Original article

Improved prognosis of young patients with breast cancer undergoing breast-conserving surgery

E. Botteri[1,8,9], P. Veronesi[2,6], J. Vila[4,10], N. Rotmensz[1], V. Galimberti[2], M. V. Thomazini[2], G. Viale[3,6], R. Orecchia[4,7], A. Goldhirsch[5] and O. Gentilini[2]

[1]Division of Epidemiology and Biostatistics, [2]Division of Breast Surgery, [3]Department of Pathology, [4]Scientific Directorate, and [5]Scientific Directory and Medical Senology, European Institute of Oncology, and [6]School of Medicine and [7]Department of Oncology, Haemato-oncology, University of Milan, Milan, Italy, [8]National Advisory Unit for Women's Health, Women's Clinic, Oslo University Hospital, and [9]Department of Bowel Cancer Screening, Cancer Registry of Norway, Oslo, Norway, and [10]Department of Breast Surgery, La Fe University Hospital, Valencia, Spain

Correspondence to: Dr O. Gentilini, Breast Surgery Unit, San Raffaele Research and University Hospital, Via Olgettina, 60, 20132 Milano, Italy (e-mail: gentilini.oreste@hsr.it)

Background: The aim of the present study was to evaluate how breast cancer prognosis has evolved over time in young women treated with breast-conserving surgery (BCS).

Methods: Data from patients younger than 40 years who had BCS and whole-breast radiotherapy in a single cancer centre between 1997 and 2010 were analysed. The patients were followed until 2016. Endpoints were local recurrence, any breast cancer-related event and death from any cause.

Results: A total of 1331 patients were included in the study. After a median follow-up of 9·3 years, 114 local recurrences, 289 breast cancer-related events and 138 deaths had occurred. Women were divided into three groups of similar size based on tertiles of the date of diagnosis: 1997–2002 (524 patients), 2003–2005 (350) and 2006–2010 (457). The risk of local recurrence was 1·42 per 100 person-years in women diagnosed in the first interval, 0·85 per 100 person-years in the second and 0·48 per 100 person-years in the third (P for trend = 0·028). The respective values were 3·01, 2·52 and 2·07 per 100 person-years for any breast cancer-related event (P = 0·004), and 1·59, 1·22 and 0·64 per 100 person-years for death (P = 0·003). Each passing year was associated with a decreasing risk of local recurrence (hazard ratio (HR) 0·93, 95 per cent c.i. 0·87 to 1·00), any breast cancer-related event (HR 0·94, 0·91 to 0·98) and death (HR 0·89, 0·83 to 0·94). A major improvement in prognosis was observed after 2005, when the classification of breast cancer molecular subtypes and use of trastuzumab were implemented in routine clinical practice.

Conclusion: In the past two decades, both local control and overall prognosis have improved significantly in young women (aged less than 40 years) with breast cancer who undergo BCS.

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Introduction

Breast cancer in young women represents a challenge from a clinical and psychological point of view, for both patients and physicians. Conventionally, women who receive a diagnosis of breast cancer before the age of 40 years are distinctively defined as 'young', as they share common disease characteristics[1,2]. Breast cancer in young women has worse prognosis[3,4] and greater likelihood of underlying hereditary genetic abnormalities[4] than breast cancer in older women. The emotional challenges and the lack of clear data on the efficacy of different treatment strategies often drive both patient and physician to opt for the most radical and extensive treatments available. In terms of surgery, mastectomy might be selected instead of breast-conserving surgery (BCS) to reduce the risk of local recurrence, thus minimizing the psychological trauma and morbidity related to local relapse of the disease and its management. Nevertheless, a recent study[5] of 1000 patients younger than 35 years showed that the type of surgery performed, BCS or mastectomy, did not influence the rate of locoregional recurrence. Moreover, a recent meta-analysis[6] including more than 22 000 young patients showed that BCS and whole-breast radiotherapy (WBRT) provide overall survival rates at least similar to those of mastectomy.

The decision whether to perform either BCS or mastectomy in young women with breast cancer should be based on reliable and contemporary risk estimates of local recurrence and other events. Therefore, a single-centre cohort study including young women diagnosed with early breast cancer, and treated with BCS and WBRT between 1997 and 2010, was conducted, with the aim of evaluating the risk of local recurrence and other events over time. The main goal was to evaluate whether the safety of BCS has improved over time and whether other components of therapy could be identified as clinically relevant, leading to improved overall outcomes. The hypothesis was that the progressive introduction of targeted treatments, more appropriate attention to the use of endocrine therapy, improved preoperative evaluation and pathological diagnosis, refinement of patient selection for surgery and better knowledge of hereditary predisposition might have led to significant improvements in outcome after BCS.

