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RESEARCH ARTICLE

Cancer Therapy and Prevention

CANTO skin: Evaluation of skin toxicity risk factors in patients treated for breast cancer

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Abstract

Skin reaction is a common toxicity during oncology management, especially followed during the radiotherapy. Its assessment and understanding of the factors influencing its occurrence, is a major issue in the management of patients treated for an early breast cancer (BC). We evaluated 8561 patients during their overall management for a BC. We focus on specific skin toxicities: erythema, fibrosis, telangiectasia and changes of skin colour. These toxicities were assessed at the baseline defined as 0-3-6 (M0), 12 (M12), 36 (M36) and 60 (M60) months. The prevalence of toxicities of interest varied over time, so at M0, 30.4% of patients had erythema while 17.7% of patients had fibrosis. At M60, the prevalence of erythema was 2%, while fibrosis remained stable at about 19%. After adjustments, at M0, there was a significant association between the onset of cutaneous erythema and obesity, the presence of axillary dissection, the type of surgery and the tumour phenotype RH+/HER2+. Concerning fibrosis, a significant association was found, at M12, with the age of the patient, obesity, Charlson score and type of surgery. Concerning the modification of skin colour at M12, we find a link between the age of

Abbreviations: 3D, tridimensional; BC, breast cancer; CI, confidence interval; IMRT, intensity-modulated irradiation; IQR, interquartile range; OR, odds ratio; RT, radiotherapy.

the patient, obesity, tobacco consumption and alcohol consumption. The prevention of this toxicity is a major issue for the quality of life. Our results allow us to understand the risk of developing skin toxicity in a patient, depending on her intrinsic, tumour or therapeutic characteristics and to implement adapted means of prevention and monitoring.

KEYWORDS
breast cancer, CANTO, risk factor, skin toxicity

What's new?

Patients with early-stage breast cancer are at risk of skin reactions, including erythema and fibrosis, following treatment. Factors associated with skin toxicity in these patients, however, remain unclear. In the present study, potential risk factors for skin reactions experienced during treatment for early-stage breast cancer were assessed among patients in the French CANTO study. Risk factors varied according to toxicity and emerged at different time points following treatment. Identified factors included obesity, surgery type, age, tumour grade and Charlson score. Comorbidity burden was a major factor in skin toxicity occurrence in patients who received treatment for early-stage breast cancer.

1 | INTRODUCTION

Skin toxicities are common in the oncological management of patients with early breast cancer. These toxicities affect patients' quality of life, as they are a clinical reflection of their disease, and have both an aesthetic and psychological impact. Skin lesions are considered as acute effects (<6 months), such as skin erythema,[1,2] or late effects (>6 months), such as fibrosis.[3-5] These toxicities can be a source of pain, discomfort and aesthetic sequelae for the patient. They occur at different stages of treatment: surgery, chemotherapy and radiotherapy. Their evaluation is clinical and, they are assessed according to CTCAEv4 grades.[6]

In our study, we are interested in a larger population and with a longer follow-up than in our first CANTO-RT study in larger population of patients.[7] We evaluate all tumour, individual and therapeutic characteristics influencing the occurrence of skin toxicity in patients treated for early breast cancer. The analysis of radiotherapy factors impacting the occurrence of these toxicities will not be addressed as already evaluated in the CANTO-RT study. All radiotherapy modalities were considered in our previous study, as well as any intra- or interindividual factors that may be associated with them. For this reason, in our study we will not focus on the modalities of radiotherapy as risk factors for skin toxicities. However, we have highlighted certain aspects of radiotherapy as risk factors for skin toxicity, such as the addition of a boost or 3D irradiation. Full results and details of the study are available in the literature.[7] Skin side effects can be more or less important depending on the treatment protocol. It is therefore essential to understand, evaluate[6,8,9] and manage them.[10,11] New therapies and drug combinations may cause new side effects.[12-14] In fact, the identification of risk factors[15-17] for the appearance of skin toxicities represents a major challenge in the treatment of patients in order to anticipate them and, to manage them in a personalised approach. Through the various CANTO studies, we are attempting to identify numerous factors influencing the occurrence of toxicity, such as fatigue[18] or cardiac toxicity.[19] With the help of a vast database reported prospectively in several major French centres, we have been

