

Time to prophylactic surgery in *BRCA1/2* carriers depends on psychological and other characteristics

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Purpose: To investigate the medical and psychosocial factors determining the time to prophylactic surgery of unaffected women carriers of a deleterious *BRCA1/2* mutation. **Methods:** Prospective study on a French national cohort of unaffected *BRCA1/2* carriers ($N = 244$); multivariate Cox proportional hazard modeling. **Results:** Median follow-up time was 2.33 years (range, 0.04–6.84 years). Time to surgery was shorter when the psychological impact of *BRCA1/2* result disclosure was stated to be higher ($P \leq 0.01$). Those who intended to opt for prophylactic surgery before being tested did so faster and more frequently after test disclosure than those who were undecided/opposed. The older the women were, the faster their uptake of risk-reducing salpingo-oophorectomy (adjusted hazard ratio >2.95 ; $P < 0.001$) was; the uptake of those with at least two children was also faster (adjusted hazard ratio = 2.51; [1.38–4.55]). Those who opted most quickly for risk-reducing mastectomy more frequently had a younger child at the time of testing (adjusted hazard ratio = 4.63 [1.56–13.74]). Time to surgery was shorter when there was a first-degree relative with ovarian/breast cancer ($P \leq 0.01$). **Conclusion:** Time to prophylactic surgery depends on the stated psychological impact of disclosure and on women's cognitive anticipation of surgery after adjusting on sociodemographic characteristics. *Genet Med* 2010;12(12):801–807.

Key Words: prophylactic surgery, *BRCA1/2*, psychosocial, breast cancer, genetic testing

Prophylactic surgery is the most effective strategy for preventing the occurrence of breast and ovarian cancer in women who are found to be carriers of a *BRCA1* or *BRCA2* mutation.^{1–3} Risk-reducing mastectomy (RRM) has been found to reduce the incidence of breast cancer,^{4–8} and risk-reducing salpingo-oophorectomy (RRSO) has proved to effectively prevent both ovarian and breast cancer.^{9–13}

In line with other countries, the French guidelines recommend risk-reducing surgery in this context.¹⁴ The latest expert committee has stated that RRSO should not be recommended before the age of 40 years and that several parameters should be taken into account, including matrimonial status and completion of childbearing. RRM should not be recommended before the age of 30 years. The incidence of risk-reducing surgery has been described in various settings most of the times on hospital series or regional registries.^{15–28} The factors affecting women's decision to undergo prophylactic surgery include age, parenthood, worry about cancer, and a prior (personal or familial) history of breast cancer. However, these studies were often performed on small numbers of unaffected participants, which meant that multivariate adjustment was not possible, or on mixed samples of affected and unaffected women, without simultaneously measuring the psychosocial variables involved.

The aim of this prospective study was to investigate the psychosocial and medical factors on which uptake and time to prophylactic surgery depend in unaffected women carriers of a deleterious *BRCA1/2* mutation. Time to RRM and time to RRSO uptake were assessed in a national multicenter cohort of French women not affected by cancer. The follow-up was up to 6 years after the disclosure of their *BRCA1/2* mutation carrier status (median follow-up was 2 years).

MATERIALS AND METHODS

Study group

Participants were identified in the French Gene Etude Prospective Sein Ovaire (GENEPSO) cohort.²⁹ The GENEPSO cohort consists of *BRCA1/2* carriers recruited in a routine consultation context since 2000 at 29 cancer genetic clinics belonging to the French National Federation of Cancer Centres' cancer genetic network. Unaffected carriers of a *BRCA1/2* deleterious mutation identified in the GENEPSO cohort up to 2006 were included. Eligible subjects were women aged 18 years or older, who were not affected by cancer but belonged to a family where a deleterious predisposing *BRCA1/2* mutation had been identified and who had consulted one of the cancer genetic clinics participating in this study for *BRCA1/2* testing.

Data collected

Women included in the cohort filled in a self-administered questionnaire before the test result delivery and again 15 days after being given the results. The follow-up also included self-administered closed questionnaires to be completed 6, 12, 24, and 60 months after test result disclosure. In parallel, the respondents' medical data were collected at cancer genetic consultations, including the test results, the type of mutation (*BRCA1* or *BRCA2*), and the familial history of ovarian and/or breast cancer.

