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ORIGINAL ARTICLE

Breast and ovarian cancer risk management in a French cohort of 158 women carrying a *BRCA1* or *BRCA2* germline mutation: patient choices and outcome

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Abstract Description of the various modalities of breast and ovarian cancer risk management, patient choices and their outcome in a single-center cohort of 158 unaffected women carrying a *BRCA1 or BRCA2* germline mutation. Between 1998 and 2009, 158 unaffected women carrying a *BRCA1* or *BRCA2* gene mutation were prospectively followed. The following variables were studied: general and gynecological characteristics, data concerning any prophylactic procedures, and data concerning the outcome of these patients. Median age at inclusion was 37 years and median follow-up was 54 months. Among the 156 women who received systematic information about prophylactic mastectomy, 5.3 % decided to undergo surgery within 36 months after disclosure of genetic results. Prophylactic salpingo-oophorectomy was performed in 68 women. Among women in whom follow-up started between the ages of 40 and 50 years, prophylactic salpingo-oophorectomy was performed, within 24 months after start of follow-up, in 83.7 and 52 % of women with *BRCA1* and *BRCA2* mutations, respectively. Twenty four women developed breast cancer. Ovarian cancer was detected during prophylactic salpingo-oophorectomy in two women (2.9 %). In this cohort of French women carrying *BRCA1/2* mutations, prophylactic mastectomy was a rarely used option. However, good compliance with prophylactic salpingo-oophorectomy was observed. This study confirms the high breast cancer risk in these women.

Keywords Breast cancer · Ovarian cancer · Prophylactic mastectomy · Prophylactic salpingo-oophorectomy · *BRCA1/2*

This study was conducted on behalf of the Institut Curie Breast and Ovarian Cancer Risk Study Group.
The members of the "Institut Curie Breast and Ovarian Cancer Risk Study Group" is given in "Appendix" section.

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Abbreviations

PM	Prophylactic mastectomy
PSO	Prophylactic salpingo-oophorectomy
MRI	Magnetic resonance imaging

Introduction

Women carrying a germline *BRCA1* or *BRCA2* mutation have a very high risk of breast and ovarian cancer. Cumulative risk of breast cancer at the age of 70 years is

estimated to be between 57 and 65 % for *BRCA1* and between 45 and 49 % for *BRCA2* mutation carriers; the risk of ovarian cancer is about 40 % for *BRCA1* and between 10 and 18 % for *BRCA2* mutation carriers [1, 2] while these risks are 12 % for breast cancer and 1 % for ovarian cancer at the age of 75 in women of the French general population [3].

The breast management of high-risk women is currently based on two types of strategies : a method designed to reduce the cancer risk or close surveillance to detect potentially curable breast cancers [4–6]. Over recent years, magnetic resonance imaging (MRI) has improved the performances of ultrasound and mammography [7, 8]. Prophylactic mastectomy (PM), *i.e.* ablation of the breast, when performed sufficiently early, is associated with a marked reduction of breast cancer risk, by 90 to 100 % [9, 10].

Some studies have considered psychological reactions and satisfaction after PM [11–13]. Generally, no negative effects on quality of life were found. Anxiety and social activities were even improved, but negative impact on sexuality and body image were also reported [12, 13]; Women who consider this option must be aware of the risk of these consequences.

In France, the 2004 guidelines [5] recommended that PM should be systematically proposed as a possible option.

Finally, a number of drugs (mainly aromatase inhibitors) are currently under investigation in clinical trials of chemoprevention such as IBIS II [14] and MAP3 [15]. In France, since March 2008, the LIBER trial has been comparing the preventive efficacy of letrozole 2.5 mg daily for 5 years vs placebo in women with *BRCA1/2* mutations [16].

Ovarian cancer screening by pelvic ultrasound has been found to be disappointing [17] and prophylactic surgery, *i.e.* resection of the ovaries and fallopian tubes or prophylactic salpingo-oophorectomy (PSO), is recommended after completion of childbearing [5, 18]. PSO is associated with an 80 % reduction of ovarian or fallopian tube cancer risk, a 50 % reduction of breast cancer risk [19] and a reduction of ovarian and breast cancer-specific mortality [10].

The present study reports the breast and ovarian cancer risk management patient choices and outcome in a single-center French cohort of 158 unaffected women carrying a *BRCA1* or *BRCA2* germline mutation.

