Breast Carcinoma Survival in Europe and the United States

A Population-Based Study

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BACKGROUND. Breast carcinoma survival rates were found to be higher in the U.S. than in Europe.

METHODS. Multiple regression analysis of breast carcinoma survival rates among women diagnosed between 1990 and 1992 was performed using clinical data from population-based case series from the Surveillance, Epidemiogy, and End Results (SEER) program (13,172 women) and the European Concerted Action on survival and Care of Cancer Patients (EUROCARE) project (4478 women).

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RESULTS. Early-stage tumors (T1N0M0) were more frequent in the SEER data (41% of cases) than in the EUROCARE data (29%). In the SEER data, early tumors were more frequent in women age ≥ 65 years (43%) than in younger women (38%), whereas the reverse was true in the European data (25% vs. 31%). In both case series, > 90% of women underwent surgery and 81–82% underwent lymphadenectomy, but the number of axillary lymph nodes evaluated was higher in the SEER data than in the EUROCARE data. The 5-year survival rate was higher in the U.S. case series (89%) than in the European series (79%). This differential was observed for each stage category evaluated: early (T1N0M0), large lymph node-negative (T2–3N0M0), lymph node-positive (T1–3N+M0), locally advanced (T4M0), and metastatic (M1) tumors. The overall relative excess risk (RER) of death was significantly higher (RER, 1.37; 95% confidence interval [95% CI], 1.25–1.50) among European women compared with U.S. women (referent group). Adjustment for stage, age, surgery, and the number of lymph nodes evaluated explained most of the excess risk (RER, 1.07; 95% CI, 0.98–1.17).

CONCLUSIONS. Transatlantic differences in the 5-year survival rates for women diagnosed with breast carcinoma between 1990 and 1992 were attributable mainly to differences in stage of disease. Resources should be invested to achieve earlier diagnosis of breast carcinoma in Europe, especially for elderly women. ***Cancer* 2004;100:715–22.** *© 2003 American Cancer Society.*

KEYWORDS: breast carcinoma, cancer registries, survival, stage, U.S., Europe.

Breast carcinoma survival comparisons between the European Concerted Action on Survival and Care of Cancer Patients (EUROCARE) project and the Surveillance, Epidemiology, and End Results (SEER) program in the U.S. have demonstrated higher survival rates for U.S. women compared with European women, particularly among elderly women.[1] International differences in breast carcinoma survival rates in Europe are also large.[2–4]

These differences are not easy to interpret. Longer survival in one country versus another may be due to the availability of better treatment, to similar treatments being more effective because diagnosis is made at an earlier stage of disease, or simply to early diagnosis without any advantage to the patient (lead-time bias). Some of the survival differences between Europe and the U.S. could, therefore, be artefactual. However, actual survival differences could reflect different patterns of care. Higher survival rates in the U.S. than in Europe might also be attributable to a higher proportion of tumors being diagnosed at an early stage as a result of more intensive diagnostic activity.

When stage at diagnosis differs between countries or regions, any survival differences should be at least partly explained by appropriate stage-adjusted comparisons. However, disease stage depends on the range and thoroughness of diagnostic procedures, particularly those able to reveal occult metastases.[5] Tumors classified as localized in an area where more intensive diagnostic investigations are performed will, on average, be more localized than tumors assigned to that stage in an area where, for whatever reason, investigations are less thorough. The corollary is that the survival of localized cases will be higher where investigations are thorough, not because of better treatment but simply because of a different de facto definition of stage at diagnosis. Advanced cases will also have higher survival where investigations are more thorough, because this group will include some early metastatic cases that would be misclassified as localized where investigations are less thorough. Therefore, stage-adjusted survival comparisons should take account of the diagnostic examinations used to determine the stage of disease. A recent study using this approach has shown that breast carcinoma survival differences in Europe are mostly attributable to differences in disease stage at diagnosis.[6]