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In all, 259 female *BRCA1/2* carriers were selected from the companion psychosocial cohort. The first questionnaire, which was filled in before test result disclosure (questionnaire M0), focused on sociodemographic data (age, marital status, education, employment, number of children, and their age) and the perceived lifetime risk of breast and ovarian cancer, and documented the women's intention to undergo prophylactic surgery if the results were positive. The second questionnaire, which was filled in 15 days after test result disclosure (questionnaire D15), focused on the psychological characteristics listed below.

Psychological variables

Perceived risks

The perceived risks of breast and ovarian cancer were measured separately with 5-point Likert-style items: "In your opinion, what is your risk of developing breast/ovarian cancer during your lifetime?" (null, low, average, high, and very high). Both measures were dichotomized to compare women who rated their risk high/very high with the other women. Perceived risk was measured at baseline (M0) and not in the D15 questionnaire.

Depression

Depression was measured using the French version of the Center for Epidemiologic Studies Depression Scale (CES-D),³⁰ a 20-item scale that is widely used in population-based studies³¹ and studies on patients with cancer.³² The threshold score of 23 has been found to be indicative of significant depressive symptoms in French women.³⁰ In this sample, the CES-D showed a high level of reliability (Cronbach's $\alpha = 0.93$).

Impact of the test result disclosure

The psychological impact of the test was measured using the 15-item Impact of Events Scale (IES).³³ The IES has two subscales focusing on intrusive and avoidance ideation about a specific event. The global IES score (Cronbach's $\alpha = 0.91$) and the intrusive ideation (Cronbach's $\alpha = 0.88$) and avoidance ideation (Cronbach's $\alpha = 0.82$) subscores were used in this study. The IES was measured 15 days after test result disclosure (using the D15 questionnaire). The IES was framed on the specific event "disclosure of the blood sample test results."

Body image

Body image was assessed using the questionnaire developed by Lodder et al.¹⁷ This scale consists of eight items measuring general body image (Cronbach's $\alpha = 0.83$) and three items measuring the breast-related body image (Cronbach's $\alpha = 0.58$). Body image was measured in the D15 questionnaire.

Statistical analysis

Time to surgery (RRSO or RRM) was calculated from the date of *BRCA* test result disclosure to the date of surgery. Subjects who did not undergo risk-reducing surgery were censored at diagnosis of cancer, death, or loss of contact for other reasons.

The relationships between the cofactors listed above (collected at M0 or D15) and RRSO/RRM were assessed using the Kaplan-Meier method and compared by performing log-rank tests. Cox's proportional hazards model was used to calculate crude and adjusted hazard ratios and their corresponding 95% confidence intervals (CIs), so that independent predictors of RRSO/RRM could be identified. The proportional hazards assumption was checked by examining the log-minus-log survival plot drawn up for each cofactor. Variables with a *P* value <0.20 in the univariate analyses were taken to be eligible for inclusion in the multivariate model. Only variables still significantly associated

with the outcome variable with a *P* value <0.05 were kept in the final model. All the statistical analyses were performed using the STATA version 9.0 software program (STATA Corp, College Station, TX).

RESULTS

Study population

Among the original 259 eligible women, 15 were subsequently excluded: 2 had RRSO before test disclosure and 13 did not complete both the M0 and D15 questionnaires. Therefore, our final sample consisted of 244 *BRCA1/2* mutation carriers (156 *BRCA1* and 88 *BRCA2*). Subjects' sociodemographic and psychological characteristics and other descriptive data are given in Table 1. The mean age of women was 39 years (SD = 10.7) at the time of inclusion; 75.4% were living with a partner and 71.3% had children. They belonged to 207 families and were registered with 26 different centers (average number of women per center = 10 [SD = 9], range = 1–62).

