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Breast cancer survival in the US and Europe: a CONCORD high-resolution study

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Novelty and impact of the work: Most of the diagnostic and therapeutic modalities used for breast cancer more than 10 years ago remain in widespread use today. Understanding the extent to which access to those modalities can explain international differences in cancer survival therefore remains highly relevant. This is the largest population-based high-resolution study, with a common protocol, standard quality-control procedures and central analyses. The modelling approach to estimate net survival is a methodological strength.

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Abstract

Breast cancer survival is reportedly higher in the US than in Europe. The first worldwide study (CONCORD) found wide international differences in age-standardised survival. The aim of this study is to explain these survival differences.

Population-based data on stage at diagnosis, diagnostic procedures, treatment and follow-up were collected for about 20,000 women diagnosed with breast cancer aged 15–99 years during 1996–98 in 7 US states and 12 European countries. Age-standardised net survival and the excess hazard of

death up to five years after diagnosis were estimated by jurisdiction (registry, country, European region), age and stage with flexible parametric models.

Breast cancers were generally less advanced in the US than in Europe. Stage also varied less between US states than between European jurisdictions. Early, node-negative tumours were more frequent in the US (39%) than in Europe (32%), while locally advanced tumours were twice as frequent in Europe (8%), and metastatic tumours of similar frequency (5–6%). Net survival in Northern, Western and Southern Europe (82–85%) was similar to that in the US (84%), but lower in Eastern Europe (72%). For the first 3 years after diagnosis the mean excess hazard was higher in Eastern Europe than elsewhere: the difference was most marked for women aged 70–99 years, and mainly confined to women with locally advanced or metastatic tumours.

Differences in breast cancer survival between Europe and the US in the late 1990s were mainly explained by lower survival in Eastern Europe, where low healthcare expenditure may have constrained the quality of treatment.

Keywords

CONCORD; net survival; excess hazard; cancer registries

Introduction

Breast cancer survival has been reported as higher in the US than in Europe[1,2]. For women diagnosed 1985–89, five-year survival was higher in each of the nine Surveillance, Epidemiology and End Results (SEER) areas than in any of the 22 European countries participating in the EUROCARE-2 study.

The first worldwide analysis of cancer survival (CONCORD[3]) provided a systematic comparison of survival for adults (15–99 years) diagnosed with a cancer of the breast, colon, rectum or prostate in one of 31 countries during 1990–94 and followed up to 1999. International differences in age-standardised survival were very wide, even after adjustment for differences in mortality from other causes of death. Breast cancer survival in the US and Canada was higher than in other countries, but differences between the US and most European regions were smaller than for women diagnosed during 1985–89[2]. The largest differences were between the US and Eastern Europe.

A population-based comparison of five-year breast cancer survival among women diagnosed in 17 territories in 6 European countries during 1990–92 and in the 9 states and metropolitan areas of the US covered by the SEER programme in 1990 showed that differences were mainly attributable to stage at diagnosis and the diagnostic procedures used to determine the stage[4].

Both the assiduity of investigation and the appropriateness of treatment by stage varied widely for women diagnosed in Europe during 1990–92 and 1996–98[5,6]. Primary treatment for breast cancer also varies greatly throughout the US[7,8]. Following the NIH Consensus Development Conference in 1990, which recommended breast-conserving surgery and radiotherapy instead of mastectomy for women with stage I and II breast cancer, the

proportion treated with breast-conserving surgery increased steadily up to 1995[9], but the percentage who also received radiotherapy and/or axillary lymphadenectomy declined[10]. Differences in protocol and calendar period make it difficult to draw firm conclusions from these studies about whether the differences in survival between Europe and the US are attributable to differences in stage, or treatment, or both.

The CONCORD protocol incorporated “high-resolution” studies designed to explain the international variations in survival for breast, colorectal and prostate cancer. The analyses involve large random samples of patients, with detailed clinical and pathological data that are not routinely abstracted by population-based cancer registries. The study reported here provides a trans-Atlantic comparison of stage, treatment and survival for women with breast cancer. The aims were to compare the stage distributions in Europe and the US; to determine whether the transatlantic differences in 5-year survival persist and, if so, to assess the extent to which they are attributable to differences in stage. We also set out to compare adherence to “standard care” for breast cancer in relation to age, stage and hormone receptor status, before widespread introduction of clinical guidelines.

Material and methods

Data on stage, diagnostic procedures, treatment and follow-up were collected for a representative sample of about 20,000 women aged 15–99 years who were registered with a diagnosis of breast cancer in the US or one of 12 European countries during 1996–98. A common protocol was used, based on the EUROCARE high-resolution protocols[5,6].

The European data were provided by 26 population-based cancer registries in 12 countries, 7 of which with national coverage, denoted by an asterisk (*). For some analyses, the data were grouped into four European regions defined by the United Nations (UN, http://unstats.un.org/unsd/methods/m49/m49regin.htm) - Northern Europe: Denmark*, Finland*, Iceland*, Sweden*; Western Europe: France (Bas-Rhin, Côte d’Or, Doubs, Isère, Tarn) and the Netherlands (Eindhoven, North East Netherlands); Southern Europe: Italy (Firenze, Genova, Modena, Palermo, Ragusa, Varese), Slovenia*, Spain (Basque Country, Castellon, Granada, Navarra); Eastern Europe: Estonia*, Poland (Cracow, Warsaw), Slovakia*. Estonia is classified by the UN as being in Northern Europe, but cancer survival has usually resembled that in Eastern European countries[11], and the data from Estonia are included here with Eastern Europe. Data from the US were provided by 7 state-wide registries: California, Colorado, Illinois, Louisiana, New York, Rhode Island and South Carolina. The US registries are part of the National Program of Cancer Registries, based at the Centers for Disease Control and Prevention.