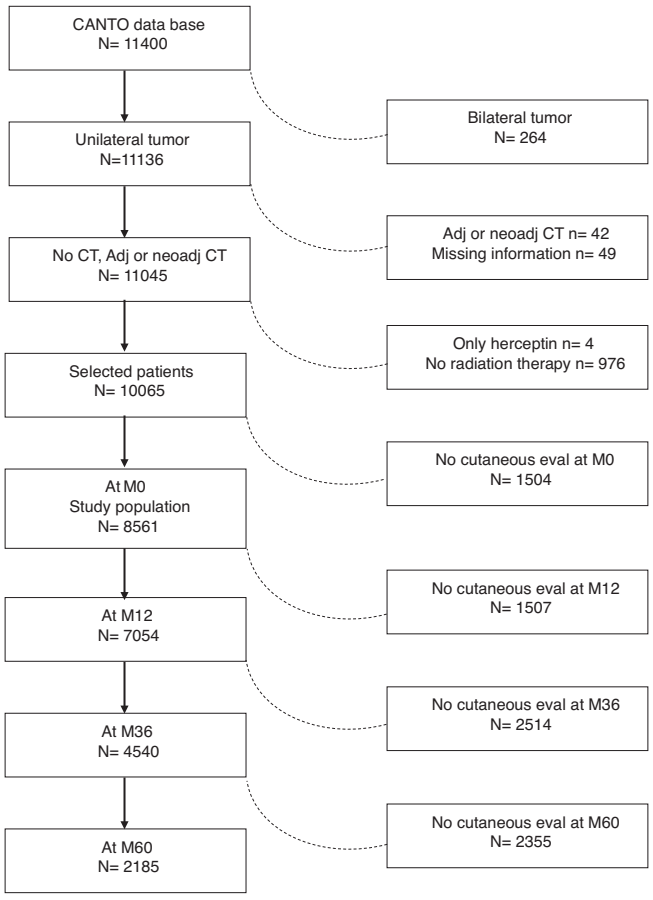

FIGURE 1 Flow chart.

TABLE 1 Characteristic of patients.

Characteristics	Class	n (8561)	%
Age at diagnosis	<50 years	2670	31.2
	50-65 years	3807	44.5
	>65 years	2084	24.3
BMI at enrolment	Normal range (18.5-24.9)	4163	48.9
	Underweight (<18.5)	180	2.1
	Overweight (25.0-29.9)	2490	29.2
	Obese (>30)	1687	19.8
	NA	41	
Obesity at enrolment	Non-obese (<30)	6833	80.2
	Obese (>30)	1687	19.8
	NA	41	
Clinical lymph node invasion	No	6957	86.6
	Yes	1080	13.4
	NA	524	
ECOG at enrolment	ECOG O	7299	94.5
	ECOG 1	403	5.2
	ECOG 2-4	19	0.2
	NA	840	
Charlson at enrolment	0	6308	81
	1	856	11
	>1	625	8
	NA	772	
Smoking status	Non-smoker	5053	59.8
	Former smoker	1867	22.1
	Smoker	1532	18.1
	NA	109	
Daily alcohol consumption	No	7230	86.6
	Yes	1118	13.4
	NA	213	
Stage TNM derived	STADE 0/I	4136	48.8
	STADE II	3499	41.2
	STADE III	848	10
	NA	78	
Oestrogen receptor	Negative	1193	14
	Positive	7340	86
	NA	28	
Progesterone receptor	Negative	2423	28.4
	Positive	6109	71.6
	NA	29	
Hormonal receptor	Negative	1154	13.5
	Positive	7380	86.5
	NA	27	
HER2	Negative	7289	85.7
	Positive	1218	14.3
	NA	54	
Phenotype	RH+/HER2−	6464	76
	RH+/HER2+	890	10.5
	RH−/HER2+	327	3.8
	RH−/HER2−	824	9.7
	NA	56	
Grade	SBR I	1517	17.9
	SBR II	4466	52.7
	SBR III	2491	29.4
	NA	87	
Mitotic index	0-9 mitoses	4820	57.7
	10-18 mitoses	1929	23.1
	>18 mitoses	1609	19.3
	NA	203	
KI67%	<20%	3630	42.4
	>20%	3045	35.6
	Not done	1886	22
Lymph node dissection	Sentinel node	5380	63.4
	Axillary node	3112	36.6
	NA	69	
Type of surgery	Conservative surgery	6764	79.1
	Mastectomy	1786	20.9
	NA	11	
Type of chemotherapy	No chemotherapy	3954	46.2
	Neoadjuvant chemotherapy	1167	13.6
	Adjuvant chemotherapy	3440	40.2

Abbreviation: BMI, body mass index.

able to analyse a large sample of patients and a vast number of factors, whether intra- or interindividual, related to treatment or tumour characteristics. At present, there are no studies in the literature evaluating the risk factors for cutaneous toxicity in such a large population and taking into account such a wide range of possible side effects and risk factors. For maximum clarity and relevance, we have focused on the skin toxicities most frequently encountered and having the most significant impact on patients. We will focus on four toxicities of interest: skin erythema, fibrosis, telangiectasia and skin colour.