Before test result disclosure, 44.3% of the women perceived their lifetime risk of developing ovarian cancer as being high/very high (Table 1); high/very high breast cancer risk perceptions were observed in 57.8% (Table 2). In addition, half of the women (55.3%) intended to have RRSO (Table 1), and more than a quarter (27.9%) intended to have RRM if their test results were positive (Table 1). The mean CES-D score was 13.7 (SD = 11.0), and 21.3% of the women were depressed (CES-D scores above 23).

The participants were followed up for a median period of 2.33 years (25–75% interquartile range [IQR] = 2.07–5.18 years, range = 0.04–6.84). During the study period, 12 women had both RRSO and RRM (4.9%), 80 had RRSO alone (32.8%), and 8 had RRM alone (3.3%). Among the remaining 144 women who underwent no prophylactic surgery, 11 were diagnosed with breast cancer at follow-up and 1 of them died; another woman died as the result of a cerebellar aneurism. No ovarian/breast cancer was observed among those who opted for RRSO/RRM, respectively, except for one woman, who developed breast cancer 2 years after RRSO.

Characteristics of women who underwent RRSO

The median time elapsing between receiving *BRCA* results and undergoing RRSO was 0.75 years (25–75%, IQR = 0.41–2.10 years) among the 92 women who opted for RRSO. Rates of RRSO did not differ significantly between centers. The median age of women was 45.6 years (25–75%, IQR = 41.1–52.4) at the time of surgery. The youngest age at RRSO was 28.3 years, and the oldest age was 72.3 years.

The Kaplan-Meier curves give the RRSO uptake versus time, stratified by age (Fig. 1A) and by the participants' "a priori" intentions concerning RRSO (Fig. 1B). The log-rank test was highly significant in both cases ($P < 0.001$). RRSO uptake within 2 years of disclosure increased drastically with age: from 1.8% (95% CI, 0.3–12.0%) among women younger than 30 years at disclosure to 14.4% (95% CI, 8.6–23.5%), 51.9% (95% CI, 39.7–65.2%), and 79.2% (95% CI, 61.8–92.3%), among women aged 31–40 years, 41–50 years, and older than 50 years, respectively. In terms of the women's a priori intentions, the rate of RRSO uptake during the 2 years after disclosure was 10.1% (95% CI, 4.3–22.6%) among those not intending before disclosure to undergo RRSO, when compared with 41.2% (95% CI, 33.3–50.3%) among those who had already made this decision.

Factors significantly correlated with RRSO uptake, as shown by the univariate and multivariate comparisons, are given in

Table 1 Descriptive data of the 244 unaffected BRCA1/2 carriers—GENEPSO cohort study

	<i>n</i> (%)
Age (yr)	
≤30	56 (23.0)
31–40	96 (39.3)
41–50	60 (24.6)
>50	32 (13.1)
Living with a partner	
No	60 (24.6)
Yes	184 (75.4)
Level of education	
Primary school	56 (22.9)
Less than high school certificate	51 (20.9)
High school certificate or higher	137 (56.2)
Children	
None/one	104 (42.6)
Two or more	140 (57.4)
Children <15 yr	
No	125 (51.2)
Yes	119 (48.8)
Has sister(s)	
No	72 (29.5)
Yes	172 (70.5)
Female first degree related has had ovarian cancer	
0	153 (62.7)
≥1	91 (37.3)
Female first degree related has had breast cancer before 50 years	
0	119 (48.8)
≥1	125 (51.2)
Intended in M0 questionnaire to undergo RRSO if the results were positive	
Certainly not/probably not	51 (20.9)
Did not know	58 (23.8)
Certainly yes/probably yes	135 (55.3)
Intended in M0 questionnaire to undergo RRM if the results were positive	
Certainly not/probably not/did not know	176 (72.1)
Certainly yes/probably yes	68 (27.9)
Gave high-perceived risk of ovarian cancer in the M0 questionnaire	
No	136 (55.7)
Yes	108 (44.3)

	<i>n</i> (%)
Gave high-perceived risk of breast cancer in the M0 questionnaire	
No	103 (42.2)
Yes	141 (57.8)
	<i>x</i> (SD)
Impact of event scale D15	19.02 (16.20)
Impact of event scale D15—avoidance score	9.60 (9.08)
Impact of event scale D15—intrusion score	9.42 (8.46)
Breast-related body image scale D15	9.32 (1.92)

