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# Variation in 'standard care' for breast cancer across Europe: A EUROCARE-3 high resolution study

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ABSTRACT

On a population-based sample of 13,500 European breast cancer patients mostly diagnosed in 1996–1998 and archived by 26 cancer registries, we used logistic regression to estimate odds of conservative surgery plus radiotherapy (BCS + RT) versus other surgery, in T1N0M0 cases by country, adjusted for age and tumour size. We also examined: BCS + RT in relation to total national expenditure on health (TNEH); chemotherapy use in N+ patients; tamoxifen use in oestrogen-positive patients; and whether $\geqslant$10 nodes were examined in lymphadenectomies. Stage, diagnostic examinations and treatments were obtained from clinical records.

T1N0M0 cases were 33.0% of the total. 55.0% of T1N0M0 received BCS + RT, range 9.0% (Estonia) to 78.0% (France). Compared to France, odds of BCS + RT were lower in all other countries, even after adjusting for covariates. Women of 70–99 years had 67% lower odds of BCS + RT than women of 15–39 years. BCS + RT was 20% in low TNEH, 58% in medium TNEH, and 64% in high TNEH countries. Chemotherapy was given to 63.0% of N+ and 90.7% of premenopausal N+ (15–49 years), with marked variation by country, mainly in post-menopause (50–99 years). Hormonal therapy was given to 55.5% of oestrogen-positive cases, 44.6% at 15–49 years and 58.8% at 50–99 years; with marked variation across countries especially in premenopause.

The variation in breast cancer care across Europe prior to the development of European guidelines was striking; older women received BCS + RT much less than younger women; and adherence to 'standard care' varied even among countries with medium/high TNEH, suggesting sub-optimal resource allocation.



## 1. Introduction

We performed a EUROCARE-3 high resolution study on breast cancer, collecting information on stage, diagnostic procedures, treatment and follow-up for a representative population-based sample of about 15,000 patients diagnosed in 1996–1998 and archived by 26 European cancer registries (CRs). Previous (EUROCARE-2) high resolution studies reported large variations in stage distribution and treatment across Europe for breast cancer, which are thought to explain a large part of the differences in breast cancer survival reported by past EUROCARE analyses.[1]

By the middle of the 1990s, large multicentre controlled clinical studies had established that, for early stage breast cancer, conservative surgery reduces discomfort, side-effects and above all improves aesthetic outcomes compared to mastectomy, without adversely affecting survival.[2–9] At around the same time it was also established that adjuvant chemotherapy for node-positive cancers[9,10] and hormonal treatment for tumours with positive oestrogen (ER) and progesterone (PR) receptors[9,11,12] reduces relapse rates and prolongs survival.

Thus, by the mid-1990s it was clear that 'standard care' should be conservative breast surgery plus radiotherapy to the residual breast for early stage breast cancer, chemotherapy for node-positive cancers, and hormonal treatment for receptor-positive disease. However, there were no European guidelines on breast cancer treatment at the time, and existing regional or national guidelines may not have reflected the best practices implied by trial results.

The aim of the present study is to analyse adherence to selected aspects of 'standard care' for breast cancer treatment across European countries, in relation to patient age, disease stage at diagnosis and hormone receptor status of the tumour. In particular we investigated the use of breast-conserving surgery plus radiotherapy (BCS + RT) in early stage (T1N0M0) breast cancer; the use of chemotherapy in node-positive (N+) disease; and the use of endocrine treatment (mainly tamoxifen) in tumours expressing oestrogen receptors (ER+). We also analysed the distribution of tumour stage at diagnosis across countries, to update the previous EUROCARE high resolution study on breast cancer.[1]

## 2. Materials and methods

We analysed data on 13,485 surgically treated breast cancer patients from 26 European CRs in 12 countries: Denmark, Estonia, Finland, France (Bas-Rhin, Côte d'Or, Doubs, Isère, Tarn) Iceland, Italy (Firenze, Genova, Modena, Palermo, Ragusa, Varese), The Netherlands (Eindhoven), Poland (Cracow, Warsaw), Slovakia, Slovenia, Spain (Basque Country, Castellon, Granada, Mallorca, Navarra) and Sweden.