The aim of our study is to identify the risk factors associated with the occurrence of these four toxicities in patients undergoing treatment for early-stage breast cancer, using the latest results from the CANTO cohort.[20]

2 | MATERIALS AND METHODS

The CANTO study (NCT01993498)[20] is a French prospective clinical multicentre study on more than 11 000 patients with

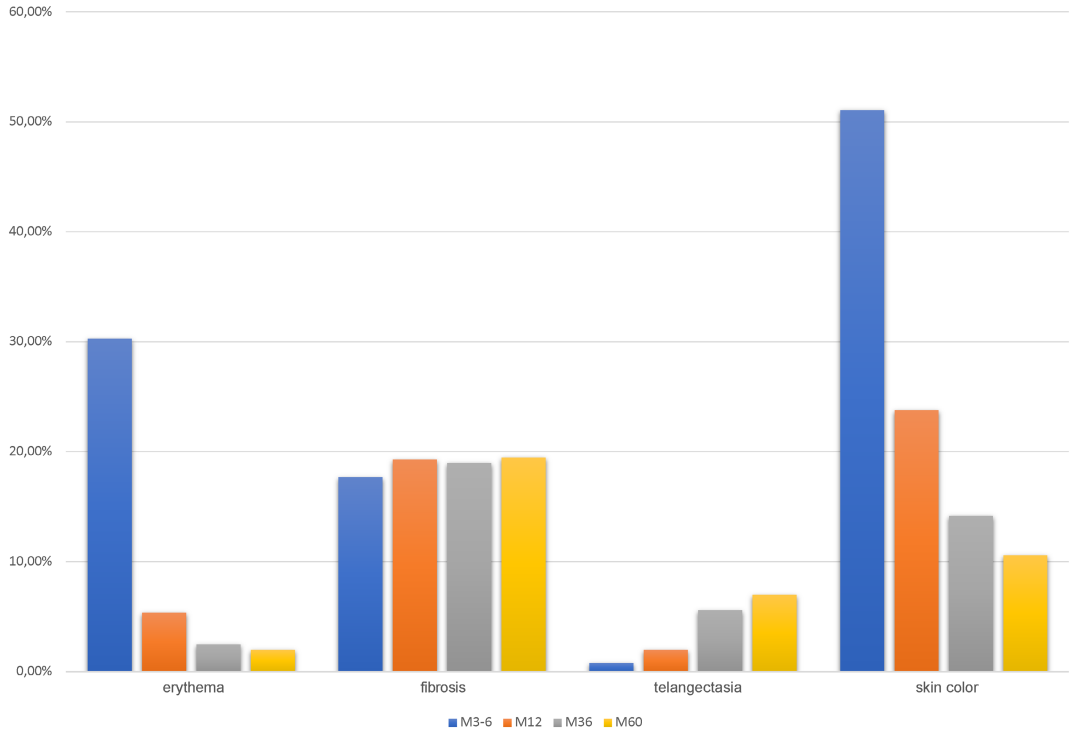

FIGURE 2 Prevalence of toxicities of interest. [Color figure can be viewed at wileyonlinelibrary.com]

stage I to III BC diagnosed and recruited between June 2012 and February 2017 in 26 French centres.

The details on the procedures of the CANTO study have been published previously.[20]

The characteristics of the patients and tumours (TNM, histology, HER2, oestrogen and progesterone receptors) were recorded from the baseline. The characteristics of the treatments and the skin toxicities (CTCAE v4.0) were evaluated at 3 to 6 (M0), 12 (M12), 36 (M36) and 60 (M60) months after the end of the primary surgery, chemotherapy or radiotherapy.

The toxicities of interest were erythema and modification of skin colour (at baseline defined as M0-3-6 months, and M12: erythema and at M12, M36 and M60: hyperpigmentation), telangiectasia, as well as fibrosis (initially at M0 presented by a postsurgery fibrosis and after M12: both postsurgical and postradiotherapy fibrosis).

The collection of data of the CANTO study was carried out using a patient booklet centred on the toxicity perceived which imitates the case report electronic forms. A clinical research nurse examines the information and records the toxicity described using the adverse event scale of the Common Toxicity Criteria (CTCAEv4). If a side effect is detected, the patient's referring physician is notified.

The objective of the study was to identify risk factors of developing skin toxicities as a function of the different characteristics of the patients and tumour, and as a function of the type of treatment received during treatment of a patient presenting an early-stage BC.

From the entire CANTO database (n = 11 400), 264 patients had bilateral BC and were excluded. Among the remaining 11 136 patients, 11 045 had complete data on the systemic treatment. Forty-two patients were excluded because they had both neoadjuvant and adjuvant chemotherapy, and 49 did not have information on the type of systemic treatment. Four patients had only received Herceptin and were also excluded. Patients who did not have radiotherapy, 976 patients, were also excluded. 8561 had a complete skin evaluation at M0 while 1504 did not have one and were excluded (Figure 1).

2.1 | Statistical analysis

Clinicopathological characteristics and demographics were assessed using descriptive statistics. Qualitative variables were expressed as counts and percentages and compared using Pearson's χ^2 or Fisher tests, while quantitative variables were expressed as mean and SD or median and interquartile range (IQR) and compared by Student's test. Multivariable logistic regression models were used to identify baseline characteristics and RT variables associated with the presence of skin toxicity (separate models for erythema at M0 and M12, cutaneous fibrosis at M0, M12 M36 and M60, telangiectasia at M12, M36 and M60 and skin colour at M12, M36 and M60). Outcomes (erythema, cutaneous fibrosis, telangiectasia and skin colour) were considered as 'Ever versus Never', whatever the grade (ie, grade I, II, III or IV vs None). All variable associated with the considered outcomes with a *P*-value minor than 10% were considered for multivariate model. No other selection was applied (nor forward or backward or mixed selection). We used the redun function (R package Hmisc) to check for redundancy in co-variates.

