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Increased risk of contralateral breast cancers among overweight and obese women: a time-dependent association

Bilal Majed · Adrien Dozol · Laureen Ribassin-Majed · Kamel Senouci · Bernard Asselain

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Abstract Breast cancer (BC) survivors are at increased risk of second cancers. Obesity is commonly recognized as a risk factor of BC in postmenopausal period and a prognosis factor in BC regardless of menopausal status. Our aim was to study whether overweight BC survivors were at increased risk of contralateral BC (CBC). Our population was a large cohort of women followed since a first BC without distant spread and/or synchronous CBC. Body mass index (BMI) was assessed at diagnosis time. Binary codings of BMI were used to oppose overweight and obese patients to the others. Survival analyses were used including Cox models. Assumed hypothesis of proportional hazards was explored using graphical methods, Schoenfeld residuals and time-dependant covariates. In case of non-proportional hazards, survival models were computed over time periods. Over 15,000 patients were included in our study. Incidence of CBC was 8.8 (8.3–9.3)/1000 person-years and increased during follow-up. A significant time-dependent association between overweight and CBC was observed. After 10 years of follow-up, we found a significant increased hazard of CBC among patients with a BMI above 25 kg/m^2: the adjusted hazard ratio was 1.50(1.21–1.86), $P = 0.001$. After 10 years of follow-up, our study found a poorer prognosis among overweight BC survivors regarding CBC events. While benefits from diet habits and weight control may be expected during the long-term follow-up, they have yet to be established using randomized clinical trials.

Keywords Contralateral breast cancer · Non-proportional hazards Body mass index · Overweight · Time-dependent covariate · Breast cancer prognosis

Abbreviations

BC	Breast cancer
BMI	Body mass index
CBC	Contralateral breast cancer
HR	Hazard ratio

Introduction

Numerous studies and literature reviews support the assumption of a poorer prognosis for overweight and obese women at the time of breast cancer (BC) diagnosis [1, 2]. Therefore, diet improvement and physical exercise are recommended among BC patients [3]. Furthermore, an observational study found a reduction of mortality among women having significant vegetable-fruit intake and physical activity [4]. However, recent clinical trials, testing whether intervention regarding diet habits could improve BC outcomes, had mixed and conflicting results [5]. Nevertheless, in these trials, the follow-up duration was limited

B. Majed (✉) · B. Asselain
Biostatistics Department, Curie Institute, 26 Rue d'Ulm, 75005 Paris, France
e-mail: bmajed@free.fr

B. Majed · K. Senouci
Arras Hospital, Epidemiology and Clinical Research Unit, SAMU/SMUR/SU/USC, Boulevard Besnier, 62000 Arras, France

A. Dozol
Groupe Hospitalier Lariboisière-Fernand Widal, Assistance Publique-Hôpitaux de Paris, Service de Santé Publique et économie de la santé, Paris, France

L. Ribassin-Majed
Université Paris Descartes, Paris V, MAP 5, Paris, France

to less than 10 years. Modification of diet and exercise habits may have an effect on prognosis on a longer term. In addition, prognosis improvement in relation to lifestyle habits may depend on the outcome of interest.

In BC prognosis studies, the main investigated endpoints in published literature are overall survival and disease free survival that includes distant, regional, and local relapses. Contralateral BC (CBC) occurrences have seldom been explored as a specific outcome among women having previously had a first BC. BC patients are recognized at an increased risk of second primary cancers including CBC, when compared to the general population [6, 7]. The cumulative incidence of CBC occurrences has been estimated to be of 4% at 5 years of follow-up [8] and more than 10% after 10 years of follow-up [7, 9]. A cumulative hazard of 20% has been reported after a follow-up of 20 years [10].

Obesity has been previously associated with an increased risk of CBC [11]; however, evidence regarding this association remains sparse. After a first occurrence of BC, a CBC event is usually considered as a second primary cancer [8].

Previously, we analyzed and confirmed the prognosis value of obesity and overweight in women BC [12]. Different end points were explored including CBC occurrences. The association between body mass index (BMI) and CBC occurrences was not statistically significant; however, descriptive analysis suggested an increase of CBC events among patients with high values of BMI on the long-term follow-up.

