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Comorbidities, age and period of diagnosis influence treatment and outcomes in early breast cancer

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Survival for breast cancer (BC) is lower in eastern than northern/central Europe, and in older than younger women. We analysed how comorbidities at diagnosis affected whether selected standard treatments (STs) were given, across Europe and over time, also assessing consequences for survival/relapse. We analysed 7581 stage I/IIA cases diagnosed in 9 European countries in 2009–2013, and 4 STs: surgery; breast-conserving surgery plus radiotherapy (BCS + RT); reconstruction after mastectomy; and prompt treatment (≤6 weeks after diagnosis). Covariate-adjusted models estimated odds of receiving STs and risks of death/relapse, according to comorbidities. Pearson's R assessed correlations between odds and risks. The *z*-test assessed the significance of time-trends. Most women received surgery: 72% BCS; 24% mastectomy. Mastectomied patients

Key words: early breast cancer, comorbidities, standard treatment, outcomes, population study

Abbreviations: BC: breast cancer; BCS + RT: breast-conserving surgery followed by radiotherapy; CCI: Charlson comorbidity index; CI: confidence interval; CR: cancer registry; ER: oestrogen receptor; OR: odds ratio; PgR: progesterone receptor

Additional Supporting Information may be found in the online version of this article.

[†]Supplementary material

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were older with more comorbidities than BCS patients ($p < 0.001$). Women given breast reconstruction (25% of mastectomies) were younger with fewer comorbidities than those without reconstruction ($p < 0.001$). Women treated promptly (45%) were younger than those treated later ($p = 0.001$), and more often without comorbidities ($p < 0.001$). Receiving surgery/BCS + RT correlated strongly ($R = -0.9$), but prompt treatment weakly ($R = -0.01/-0.02$), with reduced death/relapse risks. The proportion receiving BCS + RT increased significantly ($p < 0.001$) with time in most countries. This appears to be the first analysis of the influence of comorbidities on receiving STs, and of consequences for outcomes. Increase in BCS + RT with time is encouraging. Although women without comorbidities usually received STs, elderly patients often received non-standard less prompt treatments, irrespective of comorbidities, with increased risk of mortality/relapse. All women, particularly the elderly, should receive ST wherever possible to maximise the benefits of modern evidence-based treatments.

What's new?

This is the first Europe-wide study (37 cancer registries, 9 countries) analysing the effect of comorbidities on whether women with early breast cancer (diagnosed 2009–13) receive standard treatments. Women with no comorbidities usually received standard treatments, but elderly women often received less prompt and non-standard treatments, irrespective of comorbidities, with increased probability of relapse and mortality. All women, particularly the elderly, should receive standard treatments wherever possible to maximize the benefits of modern evidence-based approaches.

Introduction

EUROCARE, the ongoing population-based study on cancer survival across Europe, found that survival for women diagnosed with breast cancer (BC) in 2000–2007 differed between regions, with highest survival in northern and central Europe, and lowest in eastern Europe.[1] Furthermore, more advanced stage at diagnosis and lower stage-specific survival characterised women ≥75 years compared to younger women.[2] Studies on European women with early BC diagnosed in 1996–1998, and German women diagnosed 2007–2015, found that older patients received standard treatments less often than younger patients.[3,4] Comorbidities at diagnosis, patient choice, and resource availability are all likely to influence whether or not standard treatments are given, thus influencing outcomes.[1,3]

To elucidate reasons for variation in cancer outcomes across Europe, investigate use of standard treatments, and identify actions to reduce disparities, High Resolution studies are performed. These access clinical information, not normally available to population-based cancer registries (CRs), from clinical records of representative samples of cases archived by CRs. A new series of High Resolution investigations,[5] that additionally assess information on comorbidities at diagnosis, has started with the present study, making use of the updated (to May 2018) High Resolution database.

The principal aim of our study was to investigate the effect of comorbidities at diagnosis (as assessed by the Charlson comorbidity index [CCI][6]), also considering age and tumour subtype, on differences in adherence to selected components of standard treatment, for European women diagnosed with early stage BC in 2009–2013. The standard treatments considered were the proportions of women who received: (a) surgery; (b) breast-conserving surgery followed by radiotherapy (BCS + RT); (c) reconstruction after mastectomy; and (d) prompt treatment (≤6 weeks of diagnosis).[7] Surgery has long been essential for the curative treatment of early BC.[8] The other three components are among the treatment quality indicators proposed by the European Society of Breast Cancer Specialists (EUSOMA) in their 2017 update.[7]

Additional aims were to assess the influence of comorbidities on correlations between receiving standard treatments and risks of death and relapse, and to determine time-trends (1996–1998 to 2009–2013) in the proportion of women with T1N0M0 BC who received BCS + RT.

Materials and Methods

The study protocol required that each participating CR provide at least 500 *in situ* or malignant BC cases (codes C50.0–C50.9, International Classification of Diseases for Oncology[9]), diagnosed in 2009–2013 (latest years available), and followed at least to December 31, 2014.[5] Nine countries, with either national (Belgium, Estonia, Slovenia) or regional (France 16 CRs, Italy 5 CRs, Poland 4 CRs, Portugal 3 CRs, Spain 5 CRs, and Switzerland 1 CR) cancer registration, contributed by providing sufficiently high quality data (≤30% of cases with missing data for all variables analysed) (Supporting Information, Fig. S1). Most CRs provided all cases incident in 1 year of the study period. However, Belgium, Slovenia, 1 Portuguese and 2 Polish CRs used a randomised procedure balanced for month of diagnosis to select cases. France used a randomised procedure balanced for day and month of birth. One Italian and 1 Portuguese CR selected consecutive incident cases until the minimum number was reached.

Only malignant cases with stage I (T1N0M0, T0-1N1micM0) or stage IIA (T0-1N1M0, T2N0M0) BC, as defined by the 7th edition of the TNM manual[10] (Fig. S1, Supporting Information), were selected for analysis.