Statistical analysis was performed using R software Version 4.1.[21] Statistical significance was defined with a two-sided *P*-value <.05.

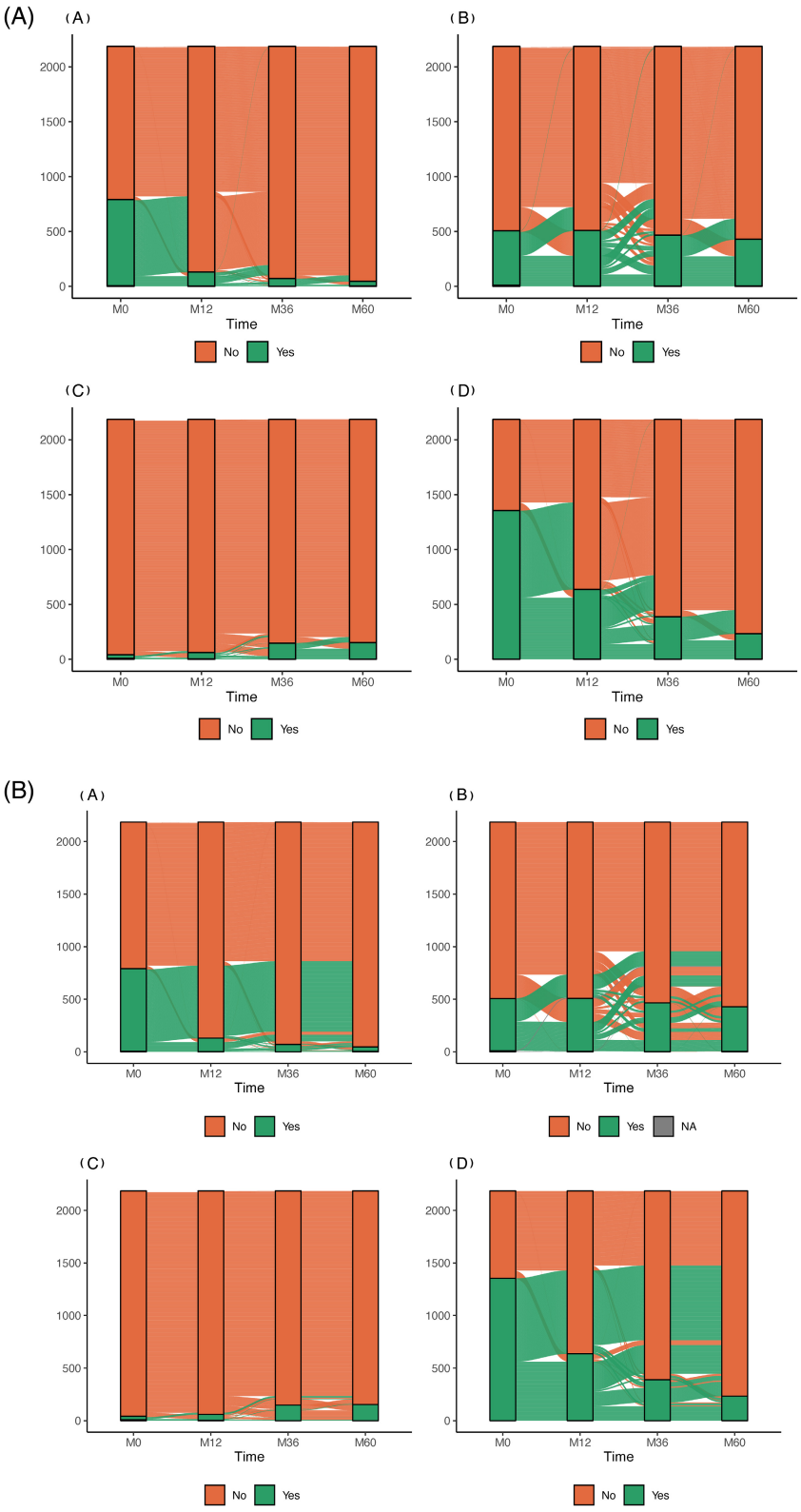

FIGURE 3 (A) Follow-up on changes in skin toxicities of interest over time (Sankey plot). (B) Evolution of skin toxicities of interest over time for a given patient (Sankey plot). [Color figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

We studied 8561 patients extracted from the CANTO database updated in June 2022. Patients had a mean age of 56.3 years and 80.2% had a BMI <30. Most patients had SBR grade 1-2, TNM 1-2, RH+/HER2−. Exactly 53.8% had received chemotherapy, and the majority of patients had breast-conserving surgery (Table 1). The prevalence of toxicities of interest evolved over time (Figure 2).

