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ORIGINAL STUDY

Satisfaction with prophylactic risk-reducing salpingo-oophorectomy in *BRCA* mutation carriers is very high and little dependent on the participants' characteristics at surgery: a prospective study

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Abstract

Objective: *BRCA* carriers are recommended to undergo prophylactic risk-reducing salpingo-oophorectomy (RRSO). Possible adverse health impacts of RRSO, particularly when done before natural menopause, can reduce the long-term satisfaction with this risk-reducing strategy. The aim of this study was to prospectively evaluate the level of satisfaction of women undergoing RRSO, also in relation to some specific characteristics at RRSO.

Methods: A prospective cohort study was performed in the Modena Family Cancer Clinic of the University Hospital of Modena (Italy). All *BRCA1/2* confirmed mutation carriers who decided to undergo RRSO were recruited between 2016 and 2019.

Results: Fifty-five women (29 *BRCA1* and 26 *BRCA2*) (mean age: 50.4 ± 7.7 years [range 35-79]) were included with a mean follow-up after RRSO of 660.9 days (1.8 years) (range 35-1,688 days) (median: 549 days). No intraepithelial (Serous Tubal Intraepithelial Carcinoma)/invasive cancers were found (0%) at RRSO. No vasomotor symptoms at 1 month after surgery were reported by 11/22 (50%) premenopausal women at RRSO. All women (100%) with new ''RRSO-caused'' vasomotor symptoms with no previous breast cancer initiated postmenopausal hormone therapy. At the final follow-up the satisfaction rate (0-100 visual analog scale points) of the participants was 96.4 ± 8.6 points (range 62-100). To the question ''Would you undergo RRSO again if it was proposed today? (0-100 visual analog scale points)'' the answer was 99.4 ± 3.2 points (range 79-100). These scores were in general very high and did not change in the different groups according to pre/postmenopausal status at RRSO, cancer survivors versus healthy women at RRSO, *BRCA* status, hormone therapy users/nonusers after RRSO, ''RRSO-caused'' symptoms versus not RRSO-caused ($P > 0.05$).

Conclusions: Findings from this prospective study suggest that satisfaction with RRSO is very high and little dependent on the participants' characteristics at surgery. Women at high risk for ovarian cancer are very satisfied with their choice of risk-reduction strategy.

Key Words: *BRCA* – Ovarian cancer – Postmenopausal hormone therapy – Risk-reducing surgery – Risk-reducing salpingo-oophorectomy – Satisfaction.

Video Summary: http://links.lww.com/MENO/A712.

The lifetime risk of ovarian cancer in women with a proven *BRCA* mutation by the age of 70 years is very high, approximately 40% in *BRCA1* mutation carriers and 18% in *BRCA2* mutation carriers.[1] Due to the proven ineffectiveness of gynecologic screening for detecting early-stage ovarian/tubal cancers,[2-4] *BRCA* mutation carriers are

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recommended to undergo a prophylactic risk-reducing salpingo-oophorectomy (RRSO) at some point in their life. According to the National Comprehensive Cancer Network guidelines, RRSO is recommended for *BRCA1* mutation carriers between the ages of 35 and 40 years or when childbearing is complete. The option of delaying RRSO until age 40 to 45 years may be considered in women with *BRCA2* mutations because there appears to be a later average age of onset (approximately 8-10 years) than in women with a *BRCA1* mutation.[5] RRSO substantially reduces the risk of ovarian and fallopian tube cancer in women who carry a *BRCA* mutation, with estimates of the reduction in risk ranging from 75% to 96%.[6-9] However, after RRSO, there is a small residual risk of developing primary peritoneal cancer. RRSO also reduces the risk of breast cancer by up to 50%,[10] though the amplitude of this protective effect has recently been widely questioned.[11,12] Despite the importance of RRSO on the long-term survival of *BRCA* mutation carriers, it is also essential to take into account other possible negative effects of RRSO, particularly when performed before natural menopause. This surgery lowers serum estrogen and androgen levels,[13] which can cause a range of symptoms including loss of libido, vasomotor symptoms like hot flashes, insomnia, mood changes, and vaginal dryness.[14] Long-term premature menopause has also been linked to a worrying impact on the cardiovascular system and bone health, and perhaps even on memory and attention.[15] However, the health benefits of RRSO should outweigh the costs of the procedure in terms of quality of life (QoL) and long-term health. Some women may benefit from postmenopausal hormone therapy (HT), consisting of either estrogen alone or combination therapy. This is an important part of treatment for women with no history of breast cancer.[16]

Previous studies have reported that women at high risk for ovarian cancer are very satisfied with their choice of RRSO, although these studies are mainly retrospective in design.[17-19] The purpose of this study was to prospectively evaluate the level of satisfaction of women undergoing RRSO in the Modena Family Cancer Clinic (MFCC), also in relation to some specific characteristics of these women.