Pathological stage was preferred; clinical stage was used if pathological stage was unavailable (typically patients not treated surgically) or if pre-operative treatment was given. For 1 Polish CR, clinical stage was never available.

CR personnel accessed the clinical records of each case to collect the after information: age at diagnosis; presence/absence of each of the 19 items of the CCI; date of diagnosis; stage; multifocality; oestrogen receptor (ER), progesterone receptor (PgR), HER2, and Ki67 status; treatments given; treatment start dates, and life status. Age was categorised as 15–54, 55–64, 65–74, and ≥75 years. A score of 0, 1, 2, 3, or 6 was assigned to each CCI item,[6] with total score calculated as the sum of the 19 items. The sum was categorised as 0 (no comorbidities), 1 (intermediate), and ≥2 (severe comorbidities).

Multifocality was categorised as present, absent, or unknown. Based on ER, PgR, HER2, and Ki67 status, six BC subtypes were defined:[11,12] luminal A, luminal B HER2−, luminal B HER2+, HER2+ non-luminal, triple-negative, and unknown (Table S1, Supporting Information). Surgery was categorised as done, not done, or unknown; type of surgery was BCS or mastectomy. If BCS was followed by mastectomy, the latter was considered the surgical treatment.

For the time-trend analyses, the proportion of women with T1N0M0 disease who received BCS + RT in 1996–1998 was accessed from Allemani *et al.*[3] Since this dataset differed from the one we used, with the possibility of compatibility problems, we only used data from the 6 countries (Estonia, France, Italy, Poland, Slovenia, and Spain) that contributed to both datasets.

Statistical analysis

Patient and disease characteristics were assessed using the chi-square test for categorical variables, with differences considered significant for $p < 0.05$. Multiple logistic regression models were used to estimate the odds (with 95% confidence intervals, CI) of receiving a standard treatment (*vs.* other treatment) according to CCI, overall and by country, adjusting for age, multifocality, and BC subtype. The country variable

Table 1. Distribution (%) of patient and disease characteristics for women with stage I/IIA breast cancer diagnosed in 2009–2013 in 9 European countries, overall and by Charlson comorbidity index (CCI)

		Charlson comorbidity index				
		CCI = 0	CCI = 1	CCI ≥ 2	Unknown	
	No (%[1])	No (%[2])	No (%[2])	No (%[2])	No (%[2])	*p*
All cases	7581 (100)	4948 (65)	1330 (18)	1230 (16)	73 (1)	
Country						‹0.001
Belgium	267 (4)	190 (71)	39 (15)	14 (5)	24 (9)	
Estonia	380 (5)	227 (60)	61 (16)	92 (24)	0 (0)	
France	1154 (15)	863 (75)	162 (14)	126 (11)	3 (0)	
Italy	1194 (16)	744 (62)	187 (16)	252 (21)	11 (1)	
Poland	1106 (15)	698 (63)	228 (21)	176 (16)	4 (0)	
Portugal	1051 (14)	592 (56)	270 (26)	188 (18)	1 (0)	
Slovenia	371 (5)	239 (64)	72 (19)	58 (16)	2 (1)	
Spain	1461 (19)	974 (67)	264 (18)	217 (15)	6 (0)	
Switzerland	597 (8)	421 (71)	47 (8)	107 (18)	22 (4)	
Age at diagnosis (years)						‹0.001
15–54	2638 (35)	2147 (81)	288 (11)	178 (7)	25 (1)	
55–64	2063 (27)	1361 (66)	388 (19)	296 (14)	18 (1)	
65–74	1759 (23)	980 (56)	387 (22)	377 (21)	15 (1)	
≥75	1121 (15)	460 (41)	267 (24)	379 (34)	15 (1)	
Stage at diagnosis						0.006
Stage I	4806 (63)	3200 (67)	807 (17)	748 (16)	51 (1)	
Stage IIA	2775 (37)	1748 (63)	523 (19)	482 (17)	22 (1)	
Cancer subtype						‹0.001
Luminal A	4586 (61)	3035 (66)	796 (17)	726 (16)	29 (1)	
Luminal B HER2−	733 (10)	495 (68)	106 (15)	122 (17)	10 (1)	
Luminal B HER2+	655 (9)	434 (66)	111 (17)	101 (15)	9 (1)	
HER2+ non-luminal	229 (3)	143 (62)	47 (21)	36 (16)	3 (1)	
Triple-negative	535 (7)	343 (64)	110 (21)	75 (14)	7 (1)	
Unknown	843 (11)	498 (59)	160 (19)	170 (20)	15 (2)	

[1]Column percentages.
[2]Row percentages.

Table 2. Distribution (%) of treatment and time from diagnosis to treatment start for women with stage I/IIA breast cancer diagnosed 2009–2013 in 9 European countries, overall and by European country