At M0, 30.3% of patients presented erythema and 17.7% postsurgical fibrosis, while between M0 and M60, the prevalence of erythema decreased from 30.3% to 2%, while the prevalence of fibrosis remained stable. The prevalence of telangiectasias remained relatively low during follow-up, increasing from 0.8% to 7% between M0 and M60. Skin colour change decreased significantly over time, from 51.1% to 10.6% (between M0 and M60). The different variations in the toxicities of interest over time (M0-M12, M12-M36 and M36-M60) are shown in Figure 3A. The specific evolution of these toxicities for each patient from M0 has been reported in Figure 3B. The toxicities presented in Figure 3A,B are mainly Grade I and II, with rare cases of Grade III toxicity and none of Grade 4 or 5 (Table 2). After adjustment, at M0, there were several statistically significant associations between the occurrence of skin erythema and the factors assessed, such as obesity, presence of axillary dissection, type of surgery (lumpectomy vs mastectomy), patient age and hormone receptor (HR)+/HER2+ tumour phenotype (OR: 0.79 [0.67-0.93] $P = .032$) (Table 3). At M12, only a few factors remained statistically associated with the occurrence of cutaneous erythema, such as obesity, the presence of an axillary dissection and the type of surgery (Table 3). Regarding fibrosis, we found a statistically significant association (at M0) between fibrosis and patient age, obesity, smoking status, tumour grade and Charlson score. Other factors related to the treatment received by the patient were also highlighted, such as the use of at least one taxane and the type of surgery (Table 4). The risk factors for the development of cutaneous fibrosis varied over time. Only obesity, Charlson score and the type of surgery performed by patients remained statistically associated with the development of fibrosis over time, particularly at the M60 assessment (Table 4). Obesity and the age of patient were the only factors found to impact telangiectasia occurrence (Table 5). At M60, only obesity was correlated with the appearance of telangiectasias. Regarding skin colour change, several individual factors were found to be associated with the occurrence of this toxicity, such as patient age, obesity, tobacco consumption and Charlson score. Other risk factors linked to the treatments received by the patient and tumour characteristics, such as tumour grade or mitotic index, were significantly associated with skin colour change (Table 6). Over the duration of the assessments, the risk factors associated with the occurrence of skin colour change evolved, in particular, an association was found between skin colour change and alcohol consumption (OR: 0.69 [0.51-0.91] $P = .009$) (Table 6). However, at M60, only the Charlson score remained statistically associated with the appearance of a skin colour change.

4 | DISCUSSION

In our study we present the latest results of the CANTO study in terms of skin toxicity. Our study allowed us to confirm the results already presented in the CANTO-RT study and extend them. Indeed, we were more interested in the intrinsic characteristics of the patients (Charlson score, tobacco consumption …), of the tumours (mitotic index, hormonal status …) but also in the systemic medical treatment

TABLE 2 Grade CTCAEv4 of toxicities of interests.

	M0 (n = 8561)				M12 (n = 7054)				M36 (n = 4540)				M60 (n = 2185)			
(%)	Grade 0	Grade 1	Grade 2	Grade 3-4	Grade 0	Grade 1	Grade 2	Grade 3-4	Grade 0	Grade 1	Grade 2	Grade 3-4	Grade 0	Grade 1	Grade 2	Grade 3-4
Erythema	69.7	22.3	7.3	0.7	94.6	4.3	0.9	0.2	97.5	2.3	0.2	0	98	1.7	0.3	0
Fibrosis	82.3	15	2.4	0.3	80.7	16.9	2.3	0.1	81	16.7	2.1	0.2	80.5	17.3	2.1	0.1
Telangiectasia	99.2	0.7	0.1	0	98	1.8	0.2	0	94.4	5.2	0.4	0	93	6.5	0.5	0
Skin colour	48.9	40.8	9.6	0.7	76.2	21.8	1.9	0.1	85.8	13.7	0.5	0	89.4	10.3	0.4	0

TABLE 3 Skin toxicity of interest: Erythema at M0 and M12 (multivariate analysis).

	M0 (n = 8561)			M12 (n = 7054)		
	N	OR [95% CI]	*P*-value	N	OR [95% CI]	*P*-value
Obesity						
No	6616		<.001	5294		<.001
Yes	1651	1.43 [1.27-1.60]		1311	2.39 [1.89-3.00]	
Type of surgery						
Conservative surgery	6549		<.001	5266		<.001
Mastectomy	1718	0.70 [0.61-0.80]		1339	0.43 [0.30-0.61]	
Axillary dissection						
No	5235		<.001	4240		.005
Yes	3032	1.28 [1.15-1.43]		2365	1.42 [1.11-1.80]	
Age at diagnosis						
50-65 years	3684	1.00 [0.90-1.12]	.025			
>65 years	2010	0.86 [0.75-0.98]				
Smoking status						
Non-smoker	4941		.055			
Former smoker	1831	0.87 [0.77-0.98]				
Smoker	1495	0.94 [0.82-1.06]				
Phenotype						
RH+/HER2−	6296		.032			
RH+/HER2+	866	0.79 [0.67-0.93]				
RH−/HER2+	314	0.93 [0.72-1.20]				
RH−/HER2−	791	1.03 [0.88-1.21]				
Mitotic index						
0-9 mitoses				3850		.084
10-18 mitoses				1532	1.32 [1.02-1.70]	
>18 mitoses				1223	1.22 [0.91-1.62]	

received (chemotherapy, surgery, targeted therapy …). In our study we have a larger recruitment because we studied also the patients who did not receive radiotherapy and the follow-up is 5 years.