Whilst BC patients are at increased risk of CBC, obesity represents a reliable BC risk factor in the post-menopausal period [13]. We hypothesized that being overweight at the time of a first BC diagnosis, may represent a risk factor for CBC during the follow-up. We also sought for a long-term association assuming a time-dependent relationship. During the follow-up, aging leads to an increase of women with a post-menopausal status. In addition, aging and BC treatment are also known to be associated with weight gain [14–16].

In the presence of an increase of BC survivors [17], of an increased CBC risk among BC patients [18] and of a worldwide obesity epidemic [19], we investigated a potential association between BMI and CBC events. Evolution of CBC hazard during the follow-up was assessed. Common explanatory factors of CBC risk were also explored.

Materials and methods

Material

The Curie Institute is a French Institute of Cancer Research and Treatment. Characteristics of recruited patients for treatment were available in a large and regularly updated data-base. Thus, we constituted a large cohort of women treated and followed since a first unilateral invasive non-metastatic BC. Period of recruitment extended from January 1981 to December 1999. Patients with synchronous CBC, defined by the occurrence of a CBC within the first 6 months of follow-up, were excluded. The aim of our study was to investigate the risk of metachronous CBC.

Weight and height were assessed at diagnosis time. Hence, patients' BMI was computed and used to define overweight and obesity, according to World health organization recommendations [20]. Two thresholds were used to define binary codings of BMI. The first coding grouped overweight and obese women using 25 kg/m^2 as a cut-off. The second coding individualized obese patients using 30 kg/m^2 as a cut-off. Patients with unavailable data regarding height or weight were excluded. They represented less than 15% of the initial eligible population.

Methods

Descriptive and univariate analysis

An estimation of CBC incidence, using the actuarial survival method, was performed to assess the evolution of CBC hazard during follow-up [21]. A Poisson regression was used to test a significant increase of incidence during follow-up. Cumulative hazard rates of CBC, using the Nelson-Aalen estimator, were also computed [22].

Documented risk factors for CBC [6, 18] such as lobular histology of the first BC, age, family history of BC, method of treatment (chemotherapy, hormonotherapy) were investigated in our population. Association between BMI and the hazard of CBC was explored, using independently the two binary codings of BMI cited above. We computed Kaplan–Meier survival curves, log-rank tests and estimation of hazard ratios (HR) using a semi-parametric survival model (Cox model) assuming proportional hazards [22].

Testing the non-proportional hazards assumption

Different strategies are proposed to verify the proportional hazard hypothesis and to handle a violation of the proportional hazard assumption when a Cox model is used [22].

A crude method is the graphical representation of survival curves to assess the assumption of proportional hazards. It can be used with variables with a limited number of categories. A complementary reliable tool to consider non-proportional hazards consists in testing the relevance of a time-dependent coefficient in the Cox model. In the usual semi-parametric proportional survival model, the hazard at

time t is modeled as: $\lambda(t, X) = \lambda_0(t) \exp\{\beta' X\}$, where $\lambda_0(t)$ is an unspecified function of time (t), β a vector of coefficients assumed constant in time, and X the matrix of covariates. Whilst a time-dependent covariate is considered, the model becomes: $\lambda(t, X) = \lambda_0(t) \exp\{\beta'(t) X\}$, where β vary according to time (t) or a function of time. We employed a logarithmic transformation of time (as a function of time) when testing proportional hazards with a time-dependent covariate. Finally, Therneau and Grumbsch [22] suggest the use of a test for non-proportionality and to assess the variation over time of a Cox model coefficient using scaled Schoenfeld residuals.

Consequently, we investigated a possible variation during follow-up of the association between BMI and CBC events using the methods cited above.

Handling an association between BMI and CBC risk in presence of non-proportional hazards

In case of non-proportional hazards, we partitioned the time axis. To this end, we defined time periods using the shape of time-dependent hazards. In each time period, common proportional HR, opposing heavier patients to others, were computed. Proportional hazards assumption was thereafter verified using Schoenfeld residuals' test.

Multivariate adjusted analyses were performed using as covariates classical CBC risk factors. We also used patients and/or tumor characteristics significantly associated to CBC events in our population.

Since CBC is considered as second primary BCs, CBC events were analyzed independently from other BC prognosis events.

R-software, including the "survival" package, was used for the data analysis.

Results

Characteristics of our population ($N = 15{,}166$) at the diagnosis time of the first BC are summarized in Table 1. The mean age was 54 years. Proportions of menopausal women without hormonal replacement therapy and non-menopausal patients were similar; menopausal women with hormonal replacement therapy represented 8% of our population. Patients with a familial history of BC represented 20% of our population. Obese patients, represented 8% and overweight patients represented 22% of our population.

