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

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Summary
Background: Breast cancer (BC) survivors are at increased risk of second cancers. Obesity is commonly recognized as a risk factor of breast cancer in postmenopausal period and a prognosis factor in breast cancer regardless of menopausal status. Our aim was to study whether overweight breast cancer survivors were at increased risk of Contralateral Breast Cancer (CBC).
Methods: 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.
Results: 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 ten years of follow-up, we found a significant increased hazard of CBC among patients with a BMI above 25kg/m²: the adjusted hazard ratio was 1.50[1.21-1.86], p=0.001.
Conclusions: After ten years of follow-up, our study found a poorer prognosis among overweight breast cancer 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.

Key-words
1. Contralateral breast cancer
2. Non proportional hazards
3. Body Mass Index
4. Overweight
5. Time-dependent covariate
6. Breast cancer Prognosis

Abbreviations
BC : Breast cancer
BMI : Body Mass Index
CBC : Contralateral Breast Cancer
HR : Hazard Ratio

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A. Introduction

Numerous studies and literature reviews support the assumption of a poorer prognosis for overweight and obese women at the time of breast cancer diagnosis[1, 2]. Therefore, diet improvement and physical exercise are recommended among breast cancer 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 breast cancer outcomes, had mixed and conflicting results[5]. Nevertheless, in these trials, the follow-up duration was limited to less than ten 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 breast cancer prognosis studies, the main investigated endpoints in published literature are overall survival and disease free survival that includes distant, regional and local relapses. Contralateral breast cancer (CBC) occurrences have seldom been explored as a specific outcome among women having previously had a first breast cancer. Breast cancer 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 breast cancer (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 breast cancer[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 breast cancer patients are at increased risk of CBC, obesity represents a reliable breast cancer risk factor in the post-menopausal period[13]. We hypothesized that being overweight at the time of a first breast cancer 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 breast cancer treatment are also known to be associated with weight gain[14-16].

In presence of an increase of breast cancer survivors[17], of an increased CBC risk among breast cancer 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.

B. Material and Methods

a. 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 breast cancer. Period of recruitment extended from January 1981 to December 1999. Patients with synchronous CBC, defined by the occurrence of a CBC within the first six 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/m² as a cut-off. The second coding individualized obese patients using 30 kg/m² as a cut-off. Patients with unavailable data regarding height or weight were excluded. They represented less than 15% of the initial eligible population.

b. Methods

i. 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 breast cancer, 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].

ii. 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 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[22].

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

iii. 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 are considered as second primary breast cancers, CBC events were analyzed independently from other breast cancer prognosis events.

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

C. Results

Characteristics of our population (N=15,166) at the diagnosis time of the first breast cancer 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 breast cancer represented 20% of our population. Obese patients, represented 8% and overweight patients represented 22% of our population.

Most breast cancers were discovered after a clinical palpation (in almost 70% of cases). Ductal breast cancers were the most frequent, in 75% of cases. Half of the tumors had hormone receptors. Stage I and II breast cancers 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 (Figure 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 breast cancer 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 25kg/m² 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 30kg/m² 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 Figure 2, Kaplan-Meier curves highly suggested 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 illustrate results using BMI 25kg/m² cut-off. These results were similar to those using the 30kg/m² 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 Figure 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 ten years of follow-up (Table 4). 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 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.

D. 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 represented by: an increase of CBC risk during follow-up of breast cancer patients, an increase of breast cancer risk among obese women in post-menopausal period and weight gain in women when aging, especially in menopausal period and after breast cancer treatment[15, 23]. Our results were achieved based on one of the largest cohort of women with breast cancer, 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 breast cancer have a significant increased risk of 50% of CBC after ten years of follow-up. After a ten-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 breast cancer 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 breast cancer 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 breast cancer 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 breast cancer 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 breast cancer 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 25kg/m² as an optimal BMI cut-off to distinguish women with increased hazard of metastasis recurrence and mortality in breast cancer[32]. However, breast cancer survivors may have had a weight increase during follow-up (while aging and becoming menopausal): overweight patients at diagnosis time of the first breast cancer may have become obese at 10 years of follow-up.