Methods

The study population was identified from a prospectively maintained breast cancer database of the European Institute of Oncology (IEO) in Milan, Italy. All women diagnosed and treated with BCS for primary invasive early-stage breast cancer (T1–3 N0–1 M0) and younger than 40 years old were selected. All patients were treated at the IEO between January 1997 and December 2010. Patients who received neoadjuvant chemotherapy, and those with evidence of metastatic disease at presentation, or bilateral, inflammatory or recurrent breast cancer were excluded from the analysis. The study was approved by the ethics committee of the IEO and by the Italian Data Protection Authority.

Data collection

Clinicopathological data were recorded including: age at surgery, date of surgery, histology, pathological tumour category, number of positive lymph nodes, oestrogen receptor (ER) and progesterone receptor (PgR) status, human epidermal growth factor receptor 2 (HER2) status, nuclear grade, proliferation index (as measured by Ki-67 immunostaining), multifocality/multicentricity, presence or absence of peritumoral vascular invasion (PVI) and an extensive *in situ* component. pT was categorized according to the AJCC staging system, seventh edition[7]. Information on ER, PgR, HER2, Ki-67, nuclear grade, PVI and extensive *in situ* component were obtained from the patient's diagnostic core biopsy and/or final surgical specimen. All tumour samples were reviewed by dedicated breast cancer pathologists. ER and PgR status was recorded as the percentage of immunoreactive cells, and classified into two groups: 0 per cent (negative receptor status) and 1 per cent or more (positive receptor status). HER2 positivity was defined as 3+ staining on immunohistochemistry, or gene amplification on fluorescence *in situ* hybridization. In the year 2000, the evaluation of HER2 became routine practice at the IEO. In the present series, information on HER2 was obtained at the time of diagnosis for almost all patients (with no retrospective evaluation). Nuclear grade was recorded as low (grade 1), intermediate (grade 2) or high (grade 3). PVI was categorized as none, focal or diffuse. Number of positive lymph nodes was categorized as none, between one and three, and more than three. Molecular subtypes were defined as: luminal A (positive for ER and/or PgR, negative for HER2, low (less than 14 per cent) Ki-67 index); luminal B (positive for ER and/or PgR, negative for HER2, high (at least 14 per cent) Ki-67 index); luminal B/HER2+ (positive for ER and/or PgR, positive for HER2); HER2+ (negative for ER and PgR, positive for HER2); and triple-negative (negative for ER, PgR and HER2). No patient underwent molecular profiling.

Treatment

All patients in the study cohort underwent BCS followed by WBRT as final locoregional treatment. After surgery, all patients were discussed in a weekly multidisciplinary meeting attended by surgeons, medical oncologists, radiation oncologists and pathologists. The type of adjuvant systemic treatment varied over the course of the study, and depended on histopathological features, staging and co-morbidities. Patients usually visited a follow-up clinic every 6 months, and had mammography with or without breast ultrasonography every year. All patients who did not attend during the final 6 months were contacted in order to update the follow-up.

Statistical analysis

Association between categorical variables and date of diagnosis categorized in tertiles (1997–2002, 2003–2005 and 2006–2010) was evaluated by the χ^2 test for trend. Primary endpoints for the survival analysis were local recurrence, any breast cancer-related event and death from any cause. Local recurrence was defined as recurrence within the ipsilateral breast, with or without involvement of the axillary/regional lymph nodes. A breast cancer-related event was defined as any breast cancer-related recurrence (local, regional and distant) or death from breast

Table 1 Characteristics of the study population, overall and by period of surgery