Most BCs were discovered after a clinical palpation (in almost 70% of cases). Ductal BCs were the most frequent, in 75% of cases. Half of the tumors had hormone receptors. Stage I and II BCs represented 85% of the cases.

Almost two-third of patients had conservative surgery. Adjuvant treatments (chemotherapy and/or hormonotherapy) were used in 49% of patients.

The median of follow-up was 10 years and the maximal follow-up was 24 years. Observed number of CBC events during follow-up was 1,370. Annual incidence of CBC was 8.8 (8.3–9.3)/1000 person-years. A significant increase of annual incidence was observed during the follow-up (Fig. 1). Cumulative hazards of CBC at 5, 10, 15, 20, and 24 years of follow-up were respectively 3.7% (3.4–4.0), 8.3% (7.7–8.8), 13.6% (12.8–14.5), 20% (18.5–21.4), and 25.5% (22.8–28.2).

Among patient characteristics (Table 1), younger age and family history of BC were highly and significantly associated with an increased risk of CBC. Menopausal status without hormone replacement was associated with a decrease of CBC risk. Patients recruited more recently were less at risk of CBC; these patients have had a shorter follow-up.

The number of axillary involved nodes was the only initial tumor characteristic associated with CBC hazard. Patients with involved axillary nodes, after axillary dissection, had a decreased risk of CBC.

Considering treatment strategies, while the use of adjuvant chemotherapy and/or hormonotherapy was associated with a reduction of CBC occurrences, neoadjuvant chemotherapy and higher doses of radiotherapy were associated with an increase of CBC events. Patients who did not benefit from a surgical treatment experienced also more CBC events during the follow-up. However, only the use of adjuvant treatments presented a statistically significant association with CBC hazard. The more important CBC risk reduction was linked to the use of an adjuvant hormonotherapy.

Whilst the association between BMI and CBC hazard was inconclusive over the total period of follow-up (Table 2), a possible violation of non-proportional hazards was considered. Over the total period of follow-up, the association between CBC risk and binary coding of BMI using the 25 kg/m^2 cut-off was close to the signification threshold of 5% in unadjusted analysis and reached signification in adjusted analysis. This result suggested that overweight and obese patients were at increased risk of CBC. Nonetheless, on one hand a modest association was found and on the other hand tests for non-proportionality were highly significant suggesting a violation of the proportional hazards assumption. The binary coding of BMI using the 30 kg/m^2 cut-off was not significantly associated to CBC hazard (over the total period of follow-up) and tests for non-proportional hazards also supported a variation of hazards over time.

We first sought for graphical signs of non-proportionality. In Fig. 2, Kaplan–Meier curves highly suggested