METHODS

Study design

A prospective single-centre cohort study was performed at the MFCC of the Azienda Ospedaliero-Universitaria di Modena between January 2016 and September 2020. Women living in the Emilia Romagna region of Italy with a family history of breast cancer, ovarian cancer, or both were invited for a first evaluation in 1 of 13 spoke centers (spoke and hub model). On the basis of their lifetime breast cancer risk, they were offered participation in a personalized surveillance program. After the first evaluation, some women were sent for a second evaluation in a hub center. The MFCC is one of four hub centers, which identifies families with an increased hereditary cancer risk. Since 1996, these centers have offered *BRCA* genetic testing to these families.

At our Institution, gynecological surveillance of *BRCA* mutation carriers includes a 6-monthly free of charge evaluation of CA 125 and CEA, together with transvaginal ultrasound (TVUS) and clinical exams. During these procedures, a dedicated specialist (G.G.) counsels women over 35 years old on the importance of RRSO, the inefficacy of screening approaches for influencing prognoses, and the reduction in mortality and premature menopause management after RRSO.

All confirmed *BRCA1* and *BRCA2* mutation carriers over 35 years old, who had completed childbearing and decided to undergo RRSO at the MFCC– following a counseling session and who agreed to participate in this prospective study were recruited between January 1, 2016 and December 31, 2019. The last follow-up was September 30, 2020.

Evaluated variables

Oncological and gynecological histories were obtained from participants during the first visit. These characteristics included age, number of pregnancies, mutation type (*BRCA1* or *BRCA2*), age of onset of menopause, and possible postmenopausal HT administration, breast cancer history, and hormone treatments for breast cancer (gonadotropin-releasing hormone analog, tamoxifen, or aromatase inhibitors), other types of pharmacological therapy, and uterine or ovarian diseases found during the transvaginal ultrasound evaluation. The mean time between counseling and acceptance of the intervention at the MFCC and the RRSO surgery was also recorded.

Histological data were also included, like ovarian or tubal alterations, in addition to immunohistochemistry analyses including p53 and B-cell lymphoma-2 expression. The p53 signature was defined as benign-appearing nonciliated tubal epithelium, overexpression of p53 but no increased cell proliferation (Fig. 1A, B). Histological analyses were performed by a single group of pathologists (Department of Pathology, Azienda Ospedaliera-Universitaria di Modena) for all surgical samples under the supervision of one author (L.B.).

After RRSO, women were evaluated 1 month after surgery, then every 6 months thereafter in accordance with the surveillance protocol. For premenopausal women undergoing RRSO, vasomotor symptoms were evaluated at the first visit according to a validated questionnaire (Greene Climacteric Scale) with items related to vasomotor symptoms (presence of hot flushes and sweating at night; items 19 and 20).[20] During this first visit and the next semiannual evaluations, each woman completed an evaluation about their satisfaction with RRSO and their willingness to undergo the surgery again (answer to the question ''Would you undergo RRSO again if it was proposed today?''). These evaluations were performed through a visual analog scale (VAS) from 0 to 100, which was directly completed by the patients.

Institutional review board approval

Ethical approval for this study was provided by the Ethics Committee of Area Vasta Emilia Nord (reference no. 515). All data were obtained from the electronic database and

