ARTICLE

Prevalent versus incident breast cancers: benefits of clinical and radiological monitoring in women with pathogenic *BRCA1/2* variants

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Women with pathogenic germline *BRCA1* or *BRCA2* variants have a higher risk of breast cancer than in the general population. International guidelines recommend specific clinical and radiological breast follow-up. This specific breast screening program has already been shown to be of clinical benefit, but no information is available concerning the use of prognostic factors or specific survival to guide follow-up decisions. We evaluated "high-risk" screening in a retrospective single-center study of 520 women carrying pathogenic germline variants of the *BRCA1* or *BRCA2* gene treated for breast cancer between January 2000 and December 2016. We compared two groups of women: the incidental breast cancer group (IBCG) were followed before breast cancer diagnosis ($N = 103$), whereas the prevalent breast cancer group (PBCG) ($N = 417$) had no specific follow-up for high risk before breast cancer diagnosis. Breast cancers were diagnosed at an earlier stage in the IBCG than in the PBCG: T0 in 64% versus 19% of tumors, ($p < 0.00001$), and N0 in 90% vs. 75% ($p < 0.00001$), respectively. Treatment differed significantly between the 2 groups: less neoadjuvant chemotherapy (7.1% vs. 28.5%, $p < 0.00001$), adjuvant chemotherapy (47.7% vs. 61.9%, $p = 0.004$) and more mastectomies (60% vs. 42% $p < 0.0001$) in the IBCG vs PBCG groups respectively. Overall and breast cancer-specific mortality were similar between the two groups. However, the patients in the IBCG had a significantly longer metastasis-free survival than those in the PBCG, at three years (96.9% [95% CI 93.5–100] vs. 92.30% [95% CI 89.8–94.9]; $p = 0.02$), suggesting a possible long-term survival advantage.

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INTRODUCTION

Women with pathogenic germline *BRCA1* or *BRCA2* variants have a high risk of breast and ovarian cancer. Their cumulative risk of breast cancer by the age of 80 years has been estimated at 72% (95% CI: 65–79%) for women with *BRCA1* variants and 69% (95% CI: 61–77%) for those *BRCA2* variants. Annual breast cancer incidence increases steadily with age, reaching a maximum between the ages of 30 and 50 years for *BRCA1* carriers, and between the ages of 40 and 60 years for *BRCA2* carriers. Thereafter, breast cancer incidence remains constant for both types of BRCA variant (20–30 per 1000 person-years) [1]. A number of national guidelines recommend specific breast screening programs, with annual mammograms and breast magnetic resonance imaging (MRI) beginning at the age of 25 or 30 years. Ultrasound scans may also be considered [2–4]. Since 2009, French national guidelines have recommended a similar radiological approach [5, 6]. Bilateral prophylactic mastectomy is an alternative to radiological surveillance [7, 8]. However, this surgery is not without complications and has a major impact on body image, anxiety and sexuality [9–11]. According to French national guidelines, it is reasonable to perform such surgery from the age of 30 years onwards [5]. Many studies have evaluated the impact of specific high-risk breast screening on the clinical characteristics of tumors in cohorts of patients with pathogenic *BRCA1* or *BRCA2* variants or patients considered at risk of breast cancer [12–24]. However, only a few studies have assessed the impact of specific screening on overall survival or relapse-free interval in susceptible women [14, 25–27]. The purpose of this observational and retrospective study was to evaluate the benefits of intensive clinical and radiological surveillance in terms of breast cancer characteristics in a French single-center cohort of women carrying pathogenic germline *BRCA1* or *BRCA2* variants. Women with genetic alterations of *BRCA1* or *BRCA2* identified at Institut Curie and treated for breast cancer were assigned to two groups. The first was a group of women receiving radiological follow-up for a high risk of breast cancer linked to genetic knowledge obtained before the diagnosis

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of breast cancer: the incident breast cancer group (IBCG). These women were cancer-free at the time of genetic testing, the variant having been detected in a relative. The women in the other group, the prevalent breast cancer group (PBCG), underwent classic breast monitoring before cancer diagnosis (annual breast examination with or without a mammogram every year, depending on family history), but their genetic status was unknown at the time of screening, they had the follow-up of women "in real life": a regular or not, follow-up with their gynecologists, and according to the family history, they could already have started the breast radiological monitoring, on an annual basis or every 18 months/2 years. The primary outcome was impact on histological and clinical tumor features. The secondary outcomes concerned prognosis: specific or overall survival and metastasis-free survival. We also investigated whether treatment decisions were modified by the knowledge of genetic status.