Table 1 Patients' features at diagnosis time

Variable	Subpopulations	N (%)	Unadjusted HR for CBC events	Variable *P* value in the survival model
Age in years	18–35	536 (3.5)	1.68 (1.33–2.12)	<0.0001
	35–50	4996 (32.9)	1.05 (0.93–1.18)	
	50–65	6421 (42.3)	1.00 (Reference)	
	65–80	2962 (19.5)	0.83 (0.70–0.98)	
	≥80	251 (1.7)	0.44 (0.18–1.06)	
Hormonal status	Pre-menopausal	6830 (45)	1.00 (Reference)	0.02
	Post-menopausal	7142 (47.1)	0.86 (0.77–0.96)	
	Hormone replacement	1194 (7.9)	0.83 (0.66–1.05)	
Family history of breast cancer	No	11970 (78.9)	1.00 (Reference)	<0.0001
	Yes	2981 (19.7)	1.46 (1.30–1.65)	
	Unknown	215 (1.4)	1.02 (0.63–1.65)	
Obesity	BMI < 30 kg/m^2	13970 (92.1)	1.00 (Reference)	0.42
	BMI ≥ 30 kg/m^2	1196 (7.9)	1.09 (0.89–1.34)	
Overweight and obesity	BMI < 25 kg/m^2	10582 (69.8)	1.00 (Reference)	0.06
	BMI ≥ 25 kg/m^2	4584 (30.2)	1.12 (1.00–1.26)	
Nature of first symptom	Mammography	3061 (20.2)	1.00 (Reference)	0.47
	Tumor	10358 (68.3)	0.96 (0.84–1.10)	
	Other/multiple signs	1747 (11.5)	1.05 (0.87–1.28)	
Period of diagnosis and treatment	1981–1985	3187 (21)	1.00 (Reference)	<0.01
	1985–1990	3950 (26.1)	1.17 (1.02–1.35)	
	1990–1995	4457 (29.4)	1.11 (0.95–1.29)	
	1995–1999	3572 (23.6)	0.90 (0.74–1.08)	
Histology of the initial breast cancer	Ductal	11280 (74.4)	1.00 (Reference)	0.69
	Lobular	1278 (8.4)	0.94 (0.77–1.15)	
	Other	1091 (7.2)	1.10 (0.91–1.34)	
	Unknown	1517 (10)	1.03 (0.86–1.23)	
Tumor size	≤1 cm	1835 (12.1)	1.00 (Reference)	0.65
	1–2 cm	3560 (23.5)	0.99 (0.83–1.18)	
	2–5 cm	6608 (43.6)	0.97 (0.82–1.14)	
	>5 cm	2008 (13.2)	1.11 (0.90–1.37)	
	Unknown	1155 (7.6)	1.02 (0.80–1.31)	
Tumor local involvement	T0	1420 (9.4)	1.00 (Reference)	0.58
	T1	4834 (31.9)	1.02 (0.84–1.25)	
	T2	6244 (41.2)	0.98 (0.80–1.19)	
	T3	1624 (10.7)	1.09 (0.86–1.40)	
	T4	818 (5.4)	1.14 (0.83–1.56)	
	Unknown	226 (1.5)	1.30 (0.86–1.97)	
Clinical nodes invasion	N0	10415 (68.7)	1.00 (Reference)	0.32
	N1	4520 (29.8)	1.09 (0.97–1.22)	
	N2–N3	161 (1.1)	0.77 (0.37–1.63)	
	NX	70 (0.5)	1.41 (0.73–2.72)	
Involved nodes after axillary dissection	0	6362 (42)	1.00 (Reference)	0.03
	1–3	2490 (16.4)	0.81 (0.68–0.96)	
	>3	1311 (8.6)	0.91 (0.72–1.15)	
	No axillary dissection	3586 (23.6)	1.07 (0.94–1.21)	
	Unknown	1417 (9.3)	1.03 (0.85–1.25)	

Table 1 continued

Variable	Subpopulations	N (%)	Unadjusted HR for CBC events	Variable *P* value in the survival model
Multifocal tumor	Unifocal tumor	12927 (85.2)	1.00 (Reference)	0.92
	Multifocal tumor	1311 (8.6)	0.96 (0.79–1.17)	
	Unknown	928 (6.1)	1.00 (0.82–1.23)	
Estrogen receptors	Negative	2580 (17)	1.00 (Reference)	0.26
	Positive	7596 (50.1)	0.89 (0.76–1.03)	
	Unknown	4990 (32.9)	0.89 (0.76-1.04)	
Progesterone receptors	Negative	3616 (23.8)	1.00 (Reference)	0.34
	Positive	7491 (49.4)	0.90 (0.79–1.03)	
	Unknown	4059 (26.8)	0.93 (0.80–1.08)	
Scarth Bloom Richardson (SBR) Grade	Non-gradable	1320 (8.7)	0.94 (0.76–1.16)	0.53
	I	3355 (22.1)	1.00 (Reference)	
	IIA	3460 (22.8)	0.94 (0.81–1.10)	
	IIB	2931 (19.3)	0.94 (0.80–1.11)	
	III	2555 (16.9)	1.10 (0.93–1.30)	
	Unknown	1545 (10.2)	1.01 (0.83–1.23)	
First treatment	Radiotherapy	2812 (18.5)	1.05 (0.91–1.21)	0.08
	Lumpectomy	7984 (52.6)	1.00 (Reference)	
	Mastectomy	2086 (13.8)	0.90 (0.75–1.08)	
	Chemotherapy	2284 (15.1)	1.18 (1.01–1.37)	
Adjuvant therapy	None	7886 (52)	1.00 (Reference)	<0.01
	Chemo and hormonotherapy	4647 (30.6)	0.92 (0.81–1.04)	
	Hormonotherapy alone	2633 (17.4)	0.75 (0.63–0.88)	
Radiotherapy delivered dose	No radiotherapy	1306 (8.6)	1.00 (Reference)	0.16
	≤50 Gy	719 (4.7)	0.95 (0.67–1.35)	
	50–75 Gy	9644 (63.6)	1.03 (0.83–1.29)	
	>75 Gy	1315 (8.7)	1.28 (0.98–1.68)	
	Unknown	2182 (14.4)	1.05 (0.81–1.36)	
Final surgical treatment	Non-conservative	4411 (29.1)	1.00 (Reference)	0.14
	Conservative	8680 (57.2)	0.99 (0.87–1.13)	
	No surgical treatment	2075 (13.7)	1.15 (0.97–1.37)	