For this study the cancer registries included in the EUROCARE-3 high-resolution study[6] made special efforts to update the follow-up to at least five years after diagnosis for all patients. The North East Netherlands registry was not included in EUROCARE-3, but it is unusual in that it routinely collects almost all the data required for high-resolution studies on all registered cancer patients, so it was able to provide such data on virtually all women with breast cancer, not just a sample.

Most European registries provided a random sample of at least 500 women diagnosed during 1996–98, as specified by the protocol. Denmark and Sweden provided a sample of women diagnosed in 1994, and Palermo (Italy) provided data for all women diagnosed in 1999, the first year for which data were available there. The Finnish cases were a population-based sample of women diagnosed in the Tampere hospital region, which is considered representative of the whole of Finland. Despite these slight departures from protocol, these cases were retained to ensure the widest possible geographic coverage. Each of the US registries provided a random sample of at least 500 women diagnosed with breast cancer in 1997.

Anonymised, individual cancer registration records were supplied for 20,150 women diagnosed with a malignant neoplasm of the breast. *In situ* tumours (1,168, 5.8%) were excluded from the analyses because they were collected systematically in the US, but not in Europe. A further 20 cases (0.1%) were excluded because they did not meet the protocol (2 with benign or uncertain behaviour, 2 with the morphology of leukaemia or lymphoma, and 16 aged less than 15 or more than 100 years). In all, 18,962 women with a primary, invasive, malignant neoplasm of the breast were included in the analysis of stage and treatment. Women whose cancer was only registered from a death certificate (23; 0.1%), or of unknown vital status (18; 0.1%), or for whom the date of last known vital status preceded the date of diagnosis (32; 0.2%), were excluded from the survival analyses, which thus involved 18,889 women.

Information on stage, diagnostic examinations, treatment and follow-up was obtained by direct examination of the clinical record. Where records were incomplete, pathology reports, hospital discharge records and other sources were consulted as necessary.

Disease stage was defined according to the 4th edition of the TNM (Tumour, Nodes, Metastasis) manual.[12] If pathological data on tumour size and lymph node status (pT and pN) were unavailable, clinical data (cT and cN) were used. Following advice from epidemiologists, pathologists and clinicians, records for which the metastatic status was unknown (MX) were considered as negative (M0), if T and N were known. Patients were grouped into six categories: early, node-negative disease (T1N0M0), larger node-negative (T2-3N0M0), node-positive (T1-3N+M0), locally advanced (T4, any N, M0), metastatic (M1) and unstaged. Within the category of early, node-negative disease, we also assessed the distribution of small tumours by size: less than 5mm (T1a), 5–10mm (T1b) and over 10mm and up to 20mm (T1c). Estrogen-receptor (ER) status was categorized as positive, negative or unknown. Age at diagnosis was categorised into four groups (15–39, 40–49, 50–69, 70–99 years) for survival analysis. Treatment comparisons were made in wider age groups: 15–49 and 50–99 years for chemotherapy and hormone therapy; 15–69 and 70–99 years for breast-conserving surgery plus radiotherapy.

Data on surgical procedures were collected in 7 categories: conservative surgery (including quadrantectomy, tumour excision, lumpectomy), simple mastectomy, any modified radical mastectomy, extended radical (Halsted) mastectomy, surgery (not otherwise specified), unknown if surgery was performed, and no surgery. When a surgical procedure was performed, axillary procedures were collected in 5 categories: for lymph-node sampling, for

axillary clearance, unspecified whether for sampling or clearance, not specified if done or not, and not done. Information was also sought on sentinel lymph-node biopsy, with or without lymphadenectomy, but sentinel biopsy was very uncommon during 1996–98. Information on biopsy or needle aspiration of the breast was coded in 5 categories as either done; not done because of refusal or death, or for specified medical contraindications, or for other or unspecified reasons; or unknown if done or not. Chemotherapy, radiotherapy and hormonal therapy were coded as yes, no or unknown.

Primary treatment for early node-negative disease was dichotomised as breast-conserving surgery with radiotherapy (BCS+RT) *vs*. all other surgical procedures, whether or not followed by radiotherapy. Chemotherapy and endocrine treatment were dichotomised as administered *vs.* not administered or unknown.

Statistical Analysis

We examined the proportion of women with early, node-negative disease who received breast-conserving surgery plus radiotherapy; the proportion of women with node-positive disease who received chemotherapy; the proportion of women with estrogen-receptor-positive tumours who received tamoxifen, and the proportion of women for whom at least 10 lymph nodes were removed and examined during lymphadenectomy, as recommended in the TNM manual for staging breast cancer from 1992 (4^{th} edition, 2^{nd} revision)[12]. Cancer registry data sets were excluded if data on stage and/or treatment were missing for 20% or more of patients. Thus Firenze and Ragusa were excluded from the analyses of chemotherapy in node-positive disease, and Firenze, Genova and Ragusa were excluded from the analyses of hormonal treatment in estrogen-receptor-positive disease.

Net survival up to five years after diagnosis was estimated by jurisdiction (registry, country and European region), age and stage using flexible parametric excess hazard models[13]. Net survival is the survival of cancer patients in the hypothetical situation when the cancer may be assumed to be the only possible cause of death; it may be interpreted as cancer survival after controlling for competing causes of death. Net survival was estimated with a modelling approach[14,15], in which the total hazard of death is considered as the sum of the cancer-related mortality hazard (excess hazard), and the hazard of death from other causes (background hazard). The background hazard is derived from life tables of all-cause mortality by sex, single year of age and calendar year in the general population of the country, region or (in the US) state from which the cancer patients are drawn. We constructed period life tables for 1994–2004 with the approaches proposed by Baili et al.[16].

Age was included as a continuous variable in all models, in order to avoid the bias in the estimation of net survival that would otherwise arise from differential loss of the oldest patients (informative censoring). Both non-linear and time-dependent (interaction with time since diagnosis) effects of age were initially modelled with cubic splines. The proportionality of the effect of tumour stage on the excess hazard was also assessed. Simpler models, with linear and/or proportional effects, were successively tested and selected using the Akaike Information Criterion for goodness of fit[17]. We also estimated the instantaneous excess risk (hazard) of death due to breast cancer, after subtracting the hazard from all other causes of death[14,15,18,19]. We present the mean excess hazard per 1,000 person-years at risk

at 1 month, 6 months and 1, 3 and 5 years since diagnosis, both by age and by stage at diagnosis after adjustment for age.