Thus, we were able to identify different risk factors for skin toxicity such as obesity, the type of surgery or the performance of an axillary dissection as risk factors for the appearance of skin erythema over time. While tumour grade, obesity and Charlson score as well as the type of surgery received by the patient are related to the onset of fibrosis over the course of the follow-up. The incidence of telangiectasia is primarily related to age and obesity, as well as to the modification of skin colour, to which is added the Charlson score and tumour grade. The burden of comorbidities is a major factor in the occurrence of skin toxicity in patients treated for early-stage breast cancer. The Charlson score is associated with the occurrence of toxicities such as fibrosis or skin colour changes. Comorbidity is a known risk factor for toxicity in patients treated for breast cancer.[22]

Neoadjuvant or adjuvant chemotherapy, was not correlated with increased skin toxicity. After surgery, the use of taxanes also favours the onset of fibrosis at M0, but it is not significantly associated with the onset of cutaneous erythema or with a modification of skin colour, as frequently described. In fact, taxanes are known in the literature and clinical practice for their skin toxicities such as rash and hand-foot syndrome, especially when the patients are treated with Docetaxel.[23-25] Thus, Sparano et al,[24] found, in a prospective phase III study showed an incidence <5.5% of grade ≥3 skin toxicities (erythema, hand-foot syndrome, pigmentation, etc). A hand-foot reaction, erythema and desquamation occurred in 3% to 4% of patients who received docetaxel vs <2% in the Anthracycline/cyclophosphamide and <0.5% in the Paclitaxel group, respectively. Furthermore, the advent of new therapeutic strategies[12,26] and therapeutic combinations,[14] potentiate the risk of skin side effects. Indeed, the use of CDK4-6 inhibitor increases the occurrence of skin toxicity as reported by Raschi et al.[27] The onset of vitiligo (ROR 8.88; 95% CI [2.95-22.46]) and bullous dermatitis was significantly associated with ribociclib (ROR 2.90; 95% CI [1.13-6.27]) while the appearance of erythema multiforme was statistically associated with the use of abemaciclib (ROR 5.80; 95% CI [2.57-11.48]). The introduction of immunotherapy in the early management of patients treated for early stage breast cancer, especially for triple negatives,[28] allowed reinforcing the therapeutic armamentarium. However, it is

TABLE 4 Skin toxicity of interest: Fibrosis at M0, M12, M36 and M60 (multivariate analysis).

	M0 (n = 8561)			M12 (n = 7054)			M36 (n = 4540)			M60 (n = 2185)		
	N	OR [95% CI]	*P*-value	N	OR [95% CI]	*P*-value	N	OR [95% CI]	*P*-value	N	OR [95% CI]	*P*-value
Smoking status												
Non smoker	4192		<.001									
Former smoker	1558	1.35 [1.17-1.57]										
Smoker	1255	1.15 [0.97-1.36]										
Age at diagnosis												
50-65 years	3111	1.13 [0.97-1.32]	.005	2629	1.30 [1.10-1.53]	<.001	1746	1.06 [0.86-1.31]	.217	831	1.35 [1.00-1.83]	.099
>65 years	804	1.34 [1.12-1.60]		1503	1.45 [1.21-1.75]		987	1.22 [0.97-1.55]		469	1.10 [0.77-1.56]	
Obesity												
No	5623		<.001	4812		<.001	3135		<.001	1497		<.001
Yes	1382	1.36 [1.18-1.58]		1141	1.55 [1.33-1.81]		723	1.64 [1.35-2.00]		336	1.82 [1.36-2.41]	
Axillary dissection												
No				3829		.173	2502		.011	1166		.417
Yes				2124	1.12 [0.95-1.33]		1356	0.75 [0.60-0.94]		667	0.88 [0.64-1.20]	
Type of surgery												
Conservative surgery	5571		<.001	4758		<.001	3092			1489		<.001
Mastectomy	1434	0.45 [0.37-0.55]		1195	0.30 [0.23-0.38]		766	0.34 [0.25-0.46]	<.001	344	0.31 [0.19-0.48]	
Clinical lymph node invasion												
No	6103		.57	5220		.227	3389			1627		.599
Yes	902	0.94 [0.76-1.16]		733	0.86 [0.68-1.09]		469	0.85 [0.61-1.16]	.301	206	0.89 [0.55-1.38]	
Charlson at enrolment												
0	5667		.03	4835		.002	3144		<.001	1493		.003
1	776	1.22 [1.01-1.47]		632	1.42 [1.17-1.73]		389	1.49 [1.16-1.91]		189	1.61 [1.12-2.28]	
>1	562	1.24 [1.00-1.53]		486	0.99 [0.78-1.25]		325	0.75 [0.54-1.02]		151	0.64 [0.39-1.02]	
Grade												
SBR I	1241		.007	1070		.017	705		.276			
SBR II	3725	0.89 [0.75-1.06]		3205	0.84 [0.70-1.01]		2054	0.84 [0.67-1.05]				
SBR III	2039	0.64 [0.48-0.85]		1678	0.64 [0.48-0.87]		1099	0.78 [0.53-1.15]				
Mitotic index												
0-9 mitoses	4025		.059	3467		.011	2263		.682	1099		.393
10-18 mitoses	1651	1.24 [1.04-1.48]		1400	1.34 [1.11-1.62]		888	1.07 [0.83-1.37]		401	1.04 [0.75-1.43]	
>18 mitoses	1329	1.18 [0.90-1.54]		1086	1.30 [0.97-1.74]		707	0.94 [0.65-1.37]		333	0.79 [0.52-1.18]	

