 (49.6)			
Radiation, yes	337 (85.1)	367 (93.2)	<0.001	400 (85.3)	NS	341 (81.8)	NS
Breast-conserving + radiation, yes	154 (88.5)	255 (96.2)	<0.01	169 (98.3)	<0.01	202 (97.6)	<0.01
Tamoxifen, yes	175 (44.2)	165 (41.9)	NS	187 (39.9)	NS	208 (49.9)	NS
Chemotherapy, yes	218 (55.1)	230 (58.4)	NS	206 (43.9)	<0.01	218 (52.3)	NS
Total	396	394		469		417	

NOTE: The characteristics in county A are the reference levels for the binomial regression analysis and the associated *P*s.
Abbreviation: NS, not significant ($P > 0.05$).
**P*s from a binomial regression analysis.
†Missing information on number of examined nodes, tumor size, detection mode, and type of surgery were under 1.7%, 1.0%, 1.0%, and 0.9%, respectively, for counties A to D.

The regional working group has supported this process by the provision of regional guidelines and yearly reports on results from each county. The regional breast cancer register has been instrumental in this interaction enabling benchmarking between the counties

The main strengths of our study are the population-based data source, high coverage rate, and availability of reliable information on diagnostic activity, tumor characteristics, and treatments. Another strength is that relative survival provides a measure of the excess mortality experienced by breast cancer patients, irrespective of whether excess mortality is directly or indirectly attributable to cancer (6). Because we estimated the relative survival of breast cancer patients using county-specific expected survival estimates, differences in general health status by county should not bias the comparison. Defining breast cancer stage from the detailed tumor characteristics in the register reduces misclassification due to different local practices of staging. Because the stages were evenly distributed over the counties, stage migration (''Will Rogers phenomenon''; ref. 8) is unlikely to have accounted for our results. However, staging in county A may have misclassified some women downwards because patients there had had fewer lymph nodes examined. This, in turn, could have lead not only to stage migration but also to missed opportunities of treatment that could create real differences in survival, as a significantly better survival is reached when ≥10 negative lymph nodes have been removed (9). Theoretically, a bias could arise if the women diagnosed with cancer in county A had poorer overall (other cause) survival than all other women there, but this is unlikely. Because the only demographic information we had was age at diagnosis, we could not study other potentially confounding patient characteristics such as social factors and comorbidity. We also did not study possible county differences in delays in diagnosis (10-12).

The study was conducted during a time period and restricted to age groups where mammographic screening was recommended and used frequently with over >80% participation. Our ability to study effects of mammographic screening is thus limited compared with an earlier study conducted in the same geographic area that found indications that a major part of the breast carcinoma mortality reduction occurring over time is due to screening (13). However, we still noted survival differences that can be interpreted as effects by early detection in county D, which is a county with screening since the late 1970s with rigorous quality control. We also noted increased survival in county A after improvement of screening performance. The association between diagnostic activity and survival may also partly be a screening effect because screening organizes diagnostic work-up and centralizes the assessment of breast cancer diagnosis and treatment to teams of experts. Increased diagnostic activity may also mirror better training in the clinical teams; experts demand full and precise information before therapy decisions. Scanty and uncertain information about tumor characterization may imply missed treatment opportunities.

Our results imply that monitoring breast cancer survival within regions is important even where the overall region seems to have similarly organized breast cancer care programs. Furthermore, clinical databases can be used to define important problems in management. In this study, diagnostic variables rather than treatment variables best explained the differences in survival by county. Either treatment guidelines had already been well promoted or adhered to or diagnostic variables are more sensitive markers of the whole management process. Our results further corroborate that paying attention to detail in breast cancer management influences important end points (1, 3), and organizational changes do improve survival.

Contribution of the Authors

Sonja Eaker has contributed substantially with the analysis and interpretation of the data and with drafting the article. Paul Dickman has contributed substantially with the analysis and interpretation of the data. Vivan Hellström has contributed substantially with the design of the study and with interpretation of the data. Matthew M. Zack has contributed substantially with the design of the study and with revising the article critically for important intellectual content. Johan Ahlgren has contributed substantially with the acquisition of the data and with revising the article critically for important intellectual content. Lars Holmberg has contributed substantially with the conception and the design of the study, interpretation of the data, and with revising the article critically for important intellectual content. All the authors have seen and approved the final version of the article.

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