Overall (all-ages) net survival estimates were age-standardised with the international cancer survival standard (ICSS) weights[20].

We used a logistic regression model to estimate the odds of women with early node-negative disease receiving breast-conserving surgery and radiotherapy (*vs.* any other surgical procedure, with or without radiotherapy) in each jurisdiction, after adjustment for age and tumour size.

Survival analyses were performed with *stpm2*[18] in Stata version 11 (StataCorp LP, College Station, TX).

Results

We included 18,962 women with invasive primary breast cancer: 15,842 women in 26 jurisdictions in 12 European countries and 3,120 women in 7 US states (Table 1). Microscopic verification was available for 98–99% of the women in each of the US states and 94% in Europe, ranging from 79% in Estonia to 100% in the Basque country (Spain). Data were available on stage for about 90% of cases in both data sets, ranging from 78% (Ragusa, Italy) to 95% or more in 8 of the 26 European registries and from 81% (New York) to 94% (Colorado and S Carolina) in the US.

Breast cancers were generally less advanced in the US than in Europe, and the stage distribution varied less between US states than between European jurisdictions. Early node-negative tumours were more frequent in the US (39%, range 33–45%) than in Europe (32%, 16–49%). Large node-negative tumours were of similar frequency (Europe 14%, 9–22%; US 14%, 10–18%), while node-positive tumours were more common in Europe (33%, 25–44%) than the US (26%, 22–29%). Locally advanced tumours were twice as frequent in Europe (8%, 0–24%) as in the US (4%, 3–6%), but the overall frequency of metastatic tumours was similar (5–6%). The proportion of tumours with unspecified stage was slightly higher in the US (11%) than Europe (8%), but up to 18–22% in three European registries (Finland; Italy: Firenze, Ragusa), while only New York (19%) differed much from the US average. Exclusion of these registries did not substantially alter the overall stage distributions in Europe or the US (data not shown).

Lymphadenectomy was reported for 13,687 (86%) women in Europe and 2,531 (81%) in the US, but it was generally more extensive in the US, where 10 or more nodes were examined in 78% (range 76–83%) of procedures, compared with 66% (23–93%) in Europe (Table 2). Among women with early node-negative tumours, the distribution of tumour size was more favourable in the US than in Europe.

More than 90% of women received surgical treatment: 91% in Europe (from 77% in Estonia to 95% or more in 10 of 26 jurisdictions) and 96% in the US (93–97%; Table 3). Among operated women, 35% had early node-negative disease in Europe, compared with 41% in the US. Among women operated for early node-negative disease, breast-conserving surgery plus

radiotherapy was received by 55% in Europe and 49% in the US, but the variability was much wider in Europe (9% in Estonia; 78–84% in four of the five French regions) than in the US (34% in S Carolina; 58% in Rhode Island). The proportion of women aged 70–99 years who received breast-conserving surgery and radiotherapy for early node-negative disease varied more between European countries and regions (4–6% in two Polish regions; 84% in Tarn) than between US states (21% in Louisiana; 47–48% in Rhode Island and California).

For early node-negative disease, and relative to Southern Europe (1,848 women, reference category), the odds of receiving both breast-conserving surgery and radiotherapy (*vs.* any other surgical procedure, with or without radiotherapy), adjusted for age and tumour size, were lower in the US (OR=0.80; 95%CI 0.69–0.94) and Northern Europe (OR=0.60; 0.50–0.72); much lower in Eastern Europe (OR=0.16; 0.12–0.20), and higher in Western Europe (OR=1.57; 1.36–1.81) (Table 4). The odds of receiving this treatment were significantly lower for women aged 70–99 years than for those aged 60–69 years (OR=0.48; 0.41–0.56), after adjustment for region and tumour size. Women with tumours of 5–10mm (T1b) received this treatment more than women with larger tumours (up to 20mm, T1c) (OR=1.31; 1.16–1.48).

Among women with node-positive tumours, 58% received chemotherapy in the 26 European jurisdictions, compared with 69% in the 7 US states (Table 5). Among women aged less than 50 at diagnosis, the overall proportion was similar in Europe and the US (90%), but the range was wider in Europe (54–100%) than the US (84–94%). Among older women, the proportion who received chemotherapy was higher, and varied less, in the US (60%, range 53–67%) than in Europe (46%, range 14–75%).

Overall, endocrine treatment in ER-positive tumours was slightly higher in the US (62%) than in Europe (55%). The proportion was similar in women aged 50 and over (63% in the US; 59% in Europe), but younger women received tamoxifen more often in the US (58% *vs.* 44%).

Overall, age-standardised net survival at five years was 81% in Europe and 84% in the US (Figure 1). Survival in Northern, Western and Southern Europe (81–84%) was similar to that in the US (84%), but it was lower in Eastern Europe (69%). Survival varied more widely between European jurisdictions (88% in Iceland to 62% in Estonia) than between US states (from 91% in Colorado to 76% in South Carolina).

Five-year age-standardised net survival was broadly similar in all European regions and the US for early, node-negative tumours (96–98%) and for large, node-negative tumours (85–90%) (Figure 2, available in web-appendix). The geographic range in survival was much wider for locally advanced disease, from 37% in Eastern Europe to 77% in Northern Europe, and 44% in the US. As with overall survival, stage-specific five-year survival was similar in Northern, Western and Southern Europe and the US. In Eastern Europe, survival for node-positive, locally advanced and metastatic tumours was lower than in other European regions or the US.