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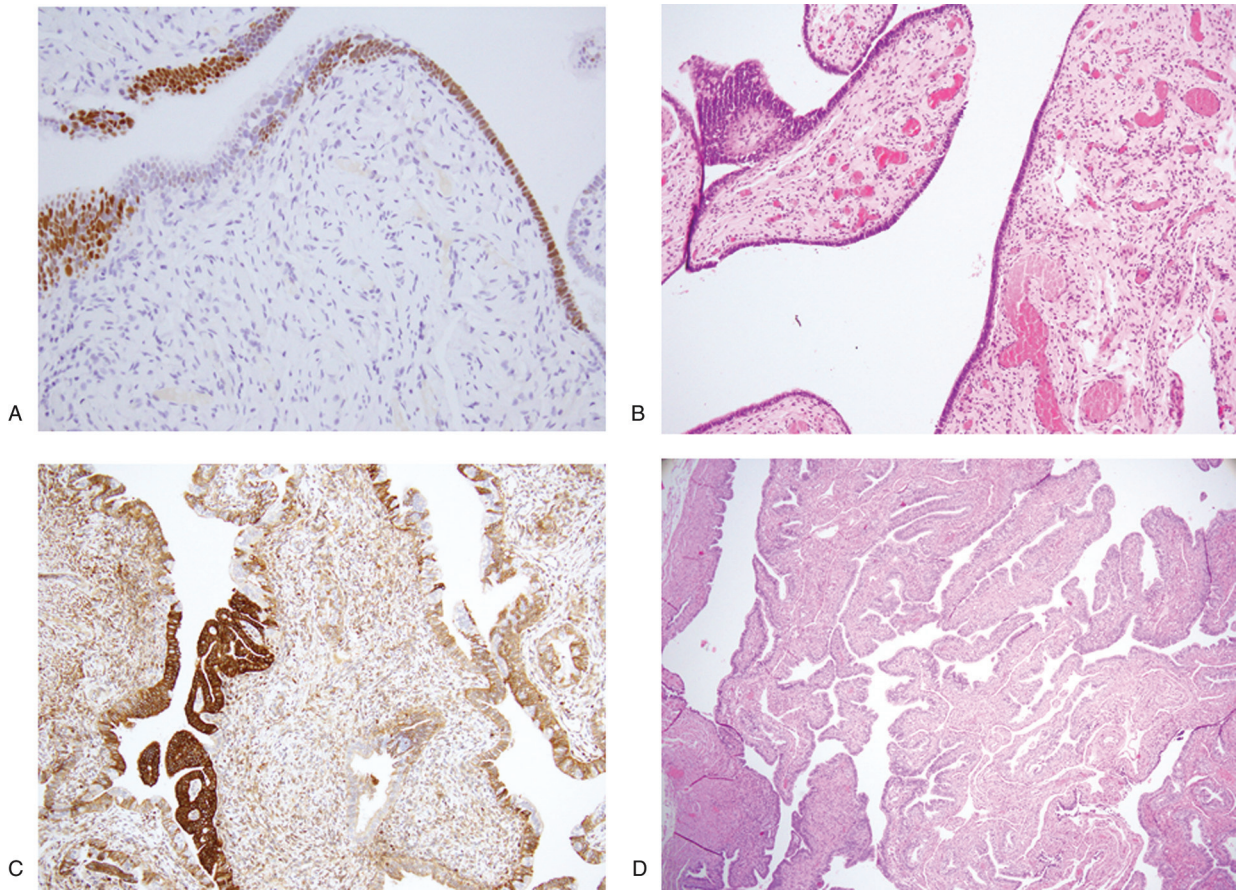

FIG. 1. p53 and Bcl-2 expression examination of the RRSO specimens: p53 signature positive 10X (**A**), hematoxylin-eosin: no atypia 4X (**B**), Bcl-2: overexpression with SCOUT 10X (**C**), hematoxylin-eosin: no atypia 4X (**D**). Bcl-2, B-cell lymphoma-2; RRSO, riskreducing salpingo-oophorectomy; SCOUT, secretory cell outgrowth.

anonymized before analysis. All patients included in the study gave their written consent for the anonymous use of their clinical data for research purposes.

Study endpoints

The primary outcome of the study was to evaluate the general degree of satisfaction with RRSO of *BRCA* mutation carriers (VAS 0-100) at the last follow-up after RRSO for each woman.

The secondary outcomes of the study were to evaluate the following: (1) willingness to undergo the surgery again (VAS 0-100; ''Would you undergo RRSO again if it was proposed today?''); (2) if specific characteristics of women undergoing RRSO influenced their satisfaction, such as pre- versus postmenopausal status at the time of RRSO, cancer survivors versus healthy women at RRSO, *BRCA* status, HT users/nonusers after RRSO, ''RRSO-caused'' versus not RRSO-caused vasomotor symptoms; (3) histological findings of RRSO specimens; (4) use of HT in these women; and (5) appearance of vasomotor symptoms in premenopausal participants at the time of RRSO.

We did not include a control group (women who refused RRSO, ''surveillance'' group) in this study because our main outcome was to evaluate the satisfaction with an intervention (RRSO) and not with a possible attitude (RRSO vs surveillance), and this intervention (RRSO) would not have happened in this control group. We are conducting another prospective study in which our inclusion criteria are different (patients who accepted RRSO vs those refusing) and not the RRSO procedure itself. However, in this different design there would have been some patients who would have changed their minds in the follow-up period and would have undergone RRSO in a second time, further confusing our satisfaction results.

