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RESEARCH ARTICLE



Cause-specific mortality after a breast cancer diagnosis: a cohort study of 10,195 women in Girona and Tarragona

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Abstract

Introduction Evidence suggests an excess of long-term mortality due to cardiovascular diseases, second tumours and other causes in patients diagnosed with invasive breast cancer (BC). Our aim was to assess this risk of death in a cohort of patients diagnosed with BC in Girona and Tarragona, northeastern Spain.

Materials and methods Using data from the cancer registries in these areas, a population-based cohort study was carried out including all the women diagnosed with BC during 1985–2004 and followed up until December 31st 2014 ($N=10,195$). The standardised mortality ratios (SMRs) were calculated for causes other than BC in the cohort at 10 years (periods 1985–1994/1995–2004) and 20 years (period 1985–1994). The impact of competing causes of death in the long-term survival was evaluated through competing risk analysis.

Results The SMRs at 10 and 20 years for all-cause mortality, except BC, were 1.21 and 1.22. The main causes of mortality showing statistically significant SMR at 10 years were other tumours (colon, lung, corpus uteri, ovary, and haematological), diabetes mellitus, diseases of the nervous system, cardiovascular diseases (after BC, the second competing cause of death among patients diagnosed > 69 years) and diseases of the kidney. Globally, the 10-year SMR was higher in the first period. After 20 years of follow-up (1985–1994 cohort), there were 48.5 excess deaths per 10,000 patient-years for causes other than BC.

Conclusions Women who did not die from BC at 10 or 20 years after the BC diagnosis had 20% higher risk of dying from other causes than women without BC. This excess risk must be clinically considered during 20 years after the BC diagnosis.

Keywords Breast cancer · Cause-specific mortality · Excess mortality · Side effects · Second tumour

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26 Abbreviations

27	BC	Breast cancer
28	RT	Radiotherapy
29	CVD	Cardiovascular disease
30	EM	Excess of mortality
31	ICD	International classification of diseases
32	SMR	Standardised mortality ratio
33	O	Observed number of deaths
34	E	Expected number of deaths
35	ED	Excess in the number of deaths
36	95% CI	95% confidence interval
37	OC	Other causes of mortality, excludes BC, cancer and CVD
38		
39	SupMat	Supplementary material
40	Gy	Dose in radiation therapy measured in grays

41 Introduction

42 Breast cancer (BC) is the most frequent tumour and the first
43 cause of cancer death in Spanish and European women in
44 recent decades [1, 2]. It is estimated that 27,700 new BC
45 cases were diagnosed in Spain during 2015 [2]. In Spain and
46 Europe, mortality from BC has significantly decreased in
47 recent decades and 5-year survival has increased [1, 3, 4] as
48 a result of early diagnosis and of therapeutic improvements
49 in chemotherapy, hormonal treatment and radiotherapy (RT)
50 [4–6]. At European level, recent estimates indicate that 12%
51 of the women who survived BC beyond 5 years of diagnosis
52 died from this cause before 10 years of diagnosis [7], and
53 evidence suggests an increased risk of cardiovascular disease
54 (CVD) and second primary tumours as a consequence of the
55 treatments (RT and some types of chemotherapy) [8–11] in
56 the long term.

57 The long-term survival of the cohort used in the present
58 study was previously analysed estimating the probability to
59 die from BC [12], and showing an excess mortality (EM)
60 at 15–20 years mainly attributed to BC. Given the average
61 of the age at the diagnosis of BC, 60 years [2, 12], and the
62 increase in women's life expectancy [12], the objective of
63 this study is to assess the causes of mortality associated with
64 the diagnosis and treatment of BC in a cohort of patients
65 diagnosed in the northeastern Spain, at 10 and 20 years after
66 the BC diagnosis.

67 Materials and methods

68 A population-based cohort study was performed using data
69 from the population-based cancer registries of Tarragona
70 and Girona. All women aged 15–84 years diagnosed with
71 invasive primary BC in these regions during the years

(periods) 1985–1994 ($N=4211$) and 1995–2004 ($N=5984$)
were included. Details of this cohort are described elsewhere
[12].

The vital status of these patients was followed until
December 31st 2014 through passive follow-up ('record
linkage' between the databases of cancer registries with
those of the Mortality Registry of Catalonia and the National
Index of Deaths of the Spanish Ministry of Health) and
active follow-up. In this process, the causes of death were
retrieved and posteriorly assessed using the International
Classification of Diseases (ICD) in its tenth edition. The
information of the patients with an ill-defined malignancy
death code (C76–C80, C97) was reviewed within the record
files of the cancer registries and in the patient's medical
records to determine the exact cause of death.

Statistical analysis

The EM was evaluated for mortality causes other than BC at
20 years for those patients diagnosed during the time period
1985–1994, and at 10 years for those diagnosed during
1985–1994, 1995–2004 and 1985–2004.

The standardised mortality ratio (SMR) was calculated as
the ratio between the observed number of deaths (O) from
a certain mortality cause at 10 and 20 years after the diag-
nosis of BC and the expected (E) deaths at that time if the
patients in the cohort experienced the same mortality rates
from that cause as the reference population [13]. Then E
was calculated by applying the age and year-specific person-
years at risk in the cohort by the corresponding cause-spe-
cific mortality rates of Catalonia, the reference population
which comprises the areas of Girona and Tarragona. The
person-years observed were defined as the period between
the BC diagnosis and the first dates reached between (a) the
date of death and (b) the date of the last-known vital status
(December 31st 2014) after the BC was diagnosed. The 95%
confidence intervals of the SMR (95% CI) were calculated
assuming that O follows a Poisson distribution [13]. Finally,
we also calculated the excess of deaths (ED), the difference
between the observed and expected cause-specific mortality
rates [13] per 10,000 patient-years, to assess the contribution
of each cause of death to the overall mortality.