The mean excess hazard was higher in Eastern Europe than in other jurisdictions at 1 month, 6 months and 1, 3 and 5 years after diagnosis, both for all ages and in each of 5 age categories (Figure 3, available in web-appendix). The difference was most marked for women aged 70–99 years. No striking differences were found between Northern, Western, Southern Europe and the US. The high excess hazard of death in Eastern Europe was mainly confined to women with locally advanced or metastatic tumours (Figure 4, available in web-appendix).

Discussion

Transatlantic differences in cancer survival have raised questions about early diagnosis and the adequacy of investigation and treatment. To our knowledge, this is the first population-based high-resolution study to use clinical data that were collected by trained abstractors from the primary medical records under a common protocol, subjected to standard quality control procedures and analysed centrally with the same statistical methods. We compared survival using clinical data on stage, diagnostic procedures and treatment. The survival differences appear likely to be related to differences in diagnosis and patterns of care shortly after diagnosis. The women were diagnosed more than 10 years ago, but most diagnostic and therapeutic approaches used at that time remain in widespread use: understanding their role in international differences in survival remains relevant.

Overall, five-year net survival was not very different in Europe (81%) and the US (84%). Differences were mainly confined to the three Eastern European countries, Estonia, Poland and Slovakia, where average five-year survival was 69%. Estonia and Slovakia are both covered by national cancer registries, and the women from those countries were thus nationally representative. Survival varied more widely between the 26 European jurisdictions than between the 7 US states.

The differences in survival between Europe and the US in the late 1990s are smaller than for women diagnosed at the beginning of the decade[3,4]. In the previous high-resolution study[4], the US data were taken from the SEER public-use data set[21] and harmonised to the extent possible with the data collected under the EUROCARE-2 high-resolution protocol. By contrast, the data for this study were collected directly from the clinical records using a standard protocol; European coverage rose from 17 to 26 registries (11 contributed to both studies), and US coverage changed from the 5 metropolitan areas and 4 states covered by the SEER program to 7 state-wide registries in the National Program of Cancer Registries (NPCR). Survival in the 1990s was lower in the NPCR territories than the SEER areas[3,22]. Finally, in the previous high-resolution study, differences in background mortality in the US were controlled with a single national life table for 1990, weighted for the proportion of Blacks, Whites and other races, whereas we were able to use state-specific life tables for each calendar year 1994–2004.

The modelling approach used to estimate net survival is a strength of this study, but it does not explain the smaller transatlantic differences than those obtained with relative survival in the previous study. We found similar patterns with all the other widely used methods for survival estimation (data not shown).

The European differences in survival were generally similar to those reported for the same countries among women diagnosed 1995–99[11]. Survival was higher than expected in Denmark (84%): the data in this study are from eastern Denmark, greater Copenhagen and Copenhagen (Zeeland), where most of the population has undergone mammographic screening since 1991[23]. In these areas, survival after mammographic diagnosis is higher than in Denmark as a whole, regardless of whether it was a screening mammography. Survival in Slovenia was lower than in other Southern European countries, and more similar to that in Eastern Europe. Variation in survival between the 7 US states was less marked than in Europe, mostly in the range 81–87%, but ranging from 91% in Colorado to 76% in South Carolina, where Blacks represent approximately 30% of the population (http://www.ipspr.sc.edu/publication/Older%20SC.pdf).

The availability of information about race in this data set would have strengthened the international survival comparisons, but information about race is not available in many European countries. Race in the US and geographical area in Europe are often considered as a proxy for socio-economic status. In future studies, it would be preferable to use life tables that are specific for race and/or socio-economic status.

Stage-specific net survival was similar in most European jurisdictions and US states. In Eastern Europe, survival from node-positive, large and metastatic tumours (N+; T4; M1) was lower than in other European regions or the US, and the proportion of metastatic tumours was also high, mainly in Estonia and Slovakia.

The mean excess hazard of death by time since diagnosis was similar in Europe and the US for women with early node-negative disease, large node-negative disease or node-positive disease, and up to five years after diagnosis. The hazard was somewhat higher in Eastern Europe for locally advanced disease, and much higher for metastatic disease, especially in the first three years after diagnosis. Adjustment for the number of examined lymph nodes, necessarily restricted to women who underwent lymphadenectomy (86%), did not modify this pattern, either overall, or within each category of stage. In other words, the geographic pattern in the mean excess hazard of death was not affected by the number of nodes examined during lymphadenectomy (data not shown). This suggests that, in contrast with the findings from the study of women diagnosed in 1990[4], stage migration does not affect the comparison of stage-specific survival between European regions and the US. This could be because the recording of stage has become more homogeneous, or because the quality and completeness of diagnostic investigation is less variable now than previously.

The mean excess hazard of death for women with late-stage disease was very high in Eastern Europe. This suggests that fewer effective treatment options were available for these women, although higher levels of co-morbidity may have restricted therapeutic options. Hormonal treatment and adjuvant chemotherapy were used more extensively in Slovakia, Estonia and Poland than in other European countries, and not just for node-positive and estrogen-receptor positive disease. Mastectomy was often used instead of breast-conserving surgery and radiotherapy, in part because radiotherapy facilities were not always available. Total national expenditure on health was low, and this is also likely to have affected the quality of treatment[6].

Data on stage were remarkably complete, because they were collected directly from clinical records. Complete data on stage and lymph nodes were unavailable for all but 5–11% of women in the 5 broad European regions, although for up to 20% in 3 of the 26 European registries. However, exclusion of women with unknown stage or lymph node status did not change the geographic pattern of the excess hazard of death within any of the categories for which stage was known. More complex analyses after imputation of missing values are unlikely to change this picture.

Pattern of care studies and survival have been conducted separately in Europe[5,6] and the US[24]. Here, we could make a direct comparison between Europe and the US with data on stage at diagnosis and treatment collected and coded with the same rules.