	All patients ($n = 1331$)	1997–2002 ($n = 524$)	2003–2005 ($n = 350$)	2006–2010 ($n = 457$)	P‡
Age (years)					0·444
< 30	147 (11·0)	56 (10·7)	33 (9·4)	58 (12·7)	
30–34	370 (27·8)	152 (29·0)	87 (24·9)	131 (28·7)	
35–39	814 (61·2)	316 (60·3)	230 (65·7)	268 (58·6)	
Histology					0·017
Ductal	1182 (88·8)	449 (85·7)	320 (91·4)	413 (90·4)	
Other	149 (11·2)	75 (14·3)	30 (8·6)	44 (9·6)	
Tumour size (pT category)					0·633
pT1	861 (65·3)	340 (65·4)	219 (63·1)	302 (67·0)	
pT2–3	457 (34·7)	180 (34·6)	128 (36·9)	149 (33·0)	
Multifocal/multicentric					0·379
No	1175 (88·3)	468 (89·3)	307 (87·7)	400 (87·5)	
Yes	156 (11·7)	56 (10·7)	43 (12·3)	57 (12·5)	
Extensive *in situ* component					0·116
No	1103 (82·9)	422 (80·5)	296 (84·6)	385 (84·2)	
Yes	228 (17·1)	102 (19·5)	54 (15·4)	72 (15·8)	
Axillary surgery					< 0·001
SNLB only	677 (50·9)	176 (33·6)	204 (58·3)	297 (65·0)	
Axillary dissection	654 (49·1)	348 (66·4)	146 (41·7)	160 (35·0)	
No. of LNs removed*	6 (2–24)	20 (2–27)	3 (1–23)	3 (2–20)	
No. of positive LNs					< 0·001
0	740 (55·6)	263 (50·2)	199 (56·9)	278 (60·8)	
1mi†	102 (7·7)	35 (6·7)	28 (8·0)	39 (8·5)	
1–3	311 (23·4)	143 (27·3)	78 (22·3)	90 (19·7)	
> 3	178 (13·4)	83 (15·8)	45 (12·9)	50 (10·9)	
Tumour grade					0·577
1	132 (10·3)	49 (9·8)	41 (12·1)	42 (9·5)	
2	489 (38·2)	207 (41·5)	106 (31·4)	176 (39·8)	
3	658 (51·4)	243 (48·7)	191 (56·5)	224 (50·7)	
Ki-67 (%)					0·196
< 20	398 (30·4)	165 (32·7)	101 (28·9)	132 (28·9)	
≥ 20	913 (69·6)	340 (67·3)	248 (71·1)	325 (71·1)	
Peritumoral vascular invasion					0·813
None	859 (64·5)	332 (63·4)	234 (66·9)	293 (64·1)	
Focal	280 (21·0)	116 (22·1)	76 (21·7)	88 (19·3)	
Diffuse	192 (14·4)	76 (14·5)	40 (11·4)	76 (16·6)	
ER status					0·413
Negative	325 (24·6)	133 (25·9)	84 (24·0)	108 (23·6)	
Positive	996 (75·4)	381 (74·1)	266 (76·0)	349 (76·4)	
PgR status					0·212
Negative	398 (30·1)	166 (32·3)	101 (28·9)	131 (28·7)	
Positive	923 (69·9)	348 (67·7)	249 (71·1)	326 (71·3)	
HER2 overexpression					0·848
No	957 (81·2)	297 (80·1)	291 (83·1)	369 (80·7)	
Yes	221 (18·8)	74 (19·9)	59 (16·9)	88 (19·3)	
Molecular subtype					0·030
Luminal A	158 (12·6)	62 (14·0)	49 (14·0)	47 (10·3)	
Luminal B	643 (51·4)	243 (54·7)	166 (47·6)	234 (51·2)	
Luminal B/HER2+	171 (13·7)	50 (11·3)	51 (14·6)	70 (15·3)	
HER2+	50 (4·0)	24 (5·4)	8 (2·3)	18 (3·9)	
Triple-negative	228 (18·2)	65 (14·6)	75 (21·5)	88 (19·3)	

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). Data were missing for some variables. †1mi, one lymph node with micrometastases only. SNLB, sentinel lymph node biopsy; LN, lymph node; ER, oestrogen receptor; PgR, progesterone receptor; HER, human epidermal growth factor receptor. ‡χ^2 test for trend.