The EUROCARE-3 high resolution study protocol specified that participating CRs had to provide data on all breast cancer cases consecutively diagnosed in a time interval between 1996 and 1998, preferably in 1997. About 500 cases per registry (roughly corresponding to a complete year's incidence) were required. If the minimum was not reached in 1 year the period could be extended backwards or forwards to reach the required number of cases.

However Denmark and Sweden provided representative samples of cases diagnosed in 1994, and Palermo provided all cases incident in 1999. These cases were included in order to ensure that the geographic area covered by the study was

**Table 1 – Number of cases and stage distribution (%) by country. Operated patients.**

| Country | Registry | No. of cases | *In situ* | T1N0M0 | T2-3N0M0 | T1-3N+M0 | T4N±M0 | M1 | NS |
|---|---|---|---|---|---|---|---|---|---|
| Denmark | National CR | 487 | 0.0 | 29.2 | 11.5 | 28.1 | 24.0 | 1.4 | 5.8 |
| Estonia | National CR | 405 | 0.3 | 21.5 | 18.8 | 40.3 | 13.6 | 3.0 | 2.7 |
| Finland | National CR | 576 | 0.0 | 35.9 | 10.1 | 29.0 | 2.8 | 1.9 | 20.3 |
| France | Bas-Rhin, Côte d'Or, Doubs, Isère, Tarn | 1484 | 0.1 | 40.6 | 15.5 | 27.6 | 2.9 | 3.2 | 10.0 |
| Iceland | National CR | 438 | 0.0 | 37.7 | 13.2 | 36.3 | 1.1 | 2.7 | 8.9 |
| Italy | Firenze, Genova, Modena, Palermo, Ragusa, Varese | 3259 | 1.4 | 33.9 | 13.0 | 33.2 | 7.5 | 3.1 | 8.0 |
| Netherlands | Eindhoven | 1219 | 0.0 | 44.5 | 13.7 | 25.4 | 6.3 | 2.1 | 8.0 |
| Poland | Cracow, Warsaw | 1058 | 0.0 | 27.1 | 15.1 | 47.0 | 3.9 | 1.2 | 5.7 |
| Slovakia | National CR | 489 | 0.2 | 24.7 | 15.3 | 40.5 | 6.5 | 11.0 | 1.6 |
| Slovenia | National CR | 718 | 0.0 | 27.9 | 18.8 | 37.5 | 9.5 | 2.5 | 3.9 |
| Spain | Basque Countries, Castellon, Granada, Mallorca, Navarra | 2882 | 5.3 | 28.1 | 18.3 | 33.6 | 6.0 | 2.4 | 6.3 |
| Sweden | National CR | 471 | 0.0 | 38.0 | 11.3 | 26.5 | 13.8 | 3.0 | 7.4 |
| All cases | | 13,485 | 1.5 | 33.0 | 15.0 | 33.2 | 6.9 | 2.9 | 7.5 |

T1N0M0 = early, T2-3N0M0 = large, node-negative, T1-3N+M0 = node-positive, T4N±M0 = locally advanced, M1 = metastatic tumours, NS = stage not specified.

as wide as possible. The Finnish population-based cases were those incident in the Tampere hospital region only, which is representative of the whole of Finland.

Information on stage, diagnostic examinations and treatment was collected according to a standardised protocol.[13] Most of the information required was obtained by examining clinical records. Where these were incomplete, additional information sources were consulted (e.g. pathology reports and hospital discharge records).

Disease stage was defined according to TNM rules (3rd edition).[14] If pathological T and N were not available, clinical stage was used. Patients were grouped into seven stage categories: in situ, early (T1N0M0), larger node-negative (T2-3N0M0), node-positive (T1-3N+M0), locally advanced (T4N±M0), metastatic (M1), and stage not specified (NS). We also assessed the distribution of T1a (⩽0.5 cm), T1b (>0.5–1 cm) and T1c (>1–2 cm) cancers in T1N0M0 cases. Age at diagnosis was categorised as 15–39, 40–49, 50–69, and 70–99 years in the logistic regression analysis and as 15–49 versus 50–99 years in the descriptive analyses; ER status was categorised as positive, negative or unknown.

Surgical treatment was categorised as BCS + RT versus other surgery, whether or not followed by RT, including conservative approaches without RT (7.4% of early stage cases) as well as mastectomy (35.3% of early stage cases). Chemotherapy and endocrine treatment were dichotomised as administered versus not administered/unknown.