Overall, women received breast-conserving surgery and radiotherapy for early node-negative breast cancer somewhat more often in Europe (55%) than the US (49%), but the distribution by age was similar. The lower proportion in the US is mainly determined by Louisiana (37%) and South Carolina (34%) and may be explained by the attitude of some US clinicians during the late 1990s, when radiotherapy may have been considered unnecessary after breast-conserving surgery[10]. Another explanation may be the paucity of radiotherapy centres and/or the distance of the nearest radiotherapy facility[25] in these two states.

After adjusting for age and tumour size within the category of early node-negative disease, the odds of being treated with breast-conserving surgery and radiotherapy were almost 60% higher in Western Europe than Southern Europe (reference), 20–40% lower in the US and Northern Europe, and more than 80% lower in Eastern Europe.

In Denmark, the low level of breast-conserving surgery and radiotherapy was probably related to the fact that most breast cancers were treated in local or regional hospitals (not specialist centres), rather than any lack of radiotherapy facilities, although the Danish national cancer plan of 2000 recognised the need to modernize and expand radiotherapy services. Most women receiving breast-conserving surgery also received radiotherapy, but breast-conserving surgery was hardly ever done in areas where breast cancer screening was not performed[26].

About 90% of women aged less than 50 years with node-positive disease received chemotherapy in both Europe and the US, in accordance with contemporary clinical protocols[27].

The proportion of women aged 50–99 years with positive lymph nodes who received chemotherapy was notably higher in the US (60% *vs.* 46%). The proportion was similar in all 7 states, but slightly lower in Illinois and Rhode Island. The finding of more active treatment for older women in the US echoes the finding for women diagnosed in 1990, and may indicate the importance of health insurance programs such as MEDICARE. The US National Institutes of Health had also recommended chemotherapy for node-positive breast cancer in 1985[28].

In the late 1990s, tamoxifen was recommended for estrogen-receptor positive tumours on both sides of the Atlantic[29,30], especially for women aged over 50 years. In the US, the proportion of women aged less than 50 years with ER+ tumours treated with hormonal therapy was 58%, higher than in Europe (44%).

The low proportion of women with early stage disease who receive breast-conserving surgery is correlated with total national expenditure on health[6]. The wider use of chemotherapy and hormonal treatment may reflect the fact that costs are lower than for surgery and radiotherapy. Taken with the findings of this study, this suggests that low healthcare expenditure in Eastern European countries may have had an important effect on the quality of breast cancer treatment, and on survival.

Differences in breast cancer survival between Europe and the US in the late 1990s were mainly explained by lower survival in Eastern Europe, where low healthcare expenditure may have constrained the quality of breast cancer treatment. Similarly wide variation has also been reported within the US, where non-Hispanic Black women were less likely to receive guideline-concordant treatment than non-Hispanic White women[8].

The need for population-based data on stage and treatment is recognised by clinicians and epidemiologists. High-resolution studies still seem to be the only valid way to collect this information. More funding should be directed to help cancer registries obtain timely high-resolution data for all registered patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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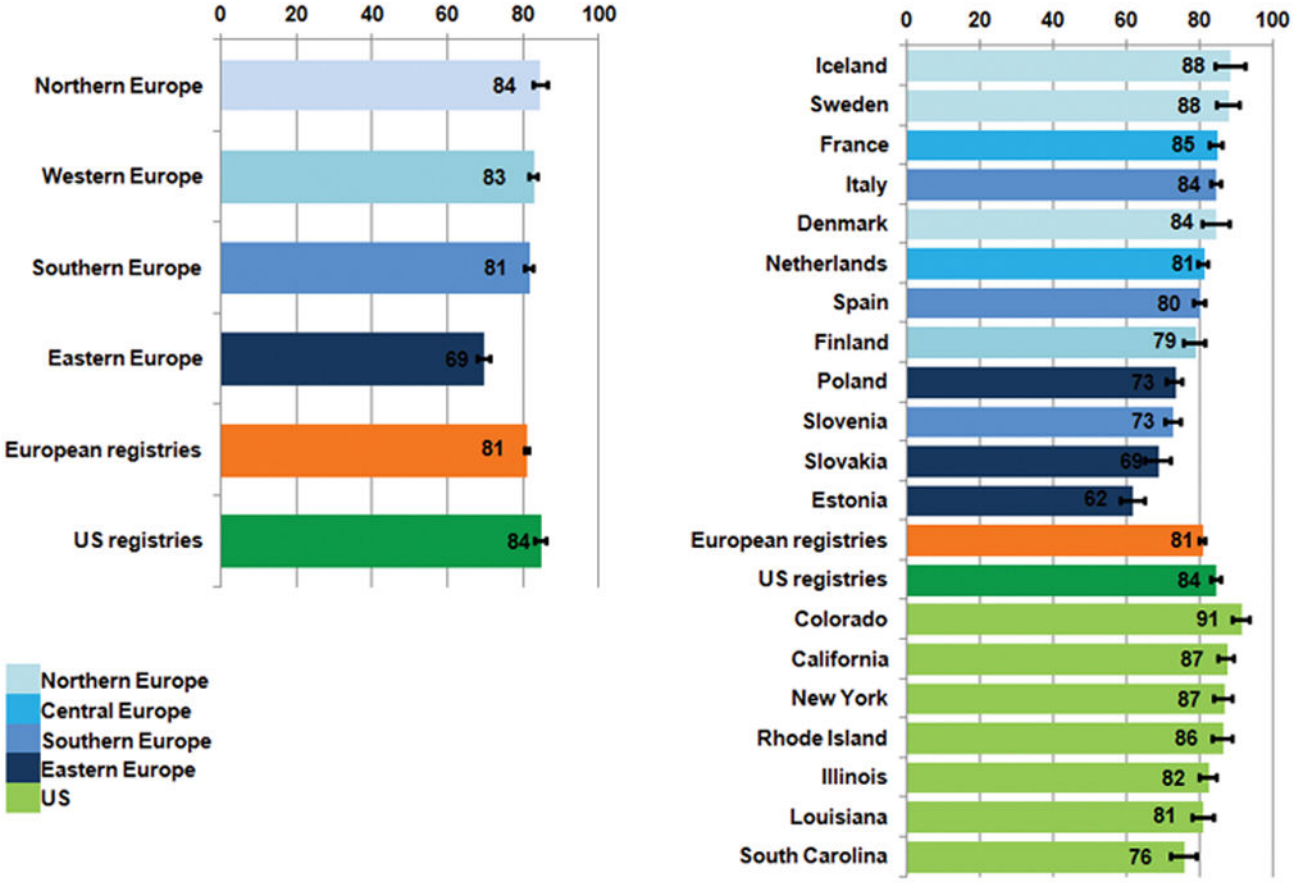

Figure 1.