Patients and methods

Cancer genetic counselling

The Paris Institut Curie (IC) family cancer clinic was set up in 1991. Screening for *BRCA1* and *BRCA2* mutations began in 1995 and 1996, respectively, in women with breast and/or ovarian cancer (index cases), with a family history of breast and/or ovarian cancer, or because of their young age at diagnosis of breast cancer (before the age of 36 years). *BRCA1/2* mutation screening comprised a search for point mutations and large gene rearrangements [20–24].

When mutation screening identified a pathogenic germline mutation, mutation-targeted genetic testing was proposed to the index case's relatives, most of whom were not affected by cancer. Genetic testing was always performed with the patient's free, informed and written consent obtained after a visit with a cancer geneticist who described the various issues involved. Genetic counselling was sometimes completed by a systematically proposed appointment with a psycho-oncologist.

Management of high-risk women

Surveillance was not systematically proposed at IC between 1992 and 1998 and only women specifically requesting surveillance were managed. From 1998 onwards, surveillance at IC was systematically proposed to all predisposed women, whether or not they were already breast and/or ovarian cancer affected. A multidisciplinary team, specifically devoted to the management of high-risk women, was composed of a large panel of physicians already involved in the management of breast and gynecological cancers.

All women were systematically asked to attend an annual radiological assessment followed by a visit with a specifically trained gynecologist according to the INSERM guidelines [4]. Mammography and breast ultrasonography were performed annually beginning at age 30 or 5 years before the age of earliest onset of breast cancer when before 34. This assessment also comprised annual breast MRI from 2003 onwards.

From 2004 onwards, women were systematically provided with detailed information about the bilateral PM option and about the possibility of future inclusion in a chemoprevention trial [5]. Women interested in PM were invited to attend a visit with a reconstructive surgeon for further information.

In order to carefully anticipate all the consequences of MP, a psycho-oncology consultation was mandatory before surgery and systematically organized. Eligibility for prophylactic surgery was validated at multidisciplinary consultation meetings. Women were asked to observe a 4-months period of reflection before PM. PM was accompanied by immediate breast reconstruction. Nipple-sparing surgery is an option that remains a subject of debate.

According to the INSERM guidelines [4, 5] ovary cancer screening with pelvic ultrasound began annually at age 35. At IC, PSO was recommended at the age of

40 years in women with *BRCA1* mutations and around the age of 50 years in women with *BRCA2* mutations (45 years for women with a family history of ovarian cancer). A psycho-oncology consultation was proposed to women reaching the recommended age of PSO, but was not mandatory. A short term hormone replacement therapy may be prescribed in case of menopausal symptoms in unaffected breast cancer women.

Cohort of high-risk women

The inclusion criteria in the present study were as follows: women carrying a pathogenic *BRCA1* or *BRCA2* mutation, wishing to be followed at IC, and in whom genetic testing was performed at IC between 1998 and 2009, unaffected by cancer at the time of disclosure of the genetic test results and during the following six months, and with a follow-up of more than 1 year. Systematic clinical data collection was initiated in 2006 and was therefore retrospective between 1998 and 2006 and prospective from 2006 onwards, but follow-up was prospective. Women were informed about follow-up data collection. This study was approved by the Institutional Review Board.

Data were extracted on 15 December 2010. Among the 636 mutation carriers followed at IC, 557 women performed genetic testing at IC beetween 1998 and 2009. On these 557, 217 women were unaffected of cancer at the disclosure of the genetic result and during six months following. On these 217, 170 women had a duration of follow-up of more than 1 year and finally 158 women were included in the register until 15 06 2009.

In order to analyze only those women who received the same information concerning prophylactic mastectomy, systematically proposed after 1st January 2004, the 156 women still cancer-free in 2004 or included after this date were selected.

The following variables were recorded:

Family history of cancer, gynecological and clinical characteristics, data concerning any prophylactic procedures and their pathological results: PSO and PM/or inclusion in the LIBER trial, data concerning patient outcome, particularly the development of breast and/or ovarian cancer.

Statistical methodology: variables and analyses

Qualitative variables are expressed as sample size and percentages with their 95 % confidence intervals (CI) and quantitative variables are expressed as the median [minimum and maximum]; a *p value* less than 0.05 was considered to be statistically significant.