Some results in our study support the hypothesis of a hormonal mechanisms 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 breast cancers. The absence of association between common breast cancer 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, 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 breast cancers[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 breast cancer prognosis[35].

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Variable	Subpopulations	N & (%)	Unadjusted HR for CBC events	Variable p-value in the Survival model
Age in years				<0.0001
	[18-35[	536(3.5)	1.68[1.33-2.12]	
	[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<30kg/m²	13970(92.1)	1.00(Reference)	0.42
	BMI≥30kg/m²	1196(7.9)	1.09[0.89-1.34]	

Overweight and obesity	BMI<25kg/m²	10582(69.8)	1.00(Reference)	0.06
	BMI≥25kg/m²	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]	

Table 1: Patients' features at diagnosis time, (Unknown: Non Available data, HR: Hazard Ratio)

Variable	Subpopulations	N & (%)	Unadjusted HR for CBC events	Variable p-value in the Survival model
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	<=1cm]	1835(12.1)	1.00(Reference)	0.65
	]1-2cm]	3560(23.5)	0.99[0.83-1.18]	
	]2-5cm]	6608(43.6)	0.97[0.82-1.14]	
	>5cm	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 to 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]	
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]	

Table 1 (continued): Tumor characteristics at diagnosis time, (Unknown: Non Available data, HR: Hazard Ratio)

Variable	Subpopulations	N & (%)	Unadjusted HR for CBC events	Variable p-value in the Survival model
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 & 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
	<=50Grays	719(4.7)	0.95[0.67-1.35]	
	]50-75Grays]	9644(63.6)	1.03[0.83-1.29]	
	>75Grays	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]	

Table 1 (continued): Delivered treatments for the first breast cancer, (Unknown: Non Available data, HR: Hazard Ratio)

BMI binary codings & 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 to 24 years of follow-up							
BMI < 30kg/m²	13970	1271	8.77[8.29-9.26]	1.00(Reference)		1.00(Reference)	
BMI ≥ 30kg/m²	1196	99	9.20[7.39-11.02]	1.09[0.89-1.34]	+	1.19[0.97-1.47]	+
Period : 0 to 10 years of follow-up							
BMI < 30kg/m²	13970	879	8.03[7.50-8.56]	1.00(Reference)		1.00(Reference)	
BMI ≥ 30kg/m²	1196	69	7.78[5.94-9.61]	0.98[0.77-1.25]		1.07[0.84-1.38]	
Period : 10 to 24 years of follow-up							
BMI < 30kg/m²	6818	392	11.09[09.99-12.19]	1.00(Reference)		1.00(Reference)	
BMI ≥ 30kg/m²	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 to 24 years of follow-up							

BMI < 25kg/m²	10582	963	8.59[8.04-09.13]	1.00(Reference)		1.00(Reference)	**
BMI ≥ 25kg/m²	4584	407	9.37[8.46-10.28]	1.12[1.00-1.26]	++	1.21[1.07-1.36]	+
Period : 0 to 10 years of follow-up							
BMI < 25kg/m²	10582	670	7.99[7.39-8.6]	1.00(Reference)		1.00(Reference)	
BMI ≥ 25kg/m²	4584	278	8.05[7.1-9]	1.02[0.88-1.17]		1.11[0.96-1.28]	
Period : 10 to 24 years of follow-up							
BMI < 25kg/m²	5339	293	10.35[9.17-11.54]	1.00(Reference)		1.00(Reference)	
BMI ≥ 25kg/m²	1929	129	14.46[11.97-16.96]	1.42[1.15-1.74]	**	1.50[1.21-1.86]	**

Table 2: Survival proportional models computed by time periods (partition of follow-up before and after 10 years). 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: + $p<0.05$, ++ $p<0.01$, +++ $p<0.001$.