MATERIALS AND METHODS

Study population

Between January 2000 and December 2016, 585 women carrying a pathogenic germline BRCA1/2 variant and treated for at least one breast cancer, were seen at Institut Curie for genetic testing or for breast cancer treatment. The study was approved by the Breast Cancer Study Group of Institut Curie and was conducted according to institutional and ethical rules concerning research on tissue specimens and patients. We excluded two women carrying double pathogenic variants (BRCA1/BRCA2 and BRCA1/CDH1), and 63 women for whom no precise data concerning the date of breast cancer diagnosis were available. The final analysis concerned 625 breast cancers in 520 women (unilateral tumors and some contralateral recurrences). Ipsilateral recurrences were not taken into account.

Study design

Two groups were defined on the basis of the type of clinical and radiological surveillance at the time of breast cancer diagnosis. The women in the IBCG were monitored according to national guidelines for high-risk group: clinical breast examination every six months, breast MRI and mammography annually, from the age of 30 years, and, ultrasound examinations if deemed necessary by the radiologist. These three imaging examinations were performed in this order, within two months. MRI examinations began before the age of 30 years in women with a familial history of breast cancer in a young relative. After the age of 65 years, women were followed annually by mammography and ultrasound (if requested by the radiologist). Women not screened in this way before breast cancer diagnosis were included in the PBCG. It was possible for a woman to switch groups between the first breast cancer and a subsequent cancer, on the basis of genetic testing. Women in the IBCG who became pregnant discontinued screening until four to six months after delivery. We included women whose breast cancers were diagnosed as a result of genetic analysis, during the first radiological screening, in the PBCG. It was therefore possible to assess the possible benefits of enhanced surveillance only from the second clinical and radiological examination onwards, not at the first round, and we took into account all breast cancers occurring during follow-up or between rounds of screening.

Outcomes

The primary outcome of this study was the oncological, clinical, and pathological characteristics of the breast cancers diagnosed in the two groups (PBCG and IBCG). The secondary outcomes were metastasis-free interval, overall and breast cancer-specific mortality, calculated by screening group.

Examinations

The imaging examinations performed in this study were mammograms (oblique and craniocaudal views for women with a history of breast cancer, and oblique views only for women with no history of breast cancer), gadolinium-chelate contrast-enhanced breast MRI, and ultrasound scans if requested by the radiologist. All of these examinations were assessed according to the Breast Imaging Reporting and Data System (BI-RADS). A screening test was considered positive if the BI-RADS assessment category was 4 or more. BI-RADS category assessment was not mandatory before 2004. For tumors diagnosed before 2004, we considered screening tests to be positive if the examination was followed by a histological examination. Multicentric tumors in a single breast were considered as single cancer, and only the size of the largest invasive component was taken into account.

Specific features of the tumors

For each cancer, clinical stage at diagnosis was reported according to the clinical or histological classification of the American Joint Committee on Cancer (AJCC). Histological type (invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC), mixed, or ductal carcinoma in situ (DCIS)) and Elston and Ellis grade were then analyzed. Hormone receptor status (considered positive if 10% or more of cells expressed hormonal receptors) and HER2/neu receptor overexpression were also noted.

Treatments

All treatments administered were recorded for each breast cancer. The type of surgery was analyzed: mastectomy or breast-conserving surgery, axillary lymphadenectomy, or sentinel node biopsy. Adjuvant or neo-adjuvant chemotherapy, endocrine therapy, and radiotherapy were recorded, together with any bilateral or contralateral prophylactic breast surgery and prophylactic salpingo-oophorectomy.