Breast cancer incidence, PM and PSO rates were estimated by Kaplan–Meier survival analysis.

The cumulative risks over time for these various events are presented by using the time of disclosure of genetic results as the origin. To facilitate interpretation of these curves, incidence rates of these various events were estimated by age-group at inclusion.

Statistical analyses were performed with R version 2.5.0 software [25].

Results

Description of the population: general and gynecological characteristics

The cohort comprised 158 women with a median age of 37 years [range: 18–66] at inclusion. One hundred and five women (66.5 %) had a *BRCA1* germline mutation and 53 (33.5 %) had a *BRCA2* germline mutation.

The characteristics of the women of this cohort are described in Table 1.

Duration of follow-up

The median duration of follow-up was 54 months [range: 13–148].

One patient died, free of disease (this woman, with a long psychiatric history, committed suicide 3 years after inclusion in the cohort). Fourteen women stopped their surveillance at the IC (8 asked to stop surveillance and 6 women changed their site of surveillance). The median duration of follow-up for these women was 51 months [range: 12–110]. To date, 143 women (90.5 %) have continued surveillance at IC and were still alive at the date of data extraction.

Inclusion in the LIBER trial

On the 158 women of the cohort, 35 women were eligible to enter the trial. Thirty of these 35 were not interested in participating in the study, and five patients were finally included. These patients had all surgical menopause (following PSO) with a minimal duration of 6 months between PSO and inclusion. One patient decided to withdraw from the study soon after inclusion due to the risk of bone side effects of letrozole. One patient decided to drop out of the trial at 16 months. Three patients are currently participating in the trial and remain unaffected.

Prophylactic mastectomy data

Prophylactic mastectomy was performed in 14 of the 158 women included in this study. PM was performed within 36 months after inclusion for 9/14 (64 %) of the women

Table 1 Clinical characteristics of women at inclusion (n = 158)

	N	%
Age		
≤30	36	22.78
[30–40]	64	40.51
[40–50]	41	25.95
>50	17	10.76
	N	Median age at inclusion (year)
Gene involved (type)		
BRCA1	105	38 [18–66]
BRCA2	53	36 [25–62]
	N	%
Family history of cancer (type)		
Breast	57	36.09
Ovary	9	5.69
Breast + ovary	92	58.22
	N (total = 158)	%
Pregnancy		
No pregnancy at inclusion	47	29.75
At least one pregnancy	111	70.25
Median age at first pregnancy at inclusion: 27 [19–37]		
Median age at last pregnancy at inclusion: 32 [22–39]		
Number of children at inclusion (total N = 111)		100
1	27	24.32
2	53	47.75
3	22	19.82
4	8	7.21
5	1	0.9
	Total	%
Menopausal status		
Premenopausal	125	79.11
Postmenopausal	33	20.89
Median age at menopause if postmenopausal at inclusion	46 [40–54]	

History of pelvic surgery prior to inclusion in the study	No	Yes	Missing value	Total
Hysterectomy	152	5	1	158
Oophorectomy	149	7 (2 unilateral, 5 bilateral)	2	158

who opted for this procedure. Overall, 5.2 % [95 % CI, 1.6–8.7 %] of women underwent PM during this period.

In order to analyze only those women who received the same information concerning prophylactic mastectomy, systematically proposed after 1st January 2004, the 156 women still cancer-free in 2004 or included after this date were selected: 13 PM were performed in this group of women. The PM rate was 5.3 % [95 % CI, 1.7–8.9 %] at 36 months (Fig. 1), corresponding to 5.4 % of women included before the age of 40, 4.9 % of women included between the ages of 40 and 50, and 5.3 % of women included after the age of 50.

No breast cancers were detected on histological examination of PM specimens.