We analysed, overall and by country, the proportion of early stage patients receiving BCS + RT; the proportion of N+ patients receiving chemotherapy; the proportion of ER+ patients receiving tamoxifen; and the proportion with 10 or more lymph nodes removed and examined during lymphadenectomy (minimum number of nodes for staging recommended by TNM during the study period).[14]

When the variable under study was not available for 20% or more of patients, the corresponding CR was excluded from the analysis. Thus the CRs of Firenze and Ragusa were excluded from the analyses on chemotherapy and hormonal treatment, and Genova was excluded from the analysis of hormonal treatment.

Differences in proportions were tested by z-test. The odds of being treated with BCS + RT (versus other surgery) in T1N0M0 patients by country, adjusted by age and tumour size were estimated using a logistic regression model.

To investigate whether use of 'standard surgical care' for breast cancer was related to regional wealth, we analysed the proportion of BCS + RT (versus other surgery) in T1N0M0 patients in relation to the mean total national expenditure on health (TNEH) in US dollars per capita purchasing power parity ($PPP), in 1994–2000.[15] TNEH was categorised as low (<1000 $PPP), medium (1000–2000 $PPP) and high (>2000 $PPP). The significance of TNEH 'exposure' trends was tested by the likelihood ratio test. Statistical analyses were performed using Stata version 9 (StataCorp LP, College Station, TX).

## 3. Results

T1N0M0 cases constituted 33.0% of the whole sample; T2-3N0M0 cases constituted 15.0%; T1-3N+M0 cases 33.2%;

**Table 2 – For T1N0M0 cases: distribution (%) of T1a, T1b and T1c disease, and proportion (%) with 10 or more lymph nodes examined, by country.**

| Country | T1N0M0[a] No. of cases | T1a[b] (⩽0.5 cm) % | T1b[b] (>0.5–1 cm) % | T1c[b] (>1–2 cm) % | 10 or more lymph nodes examined[c] % |
|---|---|---|---|---|---|
| Denmark | 142 | 7.0 | 25.4 | 67.6 | 59.2 |
| Estonia | 87 | 0.0 | 17.2 | 80.5 | 24.1 |
| Finland | 207 | 3.9 | 33.3 | 62.8 | 25.6 |
| France | 602 | 7.0 | 36.4 | 56.5 | 52.3 |
| Iceland | 165 | 4.9 | 28.5 | 63.6 | 61.2 |
| Italy | 1103 | 6.6 | 23.3 | 60.7 | 86.4 |
| Netherlands | 542 | 4.1 | 28.2 | 64.8 | 57.3 |
| Poland | 287 | 5.6 | 23.3 | 67.3 | 76.3 |
| Slovakia | 121 | 5.0 | 25.6 | 69.4 | 28.9 |
| Slovenia | 200 | 4.0 | 17.5 | 73.5 | 87.5 |
| Spain | 810 | 7.2 | 24.4 | 64.0 | 81.3 |
| Sweden | 179 | 3.9 | 35.8 | 60.3 | 41.9 |
| Total | 4445 | 5.8 | 26.8 | 63.3 | 67.9 |

[a] Percentages calculated on total number of cases.
[b] Percentages calculated on total number of T1N0M0 cases.
[c] Percentages calculated on total number of T1N0M0 cases who received axillary lymphadenectomy.

T4N ± M0 6.9%; M1 2.9%; and NS 7.5%. In situ tumours were 1.5% of the total (Table 1). Stage distribution varied across countries, with the highest proportions of T1N0M0 cases in (decreasing order) The Netherlands, France, Sweden, Iceland, Finland, and Italy. The highest proportions of T2-3N0M0 cases were in Estonia, Slovenia and Spain. The highest proportions of T1-3N+M0 cases were in Poland, Slovakia and Estonia. Denmark had the highest proportion of T4N ± M0 cases. Slovakia had the highest proportion of M1 cases. NS cases ranged from 1.6% (Slovakia) to 20.3% (Finland).

Table 2 shows the breakdown of T1N0M0 cases by size (T1a, T1b and T1c) and the proportion with 10 or more lymph nodes examined, by country. The proportion of T1N0M0 tumours varied from 21.5% in Estonia to 44.5% in the Netherlands (Table 1). Among T1N0M0 cases 5.8% were T1a, 26.8% were T1b, and 63.3% were T1c, with exact size unknown in about 4.0%. The proportion of T1a cases was highest in Spain (7.2%), Denmark (7.0%) and France (7.0%), and lowest in Estonia (0.0%). The proportion of T1b cases was about 30% in Finland, Iceland, The Netherlands, Sweden, and also France; and lowest in Slovenia and Estonia (17.5% and 17.2%, respectively). T1c cases constituted 63.3% of total cases, with highest proportion in Estonia (80.5%) and lowest proportion in France (56.5%).