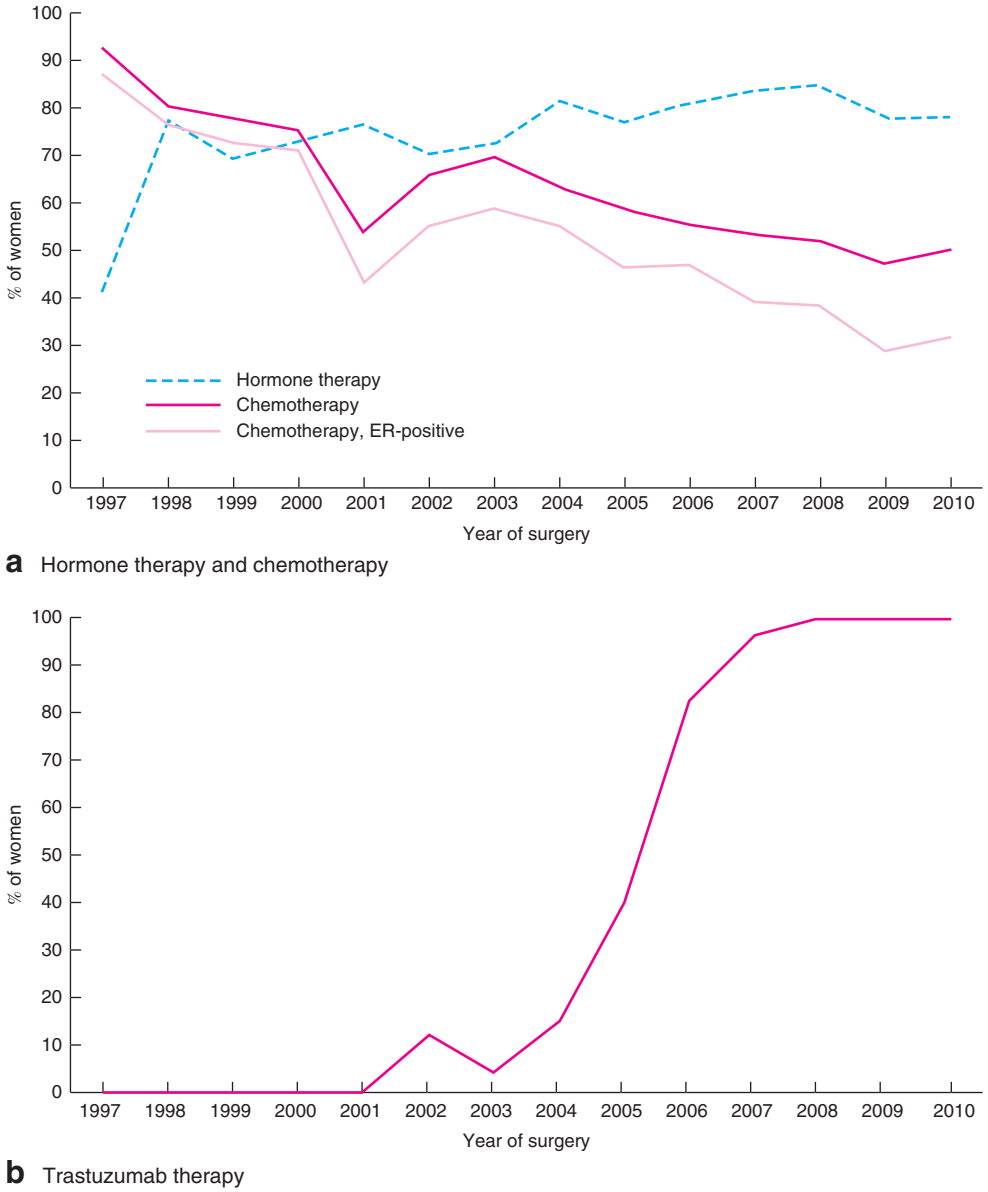

Fig. 1 Time trends in treatment from 1997 to 2010: **a** hormone therapy, and chemotherapy in all women and those with oestrogen receptor (ER)-positive disease, and **b** trastuzumab in breast cancers with human epidermal growth factor receptor 2 amplification

cancer, whereas contralateral tumours, non-breast primary tumours and deaths from other causes were considered as censoring events. Survival figures are presented as number of events per 100 person-years. Multivariable Cox proportional hazards models were applied and hazard ratios (HRs) with 95 per cent confidence intervals reported.

To investigate the shape of the relationship between date of surgery and the hazard of an event, restricted cubic spline models were used. Cubic splines are smoothly joined piecewise third-order polynomials[8]. Polynomials are fitted within intervals delimited by knots, and restrictions are placed on the resulting curve to ensure a smooth appearance at the knot points. A three-knot analysis was performed, adjusted for age, histological type, tumour size, multifocality/multicentricity, number of positive lymph nodes and molecular subtype. Results are presented as HRs, using the median value of the date of surgery (24 April 2004) as reference (HR 1·00). Restricted splines were chosen over other functions (such as polynomials)

Table 2 Univariable analysis of risk factors for local recurrence, any breast cancer-related event and death