Data analysis. Statistical analysis was performed with R Software (R Core Team, 2016). The differences in tumor characteristics between the two groups were compared by χ^2 tests, with Yates correction or Fisher's exact tests if required. A p value of less than 0.05 in a two-tailed test was considered statistically significant. Furthermore, after the diagnosis of breast cancer during the first round of monitoring, 26 women were placed in the PBCG. For the analysis of prognosis, patients assigned to the PBCG for their first cancer, and then to the IBCG for a subsequent contralateral cancer, were included in the PBCG; 41 women were in this situation. Indeed, prognosis is linked principally to the characteristics of the first breast cancer. Prognosis was analyzed in both univariate (by log rank test) and multivariate analyses, taking into account age at diagnosis, mutational status (*BRCA1* or *BRCA2*) and the occurrence of a contralateral breast cancer during follow-up.

RESULTS

The IBCG contained 155 breast tumors (24.8%) with a median follow-up of 5.4 years, and the PBCG contained 470 breast tumors (75.2%) with a median follow-up of 9.3 years (Table 1).

- Clinical and pathological data

The tumor could be detected by palpation for 30% of the IBCG tumors and 76% of the PBCG tumors ($p < 0.00001$) (Table 2). Overall, 64% of the tumors in the IBCG and 19% in the PBCG were detected at the subclinical stage (T0) ($p < 0.00001$). There was also a significant difference in clinical node status between the two groups (90% vs. 75% N0, $p < 0.00001$). No metastatic disease was reported at diagnosis in the IBCG, whereas 10 tumors were already metastatic at diagnosis in the PBCG, but this difference was not statistically significant (NS) ($p = 0.12$) (eFigure 1).

The frequency of DCIS without invasive component was significantly higher in the IBCG than in the PBCG (23.7% vs. 8% $p < 0.0001$) and in the IBCG, 24 (66.7%) were High-grade DCIS. The frequency of negative lymph nodes on pathology was significantly higher in the IBCG (81.5% vs. 63.1%, $p < 0.0001$). Histological prognosis grade for invasive breast cancer did not differ significantly between screening groups. The proportion of the triple-negative phenotype was similar in the two groups: 52.2% vs. 47% (NS).

- Sensitivity of examinations

  In the IBCG, 76% of tumors were imaged by breast MRI and 60.5% by mammography (Table 3). Complementary breast ultrasound scans were performed at diagnosis for 147 tumors (90.7%), and all three examinations were performed at diagnosis for 106 tumors. Moreover, 42.4% of these tumors

Table 1. Characteristics by group.

Number of patients: *N (%)*	IBCG (103) (%)	PBCG (417) (%)
BRCA1m	65 (64.5)	221 (53)
BRCA2m	38 (35.5)	196 (47)
BC Unilaterality	92 (89.3)	323 (77.4)
Bilaterality	11 (10.7)	94 (22.6)
Follow-up (median)	65 months (5.4 years)	111 months (9.3 years)
Age at first breast cancer	Range: 24–81, median: 42 mean: 44.3	Range: 21–80, median: 40 mean: 41.8
<30	6 (5.8)	36 (8.6)
(30–40)	29 (28.2)	165 (39.6)
(40–50)	40 (38.8)	123 (29.5)
(50–60)	19 (18.5)	65 (15.6)
≥60	9 (8.7)	28 (6.7)
BMI	$N = 102$: median:22.6 Mean: 24	$N = 406$: median: 22.5 mean: 23.5
Death during follow-up	6	64
Breast cancer	4	50
Ovarian cancer	0	8
Pancreatic cancer	1	1
Other cancer	0	4*
Other cause	1	1
Number of prophylactic salpingo-oophorectomies	83	298
Median age at surgery:	45.4 (35–71)	48.9 (31–73)

Abbreviations: IBCG: incident breast cancer group, PBCG: prevalent breast cancer group.
*: 1 cholangiocarcinoma, 2 lung cancers, and 1 colorectal cancer.

were identified by all three examinations: breast MRI, mammography, and breast ultrasound. For 29 tumors (27.3%), only one of the three examinations yielded a positive result (for example, positive breast MRI but no abnormality detected on the other two examinations). The sensitivity of the examinations was 76% for breast MRI (including all types of cancer: invasive and DCIS), 60.5% for mammography, and 76% for ultrasound scans. In total, 18 of the 32 tumors not visible on MRI (56%) were DCIS.

