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Determinants of quality of life among long-term breast cancer survivors

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Abstract
Purpose To identify the impact of clinical and socio-economic determinants on quality of life (QoL) among breast cancer (BC) survivors 5 years after diagnosis.
Methods A cross-sectional survey was conducted in women diagnosed in 2007 for primary invasive non-metastatic BC and identified through the Côte d'Or BC registry. QoL was assessed with the Medical Outcomes Study 12-item Short Form Health Survey (SF-12), the European Organization for Research and Treatment of Cancer Quality of Life (EORTC-QLQ-C30) and the breast cancer (EORTC-QLQ-BR23) questionnaires. Social support was assessed with Sarason's social support questionnaire, and deprivation was assessed by the EPICES questionnaire. Clinical variables were collected through the registry database. Determinants of QoL were identified using multivariable mixed model analysis for each SF-12 dimension. A sensitivity analysis was conducted with multiple imputations on missing data.
Results Overall, 188 patients on 319 patients (59 %) invited to participate to the survey completed the questionnaires. Five years after breast cancer diagnosis, the disease stages at diagnosis, as well as the treatment received, were not determinants of QoL. Only the age at diagnosis and comorbidities were found to be determinants of QoL.
Conclusions Five years after BC diagnosis, disease severity and the treatment received did not affect QoL.

Keywords Breast cancer · Long-term survivor · Determinant of quality of life · Social support · Socio-economics factors

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Introduction

Breast cancer (BC) is the most prevalent malignancy among women in France. Its incidence has doubled during the past 25 years [1]. Survival at 5 years after the initial diagnosis is currently 85 % [2]. Quality of life (QoL) is an important issue in BC because early diagnosis and effective methods of treatments have led to an increase in the number of long-term survivors [3, 4].

During the past decade, QoL issues pertaining to BC have been studied extensively [5–13]. Many determinants of quality of life have been identified. These include disease stage at diagnosis [10], patient's age at diagnosis [5, 7–10, 12], the treatment received [8–10, 12], comorbidity [9, 10, 12], social support [10–12], time since diagnosis

[10, 13] and socio-economic status [10–12]. However, because QoL is a subjective concept, evaluations may vary from one culture or country to another [12].

To date, few studies have been conducted in the French population, assessing the determinants of QoL in breast cancer survivors particularly in women with primary invasive non-metastatic breast cancer which represents the most common subtype of breast cancer. Using data of three French population-based cancer registries of Bas-Rhin (north-eastern France), Calvados (north-western France) and Doubs (eastern France), Klein et al. showed that 5 years after diagnosis, QoL in BC survivors was worse than that in the general population. In contrast, 15 years after diagnosis, QoL outcomes in BC survivors were similar to that in the general population [13]. Consequently, we decided to perform a population-based study on patients registered in the French regional BC registry of Côte d'Or in 2007 to identify the clinical and socio-economic determinants of QoL among BC survivors 5 years after the diagnosis. The secondary objective of this study was to describe the QoL of this population using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30 (EORTC-QLQ-C30) and its BC module Breast 23 (EORTC-QLQ-BR-23) [14, 15].

Materials and methods

Patients

A cross-sectional survey was conducted in long-term BC survivors. All women living in Côte d'Or and newly diagnosed with a primary invasive non-metastatic BC in 2007 were identified through the French regional BC registry of Côte d'Or. This registry is the only one in France that focuses on breast and gynaecological cancers. Women who died before March 2013 were excluded. In March 2013, participants were mailed a packet that included the series of questionnaires and an information letter. The letter presented the aim of the study and the legal information and asked them to participate in the study. The study was approved by the French National Data Protection Authority (CNIL).

Studied variables and endpoints

QoL, social support and social-economic status were assessed using a series of questionnaires. These questionnaires are validated self-administered instruments translated and validated in French.

The Medical Outcomes Study 12-item Short Form Health Survey (SF-12) is a validated tool to assess general quality of life (QoL) [16, 17]. The SF-12 incorporates 12 questions that generate eight scales: physical functioning (PF), role physical (RP), role emotional (RE), bodily pain (BP), social functioning (SF), mental health (MH), vitality (VI) and general health perception (GH). All of the scales were scored according to the standard scoring method described in the SF-12 scoring manual [18]. For missing items, we used the following rules:

- For two-item dimensions (physical functioning, role physical, role emotional, mental health), if one item was answered, we used the answered item and ignored missing values in the calculations.
- If both items were missing, the score was set to missing.
- For single-item dimensions (bodily pain, general health, vitality, social functioning), if the item was missing, the score was set to missing.