TABLE 4 (Continued)

	M0 (n = 8561)			M12 (n = 7054)			M36 (n = 4540)			M60 (n = 2185)		
	N	OR [95% CI]	P-value	N	OR [95% CI]	P-value	N	OR [95% CI]	P-value	N	OR [95% CI]	P-value
At least taxane												
No	3395		.042	2911		.249	1883		.155	897		.153
Yes	3610	1.18 [1.01-1.39]		3042	1.11 [0.93-1.32]		1975	1.18 [0.94-1.47]		936	1.26 [0.92-1.73]	
Phenotype												
RH+/HER2-	5378		.38							1424		.084
RH+/HER2+	708	0.90 [0.71-1.12]								178	1.05 [0.68-1.60]	
RH-/HER2+	260	1.09 [0.76-1.53]								71	0.34 [0.12-0.81]	
RH-/HER2-	659	1.15 [0.91-1.45]								160	0.89 [0.54-1.42]	

also accompanied of a risk of toxicities. In fact, PDL-1/PD-1 inhibitors can induce skin toxicity alone[13,26] or combined with chemotherapy or checkpoint inhibitors.[12,29] Thus, in the Sibaud et al study,[30] the onset of ≥grade 3 erythema was found in ~2% of patients receiving Pembrolizumab or Nivolumab monotherapy. The anti-PD1 and anti-CTLA-4 combination increases the onset of cutaneous erythema to 3% to 5%. The use of an adjuvant treatment also increases the risk of skin toxicity, such as radiotherapy[7,31] or drug treatments such as Capecitabine.[32]

Moreover, the correlation between the tumour phenotype, in particular the HR/HER2 profile, and the occurrence of skin erythema or the correlation between the mitotic index and fibrosis as well as the modification of the skin coloration at M12 is a new notion. Indeed, no study in the literature has evaluated the impact of tumour phenotype and the occurrence of skin toxicity. Some authors have evaluated the correlation between genetic mutation, such as BRCA, and increased toxicity.[33,34] It is difficult for us to date to argue the relationship between these tumour characteristics and the occurrence of skin toxicity contained in the state of the literature on this subject.

The prevalence of toxicities of interest evolves differently over time. We were able to see, via a Sankey plot analysis, that the majority of cutaneous erythema and modification of skin colour strongly decreases over time (Figures 1 and 3A). As for fibrosis, it remains globally stable over time. The fibrosis between M12 and M36 adds itself to the pre-existing postsurgical fibrosis at M0. We also observed, considerable rearrangements in the appearance and disappearance of fibrosis between M12 and M36, which indicates a reversibility of the post-treatment (surgical and radio-induced) fibrotic appearance. However, it remains globally compensated by the appearance of a later fibrosis in M36 and M60 probably postradiotherapy. About telangiectasia, there is a constant progression over time but remain marginal.

Radiotherapy is one of the fundamental treatments in the management of patients with early-stage BC. Skin toxicities constitute the main toxicity of radiotherapy and in some cases may result in the discontinuation of treatment. In our previous study,[7] we identified the radiotherapy procedures that influence the onset of skin toxicity, such as an increase in the onset of radiodermatitis in 3D techniques in comparison with IMRT, as well as increased incidence of pigmentation when a boost was used. The patient characteristics and tumour presentation associated with the occurrence of skin toxicity in patients treated for early breast cancer who have received radiotherapy have already been evaluated and reported in our previous study.

This prospective and multicentre, high level of evidence study allowed identifying numerous risk factors that favour the onset of skin toxicity. The large number of persons evaluated in our study makes it one of the biggest series on the subject. However, there are limits. In fact, the lack of data collected, and patients lost to follow-up over time decreases the power of the study. Furthermore, since the outcome measures were subjective data, there are inter- and intraevaluator variations. This characteristic is common to all studies on the subject, because to date, the evaluation of toxicities remains primarily clinical and based on visual scales.[6,9] There are new innovative means to obtain reliability and reproducibility in the analysis of skin toxicities

TABLE 5 Skin toxicity of interest: Telangiectasia at M12, M36 and M60 (multivariate analysis).

