ANTICANCER RESEARCH *40*: 1041-1048 (2020)
doi:10.21873/anticanres.14040

Treatment and Other Healthcare Use of Breast Cancer Patients With a Previous Cancer Diagnosis

SAMANTHA MORAIS[1,2], ANA RUTE COSTA[1], LUISA LOPES-CONCEICAO[1], MARIANA BRANDAO[3], MARINA BORGES[4,5], NATALIA ARAUJO[1], TERESA DIAS[4], FILIPA FONTES[1,2,4], SUSANA PEREIRA[1,4] and NUNO LUNET[1,2]

[1]*EPIUnit - Instituto de Saúde Pública, University of Porto, Porto, Portugal;*
[2]*Department of Forensic and Public Health Sciences and Medical Education, Faculty of Medicine, University of Porto, Porto, Portugal;*
[3]*Academic Promoting Team - Institute Jules Bordet, Brussels, Belgium;*
[4]*Instituto Português de Oncologia do Porto FG, EPE (IPO-Porto), Porto, Portugal;*
[5]*National School of Public Health, Universidade Nova de Lisboa, Lisbon, Portugal*

Abstract. *Background/Aim: To quantify the association between a previous cancer diagnosis and healthcare use among breast cancer (BC) patients, and estimate five-year recurrence-free survival (RFS). Patients and Methods: Women with BC were classified according to a previous cancer diagnosis (BC or other). Healthcare use during the first year and five-year RFS were obtained through clinical and administrative records. Adjusted odds ratios and hazard ratios (HR) were estimated. Results: Among 681 BC patients, 21 had a previous BC and 32 a previous non-BC. The latter were less likely to receive anthracycline-based combination chemotherapy. The former had higher odds of mastectomy and genetic testing. Five-year RFS HRs (95% confidence interval) were 2.75 (0.79-9.52) and 0.52 (0.07-3.89) for previous BC and non-BC, respectively. Conclusion: Previous cancer was associated with less anthracycline-based combination chemotherapy, and patients were more likely to undergo mastectomy and genetic testing. These findings highlight the need for assessment of previous treatments, personal genetic risk and current BC characteristics.*

The number of cancer survivors is growing, reflecting increases in the overall number of cancer cases and improvements in prognosis, due to earlier detection and improved treatment (1). In 2018, there was an estimated worldwide incidence of over 18 million cancer cases, and estimates are expected to reach nearly 30 million by 2040 (2). This has led to a growing burden associated with cancer survivorship as a higher number of individuals are diagnosed with subsequent primary cancers (3). In particular, not only are women with a first breast cancer at substantially greater risk of a contralateral breast cancer compared to the general population (4-6), but survivors of other cancer sites, namely endometrial, ovarian, colon, thyroid and Hodgkin lymphoma, also have elevated risks of breast cancer as a subsequent malignancy (7-9).

The development of multiple primary cancers has been studied for many cancers and types of treatment (10). In general, cancer survivors may be susceptible to develop a subsequent cancer due to a variety of factors, including increased genetic susceptibility, shared risk factors, effects of previous oncological treatments and a greater diagnostic surveillance (11). Moreover, patients diagnosed with a subsequent cancer pose greater challenges to medical professionals, as prior treatments and their toxicities must be taken into account when deciding the therapeutic plan for that specific patient (8).

However, there is a lack of information about the impact of a previous cancer diagnosis on the clinical management of cancer patients and their use of healthcare resources. In fact, no studies have examined this among women with breast cancer, which accounts for almost one-quarter of all cancers in women (2). Therefore, the aim of this study was to quantify the association between a previous cancer diagnosis and the treatment and other healthcare use among a cohort of breast cancer patients, and to estimate five-year recurrence-free survival (RFS).

Correspondence to: Nuno Lunet, Department of Forensic and Public Health Sciences and Medical Education, Faculty of Medicine, University of Porto, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal. Tel: +351 225513652/220426640, e-mail: nlunet@med.up.pt

Key Words: Breast neoplasm, healthcare use, second primary neoplasms, treatment.

Patients and Methods

Study design and participants. This study included women newly diagnosed with in situ or invasive breast cancer admitted to the Breast Clinic of the Portuguese Institute of Oncology of Porto (IPO-Porto) in 2012 and is based on a previously described prospective cohort study (12). For the present study, participants were eligible if they were aged 18 years or older, with histologically confirmed breast cancer, proposed for surgery, either as primary treatment or after neoadjuvant chemotherapy and, if applicable, expected to receive cancer treatments other than surgery at IPO-Porto. Those who could understand the purposes of the study and were willing to collaborate were included. Further, women with stage IV breast cancer were excluded (n=12) (Figure 1).

Data collection. Sociodemographic data were collected through face-to-face interviews using a structured questionnaire.

Information on stage and immunohistochemistry (IHC) assessment of the breast cancer diagnosed in 2012, and the existence of a previous or subsequent primary cancer was collected from clinical records. Cancer stage was classified according to the seventh American Joint Committee on Cancer staging manual (13). As per the American Society of Clinical Oncology/College of American Pathologists guidelines, tumours were considered to be hormone receptor-positive (HR+) if the expression of estrogen receptor and/or progesterone receptor was ≥1% and HER2-positive (HER2+) if they had an IHC score ≥3 or, alternatively, a score ≥2 with a FISH-amplified result (14). Breast tumours were categorized according to the following IHC-based subtypes: HR+/HER2-negative (HR+/HER2–); HER2+; triple negative (HR–/HER2–). Other primary cancers were considered when a malignancy was diagnosed in the contralateral breast or in another site or tissue, which were not a loco-regional recurrence or metastasis. Further, as per the guidelines proposed by the International Association of Cancer Registries and the International Agency for Research on Cancer, different morphologies (even with the same topography) or dissimilar topographies were regarded as multiple primary cancers, regardless of the time between diagnoses (15).