Table 2. After multivariate adjustment, the RRSO rates increased significantly with age and the number of children, and with the occurrence of ovarian cancer in a first-degree relative. Women who intended before disclosure to have RRSO if they turned out to be carriers and those who were initially undecided tended to undergo RRSO more quickly than those who said they would not have RRSO. In the latter group (*n* = 51), eight (15.7%) women actually underwent this operation. Only the IES intrusion score was still significantly associated with RRSO after multivariate adjustment. Other factors associated with RRSO uptake in the univariate Cox models (living with a partner, education, and ovarian cancer risk perception) were no longer found to be significant after multivariate adjustment, as shown in Table 2.

The type of mutated gene (*BRCA1/BRCA2*), employment status, depression, the number of cases of breast cancer among first-degree relatives, and the participants' breast cancer risk perception were not found in the univariate comparisons to be significantly associated with RRSO uptake.

Characteristics of women who underwent RRM

The median time elapsing between receiving BRCA results and undergoing surgery was 2.05 years (25–75%; IQR = 0.48–2.54 years) among the 20 women who opted for RRM. The rates of RRM uptake did not differ significantly between centers.

Median age of women who underwent RRM was 38.8 years (25–75%; IQR = 31.8–46.8; range, 28.3–51.7). Among the 12 women who underwent both types of surgery, 2 underwent RRM before RRSO, 6 had both operations concomitantly, and the remaining 4 underwent RRSO before RRM.

The Kaplan-Meier curves give the RRM uptake over time, stratified by the age of the youngest child (Fig. 2A) and by the participants' a priori intentions to undergo RRM (Fig. 2B). Women with children younger than 15 years underwent RRM significantly more frequently during the follow-up period than the others (*P* = 0.019). Factors significantly associated with RRM uptake, as shown by both univariate and multivariate comparisons, are given in Table 3.

After multivariate adjustment, the rate of RRM was significantly associated with having children younger than 15 years at the time of testing, the occurrence of breast cancer in a first-degree relative before the age of 50 years, intending before disclosure to have RRM, and immediate psychological effects of disclosure, as measured 15 days after the disclosure in terms of the IES score.

Other factors significantly associated (*P* ≤ 0.05) with RRM uptake in the univariate Cox models (number of children and breast cancer risk perception before test results) were no longer found to be significant after multivariate adjustment. Both IES

Table 2 Cox proportional hazards model for RRSO—*n* = 244 unaffected *BRCA1/2* carriers—GENEPSO cohort study

	Crude HR (95% CI)	<i>P</i>	Adjusted HR (95% CI)	<i>P</i>
Age (yr)				
≤30	0.09 (0.02–0.40)	0.001	0.17 (0.04–0.74)	0.018
31–40	1		1	
41–50	2.95 (1.80–4.83)	<0.001	2.58 (1.56–4.24)	<0.001
>50	5.36 (3.07–9.38)	<0.001	3.96 (2.21–7.11)	<0.001
Living with a partner				
No	1	0.005		
Yes	2.31 (1.28–4.15)			
Level of education				
Primary school	2.67 (1.63–4.38)	<0.001		
Less than high school certificate	2.86 (1.74–4.72)	<0.001		
High school certificate or higher	1			
Children				
None/one	1		1	
Two or more	5.83 (3.29–10.33)	<0.001	2.51 (1.38–4.55)	0.002
Has sister(s)				
No	1		1	
Yes	2.58 (1.50–4.44)	0.001	2.68 (1.51–4.75)	0.001
Female first-degree relative has had ovarian cancer				
0	1		1	
≥1	1.65 (1.10–2.47)	0.015	1.67 (1.09–2.56)	0.018
Intended in M0 questionnaire to undergo RRSO if the results were positive				
Certainly not/probably not	1		1	
Did not know	2.44 (1.06–5.61)	0.036	2.59 (1.10–6.08)	0.029
Certainly yes/probably yes	4.94 (2.36–10.34)	<0.001	3.44 (1.63–7.25)	0.001
Gave high perceived risk of ovarian cancer in the M0 questionnaire				
No	1			
Yes	1.60 (1.06–2.42)	0.025		
Impact of event scale D15	1.01 (1.00–1.03)	0.020		
Impact of event scale D15—intrusion score	1.03 (1.01–1.06)	0.002	1.03 (1.01–1.05)	0.008