	All cases	Belgium	Estonia	France	Italy	Poland	Portugal	Slovenia	Spain	Switzerland
	No (%[3])	No (%[3])	No (%[3])	No (%[3])	No (%[3])	No (%[3])	No (%[3])	No (%[3])	No (%[3])	No (%[3])
All cases (No)	7581	267	380	1154	1194	1106	1051	371	1461	597
Treatment										
Surgery	7354 (97)	255 (96)	357 (94)	1109 (96)	1175 (98)	1078 (98)	1020 (97)	348 (94)	1421 (97)	591 (99)
BCS	5450 (72)	199 (75)	237 (62)	960 (83)	979 (82)	737 (67)	477 (45)	245 (66)	1138 (78)	478 (80)
Mastectomy	1845 (24)	51 (19)	119 (31)	149 (13)	194 (16)	295 (27)	540 (51)	103 (28)	281 (19)	113 (19)
Yes, unknown type	59 (1)	5 (2)	1 (1)	0 (0)	2 (0)	46 (4)	3 (1)	0 (0)	2 (0)	0 (0)
Non-surgical treatment only	161 (2)	9 (3)	16 (4)	39 (3)	12 (1)	18 (2)	10 (1)	19 (5)	32 (2)	6 (1)
None	62 (1)	3 (1)	6 (2)	6 (1)	5 (1)	9 (0)	21 (2)	4 (1)	8 (1)	0 (0)
Unknown	4 (0)	0 (0)	1 (0)	0 (0)	2 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BCS + RT [1]	4945 (65)	184 (69)	215 (57)	898 (78)	847 (71)	658 (60)	433 (41)	222 (60)	1080 (74)	408 (68)
RT as proportion of BCS	4945 (91)	184 (93)	215 (91)	898 (94)	847 (87)	658 (89)	433 (91)	222 (91)	1080 (95)	408 (85)
Mastectomy+reconstruction	469 (6)	16 (6)	11 (3)	37 (3)	88 (7)	11 (1)	119 (11)	35 (9)	96 (7)	56 (9)
Reconstruction as proportion of mastectomies	469 (25)	16 (31)	11 (9)	37 (25)	88 (45)	11 (4)	119 (22)	35 (34)	96 (34)	56 (50)
Time from diagnosis to start of treatment (weeks) [2]	7465	264	373	1141	1185	1057	1030	367	1451	597
≤6	3338 (45)	200 (76)	256 (69)	489 (43)	556 (47)	263 (25)	191 (19)	239 (65)	681 (47)	463 (78)
>6	3728 (50)	64 (24)	114 (31)	520 (46)	500 (42)	720 (68)	819 (80)	125 (34)	739 (51)	127 (21)
Unknown	399 (5)	0 (0)	3 (0)	132 (11)	129 (11)	74 (7)	20 (1)	3 (1)	31 (2)	7 (1)

[1]BCS + RT, breast-conserving surgery followed by radiotherapy.
[2]Distribution analysed only for women for whom treatment start was known.
[3]Column percentages.

Table 3. Odds ratios[1] (ORs) of receiving surgery, breast-conserving surgery followed by radiotherapy (BCS + RT), and starting treatment within 6 weeks of diagnosis, for women with stage I/IIA breast cancer diagnosed in 2009–2013 in 9 European countries

	Surgery		**BCS + RT**		**Treatment start within 6 weeks of diagnosis**	
	OR	**95% CI[2]**	**OR**	**95% CI[2]**	**OR**	**95% CI[2]**
Age at diagnosis (years)						
15–54	1	Reference	1	Reference	1	Reference
55–64	0.77	(0.37 to 1.62)	1.38	(1.21 to 1.58)	0.83	(0.73 to 0.93)
65–74	0.55	(0.27 to 1.12)	1.10	(0.96 to 1.27)	0.87	(0.77 to 0.99)
≥75	0.04	(0.02 to 0.07)	0.31	(0.27 to 0.37)	0.97	(0.84 to 1.13)
Charlson comorbidity index[3]						
0	1	Reference	1	Reference	1	Reference
1	0.64	(0.42 to 0.96)	0.76	(0.66 to 0.87)	0.64	(0.56 to 0.72)
≥2	0.42	(0.30 to 0.61)	0.57	(0.49 to 0.66)	0.88	(0.77 to 1.00)
Multifocality						
Absent	1	Reference	1	Reference	1	Reference
Present	0.92	(0.58 to 1.45)	0.31	(0.27 to 0.35)	0.76	(0.67 to 0.86)

[1]Logistic regression models adjusted for all variables included in the table; models for BCS + RT and time from diagnosis to treatment start also adjusted for tumour subtype.
[2]CI, confidence interval.
[3]Women with unknown Charlson comorbidity index excluded.