Data regarding treatment and other healthcare use during the first year following breast cancer diagnosis in 2012 were obtained from clinical and administrative records. Information on treatment included surgery (*i.e.*, breast and axillary), systemic (*i.e.*, chemotherapy, hormone therapy and targeted therapy) and radiation (*i.e.*, external radiotherapy and brachytherapy). Data on healthcare use were obtained regarding the number of appointments [*i.e.*, outpatient visits (medical and surgical oncology, and radiation therapy), and nursing, psychology and social services appointments], and hospitalizations, which were defined taking into account percentile 75 of the distribution among those with no previous cancer (≥36 and ≥2, respectively). Finally, genetic testing was considered as having any relevant test carried out [*i.e.*, *BRCA1*/*BRCA2* mutations (hereditary breast and ovarian cancer syndrome); deletions of *MLH1* (hereditary nonpolyposis colon cancer); *TP53* mutation (Li-Fraumeni syndrome)].

Information on recurrence or death by any cause following the diagnosis of breast cancer in 2012 up to five years post diagnosis was also obtained from clinical records.

Statistical analysis. Patients' characteristics are presented as counts and proportions for all categorical variables, and median with percentiles 25 and 75 (P25-P75) for quantitative variables.

For statistical analysis, women with a breast cancer diagnosed in 2012 were divided according to the existence of a previous primary cancer: 1) no previous primary cancer (first breast cancer in 2012); 2) previous breast cancer diagnosis (breast cancer in 2012 + previous breast cancer); 3) previous non-breast cancer diagnosis (breast cancer in 2012 + previous non-breast cancer). Women with a subsequent primary cancer diagnosed in 2012 or 2013 were excluded from the analysis (n=6).

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were computed using multinomial logistic regression to quantify the association between a previous cancer diagnosis and treatment and other healthcare use in the first year following a breast cancer diagnosis in 2012. Models were adjusted for age (continuous variable), education (≤4, 5-9, ≥10), stage (0/I, II, III) and IHC-based subtypes (HR+/HER2–, HER2+, triple negative).

RFS was defined as the time between the date of breast cancer diagnosis in 2012 and the date of breast cancer recurrence or death by any cause, whichever occurred first (16). RFS was calculated using the Kaplan–Meier estimator (17). Patients who remained without an event by the end of the five-year follow-up period and those lost to follow-up were censored, considering the date referring to the last follow-up registered.

Cox proportional hazards regression analyses were used to compute hazard ratios (HR) for recurrence or death by any cause adjusted for age (continuous variable), education (≤4, 5-9, ≥10) and stage (0/I, II, III) with the corresponding 95%CI. The proportional hazards assumption was evaluated using Schoenfeld residuals.

Ethics. The study received ethical approval from the Ethics Committee of the Portuguese Institute of Oncology of Porto (ref. CES 406/011, CES 99/014 and CES 290/014) and the national research committee [Portuguese Data Protection Authority (ref. 9469/2012 and 8601/2014)]. Informed consent was obtained from all individual participants included in the study.

Results

Participants' sociodemographic and clinical characteristics according to previous cancer history are shown in Table I. Among 681 women with a breast cancer diagnosed in 2012, 21 (3.1%) had a prior primary breast cancer diagnosis and 32 (4.7%) had a previous non-breast cancer. In 2012, over two-thirds of those with a previous breast cancer were 65 or older (66.7%), while 43.6% and 43.7% of women with a first breast cancer and a previous non-breast cancer were aged between 50 and 64 years old, respectively. More than half of the women had successfully completed more than four years of education (53.3%), while close to two-thirds lived outside the Porto Metropolitan Area (63.3%). Regarding clinical characteristics, half of the patients were diagnosed with stage 0/I breast cancer in 2012 (51.5%) and over two thirds presented with HR+/HER2– tumours (76.4%). Most previous breast cancers were diagnosed more than 10 years before the current breast cancer diagnosis (71.4%), while 43.8% of previous non-breast cancers were diagnosed between five and 10 years before the present breast cancer diagnosis. The most common previous cancer sites were female genital