The SMRs were evaluated for all causes of death as
a whole, except BC, and for a grouped causes of death
according to ICD-10: (1) tumours (C00–D49), (2) dis-
eases of the blood (D50–D89), (3) endocrine organs
(E00–E89), (4) nervous system (G00–G99), (5) circulatory
system (CVD:I00–I99), (6) respiratory system (J00–J99),
(7) digestive system (K00–K95), (8) musculoskeletal sys-
tem (M00–M99), (9) genitourinary system (N00–N99), (10)
malformations and other unclassified findings (Q00–Q99).
The differences in the 10-year SMR between 1985–1994

122 and 1995–2004 were assessed through a log-linear Poisson
123 model using a time-trend effect [13].

124 We also assessed the 10-year survival under competing
125 causes of death setting [12], by comparing the cumulative
126 mortality—see supplementary material (SupMat) for sta-
127 tistical methods and tables of results related to this specific
128 analysis—due to four causes: BC, cancer (excluding BC),
129 CVD, and the group of the remaining (other) causes of death
130 (OC) stratified by age groups and cancer stage at diagnosis,
131 this latter was available in period 1995–2004 [12]. All analy-
132 ses were performed using the software R (www.cran.r.org).

133 Results

134 Among 10,195 women diagnosed with BC between 1985
135 and 2004, a total of 4127 (40.5%) had died 10 years after the
136 diagnosis: 3179 due to cancer and 948 due to other causes.
137 Among those who had died of cancer, 2857 were due to
138 BC (69% of all deaths, 73% among those diagnosed in the
139 1985–1994 period and 65% among those diagnosed between
140 1995 and 2004). Among the 4211 patients diagnosed with
141 BC between 1985 and 1994, 2797 (66.4%) had died 20 years
142 after the BC was diagnosed: 2017 of them due to cancer
143 (1781 due to BC, 64% of the total deaths) and 780 for causes
144 other than cancer. Among the 10,195 patients diagnosed
145 during 1985–2004, the all-cause SMR at 10 years was 3.18
146 (CI 95% 3.08–3.17) and 10.48 (CI 95% 10.12–10.45) for
147 dying from any tumour (including BC). According to the
148 death certificates, we finally found $N = 34$ poorly defined
149 localization or uncertain behaviour tumours (see SupMat
150 for details).

151 Table 1 shows the 10-year SMR among the 7338 patients
152 diagnosed during 1985–2004 who did not die from BC.
153 Since their all-cause SMR was 1.21, there were significant
154 SMRs in (a) tumours (SMR = 1.48), and among these in
155 colon (SMR = 1.44), lung (SMR = 2.26), bone and cartilage
156 (SMR = 7.64), uterine corpus tumour (SMR = 2.85), ovary
157 (SMR = 2.20), haematological no-leukaemia (SMR = 1.72)
158 and leukaemias (SMR = 2.05); (b) non-tumours, such as
159 in diabetes mellitus (SMR = 1.43), diseases of the nervous
160 system (SMR = 1.30), diseases of the circulatory system
161 (SMR = 1.12; “Other diseases of the heart” SMR = 1.58),
162 pathological fracture (SMR = 2.17), diseases of the genito-
163 urinary system (SMR = 1.55), kidney–ureter (SMR = 1.62)
164 and other congenital malformations (SMR = 8.72). Heart
165 failure and cerebrovascular diseases showed non-statisti-
166 cally significant SMR. The SMR in the first 10-year period
167 was higher than in the second one (SMR_{1985–1994} = 1.29;
168 SMR_{1995–2004} = 1.16) in particular in (a) tumours
169 (SMR_{1985–1994} = 1.69; SMR_{1995–2004} = 1.34), and among these
170 in lung (SMR_{1985–1994} = 3.90; SMR_{1995–2004} = 1.54), bone and
171 cartilages (SMR_{1985–1994} = 10.25; SMR_{1995–2004} = 5.53), ovary

(SMR_{1985–1994} = 3.34; SMR_{1995–2004} = 1.50) and haematologi- 172
cal no leukaemia (SMR_{1985–1994} = 2.83; SMR_{1995–2004} = 1.05); 173
and in (b) diseases of the nervous system except for men- 174
ingitis and Alzheimer’s disease (SMR_{1985–1994} = 2.37; 175
SMR_{1995–2004} = 1.10), and diseases of the kidney and ureter 176
(SMR_{1985–1994} = 2.34; SMR_{1995–2004} = 1.21). Circulatory sys- 177
tem diseases maintained a similar risk in both periods, except 178
for the group “Other heart diseases” (SMR_{1985–1994} = 1.94; 179
SMR_{1995–2004} = 1.37). 180

181 Table 2 shows the 20-year SMR among the 2430 patients
182 diagnosed during 1985–1994 and who did not die from BC.
183 Their all-cause SMR was 1.22, whereas the causes of death
184 presenting a significant SMR in tumours (SMR = 1.57) were
185 lung (SMR = 2.57), bone and cartilage (SMR = 6.42), corpus
186 uterine (SMR = 3.67), ovary (SMR = 2.51), and the haema-
187 tological ones no leukaemia (SMR = 2.14). Among non- 188
tumours, these were diabetes mellitus (SMR = 1.65), other 189
diseases of the nervous system (SMR = 1.93), diseases of 190
the circulatory system (SMR = 1.12), especially the other 191
diseases of the heart (SMR = 1.50), and diseases of the kid- 192
ney and ureter (SMR = 1.79). Heart failure (SMR = 1.28)
193 was at the limit of statistical significance. Differences in
194 10-year and 20-year SMRs were not significant (note that
195 for all-cause mortality during 1985–1994 were similar,
196 SMR_{10-year} = 1.29, whereas SMR_{20-year} = 1.22).