Unknown non-available data, *HR* hazard ratio

non-proportional hazards regarding the association between BMI and CBC. Survival curves steadily drifted apart after 10 years of follow-up; before the tenth year of follow-up, the curves were joined. In addition, the test of non-proportional hazards, using Schoenfeld residuals, was highly significant independently of the BMI coding. Graphical results suggested the presence of a significant association between BMI and CBC hazard after 10 years of follow-up. Time-dependent covariates supported a progressive increase of CBC risk among heavier patients during the follow-up, independently of the BMI coding. Figure 3 illustrates the results using BMI 25 kg/m^2 cut-off. These results were similar to those using the 30 kg/m^2 cut-off (results not shown). The consistency of the used time-dependent covariates was supported by insignificant tests regarding non-proportionality using Schoenfeld residuals. The analysis regarding the nature of non-proportionality (shape of non-proportional hazards in Fig. 3) led us to compute proportional survival models over two periods of time: before and after 10 years of follow-up.

Whilst hazards proportionality was assessed and verified, significant and consistent associations between binary codings of BMI and CBC events were found after 10 years of follow-up (Table 2). An increased risk of CBC among overweight and obese patients was highlighted in these analyses. Among overweight and obese patients, adjusted HR reached a value of approximately 1.50.

While at initial follow-up, 60% of patients were over 50 years old, at 10 years of follow-up 90% of our population was assumed to be over 50 years old. The proportion of menopausal women is assumed to have increased importantly. An interaction analysis regarding CBC hazard

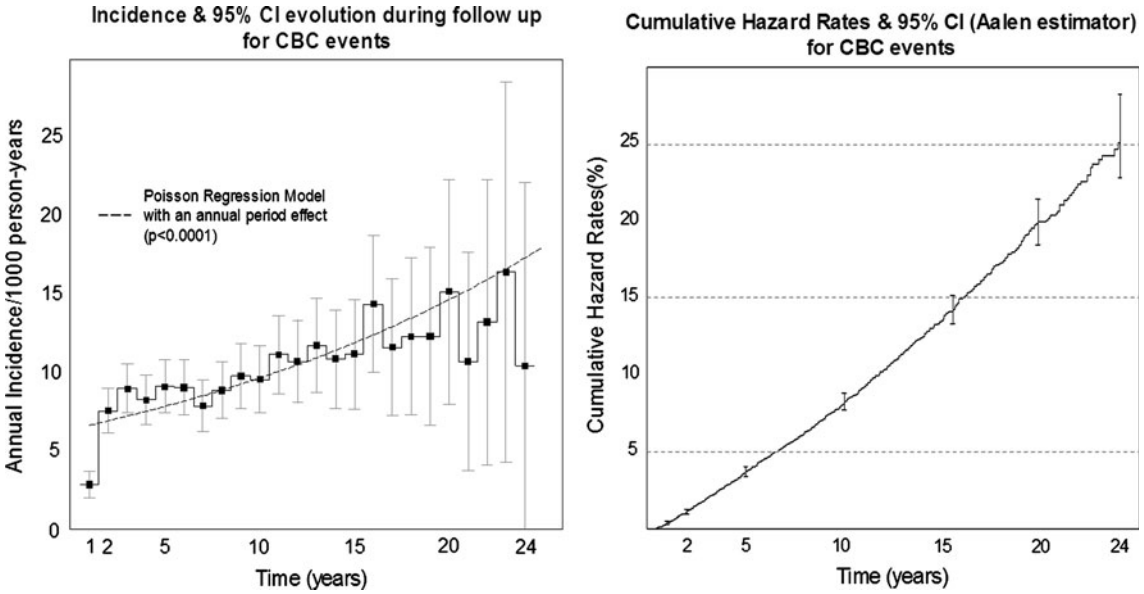

Fig. 1 Significant increase of contralateral breast cancers hazard during follow-up