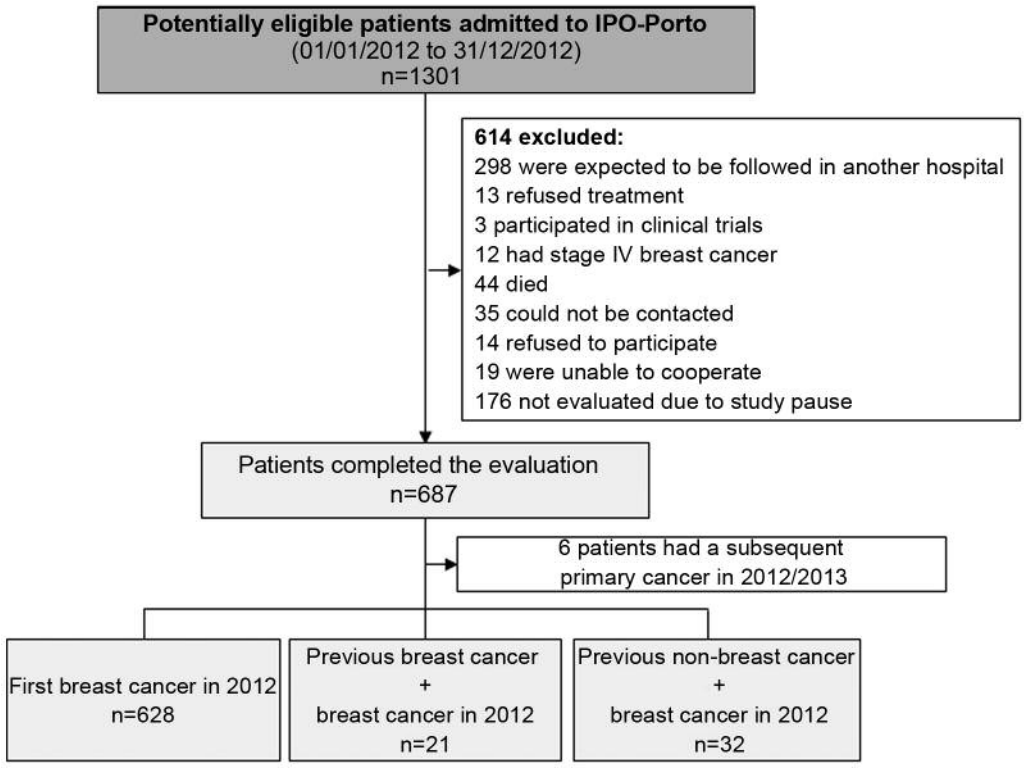

Figure 1. *Flowchart of patient inclusion in the study.*

organs (21.9%), thyroid and other endocrine glands (18.7%), digestive organs (15.6%), and melanoma and other malignant neoplasms of skin (15.6%).

Table II shows the association between a previous cancer diagnosis and treatment and other healthcare use in the first year following a breast cancer diagnosis in 2012. After adjusting for age and education, women with a previous breast cancer had higher odds of undergoing mastectomy versus breast-conserving surgery (OR=4.17; 95%CI=1.36-12.72). Regarding chemotherapy, women with a previous non-breast cancer diagnosis were significantly less likely to receive anthracycline-based combination chemotherapy (OR=0.03; 95%CI=0.01-0.20). This association was also observed among women with a previous breast cancer though was not statistically significant (OR=0.23; 95%CI=0.02-2.57). Finally, women with a previous breast cancer had significantly higher odds of undergoing genetic testing (OR=14.82; 95%CI=3.60-61.01); this was also seen for women with a previous non-breast cancer though was not statistically significant (OR=2.05; 95%CI=0.65-6.44). Estimates remained essentially the same when breast cancer stage and IHC-based subtype were added to the model (Table II).

Five-years following breast cancer diagnosis in 2012, 23 events (recurrence or death by any cause) had occurred among women with a first breast cancer in 2012, three events (recurrence or death by any cause) in women with a previous breast cancer, while no events (recurrence or death by any cause) were observed for women with a previous non-breast cancer (Figure 2). Compared to women with a first breast cancer in 2012, the age and education adjusted HRs (95%CI) were 3.43 (1.01-11.59) for women with a previous breast cancer and 0.57 (0.08-4.26) for women with a previous non-breast cancer. The corresponding age, education and stage adjusted estimates were 2.75 (95%CI=0.79-9.52) and 0.52 (95%CI=0.07-3.89).

Discussion

The present study shows that in the first year following a breast cancer diagnosis, women with a previous cancer were less likely to receive any anthracycline-based combination chemotherapy. Additionally, women with a previous cancer had higher odds of undergoing mastectomy and genetic testing.

In general, cancer treatment has evolved extensively over the past few decades shifting to less aggressive local treatment and to an increase in the use of systemic treatment (18). Regardless, patients with a previous primary cancer are an added challenge as prior treatments must be taken into

Table I. *Sociodemographic and clinical characteristics of breast cancer patients in 2012.*

Characteristics	First breast cancer in 2012 (N=628)	Breast cancer in 2012+ previous breast cancer (N=21)		Breast cancer in 2012+ previous non-breast cancer (N=32)	
	N (%)	N (%)	*p*-Value[a]	N (%)	*p*-Value[b]
Age (years)					
<50	214 (34.1)	2 (9.5)		10 (31.3)	
50-64	274 (43.6)	5 (23.8)		14 (43.7)	
≥65	140 (22.3)	14 (66.7)	<0.001	8 (25.0)	0.918
Education (years)					
≤4	289 (46.0)	13 (61.9)		16 (50.0)	
5-9	162 (25.8)	3 (14.3)		8 (25.0)	
≥10	177 (28.2)	5 (23.8)	0.317	8 (25.0)	0.895
Place of residence					
Porto Metropolitan Area	221 (35.4)	11 (52.4)		16 (51.6)	
Outside the Porto Metropolitan Area	403 (64.6)	10 (47.6)	0.111	15 (48.4)	0.067
Breast cancer stage					
0/I	327 (52.1)	7 (35.0)		16 (50.0)	
II	216 (34.4)	9 (45.0)		8 (25.0)	
III	85 (13.5)	4 (20.0)	0.315	8 (25.0)	0.161
Immunohistochemistry-based subtypes[c]					
HR+/HER2–	454 (75.8)	17 (81.0)		27 (84.4)	
HER2+	98 (16.4)	2 (9.5)		4 (12.5)	
Triple negative	47 (7.8)	2 (9.5)	0.694	1 (3.1)	0.481
Previous cancer diagnosis (years)					
≤2001	--	15 (71.4)		8 (25.0)	
2002-2006	--	4 (19.1)		10 (31.2)	
≥2007	--	2 (9.5)	--	14 (43.8)	--
Previous cancer site					
Digestive organs	--	--		5 (15.6)	
Melanoma and other malignant neoplasms of skin	--	--		5 (15.6)	
Female genital organs	--	--		7 (21.9)	
Urinary tract	--	--		3 (9.4)	
Thyroid and other endocrine glands	--	--		6 (18.7)	
Other[d]	--	--	--	6 (18.7)	--