Overall 68.8% of cases that underwent lymphadenectomy had 10 or more lymph nodes examined. The corresponding figure was 67.9% for T1N0M0 cases, range 24.1% (Estonia) to 87.5% (Slovenia). Overall 55.0% of T1N0M0 patients received BCS + RT (Fig. 1) in conformity with 'standard care.' However inter-country variation was marked, ranging from 9.0% (Estonia) to 78.0% (France). To investigate factors influencing adherence to this standard for early stage breast cancer, we analysed the odds of receiving BCS + RT (versus other surgery) in T1N0M0 patients by country, adjusted by age and tumour size (T1a, T1b, and T1c) (Table 3). Compared to France (reference) the odds of being treated with BCS + RT were lower in all other countries, even after adjusting for all the above covariates. The lowest odds ratios (ORs) were found for Eastern European countries (Estonia OR = 0.03 95% confidence interval 0.01–0.05; Poland OR = 0.05 95% CI 0.03–0.07; and Slovakia OR = 0.14 95% CI 0.09–0.21). Older women (70–99 years) had 67% lower odds of being treated with BCS + RT than younger women (15–39 years, reference group). T1b tumours had 38% greater odds of being treated with BCS + RT than T1a tumours.

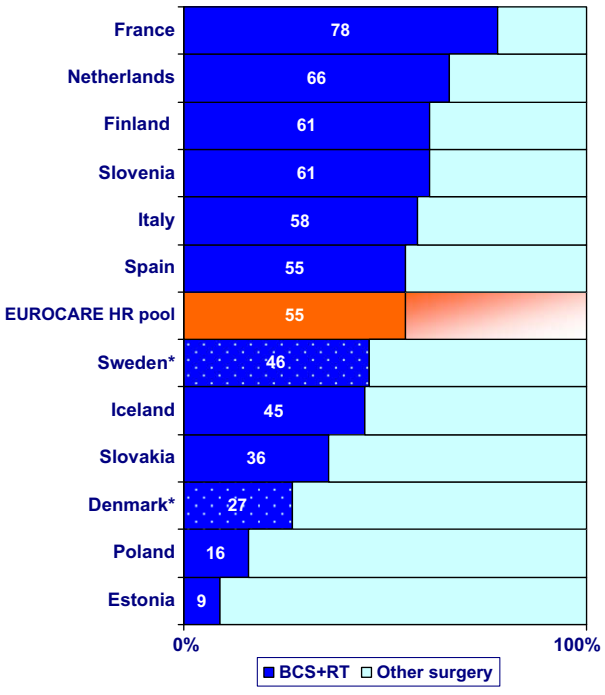



**Fig. 1 – Percentage of T1N0M0 cases receiving BCS + RT by country.**

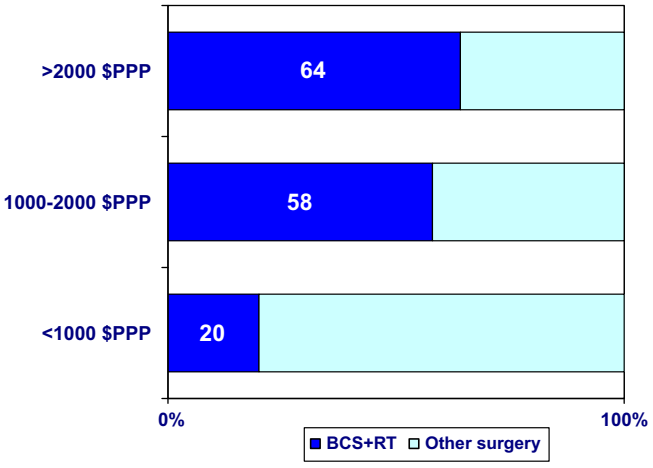
**Table 3 – Odds of being treated with BCS + RT (versus other surgery whether or not followed by RT) in T1N0M0 cases by country (adjusted by age at diagnosis and tumour size).**