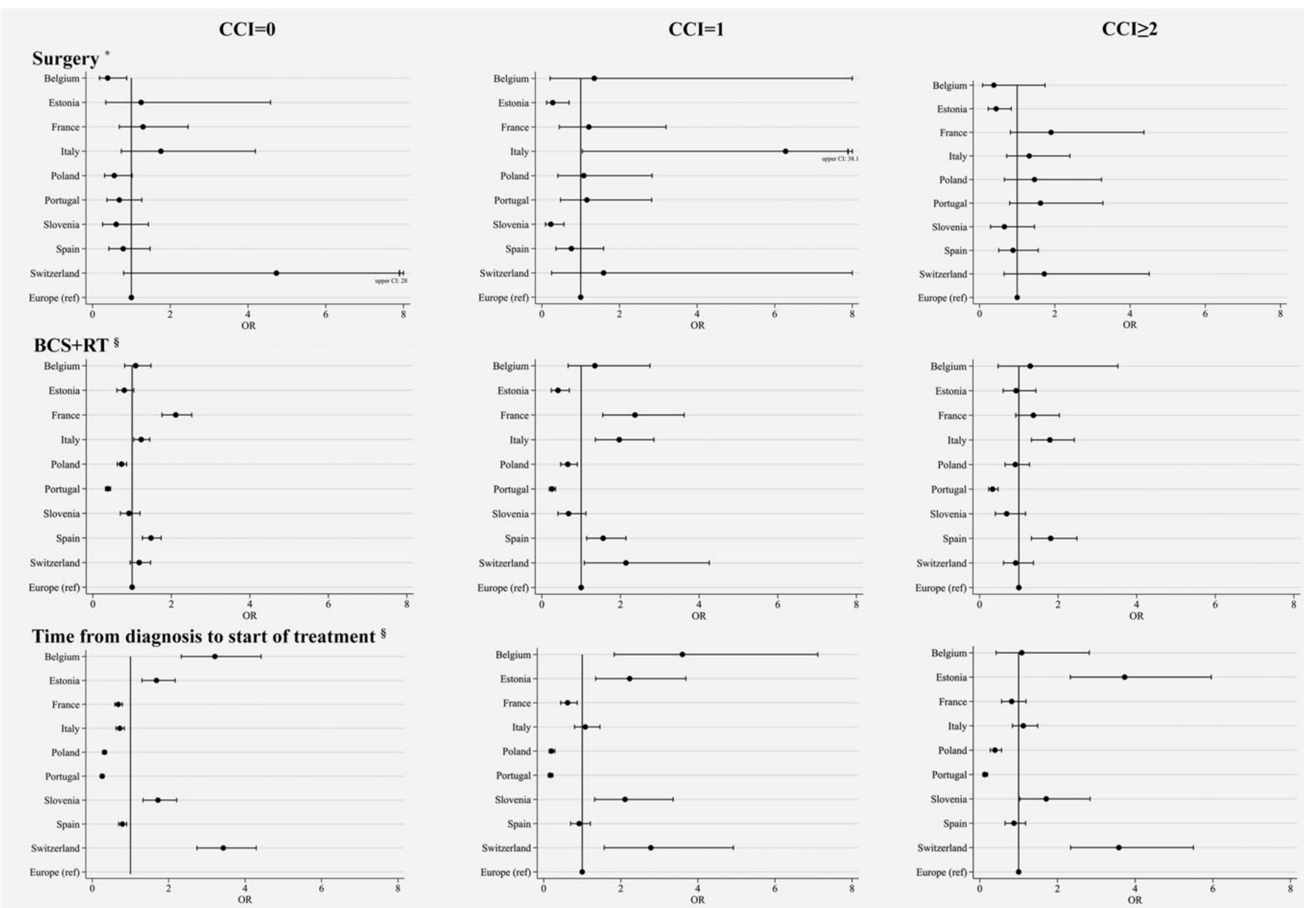

Figure 1. Odds ratios (ORs) of receiving surgery, breast-conserving surgery followed by radiotherapy (BCS + RT), and starting treatment within 6 weeks of diagnosis, for women diagnosed with stage I/IIA breast cancer in 2009–2013 in 9 European countries, according to Charlson comorbidity index (CCI). *Logistic regression models adjusted for age at diagnosis, and multifocality; §Logistic regression models adjusted for age at diagnosis, multifocality, and tumour subtype.

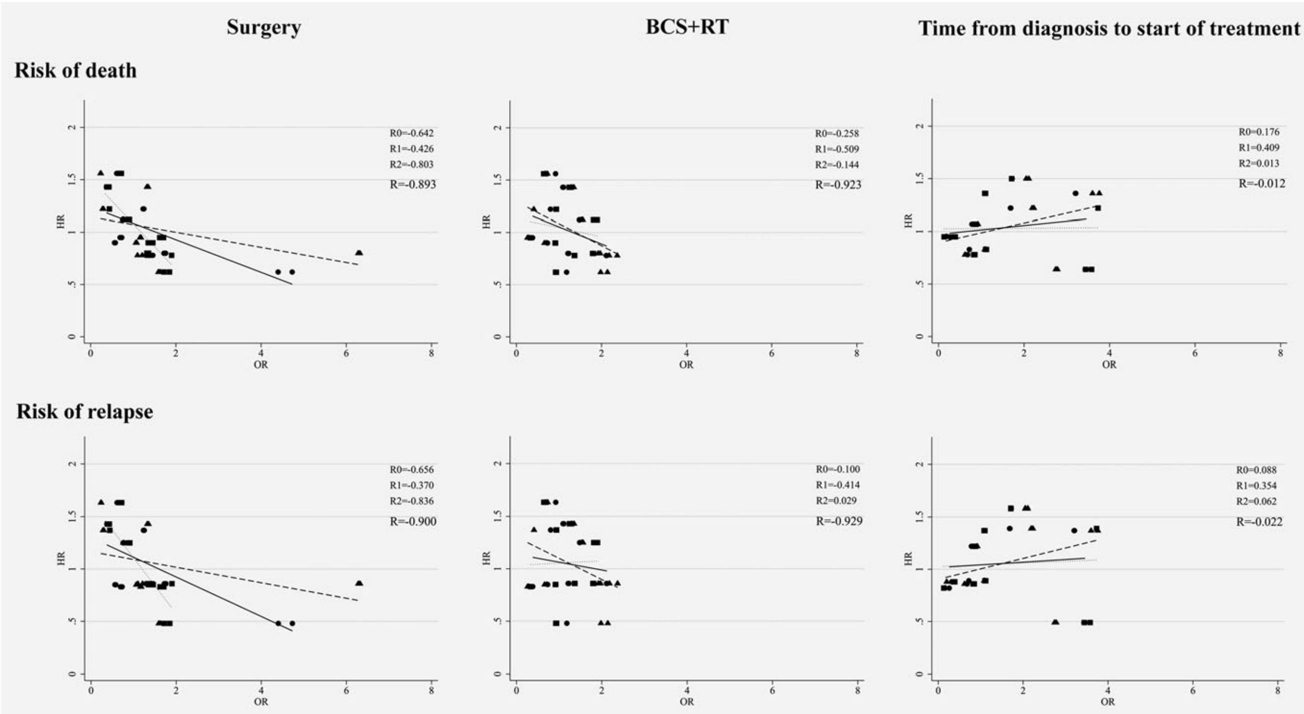

Figure 2. Scatter plots showing correlations (Pearson's R) between odds of receiving standard treatments and risks of death and relapse (locoregional recurrence plus distant metastasis), for women with stage I/IIA breast cancer diagnosed in 2009–2013 in 9 European countries, by country and Charlson comorbidity index (CCI) BCS + RT, breast-conserving surgery followed by radiotherapy; OR, odds ratio; HR, hazard ratio; Results for women in the 9 European countries with CCI = 0, 1 and ≥2 at diagnosis are indicated by circles, triangles, and squares, respectively; the corresponding Pearson's Rs are designated R0, R1, R2; Pearson's R for all women is designated R.

was incorporated into the models using the effect coding technique,[13] and the odds of treatment for each country were estimated in relation to the entire BC population.

