ANTICANCER RESEARCH *37*: 5241-5248 (2017)
doi:10.21873/anticanres.11948

Risk-reducing Salpingo–Oophorectomy in Women at Higher Risk of Ovarian and Breast Cancer: A Single Institution Prospective Series

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Abstract. *Background/Aim: Occult cancers' reported rates vary from 2-12% and serous tubal intraepithelial carcinomas (STICs) have been identified in 3-12% of the prophylactically removed tubes of women carrying a BRCA mutation. The aim of this study was to evaluate the incidence of tubal minor epithelial atypia (STIL), STIC, and occult invasive cancer and to evaluate the cancer-specific mortality in a prospective series of women at higher risk of ovarian and breast cancer undergoing risk-reducing salpingo-oophorectomy (RRSO) n a tertiary cancer center. Patients and Methods: A series of RRSO specimens (including endometrial biopsy) from women carrying a BRCA mutation, BRCA-unknown and BRCA-negative were collected between January 1998 and April 2016 at the Division of Gynecology at the European Institute of Oncology. Inclusion criteria were: asymptomatic women who had a negative gynecologic screening within 3 months prior to RRSO. Exclusion criteria were: women with ovarian/tubal cancer prior to RRSO. Results: A total of 411 women underwent RRSO. Median age at RRSO was 47.0 years (range=32–70 years); 75.2% had a history of breast cancer. Fifteen women were diagnosed with an occult cancer (7 STIC, 4 invasive cancers, 2 breast cancers metastatic to the adnexa, 2 endometrial cancer) (3.6%). Sixteen showed a STIL (3.9%). When excluding cases with preoperative positive markers, the occult invasive cancer rate drops to 1.5%. Conclusion: Our study, covering an 18-year period, shows a substantial low risk of occult cancer among a high-risk population of women undergoing RRSO. Our data still support the indication for RRSO in higher-risk patients. An endometrial biopsy should also be routinely obtained as it raises the chances of detecting occult endometrial cancers that may be otherwise missed.*

Ovarian cancer (OC) is the fifth leading cause of oncology-related death in women (1). With a family history of cancer an increased risk of this disease is observed: the lifetime risk for women with one first-degree relative affected by ovarian cancer is 3.5-7% and it increases to 15% when two first-degree relatives are affected (2).

Women who are at a higher risk of developing cancer may undergo different risk-reducing strategies, which include intensive screening, chemoprevention and surgical prophylaxis. The diffusion of more intensive screening programs for hereditary breast cancer (BC) led to early detection of this tumor.

On the contrary, OC is usually asymptomatic for long time and prevention from this tumor is still not available. Therefore, the recommendation for women carrying a *BRCA1/2* mutation is salpingo-oophorectomy (RRSO) that lowers the risk for ovarian cancer up to >95% and the risk for BC up to 50% (3). A cohort study by Domchek *et al*. proved a breast cancer specific, ovarian cancer specific and OS benefit from RRSO (4). The residual risk for peritoneal cancer after PBSO accumulates to 3.5% after 20 years of follow-up (5).

Occult cancers have been reported in prophylactically removed ovaries and fallopian tubes in women carrying a *BRCA* mutation. Reported rates vary considerably from 2-12% and seem to be influenced by patients' age at RRSO, symptoms, gynecologic screening prior to RRSO, the completeness of prophylactic surgery and the accuracy of histopathological examination (6-16).

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Key Words: Risk-reducing salpingo-oophorectomy, *BRCA* genes, breast cancer, ovarian cancer, STIC.