197 The 20-year ED for causes other than BC was 48.5 per
198 10,000 patient-years, where 7 causes with significant SMR
199 contributed to 55% (26.83 deaths out of 48.5) to that ED:
200 other heart diseases (5.04), uterine corpus tumours (4.41),
201 diabetes mellitus (4.24), lung tumour (4.02), malignant
202 hematologic tumours except leukaemia (3.09), diseases of
203 the kidney and ureter (3.02), and tumour of the ovary (3.01).

204 Finally, comparing competing risks of death 10 years
205 after the BC diagnosis by cancer stage (Figs. 1, 2; see
206 also Tables S1–S4 in SupMat) we found that: (a) in stage
207 I, patients diagnosed before 69 years were more likely to
208 die from any cancer, whereas those diagnosed later were
209 more likely to die from CVD or OC than from any cancer;
210 (b) the probability to die from CVD and OC surpasses that
211 of cancer excluding BC in stages II and III among patients
212 diagnosed > 59 years and (c) patients diagnosed in stage IV
213 had the largest probabilities to die from any cancer.

214 Discussion

215 The knowledge of the causes of death other than BC in a
216 cohort of patients diagnosed with BC sheds light in inter-
217 preting long-term mortality/survival in relation to other
218 diseases and, especially, second cancers, where we must
219 also take into account the factors other than treatment itself
220 [14]. Our study period covers two diagnostic periods: (a)
221 1985–1994, prior to a time period of improvements in RT

Table 1 Risk of death at 10 years after the diagnosis of breast cancer in the regions of Girona and Tarragona during the period 1985–1994: causes of death other than breast cancer

Groups of causes of death (ICD-10)	1985–2004			1985–1994		1995–2004		Trend-SMR
	(O)	SMR	95% CI	(O)	SMR	(O)	SMR	1995–2004/1985–1994 p value test
All causes (except breast cancer)	1267	1.21	1.14–1.28*	538	1.29*	729	1.15*	**
Infectious and parasitic diseases	15	1.04	0.58–1.72	2	0.51	13	1.22	
Tumours (except breast)	319	1.48	1.32–1.65*	140	1.69*	179	1.34*	**
Malignant tumour of lip, oral cavity and pharynx	5	1.87	0.59–4.39	1	1.04	4	2.33	
Malignant tumour of oesophagus	1	0.57	0.00–3.29	1	1.49	0	0.00	
Malignant tumour of stomach	19	1.24	0.74–1.94	5	0.73	14	1.65	
Malignant tumour of colon	43	1.44	1.04–1.94*	16	1.42	27	1.45	
Malignant tumour of rectum, recto-sigmoid junction and anus	9	1.08	0.49–2.05	4	1.15	5	1.02	
Malignant tumour of liver and biliary tract	18	1.47	0.87–2.32	8	1.59	10	1.38	
Malignant tumour of pancreas	21	1.40	0.87–2.15	7	1.40	14	1.41	
Other malignant digestive tumours	8	0.84	0.36–1.66	6	1.43	2	0.38	
Malignant tumour of larynx	1	2.30	0.00–13.20	0	0.00	1	3.45	
Malignant tumour of trachea, bronchus and lung	36	2.26	1.58–3.13*	19	3.90*	17	1.54	**
Other malignant respiratory and intrathoracic tumours	2	1.64	0.15–6.03	2	4.16	0	0.00	
Malignant tumour of bone and articular cartilages	5	7.64	2.41–17.98*	3	10.25*	2	5.53	**
Malignant melanoma of skin	2	0.93	0.09–3.40	1	1.36	1	0.70	
Other malignant tumours of skin and soft tissues	5	2.23	0.70–5.24	1	1.35	4	2.67	
Malignant tumour of cervix uteri	2	0.57	0.05–2.09	1	0.67	1	0.49	
Malignant tumour of other parts of uterus	26	2.85	1.86–4.18*	9	2.33*	17	3.23*	
Malignant tumour of ovary	26	2.20	1.43–3.23*	15	3.34*	11	1.50	**
Malignant tumour of other genital female organs	0	0.00	0.00–1.19	0	0.00	0	0.00	
Malignant tumour of kidney, except renal pelvis	2	0.54	0.05–2.00	1	0.74	1	0.43	
Malignant tumour of urinary bladder	3	0.56	0.11–1.66	2	0.94	1	0.31	
Other malignant tumours of urinary tract	0	0.00	0.00–5.73	0	0.00	0	0.00	
Malignant tumour of encephalon	6	0.88	0.32–1.93	2	0.86	4	0.89	
Other neurological and endocrine malignant tumours	2	0.99	0.09–3.64	0	0.00	2	1.53	
Malignant tumours of ill-defined, secondary and no specified sites	22	1.18	0.74–1.79	7	0.91	15	1.38	
Haematological malignant tumours, except leukaemia	26	1.72	1.12–2.52*	16	2.83*	10	1.05	**
Leukaemia	19	2.05	1.23–3.20*	7	2.05	12	2.04*	
In situ tumours	0	0.00	0.00–199.89	0	0.00	0	0.00	
Benign tumours	1	0.68	0.00–3.87	0	0.00	1	1.03	
Myelodysplastic syndrome	4	2.21	0.58–5.72	1	2.39	3	2.16	
Other tumours of uncertain or unknown behaviour	5	0.80	0.25–1.88	4	1.61	1	0.27	
Diseases of the blood and the haematopoietic organs	4	0.87	0.23–2.24	3	1.75	1	0.34	
Endocrine, nutritional and metabolic diseases	45	1.18	0.86–1.58	17	1.19	28	1.17	
Diabetes mellitus	45	1.43	1.04–1.92*	17	1.39	28	1.45	
Other endocrine, nutritional and metabolic diseases	0	0.00	0.00–0.59*	0	0.00	0	0*	
Mental and behavioural disorders	48	0.85	0.63–1.13	18	0.96	30	0.79	
Diseases of the nervous system and of the organs of the senses	65	1.30	1.00–1.66*	23	1.99*	42	1.07	
Meningitis	1	2.36	0.00–13.54	1	6.80	0	0.00	
Alzheimer's disease	37	1.17	0.83–1.62	9	1.52	28	1.07	
Other diseases of the nervous system and sense organs	27	1.49	0.98–2.17	13	2.37*	14	1.10	**
Circulatory system diseases	393	1.12	1.01–1.24*	167	1.11	226	1.13	
Chronic rheumatic heart diseases	6	0.88	0.32–1.93	3	1.06	3	0.76	
Hypertensive diseases	19	0.80	0.48–1.26	3	0.41	16	0.97	
Acute myocardial infarction	39	0.83	0.59–1.13	15	0.71	24	0.94	