Multiple exponential regression models,[14] with adjustments as above, estimated risks of death and relapse within 2 years of diagnosis, according to CCI, for all cases, and for those in each country, in comparison to the entire BC population.

Cramer's V assessed the collinearity of variables candidate for inclusion in the models. The log-likelihood ratio test assessed interactions between variables. Weak (Cramer's $V < 0.20$) and moderate ($V < 0.50$) associations between variables were found, and a significant interaction between country and CCI ($p < 0.001$) was found in the logistic models only.

Table 4. Proportions (%) of T1N0M0 breast cancer patients receiving breast-conserving surgery followed by radiotherapy (BCS + RT) in 1996–1998[1] and 2009–2013 in 6[2] European countries, for all cancer registries (CRs) in the 6 countries, and for the CRs with data for both periods

	1996–1998			2009–2013							
	(No = 3089)			All CRs in the 6 countries (No = 3563)				Only CRs with data for both periods (No = 1670)			
Country	No CRs	No cases	BCS + RT (%[3])	No CRs	No cases	BCS + RT (%[3])	p	No CRs	No cases	BCS + RT (%[3])	p
Estonia	1	87	9	1	213	75	<0.001	1	213	75	<0.001
France	5	602	78	16	788	84	0.002	5	-[4]	-	
Italy	6	1103	58	5	806	75	<0.001	2	355	73	<0.001
Poland	1	287	16	4	639	67	<0.001	1	154	66	<0.001
Slovenia	1	200	61	1	215	63	0.337	1	215	63	0.337
Spain	5	810	55	5	902	82	<0.001	4	733	80	<0.001

[1]From Allemani *et al.*[3]
[2]Countries providing data for both periods (1996–1998 and 2009–2013).
[3]Row percentages.
[4]Impossible to distinguish the CRs and hence determine numbers of cases.

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Correlations between odds of receiving a selected standard treatment and risks of death/relapse according to CCI, overall and by country, were assessed by Pearson's R. The significance of time-trends in the proportion of T1N0M0 cases given BCS + RT (by country) was assessed by the *z*-test. The analyses were performed with Stata.[15]

Results

A total of 7581 women with early BC in 9 European countries was analysed (Table 1). At diagnosis 35% were young (15–54 years), 15% were elderly (≥75 years); 63% were stage I; 61% of cancers were luminal A, 10% luminal B HER2−, 9% luminal B HER2+, 7% triple-negative, and 3% HER2+ non-luminal. For only 11% of cases was information insufficient to determine subtype.

Sixty-five percent were CCI = 0, with no information on comorbidities for 1%. France, Belgium and Switzerland had the highest proportions of CCI = 0 (71–75%), and Portugal and Estonia the lowest (56–60%) (Table 1). As expected, the proportion of women with CCI > 0 increased with advancing age at diagnosis: 7% of young *vs.* 34% of elderly women had CCI ≥ 2 ($p < 0.001$). Stage I women were slightly healthier than stage IIA women (67% *vs.* 63% CCI = 0, $p = 0.006$). More women with triple-negative, HER2+ non-luminal, or unknown subtype disease had comorbidities (CCI = 1 and CCI ≥ 2) than those with luminal disease (35–39% *vs.* 32–33%, $p < 0.001$).

Compared to those with known subtype, women with unknown disease subtype were slightly older (23% *vs.* 14% ≥75 years, $p < 0.001$) and had more comorbidities (CCI = 0: 66% *vs.* 59%; CCI = 2: 16% *vs.* 20%, $p < 0.001$), whereas age distribution was similar for women with luminal and non-luminal disease (35% *vs.* 36% 15–54 years; 14% *vs.* 11% ≥75 years, $p = 0.080$) (data not shown).

Most (97%) women received surgery: 72% BCS, 24% mastectomy (Table 2). Compared to women given BCS (Table S2, Supporting Information), mastectomied patients were older (20% *vs.* 10% ≥75 years), had more comorbidities (41% *vs.* 30% CCI ≥ 1), and more often had multifocal disease (32% *vs.* 12%). However, 37% of mastectomies were given to younger women (Table S2, Supporting Information). Of the few (2%) women given non-surgical treatment only, 89% were elderly, 70% had comorbidities, and 9% had multifocal disease (Table S2, Supporting Information).

RT was given to 91% of women who received BCS, and BCS + RT was given to 65% of women overall (Table 2). A third of the latter were young and 70% had CCI = 0 (Table S2, Supporting Information). Twenty-five percent of mastectomied women received breast reconstruction (Table 2): this subgroup constituted 6% of the entire population and in general they were young (74%) and CCI = 0 (78%) (Table S2, Supporting Information).

Among the 7465 women (Table 2) with known treatment start, 45% started promptly. They were slightly younger than those who started later (38% *vs.* 33%, $p = 0.001$), and were more often CCI = 0 (69% *vs.* 62%, $p < 0.001$) (Table S2, Supporting Information).

Odds of receiving surgery (*vs.* not/unknown), BCS + RT (*vs.* other treatment) and prompt treatment start (*vs.* late) all varied significantly with age (Table 3). For example, compared to young patients, elderly patients were less likely to receive surgery (odds ratio $[OR]_{\geq 75\ vs.\ 15\text{–}54\ years} = 0.04$ [95%CI 0.02 to 0.07]) and BCS + RT ($OR_{\geq 75\ vs.\ 15\text{–}54\ years} = 0.31$ [0.27 to 0.37]). Odds of receiving surgery, BCS + RT, and prompt treatment also decreased with increasing CCI (surgery: $OR_{CCI=1\ vs.\ CCI=0} = 0.64$ [0.42 to 0.96], $OR_{CCI\geq 2\ vs.\ CCI=0} = 0.42$ [0.30 to 0.61]); BCS + RT: $OR_{CCI=1\ vs.\ CCI=0} = 0.76$ [0.66 to 0.87], $OR_{CCI\geq 2\ vs.\ CCI=0} = 0.57$ [0.49 to 0.66]; prompt treatment: $OR_{CCI=1\ vs.\ CCI=0} = 0.64$ [0.56 to 0.72], $OR_{CCI\geq 2\ vs.\ CCI=0} = 0.88$ [0.77 to 1.00]). Finally, odds of receiving BCS + RT and prompt treatment were lower in cases with multifocality ($OR_{present\ vs.\ absent} = 0.31$ [0.27 to 0.35] and 0.76 [0.67 to 0.86], respectively).