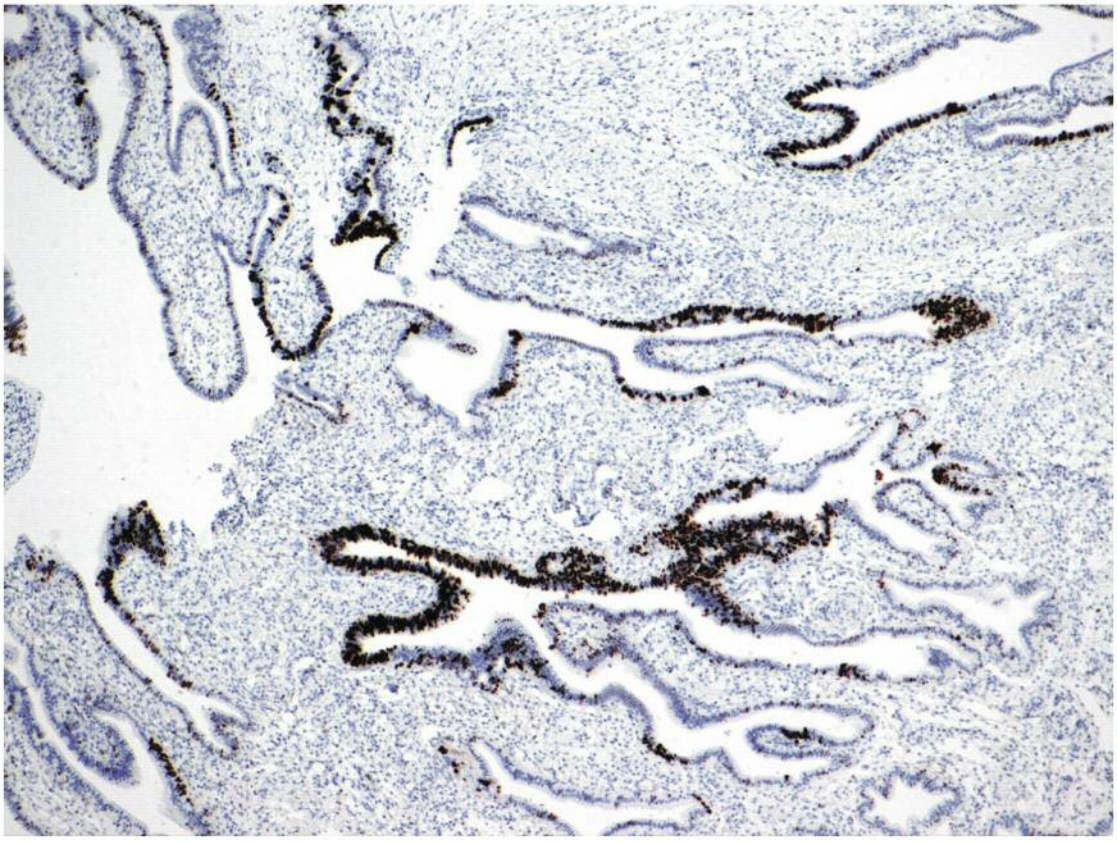

Figure 1. *IHC p53 staining in a tubal specimen in a patient with Li-Fraumeni syndrome.*

Patients and Methods

Since 1998, clinical and genetic data of all patients at higher risk of ovarian and breast cancer have been collected and recorded in collaboration with clinical geneticists, gynecologic oncologists and breast oncologists. Following internal guidelines women at high-risk for tubo-ovarian cancer (TOC) are counseled to consider RRSO by the age of 35 (*BRCA1*) or 40 (*BRCA2*), or later as soon as childbearing is completed. This applies also to women who tested negative for *BRCA* mutations (also defined as '*BRCA*-negative high-risk women') or to women with unknown *BRCA* status whose estimated lifetime risk of developing ovarian cancer is >10%. After undergoing RRSO, women continue their follow-up for breast cancer screening at the Institute. Gynecologic follow-up was standardized including CA-125 measurement, gynecologic examination and pelvic US every 6 months. Surgical specimens from prophylactic surgery of women carrying a *BRCA1-2* mutation and *BRCA* negative/unknown high-risk women were prospectively collected between January 1998 and April 2016. Inclusion criteria for prophylactic treatment were: asymptomatic women with a negative gynecologic screening (pelvic examination, transvaginal ultrasound) within 3 months prior to RRSO. Exclusion criteria: symptomatic women, patients with a positive gynecologic screening or women with ovarian/tubal cancer prior to RRSO. All women, carrying a *BRCA* mutation, enrolled in this study, had a proven pathogenic mutation (splice site mutations, nonsense mutations, frameshifts or exon deletions). Patients carrying an unclassified variant (UV) were incorporated in the group 'negative tested women'. Patients whose genetic test was unavailable were included in the *BRCA*-unknown group.