		Local recurrence		Any breast cancer		Death from any cause	
	No. at risk	No. of events	*P**	No. of events	*P**	No. of events	*P**
All patients	1331	114 (1·05)		289 (2·66)		138 (1·27)	
Age (years)			0·358†		0·280†		0·114†
< 30	147	11 (0·95)		28 (2·42)		13 (1·12)	
30–34	370	39 (1·31)		97 (3·27)		51 (1·72)	
35–39	814	64 (0·95)		164 (2·43)		74 (1·10)	
Date of surgery			0·028†		0·004†		0·003†
1997–2002	524	77 (1·42)		163 (3·01)		86 (1·59)	
2003–2005	350	25 (0·85)		74 (2·52)		36 (1·22)	
2006–2010	457	12 (0·48)		52 (2·07)		16 (0·64)	
Histology			0·294		0·010		0·068
Ductal	1182	104 (1·09)		268 (2·81)		10 (0·74)	
Other	149	10 (0·74)		21 (1·56)		128 (1·34)	
Tumour size (pT category)			0·559		< 0·001		< 0·001
pT1	861	72 (0·98)		152 (2·08)		62 (0·85)	
pT2–3	457	42 (1·21)		134 (3·87)		74 (2·14)	
Multifocal/multicentric			0·401		0·052		0·939
No	1175	97 (1·01)		245 (2·55)		122 (1·27)	
Yes	156	17 (1·36)		44 (3·52)		16 (1·28)	
Extensive *in situ* component			0·374		0·991		0·974
No	1103	89 (1·00)		239 (2·66)		113 (1·27)	
Yes	228	25 (1·27)		52 (2·65)		25 (1·27)	
No. of positive LNs			0·823†		< 0·001†		< 0·001†
0	740	62 (1·02)		125 (2·05)		51 (0·84)	
1–3	413	34 (0·98)		97 (2·79)		41 (1·18)	
> 3	178	18 (1·38)		67 (5·12)		46 (3·52)	
Tumour grade			0·228†		< 0·001†		< 0·001†
1	132	8 (0·65)		12 (0·97)		3 (0·24)	
2	483	44 (1·08)		88 (2·15)		29 (0·71)	
3	658	56 (1·10)		178 (3·49)		100 (1·96)	
Ki-67 (%)			0·361		< 0·001		< 0·001
< 20	398	29 (0·83)		54 (1·55)		19 (0·54)	
≥ 20	913	80 (1·11)		229 (3·19)		117 (1·63)	
Peritumoral vascular invasion			0·520†		< 0·001†		< 0·001†
None	859	71 (1·02)		148 (2·05)		58 (0·80)	
Focal	280	29 (1·29)		74 (3·28)		37 (1·64)	
Diffuse	192	14 (1·01)		67 (4·85)		43 (3·11)	
ER status			0·737		0·235		< 0·001
Negative	325	28 (1·12)		78 (3·11)		46 (1·84)	
Positive	996	84 (1·02)		209 (2·53)		91 (1·10)	
PgR status			0·681		0·480		0·028
Negative	398	31 (0·99)		91 (2·91)		52 (1·66)	
Positive	923	81 (1·06)		196 (2·57)		85 (1·12)	
HER2 overexpression			0·190		0·201		0·870
No	957	66 (0·88)		187 (2·49)		92 (1·22)	
Yes	221	20 (1·23)		50 (3·08)		22 (1·36)	
Molecular subtype			0·610		< 0·001		< 0·001
Luminal A	158	14 (1·00)		18 (1·29)		6 (0·43)	
Luminal B	643	54 (1·03)		156 (2·98)		71 (1·36)	
Luminal B/HER2+	171	13 (0·98)		28 (2·12)		12 (0·91)	
HER2+	50	7 (2·32)		22 (7·28)		10 (3·31)	
Triple-negative	228	14 (0·83)		41 (2·42)		30 (1·77)	

Values in parentheses are annual rate per 100 person-years. LN, lymph node; ER, oestrogen receptor; PgR, progesterone receptor; HER, human epidermal growth factor receptor. *Log rank test except †log rank test for trend.

Table 3 Multivariable Cox proportional hazards analysis of risk factors for local recurrence, any breast cancer-related event and death

	Hazard ratio		
	Local recurrence	Any breast cancer-related event	Death from any cause
Age (per year increase)	0·99 (0·94, 1·04)	0·99 (0·96, 1·02)	0·98 (0·94, 1·02)
Date of diagnosis (from 1997 to 2010) (per year increase)	0·93 (0·87, 1·00)	0·94 (0·91, 0·98)	0·89 (0·83, 0·94)
Histological type (ductal *versus* others)	1·53 (0·78, 3·02)	1·45 (0·91, 2·33)	1·09 (0·55, 2·16)
Tumour size (> 2 *versus* ≤ 2 cm)	1·31 (0·88, 1·94)	1·62 (1·27, 2·06)	1·87 (1·33, 2·64)
Multifocal/multicentric (yes *versus* no)	1·33 (0·79, 2·25)	1·18 (0·85, 1·65)	0·75 (0·44, 1·29)
Positive LNs			
0	1·00 (reference)	1·00 (reference)	1·00 (reference)
1–3	0·88 (0·56, 1·39)	1·08 (0·81, 1·44)	1·05 (0·67, 1·64)
> 3	1·19 (0·65, 2·17)	1·56 (1·10, 2·20)	2·36 (1·46, 3·8)
Molecular subtype			
Luminal A	1·00 (reference)	1·00 (reference)	1·00 (reference)
Luminal B	0·86 (0·46, 1·58)	1·62 (0·98, 2·68)	1·86 (0·79, 4·37)
Luminal B/ HER2+	0·91 (0·42, 1·97)	1·19 (0·65, 2·18)	1·35 (0·50, 3·69)
HER2+	1·98 (0·78, 5·02)	3·83 (2·03, 7·23)	3·71 (1·33, 10·41)
Triple-negative	0·76 (0·35, 1·63)	1·51 (0·85, 2·67)	3·62 (1·47, 8·90)
Peritumoral vascular invasion			
None	1·00 (reference)	1·00 (reference)	1·00 (reference)
Focal	1·23 (0·78, 1·94)	1·40 (1·04, 1·88)	1·81 (1·17, 2·81)
Diffuse	0·86 (0·44, 1·66)	1·58 (1·12, 2·23)	2·53 (1·56, 4·09)