- Treatments

  Radical mastectomy was performed for 60% of IBCG tumors vs. 42% of PBCG tumors, and breast-conserving surgery was performed for 37% (vs. 56%, $p < 0.0001$) (eFigure 2). In addition, among these 94 women who received a therapeutic mastectomy, 75 (80%) subsequently received a contralateral preventive mastectomy during the follow-up. Treatment data were missing for three women. Axillary lymphadenectomy was performed for 23.9% of the IBCG tumors (vs. 67.2% of the PBCG tumors) and sentinel node biopsy was performed for 61.3% of the IBCG tumors (vs. 26.6%); no axillary surgery was performed for 12.2% of IBCG tumors (vs 4.9%, $p < 0.0001$). Radiotherapy was performed in addition to surgery in 64.5% of cases in the IBCG (vs. 87.6% in the PBCG, $p < 0.0001$). Neoadjuvant chemotherapy was administered for 7.1% of IBCG tumors (vs. 28.5% of PBCG tumors, $p < 0.00001$) and adjuvant chemotherapy was administered for 47.7% of IBCG tumors (vs. 61.9% of PBCG tumors, $p < 0.004$) (eFigure 3). Endocrine therapy was provided for 30.3% of IBCG tumors (vs. 40.6% of PBCG tumors, $p = 0.06$), (Table 4). Significantly less neoadjuvant chemotherapy was prescribed for triple-negative breast cancer in the IBCG than in the PBCG (11% versus 40%, $p < 0.05$).
- Breast cancer-specific survival, overall survival, and metastasis-free survival

Table 2. Clinical and pathological status, according to screening program.

	IBCG $N = 155$ (%)	PBCG $N = 470$ (%)	*P* value
Diagnosis by clinical examination of the breast	**149**	**426**	**<0.00001**
Yes	45 (30.0)	325 (76.0)	
No	104 (70.0)	101 (24.0)	
Clinical tumor size (TNM stage)	**149**	**422**	**<0.00001**
0 (tumor not palpable)	96 (64.0)	79 (19.0)	
1 (<20 mm)	39 (26.0)	142 (33.0)	
2 (20-50 mm)	14 (10.0)	141 (33.0)	
3 (>50 mm)	0 (0)	47 (12.0)	
4 (extension to skin/chest wall or inflammatory)	0 (0)	13 (0)	
Clinical node involvement (TNM stage)	**149**	**421**	**<0.00001**
0	134 (90.0)	275 (75.0)	
1 (1 to 3 lymph nodes involved)	13 (9.0)	134 (32.0)	
2–3 (>4 lymph nodes involved)	2 (1.0)	12 (2.0)	
Clinical M (TNM stage)	**149**	**422**	**0.12**
M0	149 (100.0)	412 (98.0)	
M1	0 (0)	10 (2.0)	
Histological type	**152**	**463**	**<0.0001**
DCIS	36 (23.7)	35 (7.6)	
Low grade	4 (11.1)	3 (9)	**NS**
Intermediate grade	8 (22.2)	13 (37)	
High grade	24 (66.7)	19 (54)	
IDC	108 (71.0)	405 (87.5)	
ILC+/−IDC	5 (3.3)	17 (3.6)	
Other	3 (2.0)	6 (1.3)	
Unknown	3	7	
Molecular phenotype (invasive tumors)	**115**	**422**	**NS**
HER2+++	2 (1.7)	14 (3.3)	
HR−/HER2−	61 (53.0)	201 (47.6)	
HR−/HER2?	1 (0.9)	13 (3.0)	
HR+/HER2?	1 (0.9)	27 (6.4)	
HR+/HER2−	50 (43.6)	167 (39.7)	
Unknown	4	13	
Nodal status (invasive tumors)	**119**	**435**	**<0.0001**
Negative	84 (81.5)	185 (63.1)	
Positive	19 (18.5)	108 (36.9)	
Unknown	16	142	
EE Grade	**116**	**428**	**NS**
I–II	41 (36.9)	139 (33.2)	
III	70 (63.1)	280 (66.8)	
Unknown	5	9	