Each score ranges from 0 to 100 with higher scores representing a better level of QoL. Two additional scales, the physical component summary (PCS) and mental component summary (MCS), were computed from the eight scales according to the SF-12 scoring manual.

The EORTC-QLQ-C30 and its BC module Breast 23 (BR-23) are validated tools to assess QoL in cancer and more specifically BC [14].The EORTC-QLQ-C30 contains five functional scales (physical, role, cognitive, emotional and social), global health status, financial difficulties and eight symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation and diarrhoea). The BC module comprises 23 questions that generate four functional scales (body image, sexual functioning, sexual enjoyment and future perspectives) and four symptom scales (systemic therapy side effects, breast symptoms, arm symptoms and upset by hair loss).

Scores were generated if at least half of the items from the scale had been answered. In accordance with the EORTC-QLQ-C30 scoring guidelines [15], we used the following rules:

- When at least half of the items from the scale were answered, we used all the items that were completed, and we ignored any items with missing values when making the calculations.
- When more than half of the items from the scale were missing, the score was set to missing.
- For single-item measurements, when the item was missing, the score was set to missing.

These scores vary from 0 (worst) to 100 (best) for the functional and global health parameters and from 0 (best) to 100 (worst) for symptom parameters.

Perceived social support was assessed with Sarason's Social Support Questionnaire (SSQ) [19]. SSQ contains six

items measuring two scales: availability and satisfaction with the perceived social support. Each item represents a situation in which the patient should need social support, they were asked to count the number of persons providing support and to evaluate satisfaction with the support provided. The scales were scored according to Sarason's recommendations. Satisfaction scores range from 6 to 36 and availability scores range from 0 to 54. Each point of the social support availability score represents one person providing support for one item. A higher social support satisfaction score represents better perceived social support.

Socio-economic information was assessed with the "Evaluation de la précarité et des inégalités de santé pour les Centres d'Examen de Santé" (EPICES) questionnaire [20]. The EPICES questionnaire contains 11 items with two responses (yes/no) and generates one deprivation scale. The deprivation scale was scored according to the EPICES guidelines. These scores vary from 0 to 100. A threshold of 30 determines the level of deprivation with higher deprivation for a score >30.

Additionally, information was collected about patients' weight, height and education status and disease recurrence. Patients and tumour characteristics, such as age at diagnosis, Charlson's comorbidity score, cancer stage, histological Scarff Bloom and Richardson (SBR) grade, molecular subtypes (luminal or basal) and HER2 status, as well as treatments, were extracted from the Côte d'Or BC registry database. The tumour stage was categorized according to American Joint Committee on Cancer (AJCC) stage of the sixth edition TNM stage grouping [21].

Statistical analysis

The characteristics of responders and non-responders were compared using Pearson's chi-square test for categorical variables and Mann–Whitney test for age at diagnosis as a continuous variable.

The characteristics of the studied population were described. Qualitative variables were given as percentages, while continuous variables were given as means, standard deviations, medians and ranges. Age at diagnosis, body mass index (BMI) and EPICES deprivation score were described as categorical variables. The age at diagnosis cut-off was set at 65 years (younger and older). BMI cut-off was set at 25 (≤25: low and normal weight, >25: overweight). The EPICES deprivation score allowed patients to be classified as deprived or not deprived (≤30 and >30). The social support availability and satisfaction scores were categorized according to their medians. The numbers and percentages of missing scores were also provided.

A mixed model analysis was used to assess the association between each variable and each score. All variables with a P value <0.05 from univariate analyses were eligible for multivariate analyses. Correlations were tested for eligible variables. Analyses were adjusted for age and radiotherapy which were different between responders and non-responders. The results are reported as multivariable analysis coefficients, standard deviations and P values. As SF-12 QoL scores cannot be considered independent of each other, Bonferroni's correction was used to adjust the α-risk to the eight multivariable models. The significance limit was then set at 0.00625 for multivariable models.