Women undergoing PM presented certain characteristics: *BRCA1* mutation carriers (10/14), history of 2 or more

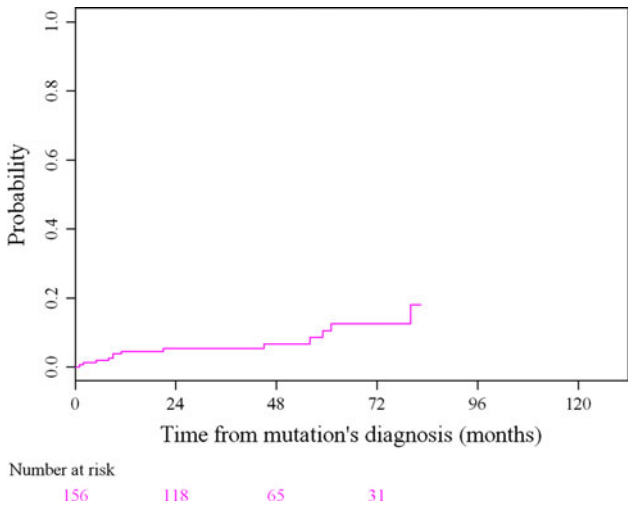

Fig. 1 Cumulative uptake of prophylactic mastectomy since inclusion among women of the cohort still unaffected in 2004 or included after 2004

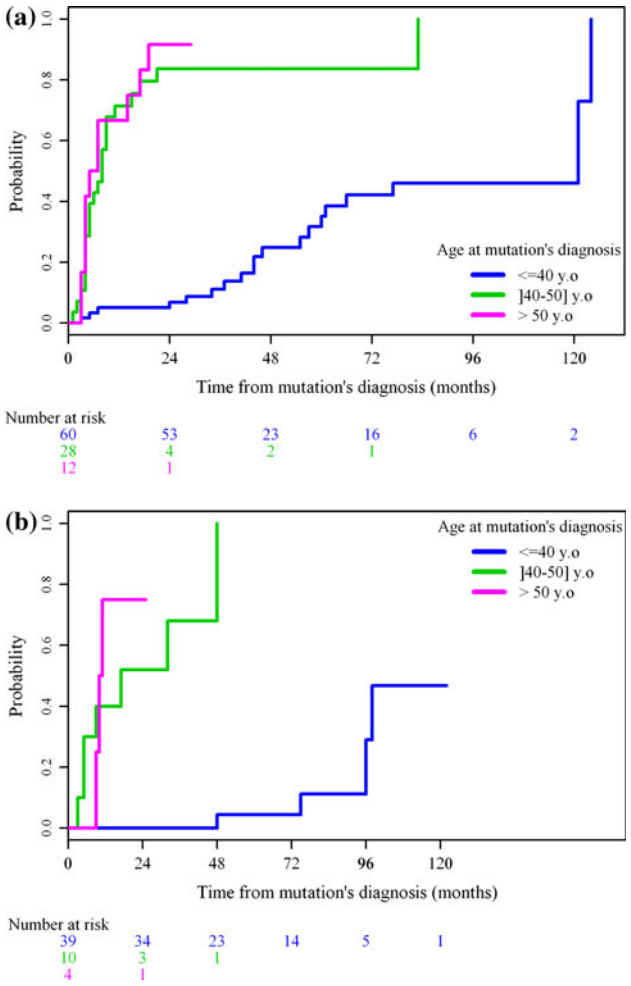

Fig. 2 **a** Cumulative uptake of prophylactic salpingo-oophorectomy since inclusion among women with *BRCA1* mutations. **b** Cumulative uptake of prophylactic salpingo-oophorectomy since inclusion among women with *BRCA2* mutations. Prophylactic surgery uptakes are presented by age-group at inclusion

breast cancers in their family (12/14), at least one relative with breast cancer before the age of 41 years (12/14), at least one young child (11/14 women had a child younger than 15).

On the 14 women who have performed PM, 6 had PIP (Poly Implant Prothèse) prosthesis. On these 6 women, 2 experienced breaks; these two women did not deny PM, but worried about complications in the long term. All the 6 women have changed their prosthesis.

Prophylactic salpingo-oophorectomy data

Five women had undergone bilateral salpingo-oophorectomy prior to inclusion; 153 women therefore had intact ovaries at the time of inclusion.

Prophylactic salpingo-oophorectomy was performed in 68 women during follow-up (54 women with *BRCA1* mutation and 14 women with *BRCA2* mutation) (Fig. 2a, b).

Among women with *BRCA1* mutation, the median age at PSO was 42.5 years [range: 34–66] and PSO was performed during the first two years after inclusion in 38.4 % [28.0–47.3] of women, in 6.8 % [0.1–13] of women included in the cohort before the age of 40 vs. 83.7 % [61.1–93.2] of women included between the ages of 40 and 50, and 91.7 % [45.6–98.7] of women included after the age of 50.