| Country | No. cases[a] | OR | 95% CI |
|---|---|---|---|
| France | 601 | 1 | |
| Denmark | 142 | 0.09 | 0.06–0.14 |
| Estonia | 85 | 0.03 | 0.01–0.05 |
| Finland | 207 | 0.43 | 0.30–0.60 |
| Iceland | 160 | 0.20 | 0.14–0.30 |
| Italy | 1000 | 0.37 | 0.29–0.47 |
| Netherlands | 526 | 0.56 | 0.43–0.74 |
| Poland | 276 | 0.05 | 0.03–0.07 |
| Slovakia | 121 | 0.14 | 0.09–0.21 |
| Slovenia | 190 | 0.42 | 0.29–0.60 |
| Spain | 774 | 0.32 | 0.25–0.41 |
| Sweden | 179 | 0.23 | 0.16–0.33 |
| *Age* | | | |
| 15–39 | 215 | 1 | |
| 40–49 | 844 | 1.16 | 0.83–1.62 |
| 50–69 | 2399 | 0.96 | 0.71–1.31 |
| 70–99 | 803 | 0.33 | 0.24–0.47 |
| *Size* | | | |
| T1a | 258 | 1 | |
| T1b | 1191 | 1.39 | 1.04–1.86 |
| T1c | 2812 | 1.08 | 0.82–1.42 |

[a] T1N0M0 cases with available information on tumor size (No. 4261).

The proportion of women receiving BCS + RT was 20% in low TNEH countries (Estonia, Poland, Slovakia); 58% in medium TNEH countries (Finland, Italy, The Netherlands, Slovenia, Spain, Sweden); and around 64% in countries with high TNEH (Denmark, France, Iceland) (Fig. 2). The association was significant (P for TNEH 'exposure' trend <0.001), and remained so after adjusting for age (data not presented).

Table 4 shows the number of N+ cases and the percentage receiving adjuvant chemotherapy, by country and age. N+ patients constituted 40.5% (no. 5194) of total cases, 28.3% of whom were under 50 years and 71.7% were 50 years or more. Overall, 63.0% (no. 3,273) of N+ patients received chemotherapy but the variation by country was marked. Chemotherapy was received much more often by premenopausal women (15–49 years; 90.7%) than by postmenopausal women (50–99 years; 52.1%, $P < 0.001$). Although a low percentage (53.3%) in this age range received chemotherapy in Denmark, and around 80% did so in Finland, Italy and Sweden, in all other countries the figure was close to or exceeded 90%. By contrast, most between-country variation in the proportion receiving




High TNEH countries: Denmark, France, Iceland
Medium TNEH countries: Finland, Italy, The Netherlands, Slovenia, Spain, Sweden
Low TNEH countries: Estonia, Poland, Slovakia

**Fig. 2 – Percentage of T1N0M0 cases receiving BCS + RT by TNEH.**

**Table 4 – Number of patients with positive nodes (N+) and percentage who received adjuvant chemotherapy, by country and age at diagnosis.**

| Country | 15–49 years | | 50–99 years | | P value |
|---|---|---|---|---|---|
| | No. of N+ cases | Chemotherapy (%) | No. of N+ cases | Chemotherapy (%) | |
| Denmark | 30 | 53.3 | 173 | 15.6 | <0.001 |
| Estonia | 62 | 98.4 | 154 | 77.3 | <0.001 |
| Finland | 49 | 81.6 | 138 | 22.5 | <0.001 |
| France | 138 | 89.9 | 362 | 51.1 | <0.001 |
| Iceland | 57 | 89.5 | 114 | 39.5 | <0.001 |
| Italy* | 274 | 83.9 | 765 | 60.9 | <0.001 |
| Netherlands | 133 | 93.2 | 325 | 15.1 | <0.001 |
| Poland | 159 | 88.7 | 380 | 46.3 | <0.001 |
| Slovakia | 88 | 95.5 | 171 | 72.5 | <0.001 |
| Slovenia | 92 | 98.9 | 244 | 67.2 | <0.001 |
| Spain | 358 | 96.9 | 769 | 69.3 | <0.001 |
| Sweden | 31 | 80.7 | 128 | 15.6 | <0.001 |
| Total | 1334 | 90.7 | 3723 | 52.1 | <0.001 |

* Italy = Genova, Modena, Palermo, Varese.

chemotherapy was confined to postmenopausal women, ranging from 15% to 16% (Denmark, The Netherlands, Sweden) to over 70% (Estonia and Slovakia).