Table 2 Survival proportional models computed by time periods (partition of follow-up before and after 10 years)

BMI binary codings and period of follow-up	*N*	Events	Incidence/1000 person-years	HR unadjusted	Tests signification (unadjusted)	HR adjusted	Tests signification (adjusted)
Obesity cut-off							
Period: 0–24 years of follow-up							
BMI < 30 kg/m^2	13970	1271	8.77 (8.29–9.26)	1.00 (Reference)	+	1.00 (Reference)	+
BMI ≥ 30 kg/m^2	1196	99	9.20 (7.39–11.02)	1.09 (0.89–1.34)		1.19 (0.97–1.47)	
Period: 0–10 years of follow-up							
BMI < 30 kg/m^2	13970	879	8.03 (7.50–8.56)	1.00 (Reference)		1.00 (Reference)	
BMI ≥ 30 kg/m^2	1196	69	7.78 (5.94–9.61)	0.98 (0.77–1.25)		1.07 (0.84–1.38)	
Period: 10–24 years of follow-up							
BMI < 30 kg/m^{22}	6818	392	11.09 (09.99–12.19)	1.00 (Reference)	*	1.00 (Reference)	*
BMI ≥ 30 kg/m^2	450	30	15.93 (10.23–21.63)	1.46 (1.01–2.12)		1.60 (1.10–2.34)	
Overweight cut-off							
Period: 0–24 years of follow-up							
BMI < 25 kg/m^2	10582	963	8.59 (8.04–09.13)	1.00 (Reference)	++	1.00 (Reference)	**
BMI ≥ 25 kg/m^2	4584	407	9.37 (8.46–10.28)	1.12 (1.00–1.26)		1.21 (1.07–1.36)	+
Period: 0–10 years of follow-up							
BMI < 25 kg/m^2	10582	670	7.99 (7.39–8.6)	1.00 (Reference)		1.00 (Reference)	
BMI ≥ 25 kg/m^2	4584	278	8.05 (7.1–9)	1.02 (0.88–1.17)		1.11 (0.96–1.28)	
Period: 10–24 years of follow-up							
BMI < 25 kg/m^2	5339	293	10.35 (9.17–11.54)	1.00 (Reference)	**	1.00 (Reference)	**
BMI ≥ 25 kg/m^2	1929	129	14.46 (11.97–16.96)	1.42 (1.15–1.74)		1.50 (1.21–1.86)	

Associations between binary codings of BMI and CBC events were unadjusted and adjusted using initial delivered treatments, tumor histology, and hormonal receptors status, number of axillary invaded nodes, patients' age, family history of breast cancer, menopausal status, and period of recruitment

Statistical tests were computed at non-adjusted and adjusted steps: *P* values regarding the tests of used covariates in survival models are coded as follow: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; *P* values regarding the non-proportionality tests (using Schoenfeld residuals) are coded as follow: + $P < 0.05$, ++ $P < 0.01$, +++ $P < 0.001$