Table 1 (continued)

Groups of causes of death (ICD-10)	1985–2004			1985–1994		1995–2004		Trend-SMR
	(O)	SMR	95% CI	(O)	SMR	(O)	SMR	1995–2004/1985–1994 p value test
Other ischaemic diseases of the heart	38	1.05	0.74–1.44	12	0.84	26	1.17	
Heart failure	73	1.20	0.94–1.51	31	1.22	42	1.19	
Other heart diseases	75	1.58	1.24–1.98*	33	1.94*	42	1.37	**
Cerebrovascular diseases	120	1.15	0.95–1.37	56	1.16	64	1.15	
Atherosclerosis	12	0.84	0.43–1.47	8	0.84	4	0.90	
Other diseases of blood vessels	11	1.16	0.58–2.08	6	1.59	5	0.87	
Diseases of the respiratory system	75	0.97	0.76–1.21	33	1.15	42	0.85	
Diseases of the digestive system	63	1.28	0.98–1.64	22	1.14	41	1.37	
Ulcer of stomach, duodenum and jejunum	2	1.19	0.11–4.38	1	1.06	1	1.39	
Non-infectious enteritis and colitis	3	3.55	0.67–10.50	1	3.56	2	3.51	
Bowel vascular disease	3	0.39	0.07–1.17	1	0.39	2	0.39	
Cirrhosis and other chronic diseases of the liver	21	1.35	0.84–2.07	8	1.16	13	1.52	
Other diseases of the digestive system	34	1.44	1.00–2.02	11	1.28	23	1.53	
Diseases of the skin and subcutaneous tissue	2	0.89	0.08–3.27	1	1.31	1	0.67	
Diseases of the musculoskeletal system and connective tissue	19	1.63	0.98–2.55	8	1.83	11	1.50	
Rheumatoid arthritis and osteoarthritis	3	1.60	0.30–4.73	2	2.78	1	0.86	
Osteoporosis and pathological fracture	14	2.17	1.18–3.64*	6	2.39	8	2.02	
Other diseases of the musculoskeletal system and connective tissue	2	0.60	0.06–2.21	0	0.00	2	0.91	
Diseases of the genitourinary system	37	1.55	1.09–2.13*	15	1.85*	22	1.38	
Diseases of the kidney and the ureter	29	1.62	1.08–2.33*	15	2.34*	14	1.21	**
Diseases of the female genital organs and disorders of the breast	0	0.00	0.00–16.03	0	0.00	0	0.00	
Other diseases of the genitourinary system	8	1.38	0.59–2.73	0	0.00	8	1.88	
Congenital malformations, deformities and chromosomal abnormalities	4	5.01	1.30–12.94*	1	3.60	3	5.72*	
Congenital malformations of the nervous system	0	0.00	0.00–138.22	0	0.00	0	0.00	
Congenital malformations of the circulatory system	0	0.00	0.00–12.57	0	0.00	0	0.00	
Other congenital malformations, deformities and chromosomal abnormalities	4	8.72	2.27–22.54*	1	7.59	3	9.06*	
Symptoms, signs and abnormal findings not elsewhere classified	25	1.22	0.79–1.80	8	1.06	17	1.30	
Cardiac arrest, death without assistance and other unknown cause of mortality	13	1.35	0.71–2.31	2	0.56	11	1.80	
Senility	4	0.72	0.19–1.86	2	0.85	2	0.62	
Rest of symptoms, signs and clinical abnormal findings	8	1.49	0.64–2.96	4	2.48	4	1.06	
External causes of mortality	32	1.21	0.83–1.71	15	1.60	17	1.00	

O observed deaths; SMR standardised mortality ratio; 95% CI 95% confidence interval of the SMR

*Statistically significant at $\alpha=0.05$

**Test for comparing whether SMR in the first 10-year period, 1985–1994, was significantly different to that of the second period, 1995–2004, at $\alpha=0.05$

222 techniques and planning [15], and (b) 1995–2004, with
223 some years before these changes took place and some years
224 after these were established [12]. In relation to the medical
225 treatments, tamoxifen was administered since 1985 to BC
226 patients diagnosed in Girona and Tarragona [12].

227 In a previous study, we showed that the largest EM
228 was due to BC [12]. In the present study, the SMRs

from certain causes other than BC were significant and
10-year risk was higher in women diagnosed in the
first decade than in the second (SMR_{1985–1994} = 1.29;
SMR_{1995–2004} = 1.15). The SMR of cancer excepting BC
was statistically significant and slightly decreased from
the first to the second decade of the study.