Abbreviations: IBCG: incident breast cancer group, PBCG: prevalent breast cancer group.
DCIS: ductal carcinoma in situ, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma.
HER2+++: human epidermal growth factor receptor-2 amplified, HR: hormone receptor status.
Positive or negative. EE grade: Elston and Ellis grade.

The two groups did not differ for overall or breast cancer-specific survival, with a follow-up of 101 months (range: 1–229 months). During follow-up, 70 deaths occurred in the two groups (Table 1). These deaths included four deaths from breast

cancer in the IBCG, 50 in the PBCG, and eight deaths from ovarian cancer, all in the PBCG. For this particular risk, which is specific to pathogenic germline *BRCA1/2* variants, 83 women in the IBCG and 298 women in the PBCG underwent prophylactic salpingo-oophorectomy at a median age of 45.4 years and 48.9 years, respectively (Table 1). Other *BRCA*-related tumors were also observed, with two women (one in each group) dying from pancreatic cancer. There were four deaths from other cancers (one cholangiocarcinoma, two lung cancers, and one colorectal cancer) and two deaths from other causes.

Four women from the IBCG and 68 from the PBCG are being treated for metastatic breast cancer. This corresponds to a statistically significant difference in metastasis-free survival rates at three years between the two cohorts: 96.9% [95% CI: 93.5–100] for the IBCG vs. 92.3% [95% CI: 89.8–94.9] for the PBCG; $p = 0.02$ (Fig. 1). This difference remained significant in multivariate analysis including mutational status (*BRCA1 versus BRCA2*) and age at first diagnosis into account (Cox model) (p-value = *0.03*).

Table 3. Sensitivity of the examinations.

	IBCG ***N* = 155 (%)**
All 3 examinations performed	106
All 3 examinations positive for cancer diagnosis	45 (42.4)
Tumors with only one positive examination	29 (27.3)
Only MRI positive	14 (13.2)
Only mammogram positive	8 (7.5)
Only ultrasound positive	7 (6.6)
Breast MRI sensitivity	97/128 (76.0)
Mammogram sensitivity	80/133 (60.5)
Ultrasound sensitivity	102/136 (75.0)

Abbreviations: IBCG: incident breast cancer group: women were followed according to the French guidelines, with a clinical examination every six months and breast MRI, mammogram+/− ultrasound annually.

DISCUSSION

The goal of this study was to evaluate the benefits of national "high-risk" breast cancer screening guidelines in terms of the characteristics of tumors and prognosis. Enhanced radiological monitoring including breast MRI is known to be beneficial for women at high risk of breast cancer. In our study, this close monitoring significantly improves the clinical detection of smaller breast cancers and lowers axillary lymph node involvement, which translates into a significantly longer metastasis-free interval.

Table 4. Breast cancer treatment according to the type of follow-up.