The objective of the current study was to improve the interpretation of differences in breast carcinoma survival between Europe and the U.S., by analyzing the impact of disease stage, age, surgery, and the number of axillary lymph nodes evaluated after lymphadenectomy on survival, using data from the population-based cancer registry networks contributing to EUROCARE and SEER. The number of lymph nodes evaluated pathologically was found to be one of the most important determinants of the lymph node stage of breast carcinoma during the early 1990s.[7]

MATERIALS AND METHODS

We used data from the EUROCARE High Resolution study, in which detailed clinical information concern-

ing stage, diagnostic examinations, and treatment was collected for 4478 European women registered with incident primary invasive breast carcinoma during 1990 in the territory of 17 population-based registries in 6 countries: Estonia (national registry), France (Bas-Rhin, Calvados, Côte d'Or, Doubs, Hérault, Isère, Somme, and Tarn), Italy (Firenze, Modena, Ragusa, and Varese), Spain (Granada), The Netherlands (Eindhoven), and the United Kingdom (Mersey and Thames). Four registries included data for 816 women diagnosed in 1991 and 47 women diagnosed in 1992 (19% of total). Details of the study design and sampling have been published previously.[4]

We included all 13,172 cases of breast carcinoma in U.S. women diagnosed in the SEER program areas during 1990. Data regarding survival and the main investigations and treatments were available in the SEER public use data base.[8] The following SEER registry areas were included: San Francisco-Oakland SMSA, Connecticut, Detroit (Metropolitan), Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, Atlanta (Metropolitan).

Only invasive tumors in women ages 15–99 years were included. Cases registered from a death certificate only and those diagnosed at autopsy were excluded because their date of diagnosis and duration of survival were unknown. The usual follow-up procedures were adopted by each registry and $\geq$ 5 years of follow-up for vital status were available for all cases.

Disease stage at diagnosis was defined using TNM characteristics.[7] For women who underwent surgery, pathologic T and N were used, whereas clinical information on T, N, and M was used for the fraction of women not treated surgically. Women were grouped into five stage categories for survival analyses: early-stage tumors (T1N0M0), large lymph node-negative tumors (T2–3N0M0), lymph node-positive tumors (T1–3N+M0), locally advanced tumors (T4M0), and metastatic tumors (M1). There also was a category for tumors of an unknown stage.

Relative survival, expressing the probability of cancer survival after adjustment for competing causes of death, was estimated as the ratio of the observed survival to the survival that would have been expected if the women had been subject only to the age-specific and sex-specific mortality rates observed in the general population.[9,10] Overall and stage-specific 5-year relative survival rates were calculated by the Hakulinen method[11] using general population life tables for women, specific for each European country or registry territory. For the U.S., the national life table was used.

Differences in 5-year relative survival rates between Europe and the U.S. were modeled with a recently developed multiple regression approach based on generalized linear models and adopting the Poisson assumption for the observed number of deaths.[12] The relative excess risks (RERs) derived from these models quantify the extent to which the hazard of death in a given region (e.g., age group) differs from the hazard in the reference category (e.g., the U.S.), after taking into account the background risk of death in the general population of each country or region.

Age at diagnosis was categorized into 4 groups ($<$ 40 years, 40–49 years, 50–69 years, and the reference group [age $\geq$ 70 years]). We used early-stage tumors (T1N0M0) as the reference group for stage. The probability of detecting axillary lymph node metastases is reported to be positively correlated with the number of lymph nodes evaluated pathologically. The number of lymph nodes evaluated was included as a determinant of lymph node status, categorized into tertiles (1–9 lymph nodes evaluated [reference], 10–14 lymph nodes examined, and $\geq$ 15 lymph nodes examined), with a fourth category of women for whom either the axilla was not evaluated surgically or this information was not available. Surgery and radiotherapy were categorized as yes, no, or no information available, regardless of the type of surgery or type and dose of radiotherapy (reference groups: women not operated and not irradiated, respectively).

We modeled the effect on the RER for Europe, compared with the U.S., of age and stage at diagnosis, surgery, the number of evaluated lymph nodes, and radiotherapy. We also tested three two-way interactions: age and stage, follow-up (categorized into five 1-year intervals) and continent, and follow-up and stage.