Statistical analysis

The characteristics of women with a *BRCA* mutation at the time of RRSO and during follow-up were analyzed and compared. In the descriptive analysis, continuous variables were summarized as the mean and standard deviation and categorical variables were reported as absolute values and percentage. Within-group comparison was performed with the *t* test for paired data. The comparison of categorical variables between groups was performed using the chi-square test or Fisher exact test, where appropriate. Statistical analysis was performed using the statistical package StatView (version 5.01.98; SAS Institute Inc, Cary, NC). Correlations were considered to be significant at $P < 0.05$.

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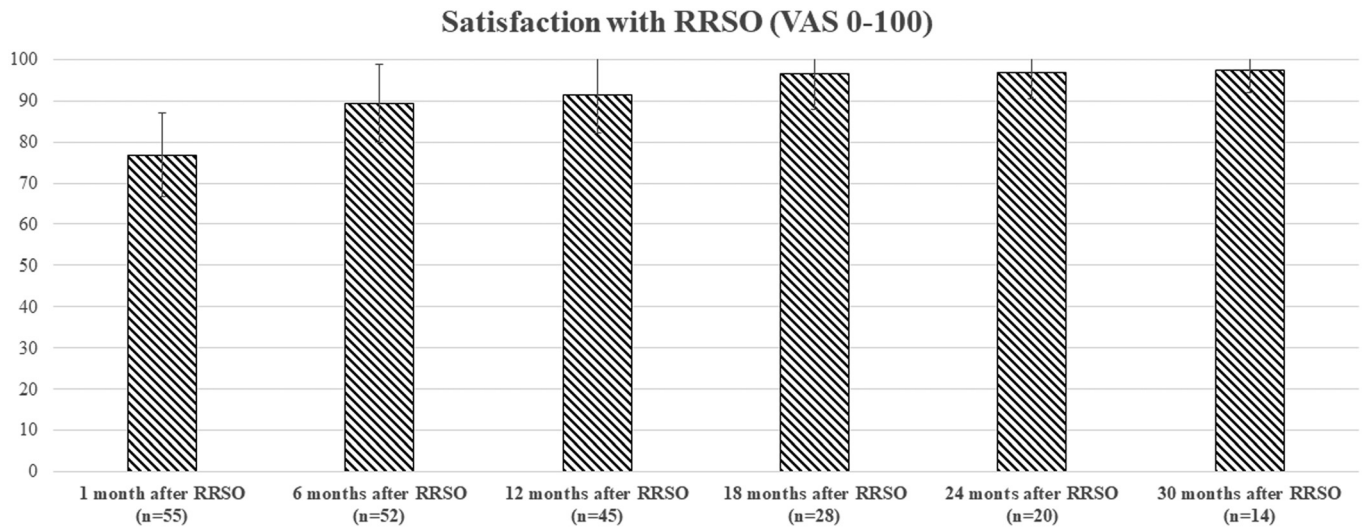

FIG. 2. Progress of the satisfaction rate, up to 30 months after RRSO. Satisfaction rate was expressed as 0-100 VAS points. RRSO, risk-reducing salpingo-oophorectomy; VAS, visual analog scale.

RESULTS

Study group

A total of 55 women (mean age at RRSO 50.4 ± 7.7 years, range 35-79 years) were included in the study, with a mean follow-up period after RRSO of 660.9 days (1.8 years, range 35-1,688 days) (Median: 549 days, 1.5 years). All the participants ($n = 55$) were evaluated at the first visit (100%) 1 month after RRSO (Fig. 2). This rate dropped to 52/55 (94.5%) at 6 months, 45/55 (81.8%) at 12 months, 28/55 (50.9%) at 18 months, 20/55 (36.4%) at 24 months and only 14/55 (25.5%) at 30 months after RRSO (Fig. 2). This was not due to women being lost to follow-up [$n = 4$ (7.3%), $n = 1$ lost after 8 months for consent withdrawal, $n = 1$ died from breast cancer 13 months after RRSO, $n = 2$ lost 13 and 17 months after RRSO for transfer to another city] but because there was not enough time to evaluate them at further follow-up visit (The last follow-up was 30th September 2020).

The characteristics of the participants are reported in Table 1. The mean time between counseling and acceptance of intervention in the MFCC and RRSO surgery was 113.6 ± 87.9 days (3.8 months, range 13-479 days; median: 74 days).