	Population *n* = 625 (%)	**IBCG *n* = 155 (%)**	**PBCG *n* = 470 (%)**	***p*- value**
Breast surgery				**<0.0001**
No	3 (0.2)	0 (0)	3 (0.6)	
Mastectomy	293 (47)	94 (60.6)	199 (42.3)	
Breast-conserving surgery	324 (52)	58 (37.5)	266 (56.7)	
Unknown	5 (0.8)	3 (1.9)	2 (0.4)	
Axillary surgery				**<0.0001**
No	42 (6.7)	19 (12.2)	23 (4.9)	
Lymphadenectomy	353 (56.5)	37 (23.9)	316 (67.2)	
Sentinel node biopsy	220 (35.2)	95 (61.3)	125 (26.6)	
Unknown	10 (1.6)	4 (2.6)	6 (1.3)	
Neoadjuvant chemotherapy				**<0.00001**
No	474 (75.9)	140 (90.3)	334 (71.0)	
Yes	145 (23.2)	11 (7.1)	134 (28.5)	
Unknown	6 (0.9)	4 (2.6)	2 (0.5)	
Adjuvant chemotherapy				**=0.004**
No	248 (39.7)	76 (49.0)	172 (36.6)	
Yes	365 (58.4)	74 (47.7)	291 (61.9)	
Unknown	12 (1.9)	5 (2.6)	7 (1.5)	
Radiotherapy				**<0.0001**
No	102 (16.3)	51 (32.9)	51 (10.8)	
Yes	512 (81.9)	100 (64.5)	412 (87.7)	
Unknown	11 (1.8)	4 (2.6)	7 (1.5)	
Hormone treatment				
No	367 (58.7)	98 (63.2)	269 (57.2)	=0.06
Yes	238 (38.1)	47 (30.3)	191 (40.6)	
Unknown	20 (3.2)	10 (6.5)	10 (2.2)	

***$p < 0.0001$, ****$p < 0.00001$.
NSS group: non specific screening group, ISP group: Intensive screening group.
Abbreviations: IBCG: incident breast cancer group.
PBCG: prevalent breast cancer group.

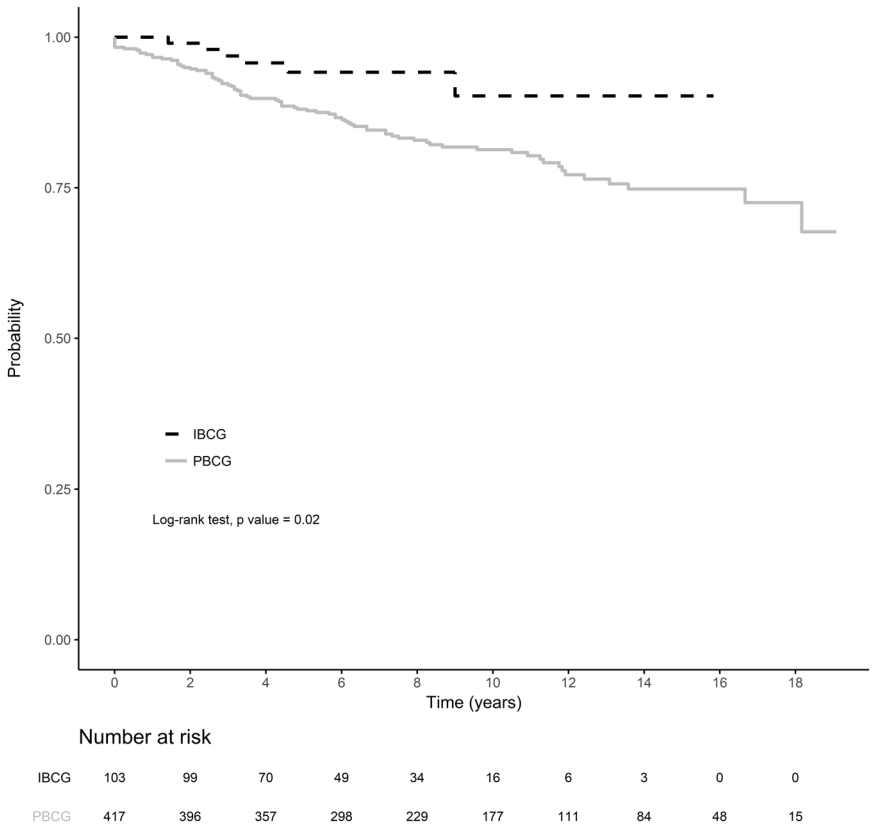

Fig. 1 Metastasis-free survival by screening group. Metastasis-free survival was compared in the two groups: IBPG (incident breast cancer group) and the PBCG (prevalent breast cancer group). Metastasis-free survival was defined as time from histological diagnosis to breast cancer-specific metastasis or death, whichever occurred first. Differences in breast cancer-specific metastasis-free survival were compared in log-rank tests. Red: IBCG group (103 women, 6 with metastasis or death). Blue: PBCG group (417 women, 82 with metastasis or death). ***$p < 0.0001$, ****$p < 0.00001$.