Among women with *BRCA2* mutations, the median age at PSO was 47.5 years [range: 41–63] and PSO was performed within the first two years and the first ten years after inclusion in 15.2 % [4.9–24.3] and 57.9 % [10.8–80] of women, respectively. No woman included before the age of 40 underwent PSO within the first 2 years after inclusion vs 52 % [6.2–75.4] of women included between the ages of 40 and 50 and 75 % [0–95.5] of women included after the age of 50.

Histological examination demonstrated ovarian cancer in 2 (2.9 %) of the 68 PSO specimens; in both cases, the ovaries had a suspicious appearance at surgery. In one case, genetic testing (*BRCA2* mutation) and inclusion were performed in a 62 years old woman. Pelvic ultrasound demonstrated atrophic ovaries and an ovarian carcinoma stage IA was diagnosed at PSO. This woman was alive and free of recurrence 21 months after surgical treatment. In the other case, genetic testing (*BRCA1* mutation) and inclusion were performed in a 50 years old woman. Preoperative pelvic ultrasound demonstrated a cystic lesion. An ovarian carcinoma stage IIIc was diagnosed at PSO. Twenty nine months after surgery and chemotherapy, a recurrence was noted.

No peritoneal disease was diagnosed after PSO with a median follow-up of 34 months [range: 0–138].

Cancer incidence data

Twenty four of the women who did not opt for PM subsequently developed breast cancer, (14 *BRCA1*, 10 *BRCA2*) with a median age at diagnosis of 43 years for *BRCA1* and 42 years for *BRCA2* and with no significant difference for the age of breast cancer diagnosis according to the two types of mutations.

Among these 24 women, 11 had performed PSO before breast cancer diagnosis, 8 women performed it after diagnosis and in 5 women, PSO was not yet recommended at the time of data extraction.

Five women developed other types of cancer: two women developed thyroid cancer *(BRCA1),* one woman developed sarcomatoid carcinoma of the pleura *(BRCA2),* one woman developed occult carcinoid appendiceal tumor *(BRCA1)* and one woman developed cervical carcinoma *(BRCA1).*

The cumulative breast cancer risk in the overall cohort was 9.9 % [95 % CI, 4.6–14.9 %] at 36 months and 16.5 % [95 % CI, 8.8–23.6 %] at 60 months of follow up (Fig. 3).

Among the 25 breast cancers (one woman presented synchronous bilateral breast cancer), 6 cancers were in situ ductal carcinomas (Stage 0) and 19 were invasive carcinomas. Among the 19 invasive tumors, 10 were stage I (pT1N0M0), 5 were stage IIA (pT0N1M0/pT1N1M0/pT2N0M0), and 2 were stage IIB (pT2N1M0) [26], with missing data for 2 cases: one woman was lost to follow-up soon after diagnosis, and one woman received upfront chemotherapy. Among the 19 invasive tumors, 13 were node-negative and 5 were node-positive (1 missing value).

Other cancer characteristics are shown in Table 2.

In one woman carrying a *BRCA1* mutation, an interval breast cancer was diagnosed 11 months after normal mammography and MRI imaging: this woman discovered a palpable breast tumor (size: 12 mm, node-negative). To elucidate the history of the disease in the five women with node-positive tumors, the breast imaging performed 6 or 12 months before diagnosis was reviewed. Imaging was classified as: ACR 3 in 2 patients (more frequent

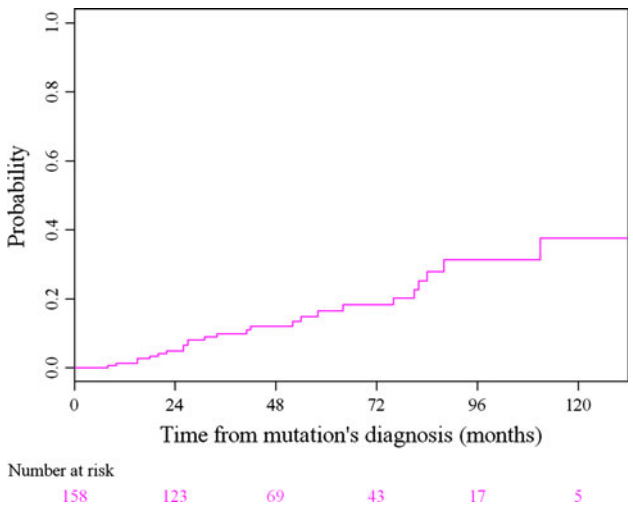

Fig. 3 Cumulative breast cancer risk since inclusion among unaffected *BRCA1/2* mutation carrier women