TABLE 1. *Characteristics of n = 55 women included in the study*

	Characteristics
Mean age at RRSO (range)	50.4 ± 7.7 (35-79) years
BRCA 1	29/55 (52.7%)
BRCA 2	26/55 (47.3%)
Nulliparous (%)	9/55 (16.4%)
Fibroids prevalence	26/55 (47.3%)
Adenomyosis prevalence	7/55 (12.7%)
Postmenopausal (%)	33/55 (60%)
Breast cancer survivors (%)	28/55 (50.9%)
Tamoxifene users (%)	4/28 (14.3%)
Aromatase inhibitors users (%)	5/28 (17.9%)
GnRH analog users (%)	2/28 (7.1%)

GnRH, gonadotropin-releasing hormone; RRSO, risk-reducing salpingo-oophorectomy.

Risk-reducing salpingo-oophorectomy specimens

The same group of pathologists performed the histological diagnoses, and no intraepithelial (STIC) or invasive cancers were found (0%). Secretory cell outgrowth was documented in 10 out of 55 cases (18.2%) (Fig. 1C, D). A p53 signature was found in 4 out of 55 (7.3%) cases (Fig. 1A, B), as the B-cell lymphoma-2 overexpression (4/55, 7.3%) (Fig. 1C). Four surgeries (7.3%) also included hysterectomy, and there were no oncological diagnoses in these patients (3/4 [75%] performed for fibroids, 1/4 [25%] for CIN3/CIS).

Vasomotor symptoms and hormone therapy after risk-reducing salpingo-oophorectomy

The frequency of vasomotor symptoms at the first follow-up after surgery, assessed using the Greene Climacteric Scale (items 19 and 20), was reported by 8/22 premenopausal women at RRSO (36.4%) as ''extremely'' frequent, 3/22 (13.6%) as ''a little'' or ''quite a bit'' frequent, and 11/22 (50%) as ''not at all''. New ''RRSO-caused'' vasomotor symptoms were reported by 11 women (real ''RRSO-caused'' symptoms participants). Three of these patients (27.3%) were breast cancer survivors. The other 8 healthy women (100%) were counseled to start postmenopausal HT (tibolone 2.5 mg/day), and all (100%) immediately initiated HT.

In the total sample, 10/27 (37%) women with no previous history of breast cancer started postmenopausal HT after the surgery ($n = 8$ with tibolone 2.5 mg/day, $n = 1$ with estradiol 1 mg/drospirenone 2 mg, $n = 1$ hysterectomized with estradiol transdermal gel 1.5 mg/day), with a mean follow-up period of 527.9 ± 389.7 days (1.4 years, range 29-1,249 days). No subsequent breast cancer diagnoses were reported in HT users during the follow-up period.

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Satisfaction rate at 12 months after RRSO

The change in satisfaction rate up to 30 months after RRSO is reported in Figure 2. At 12 months after RRSO (n = 45/55, 81.8%), the satisfaction rate (0-100 VAS points) of women included in the study was 91.2 ± 8.9 points (range 59-100) (Fig. 2). To the question ''Would you undergo RRSO again if it was proposed today?'' (0-100 VAS points), the mean score was 95.4 ± 3.5 points (range 74-100).

Satisfaction rate at the final follow-up after RRSO

At the final follow-up ($n = 55$) (ranging between 30 days and 54 months after RRSO), the satisfaction rate (0-100 VAS points) of women included in the study was 96.4 ± 8.6 points (range 62-100). To the question ''Would you undergo RRSO again if it was proposed today?'' (0-100 VAS points), the mean score was 99.4 ± 3.2 points (range 79-100).

These scores were generally very high and did not change in the different groups according to pre- versus postmenopausal status at RRSO ($P = 0.18$ and $P = 0.08$, respectively), cancer survivors versus healthy women at RRSO ($P = 0.56$ and $P = 0.66$, respectively), *BRCA* status ($P = 0.82$ and $P = 0.72$), HT users versus nonusers after RRSO ($P = 0.46$ and $P = 0.42$, respectively), and ''RRSO-caused'' versus not RRSO-caused symptoms ($P = 0.33$ and $P = 0.16$, respectively; Fig. 3A-E).