Values in parentheses are 95 per cent confidence intervals. LN, lymph node; HER, human epidermal growth factor receptor.

because of their high flexibility. Cubic splines were chosen over other-order splines because they provide sufficient flexibility for fitting data, while not requiring as many degrees of freedom as higher-order splines.

All analyses were carried out with SAS® software version 9.4 (SAS Institute, Cary, North Carolina, USA) and R software version 2.12.2 (http://www.rproject.org). $P < 0{\cdot}050$ was considered statistically significant. All reported P values are two-sided.

Results

The study population included 1331 consecutive patients younger than 40 years who underwent BCS followed by WBRT. Patient characteristics are summarized in *Table 1*. The median age at diagnosis was 35 (range 17–39) years and the median tumour size on pathology was 1·7 (range 0·05–8·0) cm. Analysis of the study population divided according to tertiles of year of diagnosis (1997–2002, 2003–2005 and 2006–2010) showed that the prevalence of breast cancer with a negative axilla increased over time ($P < 0{\cdot}001$). The use of chemotherapy decreased over time, especially in women with ER-positive breast cancer, whereas the use of hormone therapy increased slightly (*Fig. 1a*). The use of trastuzumab in patients with HER2-positive disease began in 2005–2006 (*Fig. 1b*).

After a median follow-up of 9·3 (range 0·1–18) years, 114 local events, 289 breast cancer-related events and 138 deaths had occurred (*Table 2*). The rate of local events decreased from 1·42 per 100 person-years in 1997–2002 to 0·48 per 100 person-years in 2006–2010 ($P = 0{\cdot}028$), the rate of breast cancer-related events from 3·01 per 100 to 2·07 person-years ($P = 0{\cdot}004$) and the mortality rate from 1·59 to 0·64 per 100 person-years ($P = 0{\cdot}003$). The same trends were observed in women with HER2-positive and HER2-negative breast tumours, although statistical significance was not reached for local recurrences (*Table S1*, supporting information). Notably, in patients with HER2-positive disease, the risk of breast cancer-related events and death decreased only after the introduction of trastuzumab as standard therapy for HER2-positive breast cancer in 2005–2006.

In multivariable analysis, each additional year of diagnosis was associated with a decreasing risk of local recurrence (HR 0·93, 95 per cent c.i. 0·87 to 1·00), any breast cancer-related event (HR 0·94, 0·91 to 0·98) and death (HR 0·89, 0·83 to 0·94) (*Table 3*). The HRs did not change significantly when stratified by lymph node status and pT category (data not shown). Risk factors significantly associated with increased risk of any breast cancer-related event and death were: tumour size greater than 2 cm, three or more positive lymph nodes and presence of PVI. In addition, the HER2 subtype was significantly associated with an increased risk of any breast cancer-related event (HR 3·83, 2·03 to 7·23) and death (HR 3·71, 1·33 to 10·41), whereas the triple-negative