Five-year age-standardised net survival (%), women diagnosed with primary invasive breast cancer in Europe and the US in the late 1990s: country and region

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Table 1

Stage at diagnosis for women with invasive primary breast cancer, Europe and US: availability (%) of data and distribution.

EUROPE	Registry	Period of diagnosis		Morphologically verified	Stage data available	Early node-negative (T1 N0 M0)	Large node-negative (T2-3 N0 M0)	Node-positive (T1-3 N+ M0)	Locally advanced (T4 any N M0)	Metastases (M1)	Unstaged
			No.	%	%	%	%	%	%	%	%
Denmark	*National*	1994	500	99	94	28	11	28	24	3	6
Estonia	*National*	1997	522	79	94	17	15	35	17	11	6
Finland	*National*	1996–1997	552	95	82	36	9	30	4	2	18
France	Bas-Rhin	1995	175	95	97	42	15	29	3	7	3
	Côte d'Or	1996–1997	521	99	96	43	14	31	5	3	4
	Doubs	1997	234	97	98	34	21	34	2	7	2
	Isère	1997	243	95	95	49	12	30	0	4	5
	Tarn	1997	231	98	94	36	16	28	6	8	6
Iceland	*National*	1995–1998	458	97	90	36	13	35	1	4	10
Italy	Firenze	1997	330	94	82	35	9	25	8	4	18
	Genova	1996	523	93	92	34	14	27	10	7	8
	Modena	1997	478	97	95	48	10	32	3	3	5
	Palermo	1999	580	93	89	26	13	35	9	6	11
	Ragusa	1996–1998	392	87	78	20	13	36	3	6	22
	Varese	1996–1997	1,126	97	92	32	12	33	10	5	8
Netherlands	Eindhoven	1997–1998	1,281	99	97	43	13	31	6	4	3
	NE Netherlands	1997	2,237	92	92	32	18	30	6	7	8
Poland	Cracow	1997–1998	619	84	93	23	13	44	7	5	7
	Warsaw	1996	597	96	88	23	13	42	6	4	12
Slovakia	*National*	1996	551	97	98	22	14	36	8	19	2
Slovenia	*National*	1997	882	82	91	23	15	32	11	10	9
Spain	Basque Country	1996	541	100	94	28	18	36	8	5	6
	Castellon	1995–1998	769	98	96	33	16	34	6	7	4
	Granada	1996–1997	500	95	93	16	22	38	11	6	7
	Navarra	1996–1997	500	99	93	39	13	31	4	6	7

EUROPE	Registry	Period of diagnosis	No.	Morphologically verified %	Stage data available %	Early node-negative (T1 N0 M0) %	Large node-negative (T2-3 N0 M0) %	Node-positive (T1-3 N+ M0) %	Locally advanced (T4 any N M0) %	Metastases (M1) %	Unstaged %
Sweden	*National*	1994	500	94	90	36	11	25	14	5	10
European registries			**15,842**	**94**	**92**	**32**	**14**	**33**	**8**	**6**	**8**
Northern Europe			2,010	96	89	34	11	29	11	3	11
Western Europe			4,922	95	95	37	16	30	5	6	5
Southern Europe			6,621	94	91	30	14	33	8	6	9
Eastern Europe			2,289	89	93	21	14	39	9	9	7
US	**State**										
	California	1997	458	99	92	43	12	28	4	5	8
	Colorado	1997	485	99	94	45	14	26	5	4	6
	Illinois	1997	467	99	88	37	16	22	6	8	12
	Louisiana	1997	492	99	88	37	17	25	4	6	12
	New York	1997	448	98	81	33	10	29	3	5	19
	Rhode Island	1997	403	99	87	42	11	27	3	4	13
	South Carolina	1997	367	98	94	38	18	28	5	5	6
US registries			**3,120**	**99**	**89**	**39**	**14**	**26**	**4**	**5**	**11**

Table 2

No. of lymph nodes examined among women with breast cancer who underwent lymphadenectomy, and distribution (%) of tumour size in women with early, node-negative (T1N0M0) breast cancer treated by surgery: Europe and US

				Women with early node-negative disease treated by surgery[1]			
		Lymphadenectomy	10 or more lymph nodes examined		Less than 5mm (T1a)	5 to 10mm (T1b)	Over 10mm up to 20mm (T1c)
EUROPE	**Registry**	**No.**	**%**	**No.**	**%**	**%**	**%**
Denmark	*National*	445	59	142	7	25	68
Estonia	*National*	383	23	87	0	17	80
Finland	*National*	461	33	200	4	34	63
France	Bas-Rhin	168	66	74	5	23	72
	Côte d'Or	489	47	226	8	40	52
	Doubs	220	35	79	6	27	67
	Isère	227	67	118	5	45	50
	Tarn	208	75	83	5	37	58
Iceland	*National*	393	65	165	5	28	64
Italy	Firenze	256	93	116	4	17	66
	Genova	454	84	178	9	18	58
	Modena	459	81	226	9	34	56
	Palermo	568	77	148	9	18	46
	Ragusa	299	80	77	6	17	62
	Varese	969	91	359	4	25	70
Netherlands	Eindhoven	1,172	60	542	4	28	65
	NE Netherlands	1,896	50	715	2	18	48
Poland	Cracow	516	67	144	6	26	68
	Warsaw	487	83	139	6	22	65
Slovakia	*National*	456	27	120	5	26	69
Slovenia	*National*	688	89	200	4	18	74
Spain	Basque Country	483	75	151	5	25	64
	Castellon	707	78	256	6	28	63
	Granada	431	86	82	2	22	62
	Navarra	430	86	193	11	24	65