To access the impact of the missing data on the determinants of QoL outcomes, a sensitivity analysis was conducted with multiple imputation on variables which may impact QoL [22, 23]. Multiple imputation was conducted with the fully conditional specification method and the predictive mean matching methods. Briefly, for each variable with missing values, a conditional distribution was estimated with observed cases and values were imputed randomly from a set of observed values that were closest to the predicted value for the missing value from the distribution [24].

The Statistical Analysis Software (version 9.4; SAS Institute Inc., Cary, NC) was used to analyse data.

Results

Recruitment and response

Of the 493 BC cases diagnosed in 2007, 68 were in situ cancer, 8 patients were male BC, 6 cases were concomitant BC, 34 cases were primary metastatic BC, and one case was sarcoma. Finally, 376 women were eligible for the study. Among these, 52 had died before the beginning of the study, three were lost to follow-up, and two refused to participate in any study.

The series of questionnaires was mailed to 319 patients. Of these, 188 (59 %) completed the questionnaires. For this population, the median follow-up was 70 months (range 64–78 months). The comparison of the areas of residence, as well as clinical and pathological features of responders and non-responders, is presented in Table 1. Non-responders were older than responders (mean age at diagnosis was 62.96 vs. 58.4 years) ($P = 0.004$), and more responders than non-responders had received radiotherapy ($P = 0.0091$). There were no differences between responders and non-responders for other clinical and pathological variables.

Table 1 Comparison of clinical and pathological features of patients who completed and those who did not complete the questionnaire

Variables	Responders		Non-responders		*P* value
	N = 188	%	*N* = 131	%	
Age at diagnosis	188		131		0.004[a]
Median (minimum–maximum)	59.50 (32–85)		64.00 (32–91)		
Mean (SD)	58.40 (11.86)		62.96 (13.58)		
Age					0.0025
<65	128	68.09	67	51.15	
≥65	60	31.91	64	48.85	
Missing	0		0		
Area of residence					0.7134
Urban	128	68.09	92	70.23	
Rural	60	31.91	39	29.77	
Missing	0		0		
AJCC stage					0.1682
Stage I	103	55.38	60	47.24	
Stage II/III	83	44.62	67	52.76	
Missing	2		4		
SBR grade					0.9030
Grade 1	60	32.43	42	33.07	
Grade 2 + 3	125	67.57	85	66.93	
Missing	3		4		
Molecular subtype					0.0932
Luminal	157	83.96	117	90.7	
Basal	30	16.04	12	9.3	
Missing	1		2		
HER2 status					0.4922
Negative	159	85.95	116	89.23	
Positive	26	14.05	14	10.77	
Missing	3		1		
Relapse					0.8221
No	172	92.97	122	93.85	
Yes	13	7.03	8	6.15	
Missing	3		1		
Charlson score					0.2498
= 0	144	77.84	87	69.6	
= 1	20	10.81	18	14.40	
≥2	21	11.35	20	16.00	
Missing	3		6		
Surgery: mastectomy					0.2812
No	147	78.61	93	73.23	
Yes	40	21.39	34	26.77	
Missing	1		4		
Chemotherapy					0.2462
No	102	54.55	78	61.42	
Yes	85	45.45	49	38.58	
Missing	1		4		
Trastuzumab					0.4009
No	171	90.96	123	93.89	
Yes	17	9.04	8	6.11	

Table 1 continued

Variables	Responders		Non-responders		*P* value
	N = 188	%	*N* = 131	%	
Missing	0		0		
Radiotherapy					0.0091
No	16	8.56	24	19.05	
Yes	171	91.44	102	80.95	
Missing	1		5		
Hormone therapy					0.7092
No	59	31.55	37	29.37	
Yes	128	68.45	89	70.63	
Missing	1		5		

[a] Mann–Whitney test

Socio-demographic and clinical characteristics of the studied population

Clinical and socio-demographic features of the studied population are presented in Tables 1 and 2. In summary, the main characteristics of the population were: age younger than 65 (68.09 %), an educational level less than A level (52.13 %), living in urban areas (68.09 %), BMI > 25 (50.53 %) and the absence of concomitant comorbidities at diagnosis (77.84 %). The EPICES deprivation score median was 16.56, and only 13 patients (6.91 %) relapsed. Tumours were mainly AJCC stage I (55.38 %), SBR grade II/III (67.57 %), luminal molecular subtype (83.96 %) and HER2 negative (85.95 %). Forty participants (21.39 %) had undergone mastectomy, 85 (45.45 %) had received chemotherapy, 17 (9.04 %) had received Trastuzumab, 128 (68.45 %) had received hormone therapy, and 171 (91.44 %) had received radiotherapy.