Although >90% of women received surgery, the proportion varied from 94% in Estonia and Slovenia to 99% in Switzerland (Table 2). Within-country differences (countries with regional coverage) were small (Fig. S2, Supporting Information). Between-country differences persisted after adjusting for age, multifocality, and stratifying by CCI (Fig. 1). For example, compared to all European CCI = 0 women, Belgian CCI = 0 women were significantly less likely to receive surgery (OR = 0.39 [0.18 to 0.88]), as were Estonian and Slovenian CCI ≥ 1 women (CCI = 1: $OR_{Estonia\ vs.\ Europe} = 0.28$ [0.12 to 0.70], $OR_{Slovenia\ vs.\ Europe} = 0.23$ [0.09 to 0.57]; CCI ≥ 2: $OR_{Estonia\ vs.\ Europe} = 0.44$ [0.23 to 0.84]).

Between- and within-country variations in the proportions given BCS + RT were more marked than for surgery. Thus, 41% of Portuguese women received BCS + RT (24% in central, 48% in southern Portugal; Fig. S2, Supporting Information) compared to 78% of French women (Table 2). For patients given BCS, RT administration varied from 85% in Switzerland and 87% in Italy, to 94% in France. Multivariable logistic regression models stratified by CCI and adjusted for age, multifocality, and cancer subtype (Fig. 1) showed that, compared to European CCI = 0 women, odds of receiving BCS + RT were significantly lower for Polish (0.73 [0.62 to 0.86]) and Portuguese (0.38 [0.32 to 0.45]) CCI = 0 women, and higher for French (2.11 [1.76 to 2.52]), Italian (1.23 [1.04 to 1.45]) and Spanish (1.48 [1.26 to 1.74]) CCI = 0 women.

Low odds of BCS + RT were also found for Estonian (0.41 [0.24 to 0.70]), Polish (0.66 [0.48 to 0.90]), and Portuguese (0.26 [0.19 to 0.35]) CCI = 1 women, compared to European CCI = 1 women; and Portuguese (0.33 [0.23 to 0.47]) CCI ≥ 2 women, compared to European CCI ≥ 2 women; while French (2.37 [1.55 to 3.62]), Italian (1.97 [1.36 to 2.85]) and Spanish CCI = 1 women (1.56 [1.14 to 2.14]), and also Italian (1.79 [1.32 to 2.41]) and Spanish (1.81 [1.32 to 2.48]) CCI ≥ 2 women, had high odds of BCS + RT (Fig. 1).

The proportion given mastectomy ranged from 13% in France, to 27–31% in Poland, Slovenia, and Estonia, to 51% in Portugal (Table 2). Among women given mastectomy, Poland (4%) and Estonia (9%) had the lowest proportions given reconstruction; while Italy (45%) and Switzerland (50%) had the highest proportions.

The proportion treated promptly ranged from 19% to 78% (Table 2), with highest levels for Belgium (76%) and Switzerland (78%), and lowest levels for Portugal (19%) and Poland (25%). Most of these country rankings for prompt treatment persisted regardless of CCI (Fig. 1).

Overall, risks of death/relapse increased significantly with comorbidity, being two-fold higher for CCI = 1 women, and four-fold higher for CCI ≥ 2, than CCI = 0 women (data not shown), consistent with strong inverse correlations between risks of death/relapse and odds of receiving surgery/BCS + RT, according to CCI (Pearson's $R = -0.9$, Fig. 2). However, odds of prompt treatment did not correlate with risks of death ($R = -0.01$) or relapse ($R = -0.02$).

Odds of receiving surgery in each CCI group correlated strongly and inversely with risks of death/relapse (R0-R2 range − 0.8 to −0.4; Fig. 2); while odds of receiving BCS + RT correlated moderately/weakly with death/relapse risks (R0-R2 range − 0.5 to −0.1), except in CC2 women for relapse risk ($R2 = 0$). Prompt treatment correlated weakly/not at all with risks of death/relapse (R0-*R2* ranged 0.0 to 0.2), except in CCI = 1 women, where correlations were moderate ($R1 = 0.4$).

Finally, for the 3563 women with T1N0M0 disease in the 6 countries that contributed data for the periods 1996–1998 and 2009–2013, the proportion receiving BCS + RT increased over time: from 9 to 78% in 1996–1998 to 63–84% in 2009–2013 (Table 4). The increase was steep in Estonia (from 9% to 75%, $p < 0.001$) and Poland (from 16% to 67%, $p < 0.001$); less so in France (from 78% to 84%, $p < 0.001$) and Slovenia (from 61% to 63%, $p = 0.337$), where fairly high proportions were already receiving BCS + RT in 1996–1998.

Discussion

We found that practically all women in the 9 European countries, diagnosed with stage I/IIA disease in 2009–2013, received surgery. Most received BCS, although close to a quarter received mastectomy—considerably more (31–51%) in Estonia and Portugal. Only 25% of women given mastectomy received breast reconstruction. Only about 45% of women started treatment promptly. Furthermore odds of receiving surgery and BCS + RT correlated strongly (in both cases inversely) with risks of death/relapse. Finally, although use of BCS + RT increased from 1996 to 98 to 2009–2013, variations in use of this standard treatment persisted across Europe.