subscales (avoidance and intrusion) and the breast-related body image score were borderline ($P < 0.10$) in the univariate comparisons (Table 3). The type of mutated gene (*BRCA1/BRCA2*), employment status, depression, general body image score, previous ovarian cancer in first-degree relatives, and ovarian cancer risk perception were not found in the univariate analysis to be significantly associated with RRM uptake.

DISCUSSION

As far as we know, this is the first time a prospective National Multicenter Study has been conducted on the uptake of

prophylactic surgery by unaffected women carriers of a *BRCA1/2* mutation and on the effects of psychosocial and medical factors on the time to RRSO and the time to RRM. After multivariate adjustment, women who decided before disclosure that they would have RRSO/RRM were operated on more quickly than the others. However, nearly one third of those opposed to RRSO before testing eventually changed their minds (Fig. 1B). The greater the psychological impact of the test results, the sooner the women underwent one or both types of surgery after disclosure. The time to RRSO was also found to be strikingly dependent on age group and on having completed childbearing. Only having a younger child was significantly correlated with an earlier occurrence of RRM,

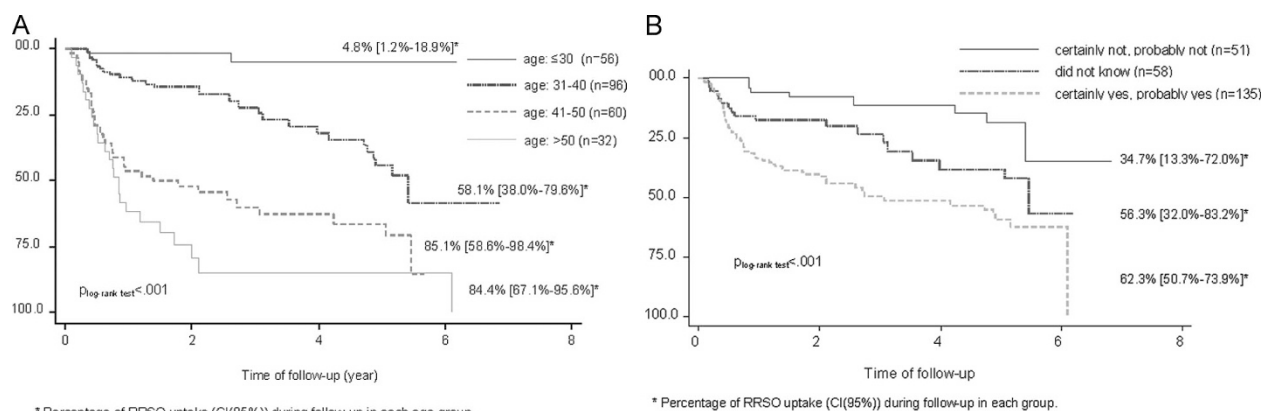


Fig. 1. A, Uptake of risk-reducing salpingo-oophorectomy (RRSO) at follow-up, in unaffected carriers of a *BRCA1/2* mutation, stratified by age at result disclosure (Kaplan-Meier) ($N = 244$). B, Uptake of RRSO at follow-up, in unaffected carriers of a *BRCA1/2* mutation, stratified by a priori intentions to undergo RRSO before BRCA testing (Kaplan-Meier; $N = 244$).