The total may not add to 681 due to missing data. May not sum to 100.0% due to rounding. [a]Breast cancer in 2012 + previous breast cancer *versus* first breast cancer in 2012. [b]Breast cancer in 2012 + previous non-breast cancer *versus* first breast cancer in 2012. [c]Immunochemistry-based subtypes were defined according to the assessment of estrogen receptor, progesterone receptor and HER2 on the surgical specimen. HR+/HER2–: estrogen receptor and/or progesterone receptor positive and HER2-negative (score <2 in immunohistochemistry and/or a score ≥2 with a non-amplified FISH test result); HER2+: HER2-positive (score ≥3 in immunohistochemistry and/or a score ≥2 with an amplified FISH test result), regardless of the estrogen and progesterone receptors status; triple negative: estrogen receptor negative, progesterone receptor negative and HER2-negative. [d]Other previous sites include: mesothelial and soft tissue, osteosarcoma, Hodgkin lymphoma and not specified.

account. We found that patients with a previous cancer had lower odds of receiving anthracycline-based combination chemotherapy, which is still part of the (neo)adjuvant chemotherapy backbone in breast cancer (19). Further, these patients also had lower odds of being submitted to radiotherapy. These findings may be a result of the prior cancer treatment received by these patients, namely radiation and chemotherapy, as there are lifetime dose limits as well as residual toxicity (8, 20, 21). For radiation in particular, patients often cannot receive radiation therapy to a specific or an adjacent area a second time as a result of dose-limiting toxicities (8, 20).

Women with a previous breast cancer diagnosis were more likely to undergo mastectomy versus breast-conserving surgery. This result remained statistically significant following adjustment for stage and IHC-based subtype, which are intermediate steps in this relation. It is possible that a more aggressive approach may be used among patients with a previous breast cancer, as previous studies have found that contralateral breast cancers are more difficult to treat than the

Table II. *Association between a previous cancer diagnosis and the treatment and other healthcare use in the first year following a breast cancer diagnosis in 2012.*

	First breast cancer in 2012	Breast cancer in 2012+ previous breast cancer			Breast cancer in 2012+ previous non-breast cancer		
	(N=628)	(N=21)			(N=32)		
	N (%)	N (%)	OR (95%CI)[a]	OR (95%CI)[b]	N (%)	OR (95%CI)[a]	OR (95%CI)[b]
Surgery							
Breast surgery[c]							
Breast-conserving	342 (54.5)	4 (19.0)	1	1	16 (50.0)	1	1
Mastectomy	286 (45.5)	17 (80.9)	4.17 (1.36-12.72)	3.30 (1.02-10.72)	16 (50.0)	1.00 (0.49-2.07)	0.93 (0.42-2.04)
Axillary surgery[d]							
None or sentinel lymph node biopsy	437 (69.6)	13 (61.9)	1	1	22 (68.7)	1	1
Lymph node dissection	191 (34.4)	8 (38.1)	1.88 (0.74-4.74)	1.11 (0.32-3.81)	10 (32.3)	1.06 (0.49-2.30)	0.60 (0.19-1.95)
Chemotherapy							
Any chemotherapy (Yes)	376 (59.9)	10 (47.6)	1.38 (0.53-3.62)	1.17 (0.37-3.73)	18 (56.2)	0.92 (0.42-2.03)	0.73 (0.29-1.82)
Timing of chemotherapy							
Neoadjuvant	35 (9.4)	0 (0.0)	--	--	2 (11.1)	1	1
Adjuvant	336 (90.6)	10 (100.0)	--	--	16 (88.9)	0.89 (0.19-4.07)	1.08 (0.20-5.73)
Chemotherapy scheme							
Anthracycline-based (Yes)[e]	371 (98.7)	9 (90.0)	0.23 (0.02-2.57)	0.05 (0.00-0.54)	15 (83.3)	0.03 (0.01-0.20)	0.01 (0.00-0.10)
Other treatments							
Radiotherapy (Yes)	469 (74.7)	12 (57.1)	0.65 (0.26-1.63)	0.54 (0.19-1.50)	21 (65.6)	0.68 (0.31-1.47)	0.51 (0.22-1.18)
Brachytherapy (Yes)[f]	127 (27.1)	2 (16.7)	0.44 (0.09-2.12)	0.79 (0.16-3.99)	5 (23.8)	0.82 (0.29-2.29)	0.87 (0.29-2.63)
Hormone therapy (Yes)	534 (85.0)	18 (85.7)	0.91 (0.26-3.21)	0.41 (0.03-5.85)	29 (90.6)	1.69 (0.50-5.66)	0.34 (0.05-2.50)
Targeted therapy (Yes)[g]	92 (14.6)	2 (9.5)	0.86 (0.19-3.85)	--	3 (9.4)	0.61 (0.18-2.06)	--
Healthcare use							
Appointments (≥36)[h]	171 (27.2)	4 (19.0)	1.13 (0.36-3.61)	0.86 (0.25-2.94)	8 (25.0)	0.91 (0.39-2.14)	0.79 (0.32-1.99)
Hospitalization (≥2)	191 (30.4)	4 (19.0)	0.57 (0.19-1.73)	0.66 (0.21-2.06)	12 (37.5)	1.38 (0.66-2.87)	1.40 (0.66-2.95)
Genetic testing (Yes)[i]	55 (8.8)	4 (19.0)	14.82 (3.60-61.01)	21.81 (5.10-93.30)	5 (15.6)	2.05 (0.65-6.44)	1.99 (0.62-6.40)