				Women with early node-negative disease treated by surgery[1]			
		Lymphadenectomy	10 or more lymph nodes examined		Less than 5mm (T1a)	5 to 10mm (T1b)	Over 10mm up to 20mm (T1c)
EUROPE	**Registry**	**No.**	**%**	**No.**	**%**	**%**	**%**
Sweden	*National*	422	49	179	4	36	60
European registries		**13,687**	**66**	**4,999**	**5**	**26**	**61**
US	**State**						
	California	397	79	198	8	31	59
	Colorado	399	78	215	12	28	57
	Illinois	376	78	171	13	32	50
	Louisiana	415	75	181	7	32	60
	New York	335	83	150	11	34	53
	Rhode Island	313	76	167	11	25	62
	South Carolina	296	76	138	9	23	62
US registries		**2,531**	**78**	**1,220**	**10**	**29**	**57**

[1] Percentages do not add to 100%: early node-negative tumours with no precise data on tumour size are not shown

Table 3

Breast-conserving surgery plus radiotherapy (BCS+RT) in early node-negative breast cancer (T1N0M0), by age: Europe and US

		All women	Surgically treated													
			Any stage		Early node-negative											
					All ages (15–99 years)				15–69 years				70–99 years			
							BCS + RT				BCS + RT				BCS + RT	
EUROPE	**Registry**	**No.**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Denmark	*National*	500	487	97	142	29	38	27	122	86	35	29	20	14	3	15
Estonia	*National*	522	404	77	87	22	8	9	73	84	7	10	14	16	1	7
Finland	*National*	552	520	94	200	38	120	60	163	82	111	68	37	19	9	24
France	Bas-Rhin	175	165	94	74	45	47	64	61	82	40	66	13	18	7	54
	Côte d'Or	521	501	96	226	45	189	84	193	85	164	85	33	15	25	76
	Doubs	234	225	96	79	35	62	78	63	80	53	84	16	20	9	56
	Isère	243	233	96	118	51	97	82	101	86	84	83	17	14	13	76
	Tarn	231	220	95	83	38	70	84	58	70	49	84	25	30	21	84
Iceland	*National*	458	438	96	165	38	74	45	139	84	72	52	26	16	2	8
Italy	Firenze	330	299	91	116	39	86	74	85	73	70	82	31	27	16	52
	Genova	523	487	93	178	37	123	69	145	81	107	74	33	19	16	48
	Modena	478	465	97	226	49	124	55	177	78	114	64	49	22	10	20
	Palermo	580	555	96	148	27	104	70	126	85	91	72	22	15	13	59
	Ragusa	392	337	86	77	23	41	53	62	81	37	60	15	19	4	27
	Varese	1,126	1,053	94	359	34	158	44	285	79	138	48	74	21	20	27
Netherlands	Eindhoven	1,281	1,219	95	542	44	359	66	428	79	300	70	114	21	59	52
	NE Netherlands	2,237	1,989	89	715	36	366	51	580	81	330	57	135	19	36	27
Poland	Cracow	619	518	84	144	28	16	11	119	83	15	13	25	17	1	4
	Warsaw	597	532	89	139	26	28	20	121	87	27	22	18	13	1	6
Slovakia	*National*	551	485	88	120	25	42	35	99	83	38	38	21	18	4	19
Slovenia	*National*	882	718	81	200	28	121	61	169	85	117	69	31	16	4	13
Spain	Basque Country	541	506	94	151	30	103	68	131	87	91	69	20	13	12	60
	Castellon	769	730	95	256	35	98	38	220	86	93	42	36	14	5	14
	Granada	500	458	92	82	18	37	45	72	88	36	50	10	12	1	10

		All women	Surgically treated													
			Any stage		Early node-negative											
					All ages (15–99 years)				15–69 years				70–99 years			
							BCS + RT				BCS + RT				BCS + RT	
EUROPE	**Registry**	**No.**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
	Navarra	500	459	92	193	42	149	77	173	90	140	81	20	10	9	45
Sweden	*National*	500	471	94	179	38	82	46	138	77	72	52	41	23	10	24
European registries		**15,842**	**14,474**	**91**	**4,999**	**35**	**2,742**	**55**	**4,103**	**82**	**2,431**	**59**	**896**	**22**	**311**	**35**
US	**State**															
	California	458	440	96	198	45	106	54	138	70	77	56	60	30	29	48
	Colorado	485	470	97	215	46	114	53	163	76	97	60	52	24	17	33
	Illinois	467	436	93	171	39	94	55	117	68	73	62	54	32	21	39
	Louisiana	492	475	97	181	38	67	37	119	66	54	45	62	34	13	21
	New York	448	430	96	150	35	77	51	95	63	55	58	55	37	22	40
	Rhode Island	403	380	94	167	44	97	58	109	65	70	64	58	35	27	47
	South Carolina	367	351	96	138	39	47	34	96	70	35	36	42	30	12	29
US registries		**3,120**	**2,982**	**96**	**1,220**	**41**	**602**	**49**	**837**	**69**	**461**	**55**	**383**	**31**	**141**	**37**

Table 4

Odds ratio (OR) for women with early node-negative disease (T1N1M0) being treated with breast-conserving surgery and radiotherapy (vs. any other surgical procedure, with or without radiotherapy) in each jurisdiction, adjusted for age and tumour size