BMI codings	Premenopausal patients	Menopausal patients without hormonal replacement	Menopausal patients with hormonal replacement
BMI<30kg/m²	1.00(Reference)	1.00(Reference)	1.00(Reference)
BMI≥30kg/m²	0.90[0.62-1.31]	1.24[0.95-1.61]	1.47[0.64-3.4]
BMI≥25kg/m²	1.00(Reference)	1.00(Reference)	1.00(Reference)
BMI≥25kg/m²	1.15[0.96-1.37] +	1.17[0.99-1.38] +	1.27[0.78-2.06]

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

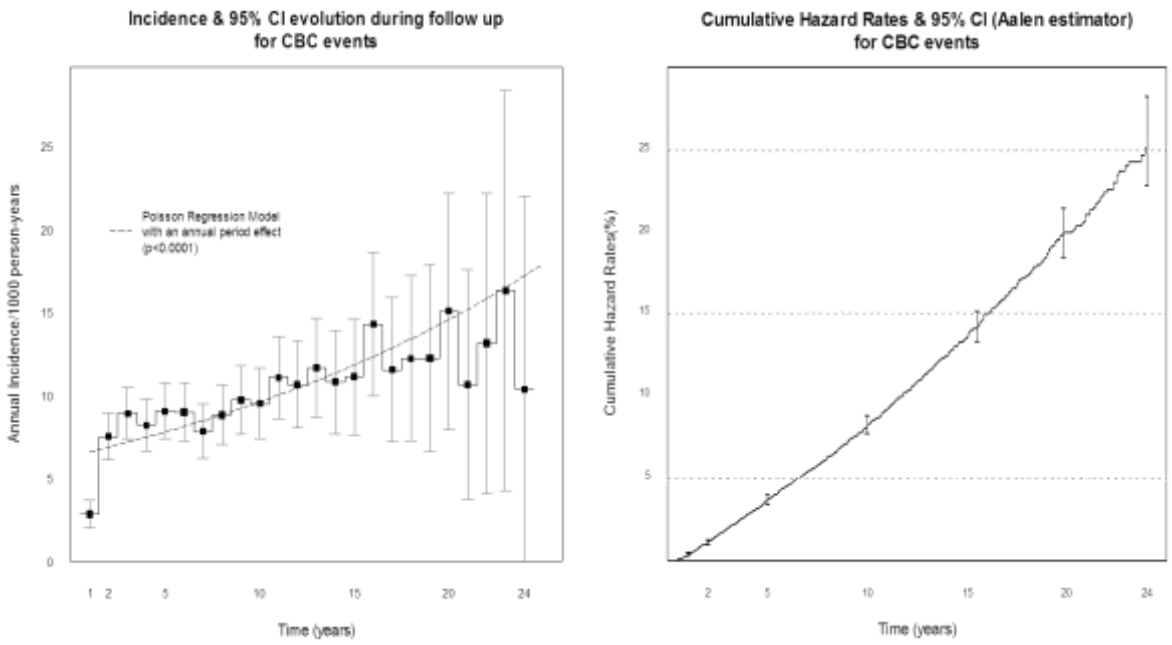

Figure 1: Significant increase of contralateral breast cancers hazard during follow up