	M12 (n = 7054)			M36 (n = 4540)			M60 (n = 2185)		
	N	OR [95% CI]	*P*-value	N	OR [95% CI]	*P*-value	N	OR [95% CI]	*P*-value
Age at diagnosis									
50-65 years	2814	1.80 [1.11-3.04]	.004	2018	1.46 [1.04-2.09]	.003	996		.483
>65 years	1595	2.35 [1.41-4.05]		1125	1.87 [1.30-2.73]		548	1.13 [0.75-1.72]	
Obesity									
No	5069		<.001	3559		<.001	1766		<.001
Yes	1222	1.97 [1.34-2.86]]		857	2.32 [1.75-3.06]		415	2.24 [1.56-3.20]	
Charlson at enrolment									
0	5087		.082						
1	676	1.75 [1.07-2.76]							
>1	528	1.22 [0.66-2.11]							

TABLE 6 Skin toxicity of interest: Skin colour at M12, M36 and M60 (multivariate analysis).

	M12 (n = 7054)			M36 (n = 4540)			M60 (n = 2185)		
	N	OR [95% CI]	*P*-value	N	OR [95% CI]	*P*-value	N	OR [95% CI]	*P*-value
Age at diagnosis									
50-65 years	2725	0.87 [0.76-1.01]	.002	1861	0.84 [0.68-1.04]	.004	904	1.10 [0.79-1.54]	.256
>65 years	1567	0.74 [0.62-0.88]		1042	0.66 [0.51-0.84]		506	0.81 [0.54-1.22]	
Obesity									
No	4903		<.001	3338		<.001	1606		.147
Yes	1195	1.85 [1.61-2.14]		779	1.73 [1.41-2.13]		372	1.30 [0.91-1.84]	
Smoking status									
Non smoker	3684		<.001						
Former smoker	1383	1.34 [1.16-1.54]							
Smoker	1031	1.34 [1.14-1.58]							
Grade									
SBR I	1097		<.001	749		.021			
SBR II	3289	0.76 [0.65-0.90]		2190	0.81 [0.64-1.02]				
SBR III	1712	0.60 [0.46-0.78]		1178	0.69 [0.53-0.90]				
Mitotic index									
0-9 mitoses	3564		.003						
10-18 mitoses	1413	1.34 [1.13-1.59]							
>18 mitoses	1121	1.18 [0.91-1.53]							
Charlson at enrolment									
0	4929		<.001	3355		<.001	1607		.009
1	659	1.60 [1.33-1.92]		415	1.64 [1.26-2.12]		205	1.32 [0.85-2.02]	
>1	510	0.93 [0.74-1.15]		347	0.70 [0.48-1.00]		166	0.44 [0.20-0.83]	
Type of surgery									
Conservative surgery	4870		<.001	3293		.008			
Mastectomy	1228	0.73 [0.62-0.85]		824	0.73 [0.57-0.92]				
Daily alcohol consumption									
No				3559		.009	1710		.783
Yes				558	0.69 [0.51-0.91]		268	0.94 [0.60-1.43]	

via ultrasonography and spectrometry.[8,35,36] However, their routine use remains difficult due to the logistics required.

Skin toxicities represent one of the most common toxicities and are sometimes difficult to live with for the patient, because they represent the visible aspect of the disease.[37,38] Thus, the evaluation of their impact on the quality of life and the cosmetic damage should be evaluated and will be the subject of a new study.

5 | CONCLUSION

In our study, we identified several intra- and interindividual risk factors, as well as treatment and tumour characteristics, that influence the occurrence of skin toxicities. Individual factors such as obesity, age and smoking interfere with the occurrence of skin toxicities such as fibrosis. While certain treatment-related factors, such as axillary lymph node dissection or the type of surgery received by the patient, increase the occurrence of cutaneous erythema.

Understanding these risk factors enables us to adapt our management of patients at risk of developing skin toxicities. With this knowledge, we can ensure personalised follow-up of these at-risk patients and set up appropriate treatment protocols to limit the occurrence of such toxicities.

Identifying the factors influencing the occurrence of toxicities is essential to understanding the side effect of our treatments and improving patients' quality of life using appropriate therapies.

AUTHOR CONTRIBUTIONS

All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version. The work reported in the article has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

Paul Cottu received honoraria from Pfizer, Lilly, Pierre Fabre, Novartis, NanoString Technologies, Seagen; advisory fees from Pfizer, Roche/Genentech, Lilly; research funding from Novartis, Pfizer; travel, accommodation, expenses from Roche, Pfizer, all outside the study. Fabrice Andrè received research funding and speaker/advisor fees (compensated to the hospital) from Roche, AstraZeneca, Daiichi Sankyo, Pfizer, Novartis and Lilly, all outside the study. The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon request.

ETHICS STATEMENT

All patients provided written informed consent. The study was approved by the French ethics committee, CPP – Ile de France 7, on 14 October 2011 (ref 11-039) and the French health authorities, ANSM, on 14 September 2011 (ref 2011-A011095-36).

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