DISCUSSION

Main findings

This prospective study included 55 women with a *BRCA1* or *BRCA2* mutation who underwent RRSO, with a mean follow-up period of 1.8 years. At the final follow-up, the satisfaction rate of the participants was extremely high

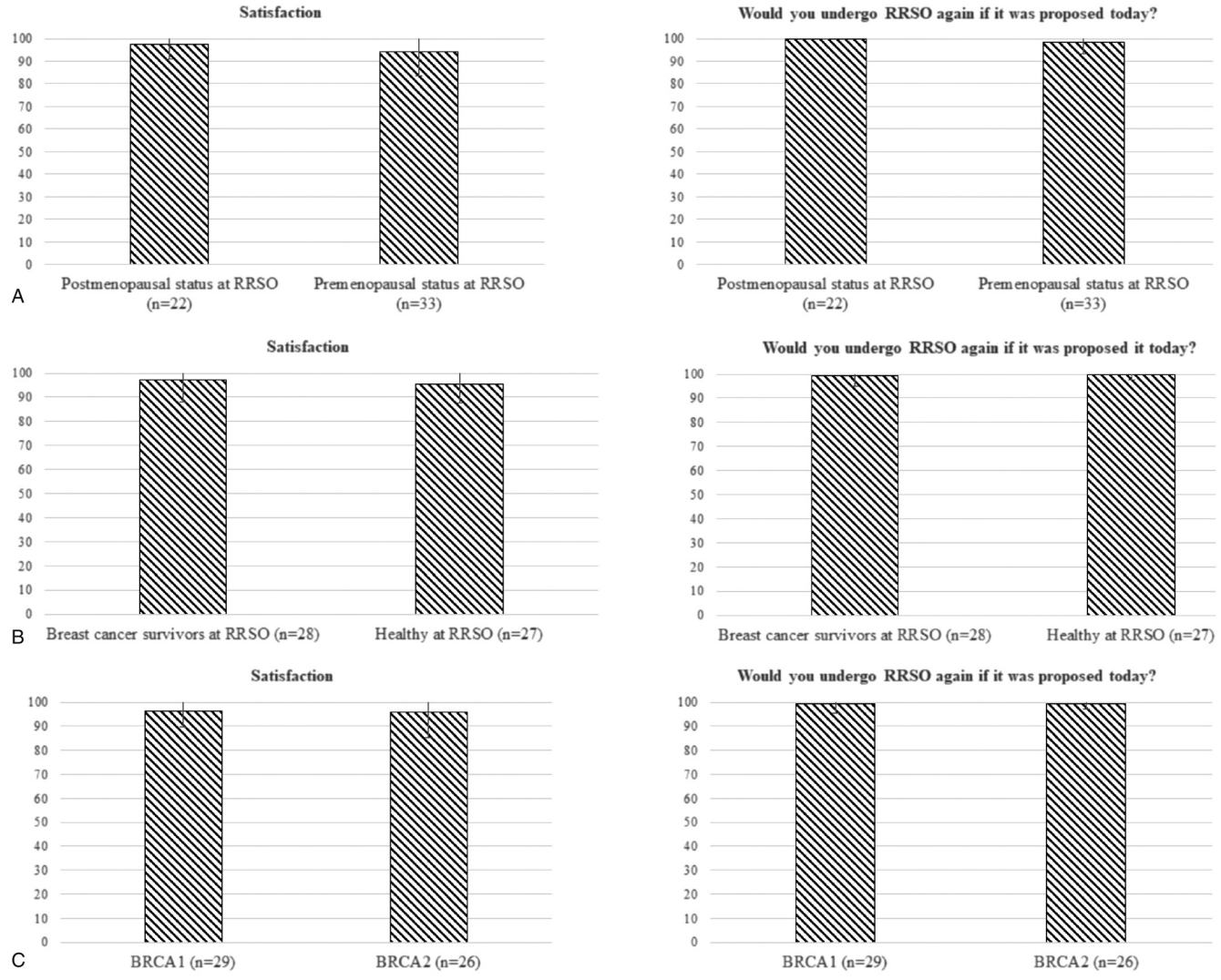

FIG. 3. Satisfaction rate (0-100 VAS points) and answer to the question ''Would you undergo RRSO again if it was proposed today? (0-100 VAS points)'' at the last follow-up visit according to pre/postmenopausal status at RRSO (**A**), cancer survivors versus healthy women at RRSO (**B**), *BRCA* status (**C**), HT users/nonusers after RRSO (**D**), ''RRSO-caused'' symptoms versus not RRSO-caused (**E**). HT, postmenopausal hormone therapy; RRSO, risk-reducing salpingo-oophorectomy; VAS, visual analog scale. *(Continued on next page)*