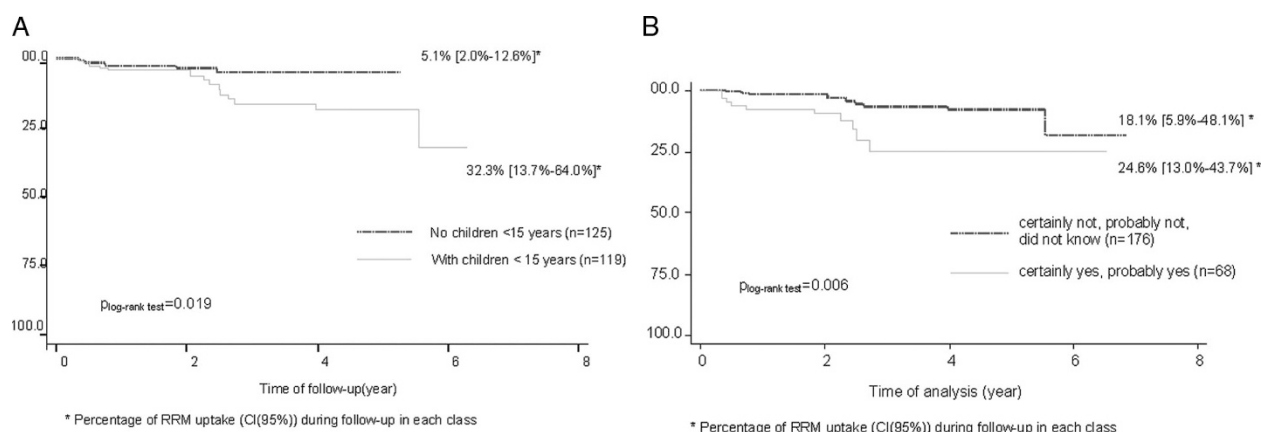


Fig. 2. A, Uptake of risk-reducing mastectomy (RRM) at follow-up, in unaffected carriers of a *BRCA1/2* mutation, stratified by children younger than 15 years at BRCA testing (Kaplan-Meier; $N = 244$). B, Uptake of RRM at follow-up, in unaffected carriers of a *BRCA1/2* mutation, stratified by a priori intentions to undergo RRM before BRCA testing (Kaplan-Meier; $N = 244$).

whereas the woman's own age was not. The occurrence of breast/ovarian cancer in a first-degree relative was also significantly associated with a shorter time to surgery. The type of gene involved (*BRCA1/2*) was not associated with the rate of RRSO/RRM uptake.

This is the first time the short-term psychological impact of *BRCA1/2* testing has been correlated with the time to uptake of prophylactic surgery, and the effects of pretest intentions on the speed and rate of uptake of RRM/RRSO after test result disclosure have been documented (Figs. 1B and 2B). Although cancer-related worry has been previously described as being associated with the decision to undergo RRM/RRSO,^{19,34,35} the stated impact of test result disclosure was found here to be a significant predictor of the uptake of preventive surgery. Women who had already made their decision before receiving their test results underwent prophylactic surgery faster than those who were undecided or opposed. However, even in the latter two categories, a nonnegligible proportion of the women opted for surgery in the long run. Further studies will have to be conducted to measure these women's satisfaction to determine how their decision making is carried out and whether their right to self-determination has been respected. Although participants

in previous studies expressed dissatisfaction with RRM when the decisions were made by their physicians,³⁶ this may not be the case if a sufficient amount of time has been devoted to provide information and counseling to women to ensure that an informed decision-making process occurred.

Time to RRSO depended on the age group. Two years after disclosure, 84% of the subjects aged 50 years and older had undergone RRSO, and this rate was still the same after 2 years of follow-up. In the younger age groups, the pattern was quite different (Fig. 1A). The authors of a previous UK study²⁷ reported that 30% of the unaffected *BRCA1/2* carriers aged 45 years and older had RRSO by the second year after test result disclosure, and this figure increased to 50% by the 4th year; in the 36–45 years age group, 50% and 70% had RRSO by the 2nd and 5th year of follow-up, respectively. Age and having at least two children are obviously decisive factors because of the deleterious reproductive and menopausal consequences of RRSO. To be able to subsequently interpret the rates of RRSO uptake, the figures should be systematically stratified on age and completion of childbearing projects at the time of *BRCA1/2* testing. In a cohort of women older than 35 years who had completed childbearing, Madalinska et al.²¹ reported that 79%

Table 3 Cox proportional hazards model for risk-reducing mastectomy (RRM)—*n* = 244 unaffected *BRCA1/2* carriers—GENEPSO cohort study