The total may not add to 681 due to missing data. May not sum to 100.0% due to rounding. 5-FU: 5-fluorouracil. [a]Adjusted for age (continuous) and education (≤4, 5-9, ≥10). [b]Further adjusted for stage (0/I, II, III) and immunohistochemistry-based subtypes (HR+/HER2–, HER2+, triple negative). [c]Patients who had breast-conserving surgery followed by mastectomy are reported as mastectomy. [d]Patients who had sentinel lymph node biopsy followed by lymph node dissection are reported as lymph node dissection. [e]Anthracycline-based chemotherapy includes: AC regimen: four or six cycles of concomitant doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2); FEC regimen: six cycles of concomitant 5-FU (500 mg/m^2), epirubicin (100 mg/m^2) and cyclophosphamide (500 mg/m^2); AC-T regimen: four cycles of concomitant doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) followed by four cycles of docetaxel (100 mg/m^2); AC-paclitaxel regimen: four cycles of concomitant doxorubicin (60 mg/m^2) and cyclophosphamide (600 mg/m^2) followed by four cycles of paclitaxel (80 mg/m^2); FEC-D regimen: three cycles of concomitant 5-FU (500 mg/m^2), epirubicin (100 mg/m^2) and cyclophosphamide (500 mg/m^2) followed by three cycles of docetaxel (100 mg/m^2). [f]Among those who received radiotherapy (n=502). [g]Targeted therapy includes trastuzumab. [h]Appointments: number of outpatient visits (medical oncology and radiation therapy), and nursing, psychology and social services appointments. [i]Genetic testing includes: *BRCA1* mutations; *BRCA2* mutations (hereditary breast and ovarian cancer syndrome); deletions in *MLH1* (hereditary nonpolyposis colon cancer); *TP53* mutations (Li-Fraumeni syndrome).

original cancer due to a more resistant biology and the inability to reuse previous effective therapy, such as anthracycline-based chemotherapy (5, 22). Nonetheless, among the 17 patients with a previous breast cancer who were submitted to mastectomy, five presented with stage IA and five with stage IIA, and of those who underwent genetic testing in the first year, none presented a *BRCA1/2* mutation, suggesting that they may have been over-treated. Likewise, among the 16 patients with a previous non-breast cancer who were submitted to mastectomy, six presented with stage IA/IB.

Several studies have found that hereditary cancer syndromes account for an estimated 5 to 10% of all cancers due to heightened susceptibility of specific cancers (23); as such, patients with multiple primary cancers are expectedly more likely to undergo genetic testing, as observed in our study. In particular, individuals with inherited mutations in *BRCA1/2,*

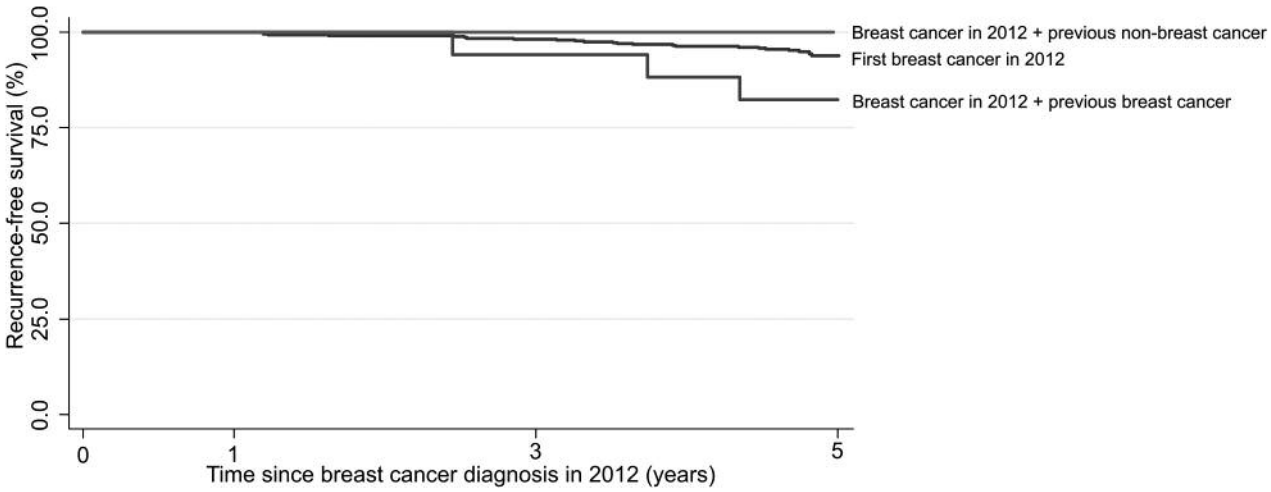

Figure 2. *Recurrence-free survival [calculated using the Kaplan–Meier estimator (17)] of breast cancer patients diagnosed in 2012 according to previous cancer diagnosis.*

TP53 (Li-Fraumeni syndrome) or *MLH1* (hereditary nonpolyposis colon cancer or Lynch syndrome) have an increased risk of developing subsequent cancers, namely of the colon and rectum, breast, uterine body and cervix, thyroid as well as connective tissues (23, 24). In fact, the most common sites of previous cancers in our study were contralateral breast, female genital organs including the cervix, thyroid and digestive organs such as the colon. Nevertheless, only 19.0% of patients with a previous breast cancer and 15.6% of patients with a previous non-breast cancer received genetic testing during the first year following breast cancer diagnosis in 2012. However, when considering younger ages at diagnosis and triple negative subtypes of breast cancer, which are important indicators for hereditary diagnostic testing (25), a larger number of women with a previous cancer diagnosis had genetic tests completed.