Table 2 Characteristics of the 25 breast cancers

Type of cancer	
In situ ductal carcinoma	6
Invasive carcinoma	19
Size of invasive tumors (mm)	
0–5	1
6–10	6
11–20	5
>20	5
Missing	2
Grade	
In situ ductal carcinoma	
Low nuclear grade	0
Intermediate nuclear grade	1
High nuclear grade	5
Invasive ductal carcinoma	
Grade I	0
Grade II	3
Grade III	13
Invasive lobular carcinoma	
Grade I	0
Grade II	2
Grade III	0
Papillary carcinoma	1
Nodal status (19 invasive)	
Negative	13
Positive	5
Missing	1[a]
Total	25
Stage	
0	6
I	10
II A	5
II B	2
Missing	2[b]

One woman presented synchronous bilateral breast cancer

[a] One case lost to follow-up soon after diagnosis

[b] One case of upfront chemotherapy; one case lost to follow-up soon after diagnosis

monitoring every 6 months was proposed and the breast cancer was diagnosed on the next imaging assessment), ACR 4 in 2 patients (a biopsy was proposed but finally postponed by both patients), and ACR 2 in 1 patient (the next assessment one year later was scored ACR 4 and led to a positive biopsy).

Discussion

This study was based on a cohort of 158 unaffected women carrying a *BRCA1* or *BRCA2* mutation followed in a single institution in France with a median follow-up of 54 months [range: 13–148].

Prophylactic mastectomy had been performed in 5.3 % of the 156 women who systematically received information about PM, 36 months after disclosure of the genetic test results. PM rates reported in the literature vary considerably, between 0 and 54 % [27]. These figures express crude rates and are difficult to compare, as observed rates depend on the age distribution and the duration of follow-up in each study, and these data are not always reported. However, in a recent single-center European study, the crude PM rate was 40 % and the majority of women underwent PM before the age of 46 [28]. Although the PM rate was lower in our study, 12 of the 14 women underwent this procedure before the age of 46.

We hypothesized that the severity of family history in terms of early age of onset and severity of breast cancer mortality could influence the woman's decision to undergo prophylactic surgery. In the present study, women who opted for PM more frequently presented a certain number of features: *BRCA1* mutation, at least 2 relatives with breast cancer, including one relative affected before the age of 41, and women who often still had young children. In the literature, a family history of breast and ovarian cancer [29, 30], a family history of breast cancer before the age of 40 [30], and mothers caring for young children [30] are reported factors influencing the woman's decision.

When analyzing PM rates, it is also important to determine whether this option was explicitly discussed with the patient and even recommended. At IC, women have been systematically provided with information about PM since publication of the French guidelines in 2004 [5]. While one of the 14 PM was performed before 2004, 13 were performed after 2004, indicating the influence of guidelines and medical information on patient decisions. The way we manage our patients (mandatory psychological evaluation, 4 months period of reflection) probably partially explains why so few patients in our cohort have chosen PM. We think that in a rigorous « Informed Medical Decision Process », all the positive and negative consequences of PM must be discussed with patients. Cultural factors affecting both women and physicians may also have an impact on the PM rate [31, 32].

Inclusion in a chemoprevention trial constitutes an alternative to PM for women wishing to reduce their breast cancer risk. In our cohort, among the 35 women eligible to the LIBER trial, only 5 (14.30 %) were actually included. Recently the overall uptake in LIBER trial among all eligible women has been estimated to 15 % [16]. The acceptability of chemoprevention remains limited, probably due to the fear of adverse drug effects.

PSO is recommended at IC at the age of 40 years in women with *BRCA1* mutation and around the age of 50 years in women with *BRCA2* mutation. Among *BRCA1* carriers, 6.8 % [0.1–13] of women included in the cohort before the age of 40 vs. 83.7 % [61.1–93.2] of women included between the ages of 40 and 50, and 91.7 % [45.6–98.7] of women included after the age of 50 underwent PSO.