Multivariable logistic modelling showed that odds of receiving surgery, BCS + RT, and prompt treatment decreased with increasing CCI, adjusting for age, multifocality, and BC subtype, and varied across countries, suggesting that comorbidities only partially explain the variations. Hence other factors contributed. Possibilities include patient and physician choice, and between-country differences in the provision of healthcare including accessibility to treatment.

As regards whether patients received BCS or mastectomy, mastectomy was usually given to women with multifocal disease (consistent with multifocality/multicentricity being a relative contraindication for BCS[8]), older women, and women with comorbidities. It is also possible that older women and those with comorbidities chose mastectomy. However mastectomy was often given to younger women (37% of mastectomies): perhaps because until recently young age was an independent risk factor for recurrence after BCS + RT; however with modern RT, conservative treatment is at least as good as mastectomy in terms of oncological outcomes.[16–18] In fact a recent Danish population-based study found that long-term overall survival and relative survival (which indirectly corrects for non-BC deaths) were better for BCS + RT than mastectomy, after adjusting for confounding variables.[19]

Recent data indicate that the proportion of women given mastectomy is increasing in the US.[20] Suggested reasons include increased availability of skin- and nipple-sparing mastectomies, with the possibility of breast reconstruction that may produce better aesthetic outcomes than BCS.[20,21] However, some women seem to prefer complete breast removal in the erroneous belief that it reduces risks of recurrence or complications.[21–23] Mastectomy also permits avoidance of RT which is a burden for many women,[24,25] but a standard part of the conservative treatment of BC because it reduces local recurrences and increases long-term survival.[17] RT was given to 91% of the women given BCS in the present study, in accord with the EUSOMA quality indicator,[7] with slightly lower proportions (85–87%) in Italy and Switzerland. Restricted access to radiotherapy[24,26] may explain why high proportions of women received mastectomy particularly in Estonia and Portugal, and may also explain why older women more often received mastectomy than younger women.[8,27] Furthermore, several medical conditions contraindicate RT[28] and in such cases mastectomy is reasonable.

As regards reconstruction after mastectomy, this was given in only 25% of cases, well short of the 40% target suggested by EUSOMA.[7] A low proportion (16%) of reconstructions was also reported by Garcia-Etienne *et al.*,[29] who prospectively analysed data from European breast units provided according to EUSOMA requirements. Possible reasons are unavailability of plastic surgeons, higher complication rates compared to mastectomy without reconstruction, and increased costs.[22] However, we found that women given reconstruction after mastectomy were younger and had lower comorbidity score than those not given breast reconstruction. This finding is consistent with younger women choosing mastectomy instead of BCS + RT.

Women who started treatment promptly were slightly younger than those who started later, and more often had CCI = 0. Furthermore, like a previous study,[30] we found little or no correlation between time to treatment start and risks of death or relapse (at 2 years), both overall and in women with CCI = 0 and CCI ≥ 2. However for CCI = 1 women delay correlated moderately (and positively) with poorer outcomes: a possible reason for this could be that, for CCI = 1 patients a quick start to treatment might imply non-optimal treatment decisions in cases for whom treatment decisions are not straightforward. Data on the effect of treatment delay on outcomes in the literature are contrasting.[31]

Although treatment decisions are increasingly driven by guidelines derived from the findings of randomised controlled trials, physicians must still reason through the best choices for an individual patient,[32] since trial findings will not be applicable to every case, particularly in those with comorbidities. Furthermore, resources may not always be available to treat according to the guidelines. Between-country differences in availability of healthcare resources arise mainly because health spending *per capita* varies substantially between European countries. In countries with relatively low gross domestic product (GDP) lack of funds may mean for example that the latest treatments are not available, radiotherapy facilities are insufficient to meet demand, or that there are insufficient physicians.[33]

In all European countries health services are financed largely by taxation or state-sponsored insurance schemes. The private sector plays a variable but limited role.[34] It has been shown that the survival of European cancer patients is related to the GDP of the country they are treated in, but only to a certain extent: in countries with similar GDP cancer survival is related the total national (public and private) expenditure on health and the total public expenditure on health.[33,35]

Recent data indicate improving 10-year relative survival for women with BC in Europe from 1999–2001 to 2005–2007,[1] in which 44% of BCs were early stage.[2] The present study revealed that use of BCS + RT increased from 1996–1998 to 2009–2013 in all countries examined, and odds of receiving this standard treatment correlated strongly with outcomes. Thus it is possible that the improvements in survival are related to increased use of current optimal treatments for early BC.

A study limitation is that we have no data on patient treatment preferences, which might contribute to understanding variations in adherence to standard treatment. This is because patient preferences are rarely noted in clinical records. Since patient input to treatment decisions is growing in importance, it is conceivable that this information might be collected in the future by treatment centres and eventually by CRs. However before it can be used in studies, the reliability and between-institute comparability of such information will need to be assessed.

A further study limitation arises because CRs may differ in how they record comorbidities, since the number of sources of information available to CRs varies. When few data sources are available, comorbidities tend to be underestimated, weakening comorbidity-related differences.

Conclusions

The present study provides an overview of important components of treatment currently being given to women with early BC across Europe, and, to our knowledge, is the first analysis of the influence of comorbidities on adherence to standard treatments, together with an assessment of consequences for short-term (2 years after diagnosis) survival. The study has shown that assessing information on comorbidities has made it possible to better understand reasons for outcome differences in European BC patients. Thus, while it is encouraging that women with no comorbidities were usually given standard treatments, with little variation across Europe, elderly patients often received non-standard and less prompt treatments, irrespective of comorbidities, which is a cause for concern. Patients with comorbidities received surgery/BCS + RT significantly less frequently than those without comorbidities with increased probability of mortality and relapse (although longer follow-up may be necessary to confirm the relation between adherence to standard treatments and survival). Nevertheless, our findings suggest that all women, particularly the elderly, should wherever possible receive standard treatment so as to maximise the benefits of modern evidence-based treatments.