Table 2 Risk of death at 20 years after the diagnosis of breast cancer in the regions of Girona and Tarragona during the period 1985–1994: causes of death other than breast cancer

Groups of causes of death (ICD-10)	1985–1994		
	(O)	SMR	95% CI
All causes (except breast cancer)	1013	1.22	1.15–1.30*
Infectious and parasitic diseases	6	0.58	0.21–1.28
Tumours (except breast)	233	1.57	1.37–1.78 *
Malignant tumour of lip, oral cavity and pharynx	3	1.67	0.31–4.93
Malignant tumour of oesophagus	2	1.69	0.16–6.23
Malignant tumour of stomach	11	1.00	0.49–1.79
Malignant tumour of colon	28	1.34	0.89–1.94
Malignant tumour of rectum, recto-sigmoid junction and anus	9	1.52	0.69–2.91
Malignant tumour of liver and biliary tract	11	1.29	0.64–2.31
Malignant tumour of pancreas	13	1.30	0.69–2.24
Other malignant digestive tumours	10	1.44	0.68–2.66
Malignant tumour of larynx	0	0.00	0.00–14.69
Malignant tumour of trachea, bronchus and lung	25	2.57	1.66–3.80*
Other malignant respiratory and intrathoracic tumours	2	2.42	0.23–8.91
Malignant tumour of bone and articular cartilages	3	6.42	1.21–19.01*
Malignant melanoma of skin	2	1.45	0.14–5.32
Other malignant tumours of skin and soft tissues	2	1.26	0.12–4.65
Malignant tumour of cervix uteri	2	0.89	0.08–3.28
Malignant tumour of other parts of uterus	23	3.67	2.33–5.52*
Malignant tumour of ovary	19	2.51	1.51–3.93*
Malignant tumour of other genital female organs	2	0.82	0.08–3.03
Malignant tumour of kidney, except renal pelvis	4	1.60	0.42–4.13
Malignant tumour of urinary bladder	4	0.99	0.26–2.56
Other malignant tumours of urinary tract	0	0.00	0.00–8.89
Malignant tumour of encephalon	5	1.20	0.38–2.82
Other neurological and endocrine malignant tumours	0	0.00	0.00–2.93
Malignant tumours of ill-defined, secondary and no specified sites	14	1.05	0.57–1.76
Haematological malignant tumours, except leukaemia	22	2.14	1.34–3.25*
Leukaemia	9	1.41	0.64–2.68
In situ tumours	0	0.00	0.00–299.76
Benign tumours	0	0.00	0.00–3.85
Myelodysplastic syndrome	1	0.73	0.00–4.20
Other tumours of uncertain or unknown behaviour	6	1.30	0.47–2.84
Diseases of the blood and the haematopoietic organs	5	1.32	0.42–3.11
Endocrine, nutritional and metabolic diseases	45	1.50	1.09–2.01*
Diabetes mellitus	41	1.65	1.18–2.23*
Other endocrine, nutritional and metabolic diseases	4	0.78	0.20–2.03
Mental and behavioural disorders	36	0.72	0.50–1.00*
Diseases of the nervous system and of the organs of the senses	58	1.51	1.14–1.95*
Meningitis	2	6.99	0.66–25.72
Alzheimer's disease	31	1.23	0.83–1.74
Other diseases of the nervous system and of the sense organs	25	1.93	1.25–2.85*
Circulatory system diseases	327	1.12	1.00–1.25*
Chronic rheumatic heart diseases	6	1.22	0.44–2.68
Hypertensive diseases	9	0.45	0.20–0.85*
Acute myocardial infarction	38	1.02	0.72–1.40
Other ischaemic diseases of the heart	26	0.86	0.56–1.27

Table 2 (continued)

Groups of causes of death (ICD-10)	1985–1994		
	(O)	SMR	95% CI
Heart failure	69	1.28	1.00–1.62
Other heart diseases	57	1.50	1.14–1.95*
Cerebrovascular diseases	104	1.19	0.97–1.45
Atherosclerosis	10	0.75	0.36–1.38
Other diseases of blood vessels	8	1.03	0.44–2.04
Diseases of the respiratory system	73	1.13	0.89–1.42
Diseases of the digestive system	37	0.98	0.69–1.35
Ulcer of stomach, duodenum and jejunum	2	1.42	0.13–5.22
Non-infectious enteritis and colitis	3	4.41	0.83–13.05
Bowel vascular disease	2	0.33	0.03–1.21
Cirrhosis and other chronic diseases of the liver	11	1.04	0.52–1.87
Other diseases of the digestive system	19	1.00	0.60–1.57
Diseases of the skin and subcutaneous tissue	2	1.05	0.10–3.87
Diseases of the musculoskeletal system and connective tissue	15	1.52	0.85–2.52
Rheumatoid arthritis and osteoarthritis	3	2.10	0.40–6.22
Osteoporosis and pathological fracture	11	1.84	0.92–3.31
Other diseases of the musculoskeletal system and connective tissue	1	0.41	0.00–2.33
Diseases of the genitourinary system	31	1.59	1.08–2.26*
Diseases of the kidney and the ureter	26	1.79	1.17–2.63*
Diseases of the female genital organs and disorders of the breast	0	0.00	0.00–20.50
Other diseases of the genitourinary system	5	1.05	0.33–2.48
Congenital malformations, deformities and chromosomal abnormalities	2	4.12	0.39–15.15
Congenital malformations of the nervous system	0	0.00	0.00–235.23
Congenital malformations of the circulatory system	0	0.00	0.00–19.26
Other congenital malformations, deformities and chromosomal abnormalities	2	7.54	0.71–27.73
Symptoms, signs and abnormal findings not elsewhere classified	20	1.13	0.69–1.74
Cardiac arrest, death without assistance and other unknown cause of mortality	9	1.13	0.51–2.15
Senility	7	1.25	0.50–2.59
Rest of symptoms, signs and clinical abnormal findings	4	0.96	0.25–2.49
External causes of mortality	27	1.36	0.90–1.98

O observed deaths; SMR standardised mortality ratio; 95% CI 95% confidence interval of the SMR