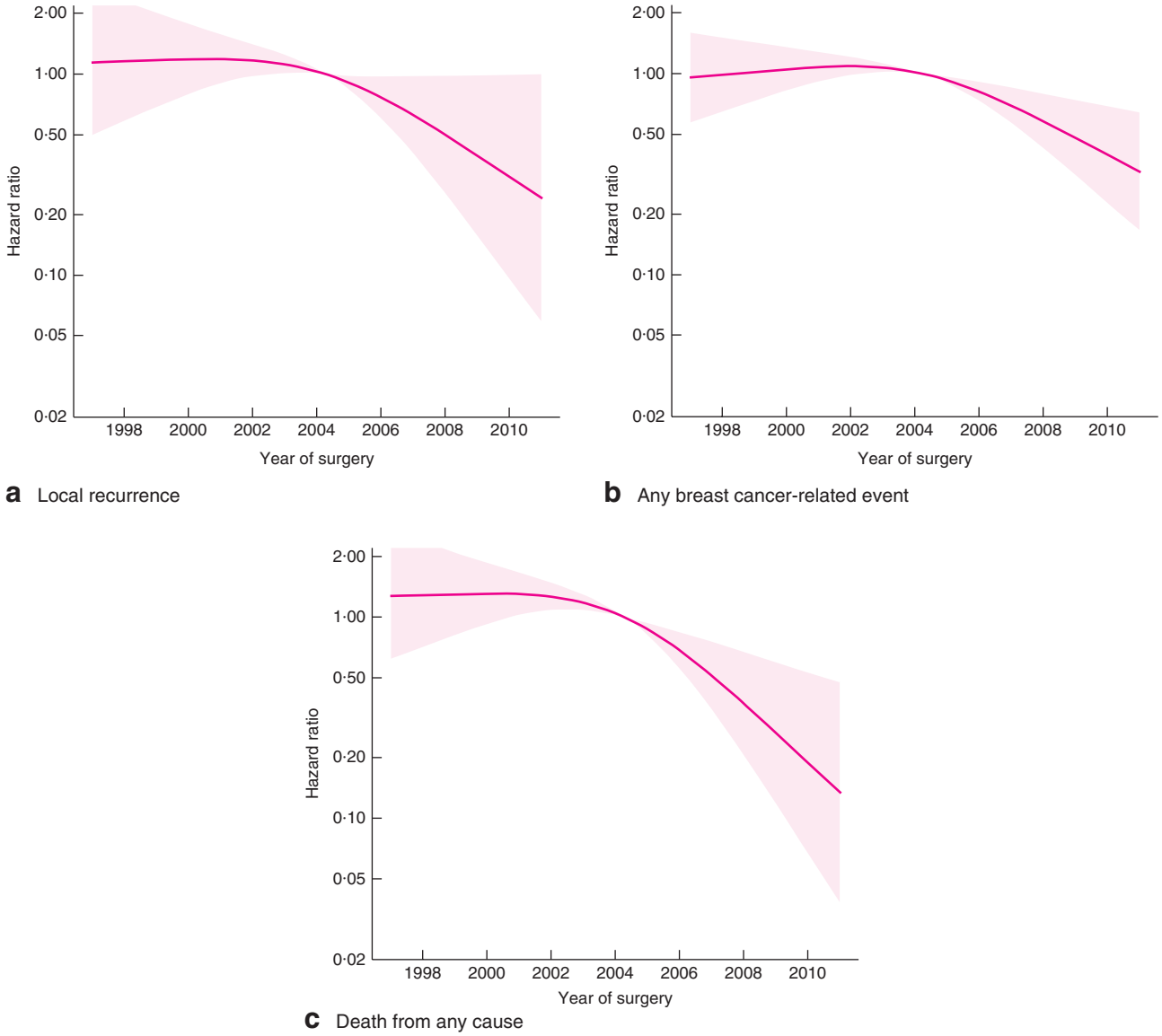

Fig. 2 Shape of the relationship between date of surgery and hazard of **a** local recurrence, **b** any breast cancer-related event and **c** death from any cause evaluated in a restricted cubic spline multivariable model, adjusted for age, histological type, tumour size, multifocality/multicentricity, number of positive lymph nodes and molecular subtype. 24 April 2004 (median value) was the reference date (hazard ratio 1·00). Shaded area represents 95 per cent c.i.

subtype was associated with increased risk of death (HR 3·62, 1·47 to 8·90).

The shape of the relationship between the date of diagnosis and the risk of local recurrence, any breast cancer-related event and death was analysed (*Fig. 2*). The risk of all three types of event was quite stable from 1997 to 2002–2003, but decreased dramatically after 2005–2006. The hypothesis of a linear trend between year of diagnosis and risk of local recurrence, any breast cancer-related event and death was tested, and rejected only for any breast-related event and death ($P = 0{\cdot}170$, $P = 0{\cdot}019$ and $P = 0{\cdot}032$ respectively).