RRSO is a minimally-invasive surgical procedure that includes laparoscopic removal of the adnexa, the collection of peritoneal washing cytology and endometrial biopsy (Pipelle). Additional minimally-invasive hysterectomy was performed if indicated (higher risk of uterine cancer, desire of the patients, etc.).

Staging for tubal intraepithelial carcinoma (STIC), when performed, consisted of laparoscopic hysterectomy, omentectomy, random peritoneal biopsies and peritoneal washing. A retroperitoneal staging was performed in case of invasive cancers.

The specific aims of the present study were to evaluate the incidence of tubal minor epithelial atypia (STIL), STIC, and occult invasive cancer in patients undergoing RRSO.

Histopathology. From 2009, a strict surgico-pathological protocol (2006 Brigham and Women's protocol for sectioning and extensively examining the fimbrial end (SEE-FIM)) was applied consisting of transverse section at 2-3 mm intervals of both tubes and ovaries (17). A haematoxylin and eosin (H&E) slide was prepared from ovaries and fallopian tubes specimens, for histology

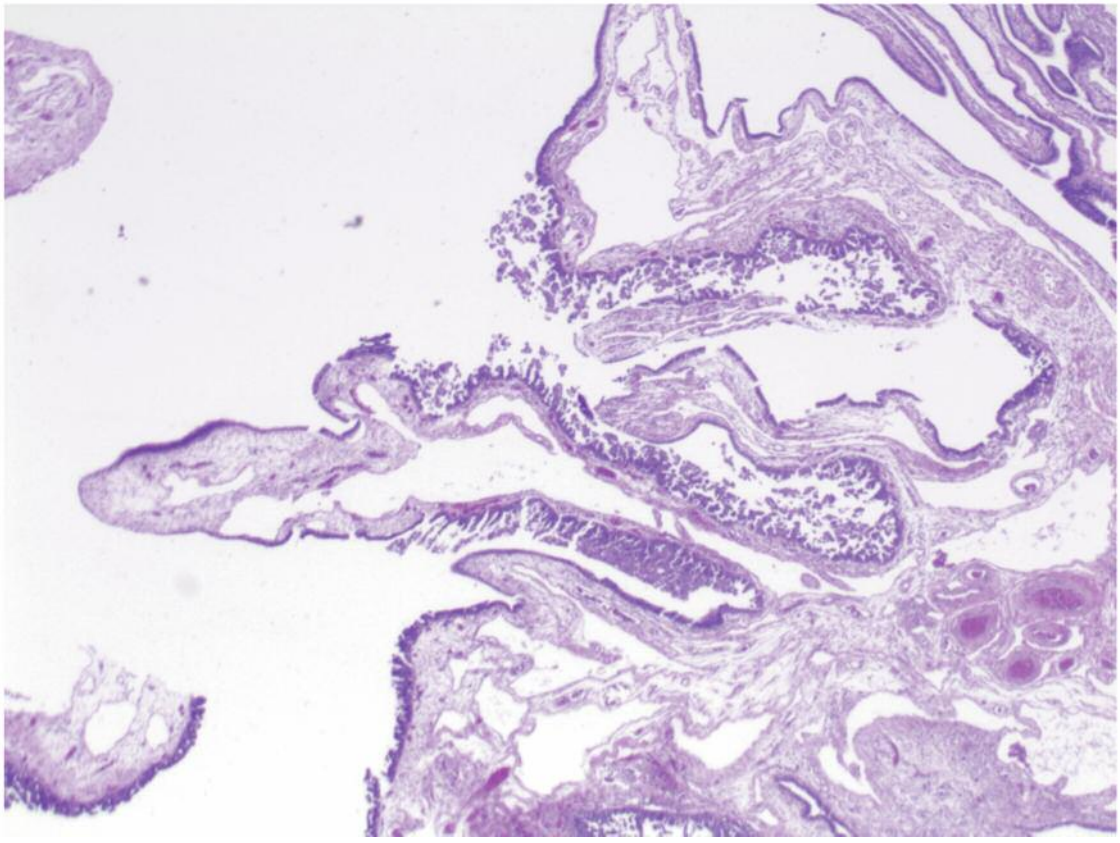

Figure 2. *Serous tubal intraepithelial carcinoma (STIC).*

and additional immunohistochemical p53 staining that can occur in both normal and neoplastic epithelium whereas immunostaining for MIB-1 (Ki67) is helpful to detect proliferative cells. Therefore, in selected cases, a MIB-1 (Ki67) staining was also performed.

Features for histological diagnosis of minor epithelial atypia (STIL) are: slightly enlarged, rounded nuclei with irregular cell membrane outlines, slightly enlarged nuclear/cytoplasmic ratio, nuclei with slight loss of polarity and inconspicuous nucleoli. Minor epithelial atypia is not visible at low power magnification. It comprises epithelial lesions that fulfill some but not all of the criteria for tubal intraepithelial carcinoma (TIC). Positive staining for p53 was not required for diagnosing STIL (Figure 1).

Tubal intraepithelial carcinoma is identifiable at low power magnification, displaying a row of dark and thickened epithelium. It is characterized by disorganized cellular crowding and nuclear stratification, and consists of secretory cells in absence of ciliated cells (Figure 2).