	No.[1]	OR	95% CI	
Jurisdiction				
Northern Europe	681	0.60	0.50	0.72
Western Europe	1,595	1.57	1.36	1.81
Southern Europe	1,848	1		
Eastern Europe	477	0.16	0.12	0.20
US	1,185	0.80	0.69	0.94
Age (years)				
15–39	244	1.33	0.99	1.78
40–49	1,039	1.44	1.21	1.70
50–59	1,558	1.38	1.19	1.60
60–69	1,614	1		
70–99	1,331	0.48	0.41	0.56
Tumour size				
Less than 5mm (T1a)	380	0.94	0.75	1.17
5–10mm (T1b)	1,650	1.31	1.16	1.48
>10mm, up to 20mm (T1c)	3,756	1		

[1] Number of women with early node-negative disease who were operated, with information on tumour size available

Table 5

Chemotherapy in node-positive disease and endocrine treatment in estrogen-receptor-positive disease, by age: registry and country

		Women with node-positive tumours											Women with estrogen-receptor-positive tumours										
					15–49 years				50–99 years							15–49 years				50–99 years			
EUROPE	Registry		Chemo-therapy		Total		Chemo-therapy		Total		Chemo-therapy			Endocrine treatment		Total		Endocrine treatment		Total		Endocrine treatment	
		No.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.	%	No.	%
Denmark	*National*	204	43	21	35	17	19	54	169	83	24	14	340	115	34	52	15	4	8	288	0	111	39
Estonia	*National*	300	236	79	81	27	76	94	219	73	160	73	110	94	85	34	31	24	71	76	69	70	92
Finland	*National*	189	71	38	52	28	41	79	137	72	30	22	376	125	33	89	24	21	24	287	76	104	36
France	Bas-Rhin	63	48	76	17	27	17	100	46	73	31	67	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
	Côte d'Or	194	110	57	67	35	58	87	127	65	52	41	396	220	56	106	27	33	31	290	73	187	64
	Doubs	94	59	63	25	27	21	84	69	73	38	55	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
	Isère	78	50	64	20	26	19	95	58	74	31	53	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
	Tarn	86	52	60	23	27	21	91	63	73	31	49	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
Iceland	*National*	178	97	54	59	33	53	90	119	67	44	37	303	162	53	77	25	32	42	226	75	130	58
Italy	Genova[1]	193	139	72	46	24	42	91	147	76	97	66											
	Modena	169	129	76	45	27	40	89	124	73	89	72	320	221	69	75	23	59	79	245	77	162	66
	Palermo	252	198	79	77	31	75	97	175	69	123	70	209	148	71	70	33	53	76	139	67	95	68
	Varese	455	250	55	131	29	90	69	324	71	160	49	685	246	36	157	23	42	27	528	77	204	39
Netherlands	Eindhoven	477	181	38	144	30	133	92	333	70	48	14	552	189	34	149	27	18	12	403	73	171	42
	NE Netherlands	823	323	39	236	29	220	93	587	71	103	18	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
Poland	Cracow	336	184	55	84	25	74	88	252	75	110	44	104	66	63	22	21	13	59	82	79	53	65
	Warsaw	290	157	54	96	33	80	83	194	67	77	40	89	61	69	26	29	10	38	63	71	51	81
Slovakia	*National*	288	219	76	99	34	91	92	189	66	128	68	93	49	53	34	37	12	35	59	63	37	63
Slovenia	*National*	402	282	70	108	27	106	98	294	73	176	60	385	227	59	88	23	24	27	297	77	203	68
Spain	Basque Country	228	190	83	87	38	84	97	141	62	106	75	260	213	82	76	29	49	64	184	71	164	89
	Castellon	327	240	73	85	26	82	96	242	74	158	65	355	290	82	86	24	70	81	269	76	220	82
	Granada	237	178	75	72	30	71	99	165	70	107	65	157	127	81	45	29	29	64	112	71	98	88
	Navarra	169	138	82	67	40	67	100	102	60	71	70	317	252	79	86	27	72	84	231	73	180	78
Sweden	*National*	159	45	28	34	21	27	79	125	79	18	14	248	123	50	41	17	7	17	207	83	116	56

EUROPE	Registry	Women with node-positive tumours										Women with estrogen-receptor-positive tumours									
					15–49 years				50–99 years						15–49 years				50–99 years		
			Chemo-therapy		Total		Chemo-therapy		Total		Chemo-therapy			Endocrine treatment		Total		Endocrine treatment		Total		Endocrine treatment	
		No.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	No.	%	No.	%	No.	%	No.	%	No.	%
European registries		**6,191**	**3,619**	**58**	**1,790**	**29**	**1,607**	**90**	**4,401**	**71**	**2,012**	**46**	**5,299**	**2,928**	**55**	**1,313**	**25**	**572**	**44**	**3,986**	**75**	**2,356**	**59**
US	**State**																						
	California	154	107	69	55	36	46	84	99	64	61	62	287	157	55	68	24	31	46	219	76	126	58
	Colorado	155	113	73	51	33	48	94	104	67	65	63	290	192	66	73	25	47	64	217	75	145	67
	Illinois	133	87	65	43	32	39	91	90	68	48	53	233	129	55	45	19	23	51	188	81	106	56
	Louisiana	155	102	66	38	25	32	84	117	75	70	60	260	116	45	40	15	18	45	220	85	98	45
	New York	155	106	68	47	30	42	89	108	70	64	59	228	147	64	42	18	20	48	186	82	127	68
	Rhode Island	128	84	66	34	27	32	94	94	73	52	55	301	245	81	68	23	52	76	233	77	193	83
	South Carolina	121	89	74	35	29	31	89	86	71	58	67	186	121	65	39	21	26	67	147	79	95	65
US registries		**1,001**	**688**	**69**	**303**	**30**	**270**	**89**	**698**	**70**	**418**	**60**	**1,785**	**1,107**	**62**	**375**	**21**	**217**	**58**	**1,410**	**79**	**890**	**63**

n/a - not available

[1] Registries were excluded if data on treatment were unavailable for more than 20% of women: Genova (hormonal treatment), Firenze and Ragusa (both treatments)