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References

1. Sant M, Chirlaque Lopez MD, Agresti R, et al. Survival of women with cancers of breast and genital organs in Europe 1999-2007: results of the EUROCARE-5 study. *Eur J Cancer* 2015;51: 2191–205.
2. Minicozzi P, Walsh PM, Sánchez MJ, et al. Is low survival for cancer in Eastern Europe due principally to late stage at diagnosis? *Eur J Cancer* 2018;93:127–37.
3. Allemani C, Storm H, Voogd AC, et al. Variation in 'standard care' for breast cancer across Europe: a EUROCARE-3 high resolution study. *Eur J Cancer* 2010;46: 1528–36.
4. Fietz T, Zahn MO, Köhler A, et al. Routine treatment and outcome of breast cancer in younger versus elderly patients: results from the SENORA project of the prospective German TMK cohort study. *Breast Cancer Res Treat* 2018;167:567–78.
5. European High Resolution studies Available at: http://www.hrstudies.eu.

6. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
7. Biganzoli L, Marotti L, Hart CD, et al. Quality indicators in breast cancer care: an update from the EUSOMA working group. *Eur J Cancer* 2017; 86:59–81.
8. Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015;26:v8–v30.
9. Fritz A, Percy C, Jack A, et al., eds. *International classification of diseases for oncology (ICD-O)*, 3rd edn. Geneva, Switzerland: World Health Organisation, 2000. 247.
10. Sobin LH, Gospodarowicz MK, Wittekind CH, eds. *TNM classification of malignant tumours*, 7th edn. Chichester: Wiley, 2010. 310.
11. Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes—dealing with the diversity of breast cancer: highlights of the St. Gallen international expert consensus on the primary therapy of early breast cancer 2011. *Ann Oncol* 2011;22:1736–47.
12. Arvold ND, Taghian AG, Niemierko A, et al. Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. *J Clin Oncol* 2011;29:3885–91.
13. Menard SW. *Applied logistic regression analysis*, 2nd edn. Thousand Oaks, CA: Sage, 2002. 111.
14. Agresti A. *Categorical data analysis*, 2nd edn. Hoboken, NJ: Wiley, 2002. 721.
15. StataCorp. *Stata statistical software, 12th release*. College Station, TX: StataCorp LP, 2011.
16. Vila J, Gandini S, Gentilini O. Overall survival according to type of surgery in young (≤40 years) early breast cancer patients: a systematic meta-analysis comparing breast-conserving surgery versus mastectomy. *Breast* 2015;24:175–81.
17. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002;347:1227–32.
18. Litière S, Werutsky G, Fentiman IS, et al. Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. *Lancet Oncol* 2012;13:412–9.
19. van Maaren MC, de Munck L, de Bock GH, et al. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in The Netherlands: a population-based study. *Lancet Oncol* 2016;17: 1158–70.
20. Mahmood U, Hanlon AL, Koshy M, et al. Increasing national mastectomy rates for the treatment of early stage breast cancer. *Ann Surg Oncol* 2013;20:1436–43.
21. Veronesi U, Stafyla V, Petit JY, et al. Conservative mastectomy: extending the idea of breast conservation. *Lancet Oncol* 2012;13:e311–7.
22. Smith BD, Jiang J, Shih YC, et al. Costs and complications of local therapies for early-stage breast cancer. *J Natl Cancer Inst* 2017;109:djw178.
23. Covelli AM, Baxter NN, Fitch MI, et al. Taking control of cancer: understanding women's choice for mastectomy. *Ann Surg Oncol* 2015; 22:383–91.
24. Athas W, Adams-Cameron M, Hunt WC, et al. Travel distance to radiation therapy and receipt of radiotherapy following breast-conserving surgery. *J Natl Cancer Inst* 2000;92:269–71.
25. Ballard-Barbash R, Potosky A, Harlan L, et al. Factors associated with surgical and radiation therapy for early stage breast cancer in older women. *J Natl Cancer Inst* 1996;88:716–26.
26. Grau C, Defourny N, Malicki J, et al. Radiotherapy equipment and departments in the European countries: final results from the ESTRO-HERO survey. *Radiother Oncol* 2014;112: 155–64.
27. Ring A, Reed M, Leonard R, et al. The treatment of early breast cancer in women over the age of 70. *Br J Cancer* 2011;105: 189–93.
28. Dilaveri CA, Sandhu NP, Neal L, et al. Medical factors influencing decision making regarding radiation therapy for breast cancer. *Int J Womens Health* 2014;6:945–54.
29. Garcia-Etienne CA, Tomatis M, Heil J, et al. Fluctuating mastectomy rates across time and geography. *Ann Surg Oncol* 2013;20: 2114–6.
30. Yoo TK, Han W, Moon HG, et al. Delay of treatment initiation does not adversely affect survival outcome in breast cancer. *Cancer Res Treat* 2016; 48:962–9.
31. Caplan L. Delay in breast cancer: implications for stage at diagnosis and survival. *Front Public Health* 2014;2:87.
32. Sniderman AD, Lachapelle KJ, Rachon NA, et al. The necessity for clinical reasoning in the era of evidence-based medicine. *Mayo Clin Proc* 2013;88:1108–14.
33. Gatta G, Trama A, Capocaccia R. Variations in cancer survival and patterns of care across Europe: roles of wealth and health-care organization. *J Natl Cancer Inst Monogr* 2013;2013: 79–87.
34. Expert Panel on effective ways of investing in Health (EXPH). Report on Access to Health Services in the European Union, 2016. Available at: https://ec.europa.eu/health/expert_panel/sites/expertpanel/files/015_access_health services_en.pdf
35. Micheli A, Coebergh JW, Mugno E, et al. European health systems and cancer care. *Ann Oncol* 2003; 14:v41–60.