PSO rates reported in the literature range from 13 to 53 % [27], but like PM rates, they are difficult to compare with the PSO rates observed in the present study. PSO may be associated with a family history of ovarian cancer and having children [33]. Analysis of the PSO curves (Fig. 2a, b) shows that, once women are included in a specific management protocol, compliance with recommendations is very high, regardless of age at inclusion, which emphasizes the importance of information and support. Early inclusion in a specific management protocol is therefore essential to effectively prevent ovarian cancer.

The proposal of low-dose hormone replacement therapy until the age of 50 also probably contributes to acceptance of this procedure [34, 35].

The cumulative breast cancer risk at 60 months was 16.5 % which leads to an annual breast cancer risk of 3.3 % [95 % CI 1.76–4.72 %], consistent with the value of 2.5 % generally reported by other groups [29, 36]. Incidence rates are closely related to the age distribution in each study. In addition, these rates may be related to the severity of the family history linked to genetic cancer risk modifiers [37].

In our cohort with breast MRI screening, 6 of the 25 incident breast cancers were in situ ductal carcinoma and 15 were stage I or IIA. This finding is in agreement with the results of the prospective study by Warner et al. [8] which identified more in situ ductal carcinoma and stage I disease, and fewer stage II to IV tumors in the MRI group compared to the control group without MRI. Nevertheless, the real value of MRI will emerge from prospective studies with mortality as end-point.

Concerning peritoneal cancer after PSO, we observed that no peritoneal disease was diagnosed with a median follow-up of 34 months. Precise estimate of the protective value of PSO still remains difficult to evaluate even in large

studies because it depends of type of gene and mutation. (HR 0, 28 [95 % IC 0,12–0,69] in the study of Domchek on 1557 *BRCA* unaffected carriers [10].

Two cases of ovarian cancer were observed. The diagnosis was suspected just before or during PSO. Both patients had performed genetic testing at an advanced age (62 and 50 years). These cases emphasize the importance of identification of these women in the population, diagnosis of the cancer predisposition, patient information and personalized management. The rate of ovarian cancer discovered at the time of PSO in this cohort was 2.94 %, fairly similar to the rates reported by Finch [38] (2.24 %) and Laki [39] (4.5 %).

Due to the poor prognosis of ovarian carcinoma, PSO is highly recommended after childbearing. On the other hand, prophylactic breast surgery remains an option [5, 40]. How can health care providers help patients to decide between these various strategies? Decision analysis models based on data of the literature are currently trying to compare the gain in terms of survival of various breast and ovarian surveillance strategies and prophylactic surgery [41, 42].We believe that this type of analysis should also take into account the age-at-death distribution. Although the impact of germline *BRCA1/2* mutation as an independent factor in breast cancer survival still remains unclear, it should be stressed that *BRCA1/2*-related tumors, especially *BRCA1*, often occur in young women and are generally triple-negative, and these features are independent indicators of poor outcome [43]. Consequently, health care providers must avoid ensuring that all breast cancer deaths can be prevented by early detection as a result of screening.

Another way to help each patient decide on the best option for her particular case is to use a formalized informed medical decision-making procedure. Decision aids have been developed to facilitate this procedure [44]. Educational-support group may also help women to decide [45]. For example, we believe that data on the long-term effects of PM, such as capsular contracture and cosmetic complications, must be evaluated and explained to these women. The patient's choices may also evolve over time: for example, the acceptability of PM could be increased by improving the patient's access to information, especially via Internet, such as the information provided by our web site: www.cancersdusein.curie.fr. The recent initiation of chemoprevention clinical trials will also provide women with a third breast management option.

Many issues have yet to be resolved, such as the efficacy of the various options in terms of mortality reduction, taking into account the response to chemotherapy and radiotherapy, the impact of PM and PSO on quality of life, and long-term adhesion to breast MRI follow-up. Long-term evaluation of patient satisfaction also needs to be performed. Answers to these questions will help to define optimal individualized management strategies.

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Ethical standards This study is in agreement with the current laws and ethical standards in France. This study was approved by the Institutional Review Board. Informed consent was obtained from each woman participating in the cohort. All authors have read and approved the manuscript as the members of the Institut Curie Breast and Ovarian Cancer Risk Study Group.

Conflict of interest The authors have no conflicts of interest to disclose.

Appendix: The Institut Curie Breast and Ovarian Cancer Risk Study Group

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