However, these potentially interesting results must be seen in the context of the biases inherent to retrospective studies. Breast cancer diagnosis (improvement of imaging) and treatment have changed considerably over the last 20 years, both in terms of the identification of pathological elements required for its management (HER2 status) and in terms of surgical (sentinel lymph node biopsy rather than lymphadenectomy) and oncological (modification of adjuvant chemotherapy) indications. All these changes can also modify the prognosis of treated breast cancers. Otherwise, the absence of precise data on breast monitoring of women in the PBCG, before cancer diagnosis does not provide a homogenous view of these patients.

Moreover, we choose not to take into account in the metastasis-free survival the lead-time bias; this statistical bias needs an adjustment in particular in breast organized screening in postmenopausal women who often present breast tumors with low grade. Koscielny and Tubiana in 1991 were able to deduce the tumor doubling time as a function of grade and axillary involvement [28]. We have no data on the natural history of those cancers, often high grade; in women carrying a germline pathogenic predisposition. Under these conditions, the lied time bias must be short and certainly not modify the data.

Furthermore, high-risk follow-up significantly increases the rate of DCIS detection. This type of breast cancer has a better prognosis, and can be managed with complementary treatments with lower levels of associated morbidity [16, 20]. Given the risk of breast cancer in this population, we do not believe that the higher rates of DCIS detection reported here are due to overdiagnosis. Another study showed that the early changes to mammary myoepithelial cell differentiation observed in sporadic DCIS were also found in healthy breast tissue from women with a predisposition to breast cancer [29].

We also report lower levels of associated treatments (neoadjuvant or adjuvant chemotherapy and complementary radiotherapy) likely to generate immediate or delayed adverse effects potentially decreasing quality of life (infertility or lymphoedema) [30, 31] that may be more frequent in women with mutations [32–35]. Thus, the monitoring of carriers of pathogenic germline BRCA1/2 variants can reduce the morbidity associated with surgical, oncological, and radiotherapy treatments, however, this follow-up could generate harmful effects (false positives, anxiety…). Women with a germline BRCA1/2 pathogenic variant have, in literature, the rate of ACR3 in MRI above 6 to 10% [36–39]. In Edmonds et al., during the first cycle the rate is evaluated at 8.5% then passes to 2% during the follow cycles [36]. In addition, in Vreemann et al., radiological false positives, as well as those leading to a negative biopsy in BRCA mutated women, were compared with women without a genetic predisposition [40]. In view of the higher risk of breast cancer in the group of women carrying a *BRCA1/2* pathogenic variant, there were significantly fewer false positives in this group. Taking into account the risk of cancer in these women (annual risk of breast cancer that varies between 1 and 2%), Furthermore, this false positive rate remains acceptable and the benefits of intensive screening outweigh the risks of harm.

Remarkably, when women know their genetic status, they often request therapeutic radical mastectomy, even though they could potentially benefit from breast-conserving surgery. Of note, breast-cancer specific mortality is identical between mastectomy and breast-conserving surgery in the general population [41]. However, in the meta-analysis performed by Valachis, the risk of ipsilateral breast cancer appears to be higher in these women seven years after the end of radiotherapy [42]. Furthermore, knowledge of their genetic predisposition provides these women with a better understanding of the risk of contralateral breast

cancer risk relative to that in non-carriers (1.5–3% increase in risk annually vs. 0.5% for non-carriers) [1, 42, 43], which can be managed by contralateral radical mastectomy. When in possession of this information, given the possibility of prophylactic surgery on the contralateral breast, which can be performed sometime after breast cancer treatment, women more frequently request a mastectomy, even when breast-conserving surgery is possible. Thus, we can identify in our IBCG population, 94 women who performed a therapeutic mastectomy and among them, 75 women (80%) had a contralateral preventive mastectomy during follow-up.