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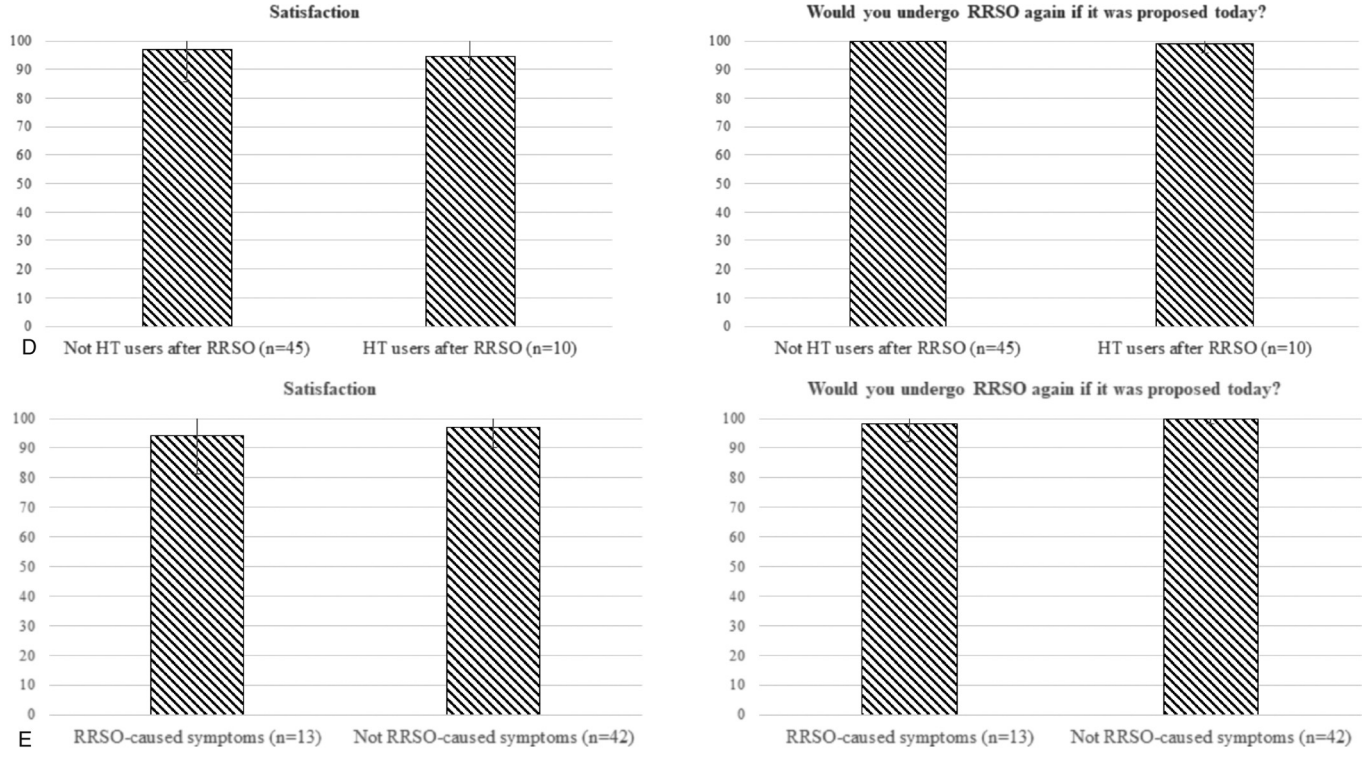

FIG. 3. (Continued).

(>95/100 points) and did not differ according to pre- versus postmenopausal status at RRSO, breast cancer survivors versus healthy women at RRSO, *BRCA* status, HT users versus nonusers after RRSO, ''RRSO-caused'' versus ''not RRSO-caused'' menopausal symptoms. The main findings of our study confirm those of previous studies that women at high risk of breast and ovarian cancer are very satisfied with their choice of this risk-reduction strategy.[17,18] In previous studies, women who chose RRSO also demonstrated higher levels of satisfaction when compared to patients who chose only periodic surveillance.[17] Swisher et al[19] found that 93% of women who chose RRSO were satisfied with their choice while only 7% expressed regret about their decision. A similarly high satisfaction rate has also been reported in several studies of women undergoing mastectomy for breast cancer risk reduction.[21,22]

Interpretation

RRSO is the more definitive option for *BRCA* mutation carriers, allowing no further room for ambivalence or conflict. It offers a permanent outcome, one that cannot be reversed. In contrast, women who undergo surveillance can theoretically still opt for RRSO at some point in the future. The possibility of being able to switch to RRSO may introduce some level of uncertainty in women who chose surveillance, possibly contributing to reduced overall satisfaction. Response shift, or the change in one's internal evaluation of well-being, could be an important reason for the high satisfaction levels demonstrated in *BRCA* mutation carriers who chose RRSO in the current study. It makes sense that once a woman has undergone RRSO, her thinking would ''recalibrate'' to accept and validate her choice of risk-reducing strategy.[17]