RESULTS

Breast carcinoma was diagnosed at a later stage in Europe than in the U.S. (Table 1). Early-stage tumors (T1N0M0) comprised 29% of all cases in the European data and 41% in the U.S. data, whereas lymph node-positive tumors were more frequent in Europe (31%) than in the U.S. (24%). Other characteristics of the case series include the percentages aged 70–99 (27% of European cases and 33% of U.S. cases), those for whom microscopic confirmation of the diagnosis was available (90% and 98%, respectively), or those for whom follow-up information was unavailable (3.0% and 2.2%, respectively).

Early-stage disease was more frequent among U.S. women aged 70–99 (43%) than those aged 15–44 and 45–49 (29% and 36%, respectively), whereas the reverse was true in European women (24% vs. 29% and 33%, respectively). In both case series, large lymph node-negative tumors (T2–3N0M0) comprised 17–21% of all tumors among younger and older women, lymph

TABLE 1
Number of Cases and Distribution by Stage of Disease at Diagnosis and Age: Women Diagnosed with Breast Carcinoma, 1990–1992, in SEER and EUROCARE Series

	SEER						EUROCARE					
		Age at diagnosis (yrs) (%)						Age at diagnosis (yrs) (%)				
Stage at diagnosis	No. of cases	All ages	15–39	40–49	50–69	70–99	No. of cases	All ages	15–39	40–49	50–69	70–99
T1N0M0	5369	40.8	28.7	35.5	43.5	42.7	1293	28.9	29.0	33.4	30.1	23.7
T2–3N0M0	2523	19.2	21.2	20.2	18.4	19.1	831	18.6	16.6	18.2	17.8	20.6
T1–3N+M0	3217	24.4	36.1	31.4	24.5	18.1	1389	31.0	39.5	33.5	32.9	24.1
T4 M0	740	5.6	5.1	5.0	4.9	6.9	304	6.8	3.7	4.0	6.0	10.7
M1	783	5.9	5.0	5.3	6.0	6.4	279	6.2	3.4	4.8	6.1	8.1
Not available	540	4.1	3.9	2.6	2.7	6.8	382	8.5	7.8	6.1	7.1	12.8
	13,172	100.0	100.0	100.0	100.0	100.0	4478	100.0	100.0	100.0	100.0	100.0

SEER: Surveillance, Epidemiology, and End Results program; EUROCARE: European Concerted Action on Survival and Care of Cancer Patients.

TABLE 2
Number of Women Who Underwent Surgery and Axillary Lymphadenectomy and Distribution by Number of Lymph Nodes Evaluated during Lymphadenectomy: Women Diagnosed with Breast Carcinoma, 1990–1992, in SEER and EUROCARE Series

	SEER	EUROCARE
Characteristics	No. of cases (%)	No. of cases (%)
Surgery	12,788 (97.1)	4040 (90.2)
Lymphadenectomy	10,790 (81.9)	3629 (81.0)
No. of lymph nodes evaluated		
1–9	1589 (14.7)	1215 (33.5)
10–14	3170 (29.4)	1120 (30.9)
15+	5473 (50.7)	1009 (27.8)
Not available	558 (5.2)	285 (7.8)
Total	10,790 (100.0)	3629 (100.0)

SEER: Surveillance, Epidemiology, and End Results program; EUROCARE: European Concerted Action on Survival and Care of Cancer Patients.

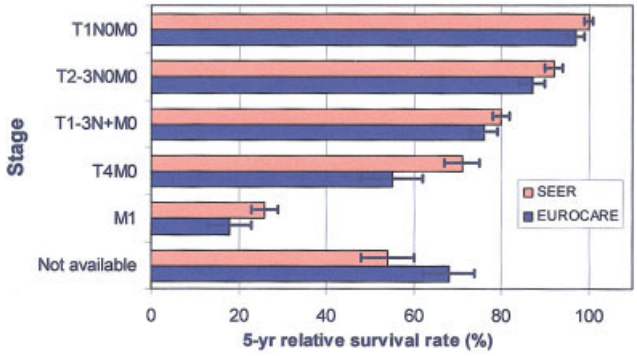

FIGURE 1. Five-year relative survival rate by stage. Women diagnosed with breast carcinoma between 1990 and 1992 in the Surveillance, Epidemiology, and End Results (SEER) program and European Concerted Action on Survival and Care of Cancer Patients (EUROCARE) series.

node-positive tumors (T1–3N+M0) were more frequent among younger women, and advanced tumors were more frequent among older women (Table 1).