Despite significant differences in breast cancer stage and axillary involvement between the groups, there was no significant difference in breast cancer-specific mortality or overall mortality. This lack of difference can be explained by the favorable prognosis for breast cancer at the five-year time point. Moreover, the presence of a pathogenic *BRCA1/2* variant is not associated with a negative prognosis. A comparison of the breast cancer-specific survival of women with breast cancer as a function of the presence or absence of such alterations, with matching according to the molecular characteristics of cancer, showed this survival to be similar in the two groups [44]. Indeed, breast cancer-specific survival may even be slightly better in the first two years after triple-negative breast cancer in women with *BRCA1/2* mutations [44]. Most of the breast cancers in our cohort were diagnosed at an early stage (less than 15% T3 or 4 in the PBCG and 0 T3 or 4 in the IBCG) [45]. It was not possible to demonstrate a benefit in terms of breast cancer-specific mortality in this study. Such a demonstration would require a very long follow-up, which was not possible for the IBCG since breast MRI was not incorporated into the French guidelines for the management of *BRCA1/2* carriers until 2009. However, metastasis-free survival seemed to be better in the IBCG than in the PBCG which could potentially result in a specific survival benefit for women in the IBCG. This finding thus indicates that close follow-up significantly decreases the risk of having metastatic breast disease, and this information is of the utmost importance for our patients. It is interesting to compare our study with that of Hadar et al., which is the most similar in design to our study [27]. Hadar et al. showed that enhanced radiological surveillance may improve patient survival, through the identification of a larger number of DCIS (although patients were older at diagnosis in his cohort and the frequency of DCIS may be higher than published rates) [15, 16, 18, 44, 45]. Our data highlight a similar pattern, and confirm the benefit of this follow-up in terms of the histological prognostic characteristics of invasive breast cancers.

The starting point for follow-up adapted to breast and ovarian cancer risk remains the targeted test or genetic analysis. However, Alegre et al., show that knowledge about genetic predisposition is poorly transmitted within families [46]. It is very important, in the context of breast surveillance to improve prognosis, to enhance communication within families, and to offer genetic analysis to any woman with personal or familial criteria for such analysis [47]. In addition, a knowledge of genetic status makes it possible to provide care in specialized units aware of the follow-up recommendations and used to these specific situations [48, 49].

CONCLUSION

This is the largest published study to date on the benefits of enhanced follow-up in women with a pathogenic germline *BRCA1* or *BRCA2* variant treated for breast cancer. It provides a number of interesting findings: close clinical and radiological surveillance improves the clinical prognosis criteria of identified breast cancers (based on tumor size and lymph node involvement), but also the histological prognosis criteria (higher proportion of DCIS). Together, these two factors lead to a significant decrease in associated treatments (neoadjuvant and adjuvant chemotherapy and radiotherapy), reducing the morbidity linked to the management of breast cancer. However, this approach has not yet displayed any proven benefits in terms of breast cancer-specific survival, although the findings for earlier signs are encouraging (significant increase in metastasis-free survival). In light of the benefits identified here, studies should be performed following women in two groups managed in different ways: enhanced clinical and radiological monitoring or prophylactic breast surgical management, because each of these options is beneficial, but has its own specific constraints. Finally, these data argue for the earliest possible identification of women with a genetic predisposition: it is imperative that women with personal or family indications for genetic analysis are correctly referred to genetic services.

DATA AVAILABILITY

The clinical data analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

Study design: CS, SMH, EMF, DSL. Data collection: CS, SMH, EMF. Data analysis: EMF, MC. Data interpretation: CS, SMH, EMF. Writing: CS, SMH, EMF. Extensive revision of the manuscript: CS, SMH, MC, CM, PC, FR, ML, EG, AD, NC, SF, FC, DSL, EMF.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

The study was approved by the Breast Cancer Study Group of Institut Curie and was conducted according to institutional and ethical rules concerning research on tissue specimens and patients.

ADDITIONAL INFORMATION

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