ER+ patients constituted 45.3% (no. 5577) of total cases, 23.1% of whom were less than 50 years and 76.9% were 50 years or over. Overall, 55.5% (no. 3094) of ER+ patients received hormonal therapy, 44.6% in premenopausal age (15–49 years) and 58.8% after menopause (50–99 years) ($P < 0.001$). There was marked variation across countries (Table 5) which was greater for premenopausal women (range 4.3% in Denmark to 73.0% in Spain) but still wide in older women (range 32.7% in Finland to 90.9% in Estonia).

## 4. Discussion

To our knowledge this is the largest European population-based study collecting information on stage, diagnostic procedures and treatment for breast cancer. Although the data refer to patients diagnosed and treated well over 10 years ago, many of these patients will still be alive today – thanks to the quality of the treatment they received then. It is also important to note that these are the most recent European high resolution population-based data available on breast cancer treatment.

This analysis has shown marked across Europe variation in compliance with 'standard care' for breast cancer treatment at the end of 1990s. Overall, just over half of early stage breast cancer patients received BCS + RT, ranging from 9.0% in Estonia to 78.0% in France. Inter-country variation was similarly wide for the use of adjuvant hormonal treatment in ER+ cancers, whereas less variation was found for the use of adjuvant chemotherapy in premenopausal N+ patients.

We decided to examine use of BCS + RT in N0 tumours even though the major trials[3,6] also recruited N+ patients.

**Table 5 – Number of operated patients positive for oestrogen receptors (ER+) and percentage who received endocrine treatment, by country and age at diagnosis.**

| Country | 15–49 years | | 50–99 years | | P value |
|---|---|---|---|---|---|
| | No. of ER+ cases | Endocrine treatment (%) | No. of ER+ cases | Endocrine treatment (%) | |
| Denmark | 47 | 4.3 | 286 | 37.4 | <0.001 |
| Estonia | 33 | 72.7 | 77 | 90.9 | 0.01 |
| Finland | 74 | 24.3 | 327 | 32.7 | 0.16 |
| France* | 104 | 26.9 | 306 | 60.8 | <0.001 |
| Iceland | 72 | 41.7 | 225 | 56.4 | 0.03 |
| Italy** | 277 | 52.0 | 931 | 50.2 | 0.59 |
| Netherlands | 138 | 10.9 | 392 | 39.8 | <0.001 |
| Poland | 46 | 45.7 | 146 | 71.2 | <0.001 |
| Slovakia | 35 | 34.3 | 57 | 61.4 | 0.01 |
| Slovenia | 81 | 27.2 | 303 | 67.3 | <0.001 |
| Spain | 348 | 73.0 | 1,029 | 81.7 | <0.001 |
| Sweden | 36 | 16.7 | 207 | 55.1 | <0.001 |
| Total | 1291 | 44.6 | 4286 | 58.8 | <0.001 |

* France = Côte d'Or.

** Italy = Modena, Palermo, Varese.

The reason for this is that N0 cancers are less advanced and only a limited proportion are likely to be multifocal or multicentric (which may contraindicate conservative surgery). Thus application of BCS + RT to N0 tumours should have been less controversial than for N+ tumours during the study period.

Although the use of BCS + RT in early stage breast cancer increased notably from the beginning of the 1990s[1] up to 1996–1998,[16] we have found that in many European countries only a relatively small proportion of these cancers were treated by BCS + RT in the second half of the decade.

The findings are comparable to those of other clinical[17,18] and population-based studies.[19] A study carried out on data from the Norwegian national Register of Hospital Discharges during 1990–1995[17] reported a lower percentage of conservative treatment (19.7%) in Norway than we found in this study for almost all European countries. A US study using data from hospital cancer registries found that 34% of stage 0–II breast cancer patients received conservative treatment in 1993–1997[18] and a population-based study on data from the Surveillance Epidemiology and End Results (SEER) program found that in 1985–1989 about 35% and in 1995 60% of women with stage I breast cancer received conservative surgery.[19]

In some cases conservative surgery for early stage cancer might be contraindicated by unfavourable prognostic factors such as multifocality, multicentricity or the presence of extensive intraductal component.[20] In the present study we did not collect information on these factors. However we did adjust for the available information (age at diagnosis and tumour size), finding that inter-country differences in the odds of receiving BCS + RT reduced only slightly after adjustment for these factors, and that inter-country differences remained significant, with lowest odds persisting in Poland, Slovakia, Estonia and Denmark.