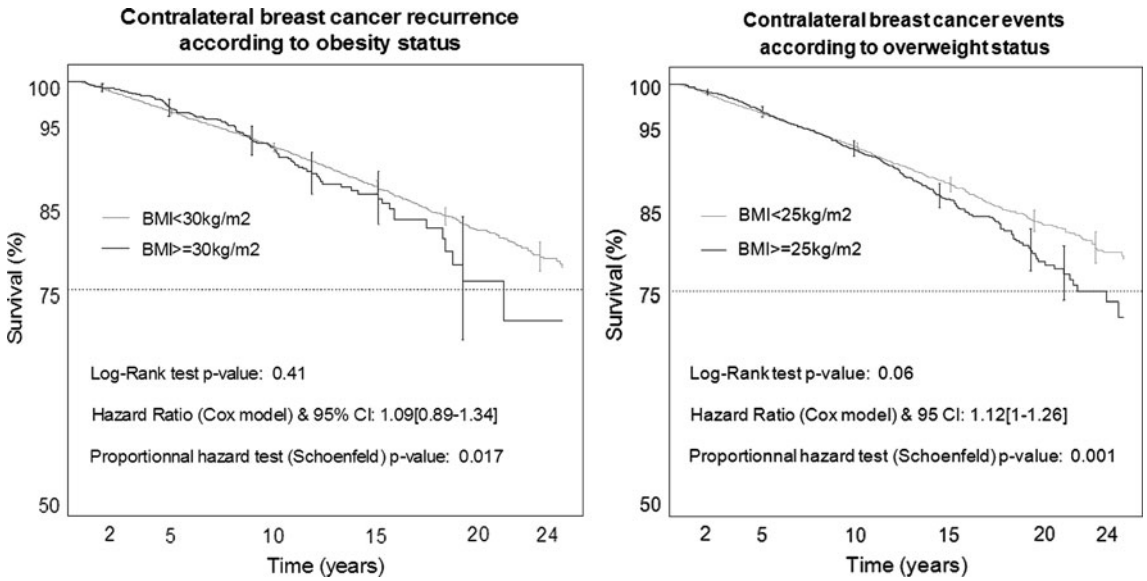

Fig. 2 Kaplan Meier survival curves indicating non-proportional hazards

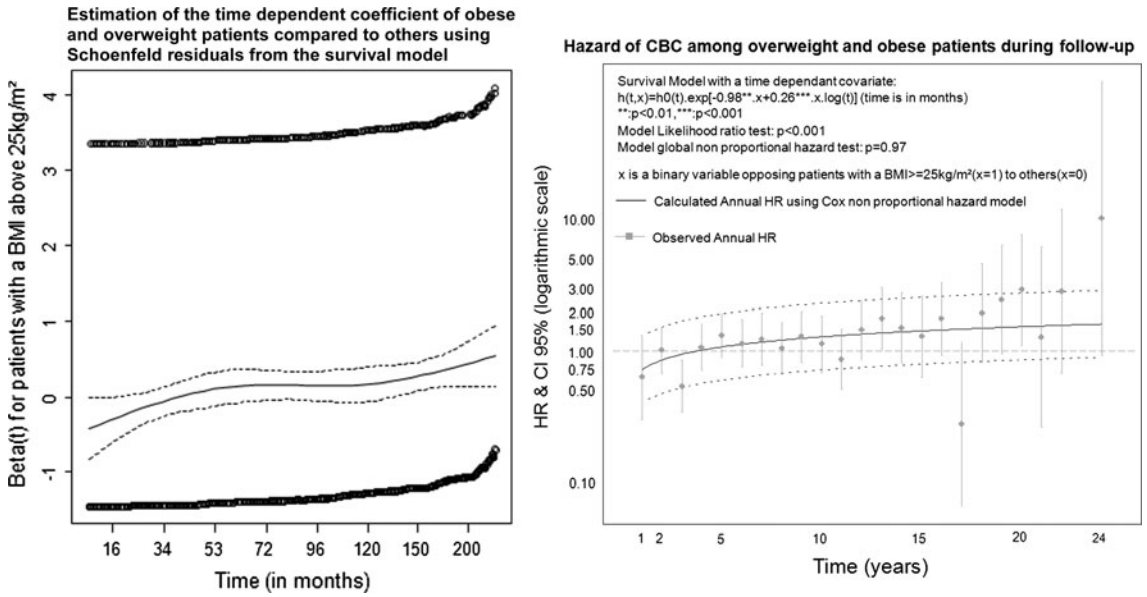

Fig. 3 Assessment of the nature of non-proportional hazards when patients' with a BMI $\geq$ 25 kg/m^2 are opposed to the others, using Schoenfeld residuals (*on the left*) and a time-dependant covariate (*on the right*)

between BMI and menopausal status at the diagnosis time was thus conducted (Table 3). The association between BMI and CBC hazard was more important among menopausal sub-populations, especially among women with a previous hormonal replacement therapy. However, on one hand, none of the associations was statistically significant (in explored sub-populations defined according to menopausal status) and on the other hand the interaction term in a global modeling strategy was insignificant. In addition, the test for non-proportionality was found to be consistent in some cases (Table 3). Consequently, interaction analysis between BMI and menopausal status was inconclusive.