Table 2 Socio-demographic features of the studied population

Variables	*N* = 188	%
Education level		
Less than A level	98	52.13
A level or more	80	42.55
Missing	10	5.32
Area of residence		
Urban	128	68.09
Rural	60	31.91
Missing	0	0.00
EPICES precarity score		
≤30	122	64.89
>30	47	25.00
Missing	19	10.11
BMI 5 years after diagnosis		
≤25	88	46.81
>25	95	50.53
Missing	5	2.66

Social support and quality-of-life features of the studied population

Social support and QoL features of the studied population are presented in Table 3.

The median social support availability score was 13, and the median social support satisfaction score was 30.

Mean of SF-12 QoL scores was all above 60, except for role physical (mean score = 59.97) and vitality (mean score = 48.77). There were less than 10 % of missing values for all SF-12 scales. Mean QLQ-30 and BR-23 functional scores were above 60, except for the future perspective scale (mean = 57.73), sexual functioning scale (mean = 16.47) and sexual enjoyment scale (mean = 53.8). Most symptoms scores were below 30, except for the fatigue score (mean = 31.85), insomnia score (mean = 38.92) and upset by hair loss score (mean = 43.48). The mean global health status was 65.29. There were less than 10 % of missing values for all QLQ-C30 and QLQ-BR23 scales, except for the sexual enjoyment scale (69.68 %) and the upset by hair loss scale (75.53 %).

Quality-of-life determinants

The univariable analysis outcomes are presented in Table 4. Variables with $P < 0.05$ were selected as candidate variables for the multivariable models. Analyses were adjusted on age and radiotherapy which were different between responders and non-responders.

The significant results of multivariable analyses are presented in Table 5. Age at diagnosis was found to be a determinant of QoL for physical functioning (PF;

Table 3 Social support and quality-of-life features of the studied population

Variables	$N = 188$	Mean (SD)	Median (min–max)
Social support questionnaire SSQ6			
Social support availability	161	15.22 (9.91)	13.00 (30–54)
Social support satisfaction	146	28.23 (7.05)	30 (6–36)
Quality-of-life questionnaires SF-12			
General health	188	61.38 (22.06)	60 (0–100)
Physical functioning	188	69.55 (32.19)	75 (0–100)
Role physical	188	59.97 (28.06)	56.25 (0–100)
Role emotional	186	61.36 (25.76)	62.50 (0–100)
Bodily pain	187	68.45 (27.20)	75 (0–100)
Mental health	187	63.84 (20.98)	62.50 (0–100)
Vitality	183	48.77 (25.58)	50 (0–100)
Social functioning	187	71.39 (27.01)	75 (0–100)
Composite scores			
PCS	182	45.62 (10.46)	47.61 (5.98–64.34)
MCS	182	44.07 (10.65)	45.23 (14.07–67.58)
EORTC-QLQ-C30			
Global health	188	65.29 (19.06)	66.67 (0–100)
Physical functioning	186	81.41 (19.64)	86.67 (20–100)
Role functioning	187	80.03 (27.04)	83.33 (0–100)
Emotional functioning	185	73.20 (26.10)	83.33 (0–100)
Cognitive functioning	187	81.37 (23.42)	83.33 (0–100)
Social functioning	187	84.67 (24.31)	100 (0–100)
Fatigue	184	31.85 (24.86)	33.33 (0–100)
Nausea and vomiting	185	4.32 (12.26)	0 (0–66.67)
Pain	187	25.22 (26.68)	16.67 (0–100)
Dyspnoea	181	22.47 (26.96)	0 (0–100)
Insomnia	185	38.92 (35.42)	33.33 (0–100)
Appetite loss	185	7.39 (17.70)	0 (0–100)
Constipation	186	17.02 (27.34)	0 (0–100)
Diarrhoea	184	9.24 (18.90)	0 (0–100)
Financial difficulties	184	9.42 (24.55)	0 (0–100)
EORTC-QLQ-BR23			
Body image	181	72.94 (28.73)	83.33 (0–100)
Sexual functioning	169	16.47 (21.21)	0 (0–83.33)
Sexual enjoyment[a]	57	53.80 (25.78)	66.67 (0–100)
Future perspective	179	57.73 (33.44)	66.67 (0–100)
Systemic therapy side effects	184	17.33 (16.06)	14.28 (0–100)
Breast symptoms	187	16.84 (19.50)	8.33 (0–100)
Arm symptoms	186	18.34 (21.71)	11.11 (0–100)
Upset by hair loss[b]	46	43.48 (37.76)	33.33 (0–100)