Among women aged 70–99 who underwent surgery, disparities in pathologic tumor size were marked. The smallest tumors represented 3% of the U.S. series and 1% of the European series (T1a, $\leq$ 5 mm in greatest dimension), with corresponding percentages of 16% and 6%, respectively, for T1b (6–10 mm in greatest dimension) and 35% and 31%, respectively, for T1c (11–20 mm in greatest dimension) (data not shown).

Most women were treated surgically (90% in EUROCARE data, 97% in SEER data; Table 2). Lymphadenectomy was equally common in both series (81–82%), but was more extensive in the U.S. than in Europe. For example, approximately half of the U.S. women (51%) had $\geq$ 15 lymph nodes evaluated, compared with less than one-third of European women (28%).

The overall 5-year relative survival rate was 89% in the U.S. series and 79% in the European series (Fig. 1). Survival was higher in the U.S. for each stage category, except for women whose disease stage at diagnosis was unknown. Survival was similar for early-stage tumors (100% in the U.S. series and 97% in the European series) but the difference increased with advancing stage and was maximal for locally advanced tumors (T4M0, 71% vs. 55%).

The age-adjusted RER of death was significantly higher in Europe than in the U.S. (RER, 1.37; 95% confidence interval [95% CI], 1.25–1.50) (Table 3, Model 1). The excess risk for women age $<$ 40 years was significantly higher than for women ages 70–99 years (RER, 1.61; 95% CI, 1.36–1.91). The overall excess

TABLE 3
RER of Death by Age, Disease Stage, and Treatment: 17,650 Women Diagnosed with Breast Carcinoma, 1990–1992, in SEER and EUROCARE Series

		Model 1		Model 2		Model 3		Model 4	
Characteristics	**No. of women**	**RER**	**95% CI**	**RER**	**95% CI**	**RER**	**95% CI**	**RER**	**95% CI**
Region									
SEER	13,172	1		1		1		1	
EUROCARE	4478	1.37	1.25–1.50	1.20	1.09–1.31	1.12	1.03–1.22	1.07	0.98–1.17
Age (yrs)									
15–39	1238	1.61	1.36–1.91	1.86	1.58–2.18	1.38	1.19–1.60	1.37	1.18–1.59
40–49	3136	1.06	0.91–1.24	1.16	1.01–1.34	0.88	0.78–1.00	0.88	0.78–1.00
50–69	7723	1.10	0.96–1.26	1.24	1.10–1.41	0.98	0.89–1.09	0.98	0.89–1.09
70–99	5553	1		1		1		1	
Surgery									
No	1211			1		1		1	
Yes	16,439			0.10	0.09–0.11	0.38	0.34–0.43	0.53	0.46–0.59
Stage									
T1N0M0	6662					1		1	
T2–3N0M0	3354					4.87	3.67–6.47	4.54	3.45–5.96
T1–3N+M0	4606					10.44	8.03–13.58	10.54	8.20–13.54
T4M0	1044					17.22	13.03–22.76	14.91	11.39–19.51
M1	1062					48.35	36.88–63.38	35.16	26.98–45.81
Not available	922					12.55	9.33–16.88	8.49	6.34–11.38
Evaluated lymph nodes									
1–9	2977							1	
10–14	4302							0.92	0.79–1.08
15+	6509							0.88	0.76–1.02
Not available	3862							1.80	1.54–2.11

RER: relative excess risks; SEER: Surveillance, Epidemiology, and End Results program; EUROCARE: European Concerted Action on Survival and Care of Cancer Patients; CI: 95% confidence interval.