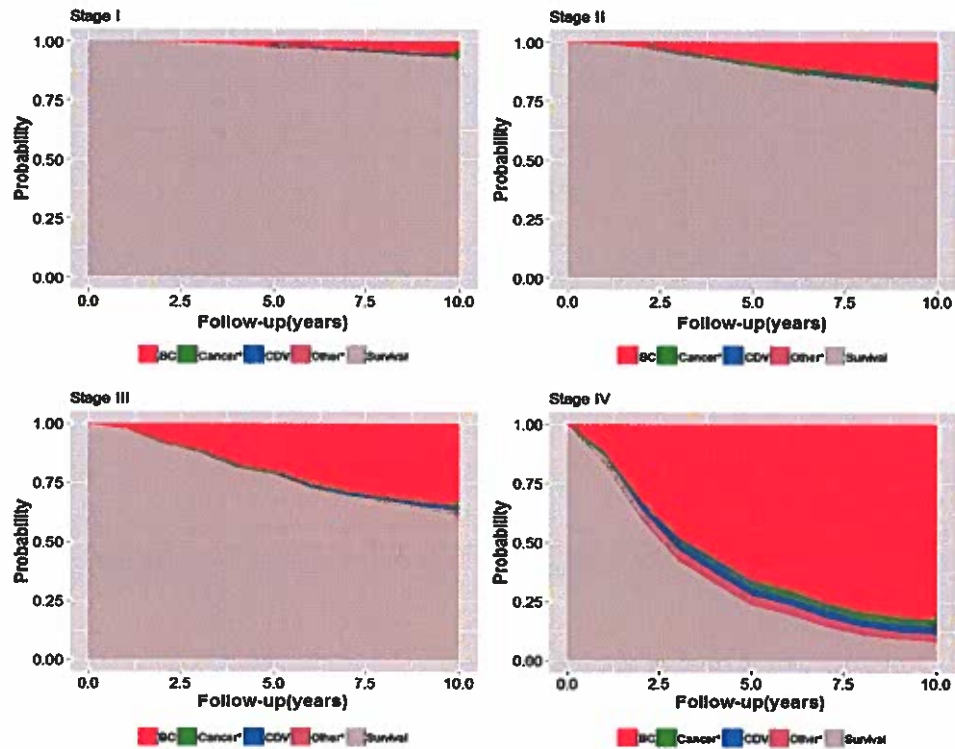
*Statistically significant at $\alpha=0,05$

235 Cancer causes

236 The SMR for lung cancer was statistically significant
 237 (SMR = 3.90) among patients diagnosed in 1985–1994 but
 238 not in those diagnosed later. Two cohort studies carried out
 239 in the mid-80 s found higher risk of lung cancer after the BC
 240 diagnosis, suggesting an association between this cancer, as
 241 second tumour, and side effects of RT [15, 16]. In the line
 242 of these studies, at the beginning of 1990s, the sites that
 243 typically received the highest radiation exposures (> 1 Gy)
 244 were oesophagus, lung, pleura, bone and soft tissues, which
 245 were irradiated with higher doses than those at the end of
 246 the 1990s [17, 18]. In our regions, changes in radiation expo-
 247 sures were introduced in the year 2000 [12], and this could
 248 be the reason for the decrease of the SMR in 1995–2004.

249 The proportion of women with locoregional BC who are
 250 treated with RT has increased over the years, and the tech-
 251 niques used in RT have improved substantially by decreas-
 252 ing the volumes of non-breast-irradiated tissues. Likewise,
 253 the post-surgery conservative RT of the breast after partial
 254 mastectomy would also decrease the doses compared to the
 255 post-mastectomy RT and this would entail a non-increased
 256 risk of lung cancer compared to the non-use of the RT [17,
 257 18]. In a cohort recruited from 1973 to 2005, there was a
 258 small but significant increase in the risk of lung cancer and
 259 other regions receiving high doses after conservative surgery
 260 [17]. We must take into account two factors: lung cancer
 261 mortality rates among women in Girona and Tarragona were
 262 very low in 1985–1994 [19] as well as smoking prevalence
 263 in the study cohort. On the other hand, death certificates

(a) ≤ 59



(b) [60-69]

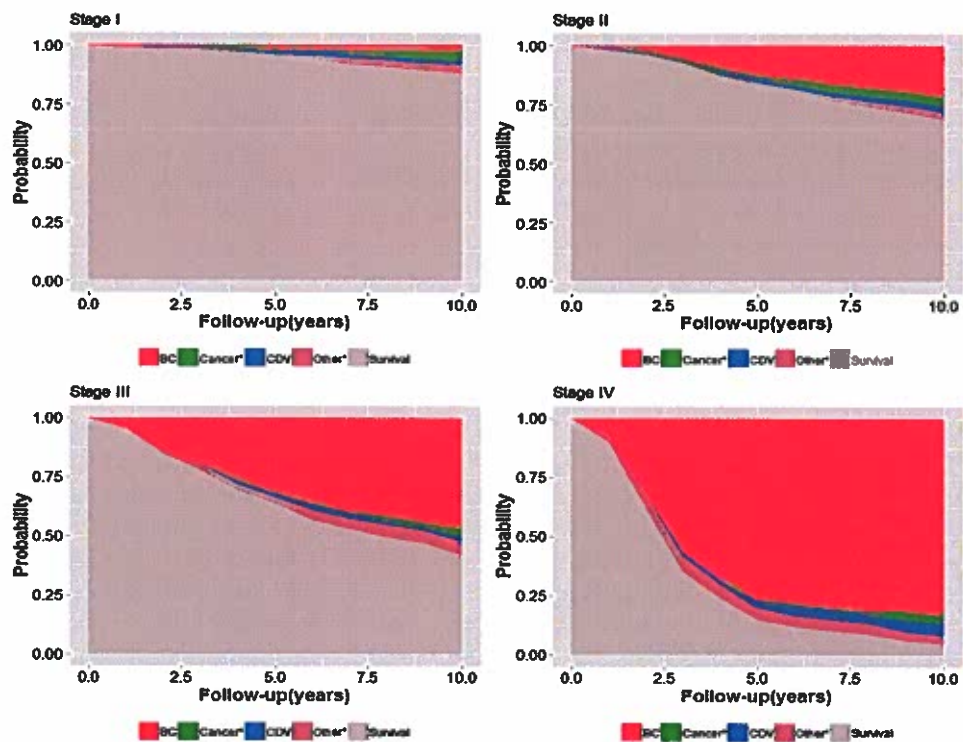


Fig. 1 Cumulative probability of cause-specific mortality and survival probability by age groups and across stages of BC at diagnosis during 1995–2004: a patients diagnosed of BC at ages ≤ 59 years; b

patients diagnosed of BC comprised from 60 to 69 years of age. BC breast cancer; Cancer* cancers other than BC; CDV cardiovascular; Other* other causes of death