We also found that patients with a previous breast cancer had a trend for worse five-year RFS, which is in line with the literature: a contralateral breast cancer diagnosis is negatively associated with survival (26-28). This may not only be related with a more aggressive breast cancer biology, but also with the fact that patients with a previous breast cancer were generally older and as such may have more co-morbidities. Additionally, the cumulative toxicity of treatments for both breast cancers (*i.e.*, chemotherapy, radiotherapy, endocrine therapy) may also impair survival. On the other hand, after adjusting for age, education and stage, patients with a previous non-breast cancer did not have a significantly worse five-year RFS, albeit the lower use of anthracycline-based chemotherapy, which is generally associated with better outcomes (29, 30). However, this analysis is essentially exploratory since the number of events (recurrence or death by any cause) was very small, and a poorer survival of patients with a previous cancer cannot be excluded.

Strengths and limitations. The systematic and thorough evaluation of the treatment and other healthcare use during the first year following a breast cancer diagnosis is a methodological strength of the present study. Data were collected from clinical records by health professionals and other healthcare use data were obtained from administrative records, which allowed us to have high quality data with a low level of missing information.

Our study evaluated essentially women with early breast cancer, which limits generalizability to those with more advanced disease; and women with a subsequent cancer diagnosis in 2012 or 2013 were excluded as this would have influenced the outcome under study. Furthermore, all patients were selected and treated in the same institution; however, IPO-Porto is the largest hospital providing care to cancer patients in Northern Portugal and receives patients referred from a wide geographical area.

The uptake of genetic testing among patients in our study was low, even among those with a previous breast cancer (19.0%), but this may be related to the timing of the analysis: back in 2012/2013, access to genetic testing was lower than what it is nowadays (31), therefore the values presented may no longer reflect current clinical practice. However, it is also possible that women underwent genetic testing outside of IPO-Porto or the time period considered in the current analyses (*i.e.*, before or more than one year following the breast cancer diagnosis in 2012), and this information may not have been available to us for all patients.

Although there were a small number of cases in some strata, the associations found were strong and therefore there was sufficient statistical power. However, as we have a large heterogeneity in the previous non-breast cancer sites, we were unable to perform subgroup analysis, which may have yielded

more consistent results. Similarly, it may have been interesting to evaluate previous cancer treatments received in order to examine possible toxicity levels. However, considering the sample size, these analyses would likely not have yielded meaningful results. Regardless, this is one of the first studies evaluating the association between a previous cancer diagnosis and the treatment and other healthcare use among a cohort of breast cancer patients.

Conclusion

The increasing number of breast cancer patients being diagnosed who have a previous cancer diagnosis requires a specific investigation to understand its impact on the clinical management of these patients and their use of healthcare resources. Our study provides evidence that a previous cancer diagnosis is associated with a lower use of anthracycline-based combination chemotherapy and that these patients are more likely to undergo genetic testing. Furthermore, patients with a previous breast cancer had a higher chance of undergoing a mastectomy, even if they presented with a low-stage disease, which suggests that these patients may have been locally over-treated. Five-year RFS also tended to be worse among patients with a previous breast cancer. As such, these findings highlight that in patients with a previous cancer diagnosis, there is a need for a careful assessment of previous treatments and toxicities, of personal genetic risk and of the present breast cancer's characteristics, in order to avoid over- or under-treatment. A comprehensive and personalized approach is paramount, in order to improve survival and reduce morbidity among patients with multiple cancers.

Conflicts of Interest

Mariana Brandão has received a travel grant, unrelated to this study, from Roche/GNE, and the Institut Jules Bordet has received research grants, unrelated to this study, from Roche/GNE, Radius, AstraZeneca, Lilly, MSD, GSJ/Novartis, Synthon, Servier and Pfizer. Marina Borges has received travel grants, unrelated to this study, from Roche and Janssen. All other Authors declare that they have no conflict of interest (Samantha Morais, Ana Rute Costa, Luisa Lopes-Conceição, Natália Araújo, Teresa Dias, Filipa Fontes, Susana Pereira and Nuno Lunet).

Authors' Contributions

SM performed the statistical analysis and interpreted the data, drafted and revised the manuscript. LC, MB, MB, NA and FF collected the data. ARC, LC, NA, MB, MB, FF, TD and SP critically reviewed the manuscript and made important intellectual contributions. NL supervised the analysis and interpretation of data and reviewed the manuscript. SP and NL conceived, designed and implemented the cohort. NL defined the study hypothesis. All Authors contributed to the discussion of the results. All Authors read and approved the final version of the manuscript.

Acknowledgements

This study was funded by FEDER through the Operational Programme Competitiveness and Internationalization and national funding from the Foundation for Science and Technology – FCT (Portuguese Ministry of Science, Technology and Higher Education), under the project "A five-year prospective cohort study on the neurological complications of breast cancer: frequency and impact in patient reported outcomes" (POCI-01-0145-FEDER-016867; ref. PTDC/DTP-EPI/7183/2014), and the *Unidade de Investigação em Epidemiologia – Instituto de Saúde Pública da Universidade do Porto* (EPIUnit) (POCI-01-0145-FEDER-006862; ref. UID/DTP/04750/2019). SM and LC were also funded under the scope of the project "NEON-PC - Neuro-oncological complications of prostate cancer: longitudinal study of cognitive decline" (POCI-01-0145-FEDER-032358; ref. PTDC/SAU-EPI/32358/2017). Individual grants attributed to ARC (SFRH/BD/102181/2014) and NA (SFRH/BD/119390/2016) were co-funded by FCT and the *Programa Operacional Capital Humano* (POCH/FSE). Data management activities up to the first year of follow-up were supported by the Chair on Pain Medicine of the Faculty of Medicine, University of Porto and by the Grünenthal Foundation – Portugal.