Discussion

Our survey highlighted a relevant increased risk of CBC during the long-term follow-up among obese and overweight patients. We formulated and corroborated this association considering common epidemiologic evidences

Table 3 Interaction analysis between BMI and menopausal status at the diagnosis time regarding CBC events

BMI codings (kg/m^2)	Premenopausal patients	Menopausal patients without hormonal replacement	Menopausal patients with hormonal replacement
BMI < 30	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
BMI ≥ 30	0.90 (0.62–1.31)	1.24 (0.95–1.61)	1.47 (0.64–3.4)
BMI < 25	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
BMI ≥ 25	1.15 (0.96–1.37) +	1.17 (0.99–1.38) +	1.27 (0.78–2.06)

Hazard ratios with 95% CI, *P* values of used BMI codings and test results of non-proportionality (using Schoenfeld residuals) are reported as in Table 2

represented by the following: an increase of CBC risk during follow-up of BC patients, an increase of BC risk among obese women in post-menopausal period and weight gain in women when aging, especially in menopausal period and after BC treatment [15, 23]. Our results were achieved based on one of the largest cohort of women with BC, with a high number of CBC events and an important duration of follow-up.

In spite of the observational setting of our study, our results indicate that overweight and obese patients at the diagnosis time of a first BC have a significant increased risk of 50% of CBC after 10 years of follow-up. After a 10-year period of follow-up, almost all patients are assumed to be menopausal and patients initially overweight may have maintained or increased their weight.

Some authors formerly documented a significant association between BMI and the hazard of CBC. Dignam et al. [11] asserted that obesity may compromise the long-term welfare of BC survivors. An increase of approximately 60% of CBC risk was observed among obese patients when compared to normal BMI and underweight patients. However, the association found in our study is time-dependent. Nonetheless, in some BC studies, several prognosis factors have been identified with a time-dependent effect that decreases during the follow-up [24–26]. On the contrary, we found that CBC hazard is increased during the long-term follow-up among overweight and obese patients. Our results can suggest that the benefit of diet habits improvement, physical exercise and weight control may be effective among long-term survivors. However, long-term improvement of BC prognosis in relation to lifestyle modifications has yet to be demonstrated by clinical trials.

The epidemiological results, found in our study, are in accordance with previously published data [6, 8, 18, 27]. Annual incidence of CBC increases during the follow-up of BC survivors. Common CBC risk factors were confirmed in our population, apart from tumor lobular histology and hormone receptors [18, 27–31]. When considering BMI as an independent risk factor for CBC, CBC events are expected to increase along with improved BC survival [29] and the given worldwide epidemic of overweight and obesity [19].

Hazard of CBC is increased among overweight and obese patients in a similar degree during the long-term follow-up. This result is in accordance with a previous paper that validated 25 kg/m^2 as an optimal BMI cut-off to distinguish women with increased hazard of metastasis recurrence and mortality in BC [32]. However, BC survivors may have had a weight increase during follow-up (while aging and becoming menopausal): overweight patients at diagnosis time of the first BC may have become obese at 10 years of follow-up.

Some results in our study support the hypothesis of a hormonal mechanism to explain the association between BMI and CBC hazard [1]. In the interaction analysis (Table 3), most important associations between CBC and BMI were observed among menopausal patients who had a previous hormonal replacement therapy [33]. The association between BMI and CBC hazard was significant over the long-term follow-up; this may be linked to an increase of menopausal women and possibly obese patients over time. Finally, there was a significant protective effect of adjuvant hormonal therapy.

CBC events were considered in our study as second primary cancers, independently from other outcomes following initial BCs. The absence of association between common BC prognosis factors and CBC hazard supports this assumption. Nevertheless, different strategies considering competing risks or multistate modeling approaches have been previously compared for the assessment of CBC hazard. Results did not indicate a better relevance of the above modeling strategies [8].

Despite our large scale population and an important number of CBC events, other multicentre studies are required to confirm our results. Nonetheless, the proportional hazards assumption is encouraged to be systematically tested when assessing the association between BMI and CBC. The accordance between the different methods used in our study (to test the proportional hazards assumption) indicates a reliable appraisal of the nature of the link between overweight and CBC hazard during follow-up.

Benefits from improved diet habits and lifestyle may possibly reduce CBC occurrences during the long-term follow-up. Albeit, CBC are usually diagnosed as in situ cancers and are often less extended tumors than the first BCs [34].

Our results support the need of assessments during the long-term follow-up of diet and lifestyle interventions. Randomized controlled trials are required to establish the usefulness of dietary improvements, weight loss and increase in physical activity in BC prognosis [35].

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Conflict of interest None.

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