RRSO appears to positively impact cancer-related anxiety and overall perception of risk while negatively impacting sexual functioning and menopause-related symptoms. However, the impact on general QoL after RRSO is still debated. Many studies have examined the impact of RRSO on various aspects of QoL, with cohorts differing in age, menopausal status, and time interval from surgery. Previous larger studies observed no decline in overall QoL post-RRSO in *BRCA* mutation carriers,[23,24] but there were declines in specific domains, particularly vasomotor, physical, and sexual symptoms.[23] On average, fewer symptoms were observed among HT users than nonusers, but HT use did not completely eliminate the symptoms. Previous findings suggest that there is a significant impact of early RRSO on various menopausal symptoms and sexual functioning, which are sustained several years postsurgery and are not entirely restored to presurgical levels with HT use. The impact of RRSO on QoL appears to be immediate and sustained[23]; however, there is no worsening of symptoms over time. This was confirmed by our study, in which we observed a slight increase in satisfaction rate of women who underwent RRSO over time.

Several authors have reported decreased sexual function and sexual desire after RRSO, particularly in the first year after RRSO.[25-27] Only one study prospectively assessed sexual function in women with a *BRCA* mutation before RRSO, at 1 year post-RRSO[28] and at 3 years post-RRSO,[23] showing a

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significant decline in sexual function, particularly pleasure and discomfort domains. However, the concomitant presence of depression seems to be a significant risk factor for sexual dysfunction in these patients, and this disease may be underdiagnosed and undertreated.[26]

Despite this, our data suggest that women who chose RRSO were willing to accept the trade-offs of an increased likelihood of experiencing menopausal symptoms, sexual dysfunction, and possible decreased QoL for a significantly reduced risk of developing ovarian cancer. This may occur because women with intact ovaries have reduced menopausal symptoms but greater concern about cancer than women who have undergone RRSO.[29]

Women can be prescribed HT to alleviate symptoms associated with natural or surgical menopause.[16] In our study, all women who were premenopausal at the time of surgery and had no previous breast cancer diagnosis initiated HT following surgery in comparison to less than half of the participants in other studies.[23] This high use of HT among participants, due to specific and detailed counseling performed at our MFCC, may contribute to the high satisfaction rate with RRSO demonstrated in our study.

There is an additional element of complexity in the care of *BRCA* mutation carriers with a personal history of breast cancer given that treatment regimens (ie, chemotherapy) have also been shown to impact the severity of menopausal symptoms and sexual functioning.[30] Moreover, HT is currently contraindicated in women with a personal history of disease and was not used in our study of breast cancer survivors.[16]

Limitations

The findings reported in this study should be interpreted within the context of its limitations. Firstly, the study sample was comprised exclusively of clinical research participants at a single institution. Furthermore, our sample size was relatively small, precluding robust analyses of subgroups. In our study, the mean age at RRSO was higher than that reported in other studies[7,8,11,12,23,28] and established by guidelines[5] and this could influence the satisfaction rate with RRSO. This issue was just discussed in a recent study and it could be related in our region to the age at genetic testing or to the trend to delay the RRSO procedure to the age of the natural menopause.[9] Moreover, in this first study, we did not include a control group (women who refused RRSO). This was done because our main outcome was to evaluate the satisfaction with an intervention (RRSO), and this intervention would not have happened in this control group. However, satisfaction with a possible attitude in *BRCA*-mutation carriers (RRSO vs surveillance) will be the focus of a separate ongoing trial. The strengths of this study include its prospective design and the relatively long follow-up period, allowing for the evaluation of long-term satisfaction with RRSO.

CONCLUSIONS

In summary, the findings of this prospective analysis suggest that, in our patient population and using our approach to counsel women with *BRCA* mutations, satisfaction with RRSO is very high and mostly independent of participant characteristics at the time of surgery. Our results suggest that women who chose RRSO were willing to accept the trade-offs of an increased likelihood of experiencing menopausal symptoms, sexual dysfunction, and potentially decreased QoL for a significantly reduced risk of developing ovarian cancer. For these reasons, we can continue to recommend this procedure without hesitation to all patients with these mutations[15] within the age range set by the guidelines.[5] However, it is critical to continue to explore other long-term health consequences of RRSO for these satisfied women, including its impacts on cognitive function, cardiovascular system and bone mineral density.

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