References

1 Parry C, Kent EE, Mariotto AB, Alfano CM and Rowland JH: Cancer survivors: A booming population. Cancer Epidemiol Biomarkers Prev *20(10)*: 1996-2005, 2011. PMID: 21980007. DOI: 10.1158/1055-9965.epi-11-0729

2 Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, Znaor A, Soerjomataram I and Bray F: Global cancer observatory: Cancer today. Lyon, France: International Agency for Research on Cancer; 2018 (Available from: https://gco.iarc.fr/today)

3 Ye Y, Neil AL, Wills KE and Venn AJ: Temporal trends in the risk of developing multiple primary cancers: A systematic review. BMC Cancer *16(1)*: 849-849, 2016. PMID: 27814758. DOI: 10.1186/s12885-016-2876-y

4 Aalders KC, van Bommel AC, van Dalen T, Sonke GS, van Diest PJ, Boersma LJ and van der Heiden-van der Loo M: Contemporary risks of local and regional recurrence and contralateral breast cancer in patients treated for primary breast cancer. Eur J Cancer *63*: 118-126, 2016. PMID: 27299664. DOI: 10.1016/j.ejca.2016.05.010

5 Schaapveld M, Visser O, Louwman WJ, Willemse PH, de Vries EG, van der Graaf WT, Otter R, Coebergh JW and van Leeuwen FE: The impact of adjuvant therapy on contralateral breast cancer risk and the prognostic significance of contralateral breast cancer: A population based study in the Netherlands. Breast Cancer Res Treat *110(1)*: 189-197, 2008. PMID: 17687645. DOI: 10.1007/s10549-007-9709-2

6 Cluze C, Delafosse P, Seigneurin A and Colonna M: Incidence of second cancer within 5 years of diagnosis of a breast, prostate or colorectal cancer: A population-based study. Eur J Cancer Prev *18(5)*: 343-348, 2009. PMID: 19436213. DOI: 10.1097/CEJ.0b013e32832abd76

7 Curtis R, Freedman D, Ron E, Ries L, Hacker D, Edwards B, Tucker M and Fraumeni JJ: New malignancies among cancer survivors: SEER Cancer Registries, 1973-2000. Bethesda, MD: National Cancer Institute. NIH Publ. No. 05-5302; 2006.

8 Vogt A, Schmid S, Heinimann K, Frick H, Herrmann C, Cerny T and Omlin A: Multiple primary tumours: Challenges and

approaches, a review. ESMO Open *2(2)*: e000172-e000172, 2017. PMID: 28761745. DOI: 10.1136/esmoopen-2017-000172

9 Zafon C, Obiols G and Mesa J: Second primary cancer in patients with papillary thyroid carcinoma. Anticancer Res *33(1)*: 337-340, 2013. PMID: 23267166.

10 Travis LB, Wahnefried WD, Allan JM, Wood ME and Ng AK: Aetiology, genetics and prevention of secondary neoplasms in adult cancer survivors. Nat Rev Clin Oncol *10*: 289, 2013. PMID: 23529000. DOI: 10.1038/nrclinonc.2013.41

11 Travis LB: The epidemiology of second primary cancers. Cancer Epidemiol Biomarkers Prev *15(11)*: 2020-2026, 2006. PMID: 17057028. DOI: 10.1158/1055-9965.epi-06-0414

12 Pereira S, Fontes F, Sonin T, Dias T, Fragoso M, Castro-Lopes J and Lunet N: Neurological complications of breast cancer: Study protocol of a prospective cohort study. BMJ Open *4(10)*: e006301, 2014. PMID: 25351600. DOI: 10.1136/bmjopen-2014-006301

13 Edge SB and Compton CC: The American Joint Committee on Cancer: The 7th edition of the AJCC Cancer Staging Manual and the future of TNM. Ann Surg Oncol *17(6)*: 1471-1474, 2010. PMID: 20180029. DOI: 10.1245/s10434-010-0985-4

14 Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, Dowsett M, Fitzgibbons PL, Hanna WM, Langer A, McShane LM, Paik S, Pegram MD, Perez EA, Press MF, Rhodes A, Sturgeon C, Taube SE, Tubbs R, Vance GH, van de Vijver M, Wheeler TM and Hayes DF: American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol *25(1)*: 118-145, 2007. PMID: 17159189. DOI: 10.1200/jco.2006.09.2775

15 Working Group Report: International rules for multiple primary cancers (ICD-0 third edition). Eur J Cancer Prev *14(4)*: 307-308, 2005. PMID: 16030420.