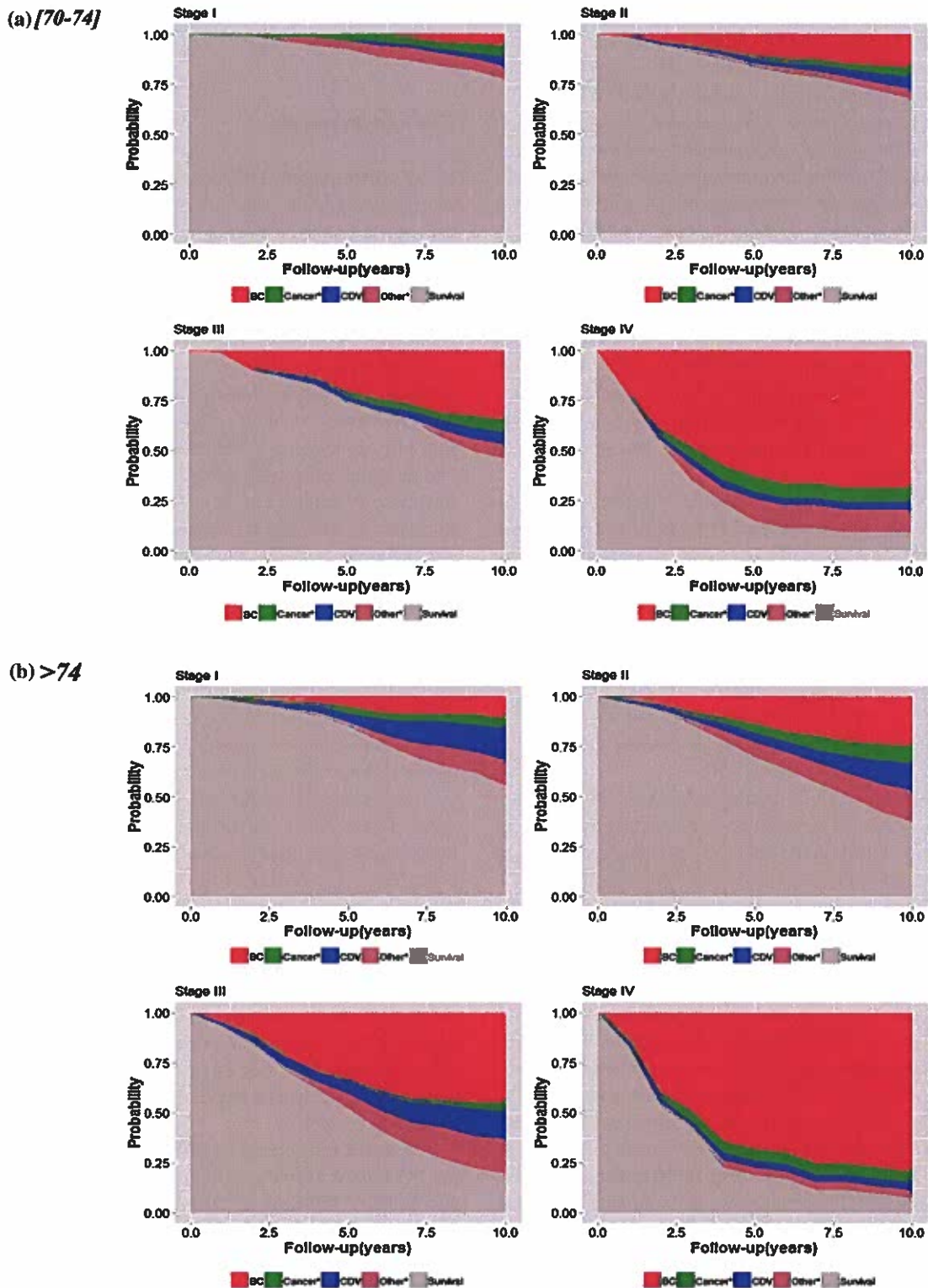


Fig. 2 Cumulative probability of cause-specific mortality and survival probability by age groups and across stages of BC at diagnosis during 1995–2004: **a** patients diagnosed of BC at ages (70–74) years

and **b** patients diagnosed of BC beyond 74 years. *BC* breast cancer; *Cancer** cancers other than BC; *CDV* cardiovascular; *Other** other causes of death

might be coding some lung cancer metastases as primary lung cancer [19]. In absolute terms, lung cancer is the second most involved type of cancer after BC, so it is important to monitor this risk in patients treated with RT [17, 18].

Evidence suggests an increased risk of bone and soft tissue tumours after BC in population-based studies about second cancers, where sarcomas and angiosarcoma are the most frequent tumours associating its risk with RT [20]. In our study, the incidence of these tumours is very low ($n=3$), but we found an SMR = 10.25 of the malignant tumours of bone and articular cartilages among women diagnosed during 1985–2004. However, this could be an effect of tumour misclassification. We did not find an increased risk in bone tumours among women diagnosed during 1995–2004, either in soft tissue tumours—in either of the two periods—or in esophageal cancers. The results observed in our study suggest that the doses of RT applied in the BC were lower in the second period.