Discussion

This study evaluated the contemporary risk estimates of breast cancer events in young patients undergoing BCS, as this information might help both physicians and patients

to make an informed decision about the appropriate surgical treatment. In everyday practice, physicians are often prone to recommend, and patients to prefer, mastectomy over BCS, owing to a belief that a more radical surgical approach would provide a better prognosis. This attitude is based on the increased cumulative incidence of ipsilateral breast tumour recurrence after BCS in young women compared with older women with breast cancer[9,10]. In addition, the tumour biology of breast cancer is more aggressive in young patients[3,4], leading to a worse outcome than in older premenopausal women[3]. A recent meta-analysis[6] including more than 22 000 patients nevertheless showed that type of surgery did not affect overall survival in young patients with breast cancer. Actually, BCS was associated with borderline significantly better overall survival compared with mastectomy (HR 0·90, 95 per cent c.i. 0·81 to 1·00). Furthermore, a cohort study[5] of 1000 patients younger than 35 years from the Netherlands Cancer Registry reported that type of surgery, either BCS or mastectomy, did not affect risk of local recurrence in the entire cohort and in molecular subtype groups.

In the present large single-centre retrospective analysis of young women with breast cancer treated with BCS and WBRT, the risk of local recurrence, breast cancer-related events and death decreased significantly over time. A dramatic improvement in prognosis was observed after 2005, when the use of trastuzumab was implemented in routine clinical practice. However, prognosis did not improve only in patients with HER2-positive disease. This could be explained by the widespread use of classification of breast cancer molecular subtypes, which led to more accurate treatment strategies for all patients, and by general improvements in diagnostic ability and the introduction of new effective systemic treatments[11,12]. Better diagnostic ability was evident in both the preoperative evaluation and pathological analysis. The increasing use of MRI in young women might also have improved the correct selection of patients for BCS, and the introduction of molecular subtypes allowed more tailored treatments. In the study reported by Aalders and co-workers[5], the proportion of patients receiving chemotherapy remained stable throughout the entire observation period (from 2003 to 2008), with more than 90 per cent of patients younger than 35 years undergoing chemotherapy.

It is interesting to note how adjuvant treatment changed over time in the present series, with a progressive reduction in administration of chemotherapy, which paralleled greater and more accurate use of endocrine therapy. The choice of adjuvant treatment was based more on the biology of the disease (molecular subtype categorization) and its stage (such as lymph node involvement) rather young age, which is considered an independent factor for recurrence[13]. One of the major advances was clearly the introduction of trastuzumab as standard treatment in patients with HER2-positive disease. In the present study, patients with the luminal B/HER2+ subtype did not have a significantly worse prognosis than those with luminal A cancer, whereas women with the HER2+ subtype had a worse prognosis than those with luminal A cancer.

The incidence of ipsilateral breast tumour recurrence decreased by 7 per cent each year, going from 1·42 per 100 person-years in those treated up to 2002 to 0·48 per 100 person-years in those treated after 2005. A 10-year local relapse rate of 4·8 per cent is much better than that reported previously in young women[8,9]. Tumour size affected breast cancer-related events and risk of death independently, but had no impact on local recurrence, consistent with the findings of Aalders *et al.*[5], and suggesting that tumour size itself should not be an *a priori* contraindication to BCS.

This study has all the limitations of a retrospective analysis. For example, the outcome of these young patients might in part have improved over time owing to the constantly improving selection of patients for BCS as initial treatment. The increased referral for genetic consultation and genetic testing might have contributed to the selection of patients without an increased genetic predisposition for BCS. Unfortunately, information on the number of women who did not choose BCS because of genetic predisposition is not available in the data set. In addition, the use of primary systemic therapy might have progressively excluded patients with a poor prognosis from initial BCS. However, this was unlikely to have affected the results as the proportion of women receiving neoadjuvant therapy followed by BCS was constant during the study period (around 14 per cent of all women who underwent BCS).

On the other hand, the present study has several strengths. Data were collected from a single referral cancer centre where all the information had been entered prospectively into a dedicated institutional database. The large number of patients and long follow-up gave a reliable perspective on how prognosis changed over time in this subset of patients with an increased risk of recurrence and death. It is valuable for young patients with breast cancer to realize that they can safely undergo a limited, non-mutilating, surgical procedure and achieve a good oncological outcome, which has improved constantly over the past two decades. Although there are no prospective randomized trials specifically designed for this age group, the present analysis, along with data from the large Dutch cohort[5], confirm that good outcomes can be achieved with BCS. The rate of ipsilateral breast

tumour recurrence after BCS currently appears to be reasonably low, and certainly much lower than in the past. In addition, the meta-analysis by Vila and colleagues[6] provides robust evidence that mastectomy *per se* in young patients does not provide better outcome in terms of overall survival. Therefore, whenever technically feasible, and after thorough preoperative evaluation, BCS should also be the first option in young patients with breast cancer, at least when increased genetic risk has not been demonstrated.

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Supporting information

Additional supporting information may be found online in the supporting information tab for this article.

Table S1 Risk of recurrence and death over time according to molecular subtype and human epidermal growth factor receptor 2 overexpression (Word document)