16 Hudis CA, Barlow WE, Costantino JP, Gray RJ, Pritchard KI, Chapman JA, Sparano JA, Hunsberger S, Enos RA, Gelber RD and Zujewski JA: Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: The STEEP system. J Clin Oncol *25(15)*: 2127-2132, 2007. PMID: 17513820. DOI: 10.1200/jco.2006.10.3523

17 Kaplan EL and Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc *53(282)*: 457-481, 1958. DOI: 10.2307/2281868

18 Falzone L, Salomone S and Libra M: Evolution of cancer pharmacological treatments at the turn of the third millennium. Front Pharmacol 9(1300), 2018. PMID: 30483135. DOI: 10.3389/fphar.2018.01300

19 Curigliano G, Burstein HJ, Winer EP, Gnant M, Dubsky P, Loibl S, Colleoni M, Regan MM, Piccart-Gebhart M, Senn HJ, Thurlimann B, Andre F, Baselga J, Bergh J, Bonnefoi H, Brucker SY, Cardoso F, Carey L, Ciruelos E, Cuzick J, Denkert C, Di Leo A, Ejlertsen B, Francis P, Galimberti V, Garber J, Gulluoglu B, Goodwin P, Harbeck N, Hayes DF, Huang CS, Huober J, Hussein K, Jassem J, Jiang Z, Karlsson P, Morrow M, Orecchia R, Osborne KC, Pagani O, Partridge AH, Pritchard K, Ro J, Rutgers EJT, Sedlmayer F, Semiglazov V, Shao Z, Smith I, Toi M, Tutt A, Viale G, Watanabe T, Whelan TJ and Xu B: De-escalating and escalating treatments for early-stage breast cancer: The St. Gallen International Expert Consensus Conference on the primary therapy of early breast cancer 2017. Ann Oncol *28(8)*: 1700-1712, 2017. PMID: 28838210. DOI: 10.1093/annonc/mdx308

20 American Cancer Society. Cancer treatment & survivorship facts & figures 2019-2021. Atlanta, GA, USA, 2019.

21 Almstedt K, Fasching PA, Scharl A, Rauh C, Rack B, Hein A, Hack CC, Bayer CM, Jud SM, Schrauder MG, Beckmann MW and Lux MP: Mitomycin C and capecitabine (MiX trial) for therapy of patients with metastasized, breast cancer pretreated with anthracycline. Anticancer Res *36(1)*: 419-425, 2016. PMID: 26722076.

22 Font-Gonzalez A, Liu L, Voogd AC, Schmidt MK, Roukema JA, Coebergh JW, de Vries E and Soerjomataram I: Inferior survival for young patients with contralateral compared to unilateral breast cancer: A nationwide population-based study in the Netherlands. Breast Cancer Res Treat *139(3)*: 811-819, 2013. PMID: 23760860. DOI: 10.1007/s10549-013-2588-9

23 Garber JE and Offit K: Hereditary cancer predisposition syndromes. J Clin Oncol *23(2)*: 276-292, 2005. PMID: 15637391. DOI: 10.1200/jco.2005.10.042

24 Nagy R, Sweet K and Eng C: Highly penetrant hereditary cancer syndromes. Oncogene *23(38)*: 6445-6470, 2004. PMID: 15322516. DOI: 10.1038/sj.onc.1207714

25 Working Group of the BeSHG/College. Guidelines for hereditary breast and/or ovarian cancer syndrome diagnostic testing criteria, 2018.

26 Qiu R, Zhao W, Yang J, Shen Y, Wang B, Li P, Zhao A, Tian Q, Zhang M, Yi M, Yang J and Dong D: Comparative analysis of outcomes and clinicopathological characteristics of synchronous and metachronous contralateral breast cancer: A study of the SEER database. J Breast Cancer *22(2)*: 297-310, 2019. PMID: 31281731. DOI: 10.4048/jbc.2019.22.e18

27 Xiong Z, Yang L, Deng G, Huang X, Li X, Xie X, Wang J, Shuang Z and Wang X: Patterns of occurrence and outcomes of contralateral breast cancer: Analysis of SEER data. J Clin Med 7(6), 2018. PMID: 29857526. DOI: 10.3390/jcm7060133

28 Heinavaara S and Hakulinen T: Relative survival of patients with subsequent cancer. J Cancer Epidemiol Prev *7(4)*: 173-179, 2002. PMID: 12846488.

29 Di Leo A, Desmedt C, Bartlett JM, Piette F, Ejlertsen B, Pritchard KI, Larsimont D, Poole C, Isola J, Earl H, Mouridsen H, O'Malley FP, Cardoso F, Tanner M, Munro A, Twelves CJ, Sotiriou C, Shepherd L, Cameron D, Piccart MJ and Buyse M: HER2 and TOP2A as predictive markers for anthracycline-containing chemotherapy regimens as adjuvant treatment of breast cancer: A meta-analysis of individual patient data. Lancet Oncol *12(12)*: 1134-1142, 2011. PMID: 21917518. DOI: 10.1016/s1470-2045(11)70231-5

30 Ghanbari S, Ayatollahi SM and Zare N: Comparing role of two chemotherapy regimens, CMF and anthracycline-based, on breast cancer survival in the Eastern Mediterranean region and Asia by multivariate mixed effects models: A meta-analysis. Asian Pac J Cancer Prev *16(14)*: 5655-5661, 2015. PMID: 26320431. DOI: 10.7314/apjcp.2015.16.14.5655

31 Singer CF, Balmana J, Burki N, Delaloge S, Filieri ME, Gerdes AM, Grindedal EM, Han S, Johansson O, Kaufman B, Krajc M, Loman N, Olah E, Paluch-Shimon S, Plavetic ND, Pohlodek K, Rhiem K, Teixeira M and Evans DG: Genetic counselling and testing of susceptibility genes for therapeutic decision-making in breast cancer-an European consensus statement and expert recommendations. Eur J Cancer *106*: 54-60, 2019. PMID: 30471648. DOI: 10.1016/j.ejca.2018.10.007

Received December 13, 2019
Revised January 9, 2020
Accepted January 13, 2020