In the line of our study, several studies have noted an increased risk of developing uterine corpus tumours after a BC [16, 21]. In some studies this risk has been linked with shared reproductive factors such as nulliparity or late age at diagnosis [16], therapies, such as tamoxifen in invasive BC [22], or shared risk factors [16, 21–23]. Certain studies have shown an increased risk of developing endometrial cancer after BC regardless of oestrogen receptor or progesterone status [23], raising a concern whether common etiological factors among BC subtypes might increase the susceptibility to develop endometrial cancer [23].

Risk of ovarian cancer mortality has also been reported in several studies of second tumours after the treatment of BC [16, 19, 21, 24]. Individuals with germline mutations in cancer susceptibility genes, such as BRCA1 and BRCA2, are at high risk of developing breast and ovarian cancer [21, 24], whereas increased mortality of ovarian cancer can be explained by shared inherited susceptibility genes such as BRCA1 or BRCA2, especially in young women [24].

Leukaemia mortality showed a significant 10-year risk (SMR_{1985–2004} = 2.05). Therapy-associated secondary leukaemias might occur between 0.3 and 0.5% after anti-neoplastic therapy of solid tumours such as cancers of the breast, lung, testicles and ovaries, and sarcomas [25]. Risk of other haematological malignant tumours was found in the 1985–1994 cohort. This risk could be explained by side effects of RT [25]. In our study, we did not find a significant SMR from other types of malignant tumours (head and neck, thyroid, melanoma or others).

Significant risk for colon cancer after 10 years of BC diagnosis was also detected (SMR_{1985–2004} = 1.44). The studies about time interval to colorectal cancer since BC diagnosis note that most women develop their second malignancy between 1 and 10 years [26], therefore, evidence suggests that women diagnosed with BC before 50 years of age

should start colorectal screening 5 years earlier than the general population [26].

Non-cancer causes

In our previous study [12], we suggested that CVD and OC mortality might increase with older age at diagnosis. In the present study, the competing risk analysis showed that the probability to die from non-cancer surpassed that of cancer (except BC) among patients diagnosed in stages II–III independent of the age at the diagnosis of BC, whereas in stage I, this pattern was observed in elderly patients.

In our study, we observed a significant SMR for diabetes mellitus. Pre-existing diabetes mellitus in women with BC has been associated with a 37% increased risk for all-cause mortality and with a 17% increased risk for BC mortality and mortality of women with BC is significantly increased for diabetic patients compared with non-diabetic patients [27]. The links between diabetes and BC are explained by common risk factors (overweight/obesity, dietary errors, physical inactivity), biological changes and the impact of some anti-diabetic treatments or hormonotherapy. These studies conclude that physicians facing a diabetic patient treated for BC have a role in choosing the best anti-diabetic treatment and implementing the lifestyle modifications [27].

The slight EM from diseases of the circulatory system is the one that produces a greater increase in deaths per 10,000 patient-years since deaths from this type of diseases represent the first cause of mortality in women in the populations of Girona and Tarragona. The ED corresponding to the group “Other heart diseases” might be due to poor certification and/or coding of the cause of death. It has been determined that cardiac mortality is positively correlated with the cardiac dose–volume [28]. RT regimens used in BC treatment during 1989–2005 increased the risk of cardiovascular disease, whereas anthracycline-based chemotherapy regimens increased the risk of congestive heart failure [29]. In our study, EM was only observed among women diagnosed in 1985–1994 and after 20 years of follow-up, possibly because the irradiation doses in 1995–2004 were lower than in 1995–2004.

We found a significant SMR for diseases of the nervous system except for meningitis and Alzheimer’s disease for the 1985–1994 cohort. The real cause of death of these women is difficult to validate, but evidence suggests that chemotherapy and RT could lead to long-term side effects in brain [28].

Mortality by “Osteoporosis and pathological fracture” was only observed for the global period possibly because of the few number of deaths for this cause. On the other hand, certain percentage of these deaths has been probably caused by bone metastases and, therefore, primarily by BC.

367 Finally, we found a significant SMR for diseases of kidney
368 and ureter in the first decade that was not statistically
369 significant in the second decade. It has been hypothesised
370 that chronic kidney disease could be a risk factor for mortality
371 in patients with BC, but in a recent study, this disease
372 does not appear to have a significant impact on outcomes in
373 these patients [30]. In our study, we reviewed the clinical
374 records of 50% of the death certificates as well as all registry
375 records of diseases of kidney and ureter, and we found that
376 a non-negligible proportion of cases suffered from chronic
377 renal failure before the diagnosis of BC.

378 Strengths and limitations

379 The main strengths of this study are: (a) it is population-
380 based, and this allows obtaining unbiased results, and (b)
381 it has long follow-up. The main limitation lies in the potentially
382 limited quality of the data since death certificates
383 might present quality problems of various kinds [12, 19].
384 An effort was made for minimising that issue by determining
385 the exact type of cancer among deceased patients with
386 poorly defined tumours. We noted two other limitations: (a)
387 the design of this study has not allowed to evaluate the risk
388 of death by contralateral BC and (b) the treatment received
389 by each patient could not be retrieved from registry records
390 [12], therefore, it was not possible to study the association of
391 the different types of treatment with the causes of mortality
392 in the cohort.

393 Conclusions

394 In our study, at 10 and 20 years after the diagnosis of BC,
395 women who did not die from BC had a 20% excess risk of
396 dying from other causes than BC. This excess risk of dying
397 from these causes must be considered clinically for at least
398 20 years after the diagnosis of BC.

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404 Compliance with ethical standards

405 **Conflict of interest** The funders had no role in the design of the study,
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408 The authors state that there are no conflicts of interest concerning this
409 study.

410 **Research involving human participants and/or animals** This article
411 does not contain any studies with human participants or animals per-
412 formed by any of the authors.

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