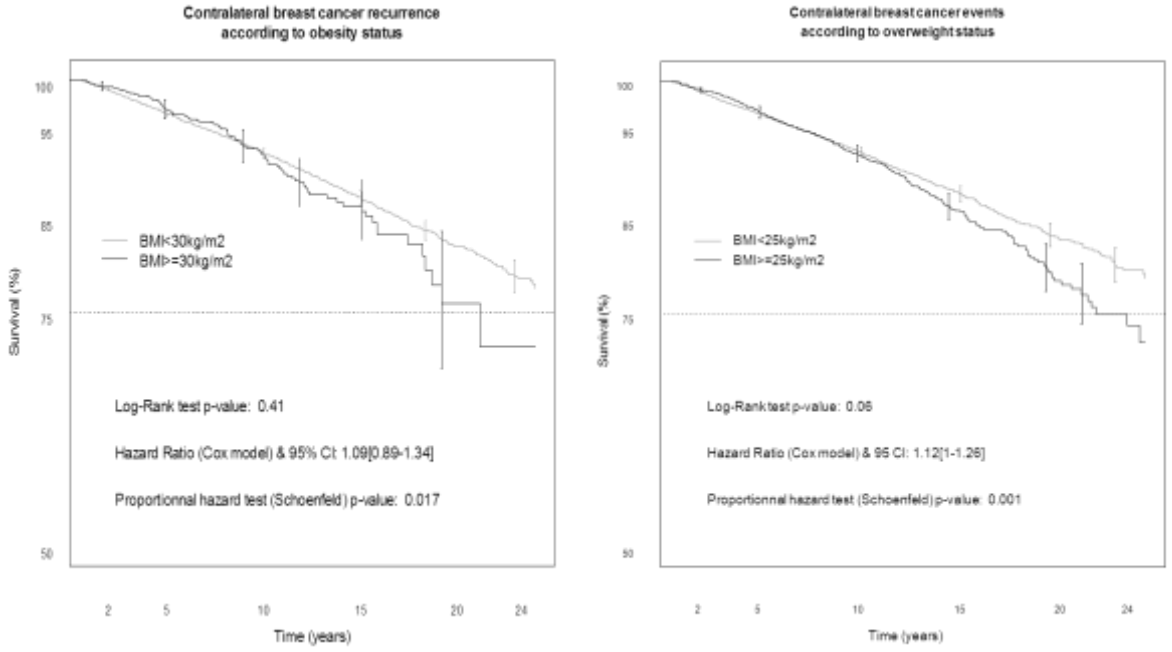

Figure 2 : Kaplan Meier survival curves indicating non-proportional hazards

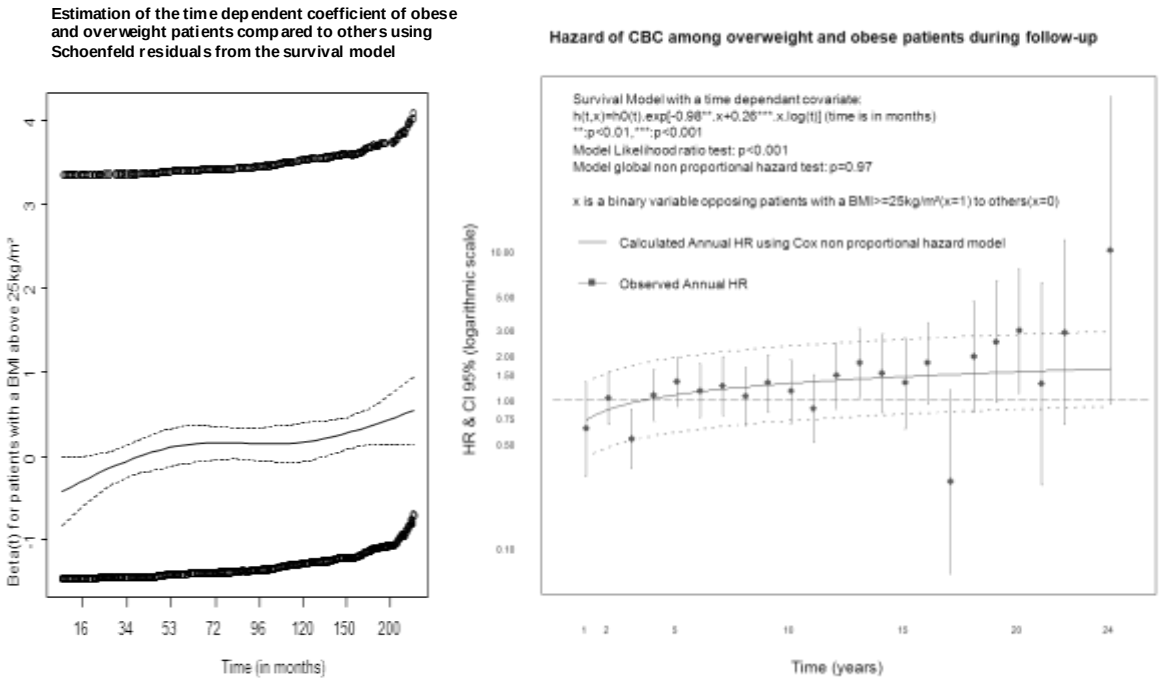

Figure 3: Assessment of the nature of non-proportional hazards when patients' with a BMI≥25kg/m² are opposed to the others, using Schoenfeld residuals (on the left) and a time dependant covariate (on the right).