[a] Sexual enjoyment score is not generated if participants answered they had no sexual activity (item 15)

[b] Upset by hair loss score is not generated if participants answered they had no hair loss (item 4)

$P < 0.0001$) and role physical (RP; $P = 0.0034$). Older subjects had a worse QoL for these dimensions.

The Charlson comorbidity score was found to be a determinant of QoL for PF ($P = 0.0003$) and general health (GH) ($P = 0.0027$). Subjects with two or more comorbidities had a worse QoL than did subjects with no comorbidity on both scales.

Moreover, there was an interaction between the deprivation and the stage at diagnosis of the breast cancer. Deprived patients with early stage at diagnosis (AJCC

Table 4 Selection of variables following univariable analysis (based on *P* values)

Variables	SF-12 dimensions							
	PF	RP	BP	GH	VT	SF	RE	MH
Education level	<0.0001[a]	0.0057[a]	0.0038[a]	0.0139[a]	0.1200	0.5467	0.0133[a]	0.1081
BMI	0.0271[a]	0.0018[a]	0.0061[a]	0.1014	0.0214[a]	0.8261	0.2334	0.7021
Area of residence	0.8008	0.8966	0.2766	0.8211	0.8592	0.7148	0.7835	0.9026
Charlson	<0.0001[a]	0.0199[a]	0.0163[a]	0.0026[a]	0.0341[a]	0.0204[a]	0.0118[a]	0.8364
Ajcc stage	0.7648	0.7436	0.8813	0.6571	0.3342	0.1188	0.1426	0.0281[a]
SBR grade	0.2886	0.3609	0.0532	0.1238	0.0594	0.3188	0.7538	0.9115
Molecular subtypes	0.7096	0.6427	0.7026	0.2742	0.9455	0.5038	0.7551	0.2401
HER2 status	0.3090	0.8973	0.7284	0.2610	0.9339	0.6195	0.3249	0.7569
Relapse	0.6608	0.0381[a]	0.5049	0.0511	0.9211	0.5649	0.4185	0.2741
Mastectomy	0.4063	0.0441[a]	0.8384	0.7642	0.8407	0.8721	0.5530	0.7609
Chemotherapy	0.6421	0.7126	0.0605	0.8415	0.6059	0.2892	0.3125	0.6764
Trastuzumab	0.0418[a]	0.0991	0.1956	0.9679	0.3014	0.7170	0.7484	0.5276
Hormone therapy	0.6923	0.2637	0.7268	0.9397	0.8542	0.3596	0.8338	0.3178
Epices score	<0.0001[a]	0.0079[a]	0.0020[a]	0.0631	0.0052[a]	0.0716	0.0007[a]	0.0008[a]
Social support availability	0.0157[a]	0.0358[a]	0.0206[a]	0.5972	0.0215[a]	0.1098	0.0048[a]	0.0175[a]
Social support satisfaction	0.5326	0.8752	0.0789	0.6633	0.0678	0.0211[a]	0.1350	0.0310[a]

PF physical functioning, *RP* role physical, *BP* bodily pain, *GH* general health, *VT* vitality, *SF* social functioning, *RE* role emotional, *MH* mental health

[a] Variable selected as candidate variable for multivariable models

Table 5 Determinants of quality of life in the studied population

SF-12 dimensions	Variables	Coefficient	SD	*P* value[a]
Physical functioning	Age at diagnosis			<0.0001
	<65	Reference		
	≥65	−26.47	5.34	
	Charlson score at diagnosis			0.0003[b]
	0	Reference		
	1	9.67	8.1	0.2346
	≥2	−29.84	7.63	0.0001
Role physical	Age at diagnosis			0.0034
	<65	Reference		
	≥65	−15.68	5.25	
General health	Charlson score at diagnosis			0.0027
	0	Reference		
	1	−5.41	5.12	0.2921
	≥2	−17.42	5.03	0.0007
Mental health	Interaction between EPICES precarity score × AJCC stage			<0.0001[b]
	AJCC stage I × Epices ≤ 30	Reference		
	AJCC stage I × Epices > 30	−27.56	5.92	<0.0001
	AJCC II/III × Epices ≤ 30	1.97	4.19	0.6388
	AJCC II/III × Epices > 30	4.11	5.21	0.4322