	Crude HR (95% CI)	<i>P</i>	Adjusted HR (95% CI)	<i>P</i>
Age (yr)				
≤30	1			
31–40	0.77 (0.26–2.29)	0.635		
41–50	1.13 (0.36–3.53)	0.828		
>50	0.48 (0.06–4.04)	0.500		
Level of education				
Primary school	1.87 (0.67–5.27)	0.234		
Less than high school certificate	1.67 (0.58–4.98)	0.360		
High school certificate or higher	1			
Children				
None/one	1			
Two or more	4.88 (1.42–16.76)	0.012		
Children aged <15 yr				
No	1		1	
Yes	3.14 (1.14–8.65)	0.027	4.63 (1.56–13.74)	0.006
Female first degree related who had breast cancer before 50 years (idem)				
0	1		1	
>1	3.78 (1.26–11.31)	0.017	3.62 (1.19–11.03)	0.024
Intended in M0 questionnaire to undergo RRM if the results were positive				
Certainly not/probably not/did not know	1		1	
Certainly yes/probably yes	3.22 (1.33–7.76)	0.009	2.60 (1.06–6.39)	0.037
Gave high perceived risk of breast cancer in the M0 questionnaire				
No	1			
Yes	2.96 (0.99–8.87)	0.052		
Impact of event scale D15	1.02 (1.00–1.05)	0.054	1.03 (1.01–1.06)	0.016
Impact of event scale D15—avoidance score	1.04 (1.00–1.08)	0.075		
Impact of event scale D15—intrusion score	1.04 (1.00–1.09)	0.080		
Breast-related body image scale D15	1.26 (0.99–1.61)	0.065		

HR, hazard ratio; RRM, risk-reducing mastectomy.

underwent RRSO within 1 year of attending a systematically organized gynecological consultation, but age-related effects were still observed in this fairly homogeneous group. On the whole, it can be said that long-term clinical follow-up must be made available to young women at *BRCA1/2* result disclosure and that the highest predictable rate of RRSO uptake by premenopausal and menopausal women is about 80%.

RRM was undergone by 8% of the women included in this study, which is very low compared with what is observed in other countries, Denmark in particular,²⁸ but not surprising in the French context if we compare a priori attitudes toward prophylactic surgery.³⁷ No effect of the participants' age on the uptake of RRM was observed, whereas having young children

was found to be a significant factor (Table 3). Previous authors have assumed that mothers of young children prize their life expectancy more than their body image.¹⁷

Some authors have observed,^{19,36} contrary to others,³⁵ that there exists an association between the uptake of prophylactic surgery and a history of cancer in first-degree relatives. It was established in this study that having a first-degree relative with breast/ovarian cancer contributes significantly to women's decision to undergo RRM/RRSO.

Our study admittedly had some limitations. First, we learned from the main GENEPSO cohort study that we had some overestimation of the practice of prophylactic surgery among responders who agreed to complete self-administered psychosocial

questionnaires. Second, the uptake rates of prophylactic surgery may have been higher because questions were provided in this study on these issues. Taking into account these limitations that possibly overestimate the crude RRM/RRSO uptake data, the uptake of RRM was still very low in this study in comparison with the data published in other countries.^{16,20,24,25,27,28} Finally, using pretest risk perception instead of posttest risk perception not available at 15 days is likely to have underestimated the effect of risk perception on prophylactic surgery. This limitation has to be kept in mind in interpreting the association between risk perception and subsequent behavior.

When promoting BRCA testing for younger women who are not eligible for RRSO/RRM according to the medical guidelines, one should not forget that the concern for prophylactic surgery will usually only arise several years after test disclosure. It is necessary to organize and maintain suitable clinical surveillance and informed decision making for younger unaffected women carriers of a BRCA1/2 mutation taking into account that the psychological impact of test result may be associated to women opting for surgery rapidly after testing. Because guidelines are updated regularly in the light of new evidence-based knowledge, it is important to keep in touch with carriers. Long-term prospective follow-up protocols should be set up for the youngest generations of familial mutation carriers to be able to assess as accurately as possible the personal and familial consequences of breast/ovarian cancer genetic testing and mutation carriers' subsequent preventive behavior.

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