risk was reduced to 1.20 (95% CI, 1.09–1.31) by adjustment for surgery (Model 2). As would be expected, women treated surgically had a much lower hazard of death than the minority who did not undergo surgery (RER, 0.10; 95% CI, 0.09–0.11) and the RER for each age group was higher after this adjustment. After inclusion of stage of disease at diagnosis (Model 3), the overall risk for European women decreased to 1.12 (95% CI, 1.03–1.22) and the age-specific excess risks were smaller than with adjustment for surgery alone. Tumor stage at diagnosis was found to be strongly and significantly associated with prognosis. With respect to the reference category of early tumors (T1N0M0), the RER increased from 4.87 to 48.35 for progressively more advanced disease. For women with breast carcinoma of unknown stage, the risk was 12.55-fold.

Adjustment for the number of lymph nodes evaluated to determine stage (Model 4) further reduced the excess risk of death among the European women, which was no longer significantly higher than that for U.S. women (RER, 1.07; 95% CI, 0.98–1.17). Age-specific risks were unchanged by this adjustment, but the RER decreased slightly in most categories of stage. Women who underwent excision of ≥ 15 lymph nodes were found to have a slightly lower risk than women with < 10 lymph nodes evaluated, whereas women who did not undergo lymphadenectomy, or for whom the number of lymph nodes evaluated was not available, had a significantly high risk (RER, 1.80; 95% CI, 1.54–2.11).

The addition of adjuvant radiotherapy (performed or not) to the last model did not appear to change the level or significance of the excess risk for European women (RER, 1.08; 95% CI, 0.99–1.18) and the excess risks for other factors changed very little. Excess risks were similar among women who were irradiated (RER, 0.93; 95% CI, 0.86–1.02) and those not irradiated (reference group), or those for whom the information was not available (RER, 1.04; 95% CI, 0.38–2.87). The interactions between stage and follow-up and stage and age were found to be individually significant, but their inclusion in the model only slightly altered the excess risks for European women or the goodness of fit of the model. Results were omitted from Table 3 for simplicity (they are available on request).

DISCUSSION

The current study indicates that the higher survival of women diagnosed with breast carcinoma in 1990 in areas of the U.S. covered by the SEER program compared with women in the 17 European countries or regions participating in the EUROCARE study was attributable mainly to differences in disease stage at diagnosis. Proper adjustment for surgery, stage, and the adequacy of staging investigations accounted for much of the difference in risk of death between the two population-based case series. Tumors were diagnosed earlier in the U.S. than in Europe. Even among the early (T1) tumors, a higher proportion of U.S. women had small tumors (< 6 mm greatest dimension; T1a) compared with European women. These tumors are often diagnosed when asymptomatic, which suggests more intensive early diagnosis and detection of asymptomatic tumors in the U.S. than in Europe.

Adjustment of the RER for age, surgery, stage, and the number of lymph nodes evaluated greatly reduced the differences between Europe and the U.S..

The study design did not allow us to distinguish how much of the difference in survival between the European and U.S. case series is due to lead time and how much to postponement of death. However, most studies of breast carcinoma screening have shown that diagnosis at an earlier stage is associated with reduced mortality.[13–17]

The higher proportion of early tumors among U.S. women age ≥ 65 years helps to explain the finding that age appears to bear little relation to prognosis in the U.S., whereas survival decreases sharply with increasing age at diagnosis in Europe.[1] Survival differences between the U.S. and European series in the current study data were confined to elderly women.

Survival for all stages of disease was higher for women in the U.S. than in Europe (Fig. 1). At first glance this might suggest that breast cancer treatment in the U.S. is more effective than in Europe. However, the average number of axillary nodes examined was higher in the U.S. series, indicating a more thorough search for occult metastasis. The node-negative category in Europe may therefore have included a higher proportion of misclassified tumors, which were in fact node-positive, than in the U.S. The fewer nodes examined, the higher the probability of misclassifying some node-positive tumors as node-negative: note that the practice of sentinel node sampling was not widespread in 1990. Inclusion of the number of nodes examined in the model improved the adjustment for stage of the relative excess risks, and the relative excess risk of death in Europe was no longer significantly higher than in the U.S. The improved adjustment is reflected by the fact that women with ≥15 axillary nodes examined have a smaller relative excess risk than women for whom fewer nodes were examined. Within a given stage category, a higher number of nodes examined implies a less advanced tumor. Unfortunately, we do not have information on bone, liver or lung scans performed, but the higher survival in the U.S. of both locally advanced cases and cases with distant metastasis might reflect a more thorough diagnostic examination in U.S. women. Only women for whom data regarding stage were not available had higher survival in the European series. Women who did not undergo accurate diagnostic workup are more likely to have been included in this group in the U.S. data than in the European data. Unstaged cases in the European series had survival similar to the overall overage, suggesting that this group was broadly representative of all patients, and that stage was more often unavailable in Europe simply because the information was missing from the clinical records.