Analyses are adjusted on age and radiotherapy which are different between responders and non-responders

[a] The significance limit is adjusted with Bonferroni's correction and is set at 0.00625

[b] Global *P* value of the variable

stage I) had worse QoL than non-deprived patients early stage at diagnosis ($P < 0.0001$). However, there were no differences in terms of QoL between deprived or non-deprived patients with advanced stage (AJCC stages II/III) and non-deprived patients with early stage.

Sensitivity analysis

The significant results of multivariable analyses on the imputed data set are presented in Table 6. Age at diagnosis was found to be a determinant of QoL for PF ($P < 0.0001$) and RP ($P = 0.0052$). Older subjects had a worse QoL for these two dimensions.

The Charlson comorbidity score was found to be a determinant of QoL for PF and GH. Subjects with two or more comorbidities had a worse QoL than did subjects with no comorbidity on both scales ($P = 0.0004$ for PF, $P = 0.0044$ for GH).

Discussion

Early diagnosis and effective methods of treatments for BC have led to an increase in the number of long-term survivors. As Klein et al. [13] found that QoL in French BC survivors was worse than that in the general population 5 years after diagnosis, there was a need to investigate the determinants of QoL in this population. A cross-sectional survey was thus conducted in women living in Côte d'Or and diagnosed in 2007 for a primary invasive non-metastatic BC. Patients were identified through the French regional BC registry of Côte d'Or. This registry provides exhaustive population-based data and is the only one in France to focus on BC.

One hundred eighty-eight patients (59 %) participated in the survey. This response rate can be explained by the length of the series of questionnaires, the age of the patients and the good health of the studied population. Indeed, some patients declared that they did not feel concerned by this study about cancer survivors because they felt cured of their BC. Moreover, non-responders were older than responders. This result is found in many cross-sectional studies that assess QoL in older populations [7, 13]. One surprising result was that the proportion of responders who had received radiotherapy was significantly greater than the proportion of non-responders who had received radiotherapy. This result was not found with more aggressive treatments such as chemotherapy or mastectomy.

Overall, the QoL questionnaires had a good rate of completion in responders, except for some QLQ-C30 and QLQ-BR23 scales (sexual functioning, sexual enjoyment and upset by hair loss). The sexual functioning scale is usually known to have worse response rates than the other scales. The sexual enjoyment and upset by hair loss scores were not scaled if the patient had no sexual activity and no hair loss, respectively.

Results of this study showed that overall the QoL scores in responders were good. These results were found with the SF12 generic questionnaire as well as the QLQ-C30 and QLQ-BR23 cancer-specific questionnaires with most SF-12 QoL scores and QLQ-C30 and QLQ-BR23 functional scores above 60 and most QLQ-C30 and QLQ-BR23 symptoms scores below 30. Indeed in the systematic

Table 6 Analysis on imputed data set: determinants of quality of life in the studied population

SF-12 dimensions	Variables	Coefficient	SD	*P* value
Physical functioning	Age at diagnosis			<0.0001
	<65	Reference		
	≥65	−20.59	4.43	
	Charlson score at diagnosis			
	0	reference		
	1	8.88	6.57	0.1766
	≥2	−23.07	6.45	0.0004
Role physical	Age at diagnosis			
	<65			
	≥65	−11.8	4.22	0.0052
General health	Charlson score at diagnosis			
	0			
	1	−4.04	5.05	0.4242
	≥2	−14.14	4.97	0.0044

Analyses are adjusted on age and radiotherapy which are different between responders and non-responders