Lack of radiotherapy facilities may be another reason why mastectomy was performed rather than conservative surgery: mastectomy is more likely to be a definitive treatment than conservative surgery without RT, which is characterised by a fairly high rate of locoregional recurrences[4] requiring further treatment and increasing overall treatment costs. The countries with the highest proportions of early stage breast cancer cases receiving BCS + RT were also those with the highest numbers of RT units per million inhabitants. Thus, during 1996–1998 there were 6–9 RT units per million in France, The Netherlands and Finland, but only 2–3 units per million in Italy and Spain.[15]

It has also been reported that low use of adjuvant RT is related to long distance between the patient's home and the RT centre.[21] We did not have access to information on distances in our study and could not verify an influence of this factor in the use of RT. In Denmark, failure to perform BCS + RT was probably related to the fact that most breast cancers were treated in local or regional hospitals (instead of specialist centres) rather than lack of RT facilities, even though the Danish national cancer control plan of 2000 recognised the need to modernise and expand RT services.[22] Most patients receiving BCS in Denmark also received RT, but BCS was hardly ever performed in areas with no breast cancer screening.

Consistent with other studies,[23] the odds of being treated with BCS + RT decreased with increasing age at diagnosis, suggesting that elderly patients received less appropriate care than younger patients, particularly since older women have lower risk of relapse than younger patients, irrespective whether the treatment is conservative or mastectomy.[4,24] In the SEER network, which covers about 10% of the US population, older patients also received BCS + RT less often than younger patients.[25]

In accordance with the clinical protocols available during the study period,[9] more than 90% of patients aged 15–49 – who were presumably premenopausal at diagnosis – received adjuvant chemotherapy, with low variation across countries. The low frequency of chemotherapy in Denmark (53.3%) could be due to adherence to the Danish Breast Cancer Study Group guidelines[26] which recommended the premenopausal women with receptor-positive tumours should receive chemotherapy or ovarian ablation. The proportion of Finnish postmenopausal women receiving chemotherapy was low during the study period because of an ongoing trial evaluating adjuvant anti-estrogens plus toremifen versus tamoxifen: all hormone receptor-positive postmenopausal women were enrolled and only receptor-negative patients received chemotherapy.[27]

Approximately 60% of menopausal patients (50–99 years) with ER+ cancers received tamoxifen, with marked inter-country variation, although differences were narrower compared to younger women. Information on ER status was complete for most countries, with overall proportion with unknown ER status at about 15%. However, underreporting may partly explain low use of hormonal therapy for ER+ cancers in Denmark, Finland and The Netherlands. It also seems that it was policy in these countries not to prescribe tamoxifen to patients with negative axillary lymph nodes, irrespective of ER+ status.

The Eastern European countries of Slovakia, Estonia, and Poland were characterised by extensive use of hormonal treatment and adjuvant chemotherapy, not confined to women with N+ and ER+ disease; BCS + RT for early stage breast cancer was also used less than in other European countries at that time, while stage at diagnosis was more advanced. Thus, in Eastern Europe medication appeared to be the mainstay of breast cancer treatment, and was probably used in an attempt to mitigate a lack of surgical facilities. Costs of medical treatment are almost certainly lower than for surgery and radiotherapy. In this connection it is noteworthy that the proportion of early stage breast cancer cases receiving conservative treatment is directly related to national expenditure on health (TNEH) (Fig. 2), strongly suggesting that the low expenditure on health characterising Eastern European countries had an important effect on the quality of treatment.[28]

Although inter-country variation in adherence to 'standard care' was related to TNEH, adherence varied even among medium/high TNEH countries (Fig. 2) suggesting lack of updating or a conservative medical culture, with the further implication that, in the late 1990s, the allocation of available resources for breast cancer control was not optimal in many European countries.