Adjustment of the RER for stage was improved by the inclusion of the number of lymph nodes evaluated. When many lymph nodes were evaluated pathologically, cases classified as lymph node negative are less likely to be truly lymph node positive and some cases classified as lymph node positive will have only minor lymph node involvement. This improved adjustment is reflected by a smaller excess risk for cases with ≥ 15 lymph nodes evaluated and a slight increase in the excess risk for the lymph node-positive category, whereas other stage-specific risks decreased.

Nearly all women underwent surgery. Those who did not were most likely deemed unlikely to benefit from surgery because their tumor stage was too advanced. Surgical intervention therefore may be considered a proxy for stage of disease. Inclusion of surgery in the model had the effect of a crude adjustment for stage.

After full adjustment for stage, the residual excess risk of death in the final model for European versus U.S. women was small (7%) and was not statistically significant. Such a small difference might well depend on residual misclassification of tumor stage or staging procedures. This small excess risk, if real, could also be attributable to differences in adjuvant therapy. However, inclusion of information on radiotherapy did not appear to change the estimated excess risk for women in Europe. More detailed information concerning the type and dose of adjuvant radiotherapy, chemotherapy, and hormone therapy is needed to explore this issue.

We have considered Europe and the U.S. in these

analyses as two homogeneous regions, to provide a broad overview of breast carcinoma survival between the two continents. However, the SEER program and the EUROCARE project cover only 10% and 14%, respectively, of the general population in the countries involved,[18] which may not be entirely representative of the corresponding national populations. The national life tables used for the U.S. may not reflect the background mortality in contributing areas as closely as in the European series. The difference in breast carcinoma survival between the European and U.S. series may, in part, be due to the particular regions included. However, this cannot be the only explanation because survival in 22 European countries or regions for which comparable data are available is reported to be lower than in any of the U.S. areas covered by the SEER program.[18] The CONCORD study may further elucidate these differences.[1]

In Europe, large differences in survival for breast carcinoma have been observed.[2–4,18–20] European areas with both high and low survival were represented in the current study. The overall 5-year relative survival rate ranged from 74% to 82% in France, Italy, and The Netherlands and from 66% to 76% in Spain, Estonia, and the U.K. These differences were attributable to differences in stage at diagnosis and treatment.[6] European regions with low survival contributed approximately 50% of the total number of women in the European component of the current study. The inclusion of other European countries with high breast carcinoma survival rates (e.g., Sweden, Iceland, Norway, and Finland)[19,20] would have reduced further the residual excess risk of death in Europe.

Breast carcinoma survival rates vary less widely between the SEER registry areas than between the countries contributing to EUROCARE. Socioeconomic status (SES) influences survival rates in both the U.S. and Europe,[21–23] but we did not include this factor because comparable data were not available. Breast carcinoma survival differences in the U.S. are related to race and SES.[24–26] Differences in outcome have also been reported by type of healthcare delivery.[27–29] The type of health insurance also influences survival rates.[30] However, the inclusion of European countries with a wide range of breast carcinoma survival rates may reflect to some extent the range of social and racial factors influencing cancer survival rates in the U.S..

The results of the current study suggest that most differences in breast carcinoma survival rates between Europe and the U.S. can be explained by earlier diagnoses in the U.S.. The results suggest that more resources should be invested to achieve earlier diagnosis of breast carcinoma in Europe, especially for elderly women.

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