[a] The significance limit is adjusted with Bonferroni's correction and is set at 0.00625

review made by Mols et al. [10], the authors reported that long-term survivors of breast cancer experienced good overall QoL in most studies. Comparison of our data to those reported by Klein et al. [13] on breast cancer survivors randomly selected from three French population-based cancer registries of Bas-Rhin (north-eastern France), Calvados (north-western France) and Doubs (eastern France) matched to healthy controls stratified for age and place of residence showed results similar to those of breast cancer survivors 5 years after diagnosis but lower QoL in comparison with controls. One explanation for this good QoL 5 years after BC may be that, at this time, treatment effects are attenuated, and in the absence of relapse, survivors generally have a good QoL. Some would also argue that our population was selected in that responders may be healthier than non-responders. Although we cannot reject this hypothesis, comparison of the clinical and pathological features of responders and non-responders showed that several factors that can affect global health, such as the presence of comorbidities, were no different between responders and non-responders. As found by Ganz et al. [25], disease-free breast cancer survivors report high levels of QoL between 5 and 10 years after diagnosis.

One important finding was that clinical variables related to BC, such as the AJCC stage at diagnosis, the SBR grade at diagnosis, molecular subtypes and treatment received (mastectomy, chemotherapy, radiotherapy, trastuzumab and hormone therapy) did not have a significant relationship with any SF-12 scales. This result suggests that 5 years after diagnosis, QoL is not affected by disease severity at diagnosis and the treatment received. Lu et al. [12] showed similar results in a study which aimed to evaluate changes in QoL and identify medical and socio-demographic predictors of QoL among 2232 Chinese BC survivors 3 years after diagnosis. Even if individuals with relapsed disease might be assumed to have worse QoL, in this study, we failed to show a significant relationship between the disease relapse with any SF-12 scales. One explanation could be a lack of power; only 7 % of the responders had a relapsed disease.

In this study, patients' characteristics such as the BMI, the area of residence and the education level did not have a significant relationship with any SF-12 scales. Lu et al. [12] reported similar results. Indeed, they did not find BMI to be a predictor of QoL, but reported that education level was a predictor of QoL. Studies on American populations [26, 27] reported that the education level was not a predictor of QoL. However, this difference in the relationship between QoL and education level can be explained by cultural and healthcare system differences among countries.

Age at diagnosis and comorbidities were both found to be determinants of QoL for PF, RP and comorbidities alone for GH. Ultimately, these results are not exclusive to a population of BC survivors, as the same factors are determinant of the QoL in the general population. Indeed, age is found to be a determinant of QoL in the general population: older people usually report a worse physical functioning than do younger people. In the same way, the population with several comorbidities had a worse QoL than the population with no comorbidities [28]. Then 5 years after the disease, QoL for BC survivors seems to be affected by the same factors as those that affect the general population.

There were some differences between the results obtained from analyses of real dataset and those from analyses following the imputation of missing data. Indeed, results obtained from analyses of real dataset showed a significant interaction between the deprivation and the stage at diagnosis of the BC. Deprived patients with early stage at diagnosis (AJCC stage I) had worse QoL than non-deprived patients with early stage at diagnosis ($P < 0.0001$). However, there were no differences in terms of QoL between deprived or non-deprived patients with advanced stage (AJCC stages II/III) and non-deprived patients with early stage. This interaction was no longer significant after multiple imputations. These results highlight the interest of imputation methods when incomplete datasets are used. Indeed, there was a high rate of incomplete questionnaires for the SSQ (14 % for the availability score, 22 % for the satisfaction score) and EPICES questionnaires (10 %). The main reasons for the missing items were that patients did not understand how to complete the questionnaires and some patients declared that they did not feel concerned for some questions. In the real dataset analysis, SSQ scores and EPICES scores were generated only if all the items of the questionnaire were answered. Because of the high rate of incomplete questionnaires for SSQ and EPICES, this method generated a considerable bias in the results. Multiple imputations made it possible to correct for this bias and to provide more accurate results.

In conclusion, the results of this study showed that disease stage, being treated for BC, the education level and deprivation were not determinants of QoL among BC survivors 5 years after diagnosis. The major determinants of QoL in BC survivors 5 years after diagnosis were age and comorbidities. Since age and comorbidities are also determinants of QoL in the general population [28, 29], we can assume that 5 years after diagnosis, BC survivors are almost cured. Future studies should focus on social support, socio-economic factors and social reinsertion.

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Compliance with ethical standards

Conflict of interest None.

Ethical approval Côte d'Or breast and gynaecological cancer registry has agreement of "Commission Nationale de l'Informatique et des Libertés (CNIL)" DR-2012-038 for collecting data, recording data and carrying out studies with these data.

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