Differences in stage distribution at diagnosis, highlighted in the previous HR study on breast cancers diagnosed in 1990–1992[1] were still evident in the present study, which analysed cases diagnosed approximately 5 years later. The

proportion of early stage cancers diagnosed depends on diagnostic activity.[29,30] Thus, countries with national screening during the study period (The Netherlands, Finland and Sweden) had high proportions of T1N0M0 and low proportions of M1 cases. By contrast, the distribution of T1a, T1b and T1c cases (among T1N0M0 tumours) did not vary much across countries: in all countries the most common size was T1c (1–2 cm). The proportions of in situ and T1a (⩽0.5 cm) cancers – another indicator of diagnostic activity – were relatively high in Italy and Spain, countries also characterised by high numbers of lymph nodes examined during lymphadenectomy, in accord with the TNM manual.[14] However, the data on in situ tumours are likely to be incomplete since these tumours were not recorded uniformly by CRs. Sentinel node biopsy was not widely practised during the study period, so sampling at least 10 axillary nodes was the standard.

The high proportion of women presenting with advance disease in Poland, Slovakia and Estonia suggests diagnostic delay, probably reflecting lack of educational programmes inform women about the disease, or inadequate diagnostic facilities. High proportions of advanced tumours at diagnosis are likely to be the main cause of poor survival in these countries.[28,31] In Denmark the high proportion of T4 tumours (24%) was also due to lack of effective programs for early diagnosis in the study years.[32] The relatively high proportion cases with NS stage in Finland (20.3%) is due to the fact that the recorded stage was often pre-operative, whereas the definitive stage was not systematically entered in the database (Kaija Holli, personal communication).

Formal comparison of stage distribution in the present study with that of the previous high resolution study on breast cancer is impossible, because only 12 registries (Bas-Rhin, Côte d'Or, Doubs, Isère, Tarn, Firenze, Modena, Ragusa, Varese, Eindhoven, Estonia, Granada) were included in both studies. For CRs with both sets of data, the proportion of early stage tumours increased from 1990–1992 to 1996–1998.[16] During the 1990s breast cancer screening programmes were started or consolidated in France, Italy, Spain and The Netherlands, and the earlier stage at diagnosis in the CRs of these countries is likely to be mainly due to screening.[29,30,33] The increase in proportion of early stage cancers in Estonia is likely to be due to improved oncological care in the country over the two study periods, since screening was introduced from 2002 (www.cancer.ee). It is likely that a similar improvement in stage distribution at diagnosis was present in countries for which comparison over the two periods was not possible.

It is important to emphasise the population-based nature of our study, involving analysis of a representative sample of all surgically treated cases incident in the selected CRs during the study period. However, it is difficult to obtain complete diagnostic, prognostic and treatment information on such cases and herein lies a potential weakness of the study. To reduce the impact of incompleteness, we excluded CRs with unknown information on treatment in more than 20% of cases, thereby keeping overall data quality fairly high. Most of CRs retained in the analyses had very low proportions with missing treatment information (generally less than 5%). As noted above, information on ER status was complete for most countries, and the overall proportion with unknown ER status was 15%. Another potential weakness is that time period of cases sampling was not the same for all CRs. Denmark and Sweden were doing their own high resolution study and we included their already available 1994 clinical data, in view of the high cost of collecting new data. It was important to include data from Palermo which is in an area of Italy with few CRs and where survival is lower than in other Italian regions: 1999 was the first year for which complete Palermo data were available. Since diagnostic and therapeutic procedures in 1994 and 1999 did not differ greatly from those in 1996 to 1998, inclusion of these years is unlikely to greatly affect study results. Finally, Varese and Eindhoven sent cancer incidence for 2 years (1996–1997 and 1997–1998, respectively). We included both years in view of the resources expended to collect the data: the distribution of the analysed variables were similar for different years.

To conclude, the present study on breast cancers diagnosed mainly in 1996–1998 has revealed large differences in care for this cancer across Europe. During the study period national protocols had been developed and disseminated, but standard European guidelines were still not available. The first meta-analysis on systemic treatment for early breast cancer was published in 1992[11]; only in 1998 was a comprehensive series of meta-analyses published[10,12] when it was also becoming evident that guidelines for breast cancer management might be useful (www.eusoma.org). The effect of European guidelines should be evident for patients diagnosed more recently. Thus, high resolution studies on patients diagnosed and treated more recently should make it possible to assess the effect of guidelines and indicate whether the less-than-optimal allocation of resources for the treatment of breast cancer suggested by our late 1990s data has been remedied.

## Conflict of interest statement

None declared.

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