Histological features of tubal invasive carcinoma are identical to TIC, but with the addition of an invasive component (18).

Occult cancer is defined as a clinically unapparent invasive malignancy of the epithelium of the ovary or fallopian tube diagnosed at histopathological examination, according to the guidelines of the International Federation of Gynecology and Obstetrics (FIGO). Therefore, occult cancer refers to an invasive malignancy and not to an *in situ* component.

Table I. *Mutational status of patients undergoing RRSO.*

Type of mutation	N° of patients	%
BRCA1	157	38,2
BRCA2	119	29
BRCA1-2	14	3,4
BRCA-negative	60	14,6
BRCA-unknown	61	14,8
Lynch syndrome	6	1,5
BRCA1 – Lynch syndrome	2	0.5
Li-Fraumeni	1	0.2

RRSO: Risk reducing salpingo-oophorectomy; BRCA: breast-related cancer antigens.

Results

From January 1998 to April 2016, 411 high-risk women underwent prophylactic surgery. Distribution by type of mutation is shown in Table I. Menopausal status, family history and age distribution are shown in Table II. A positive

Table II. *Demographics*.

	BRCA1 (N=157)	BRCA2 (N=119)	BRCA1-2 (N=14)	BRCA-negative (N=60)	BRCA-unknown (N=61)	Total (N=411)
Menopausal status						
Premenopausal	96	40	7	15	26	184 (44,8%)
Postmenopausal	61	79	7	44	35	226 (55%)
Not Available				1		1 (0,2%)
Familiarity						
Positive	149 (94,9%)	110 (92,4%)	13 (99,9%)	56 (93,3%)	53 (86,9%)	381 (92,7%)
Negative	8 (5,1%)	6 (5%)	1 (0,1%)	4 (6,7%)	8 (13,1%)	27 (6,6%)
Not Available		3 (2,5%)				3(0,7%)
Age						
Median age at RRSO	44 (31-68)	45 (34-70)	45,5 (31-61)	50 (38-68)	49 (40-73)	47 (31-73)
BC prior to RRSO	116 (73,9%)	99 (83,2%)	11 (78.6%)	47 (11,4%)	36 (8,76%)	309 (75,2%)
Median age at first BC	38 (24-60)	40 (24-59)	42 (30-50)	43 (27-60)	43,5 (32-57)	40 (24-60)

N: Number; BRCA: breast related cancer antigens; RRSO: risk reducing salpingo-oophorectomy; BC: breast cancer.

Table III. *Findings at RRSO*.

	BRCA1	*BRCA2*	*BRCA1-2*	*BRCA*-negative	*BRCA*-unknown	Total
Occult invasive cancers	2 (1.3 %)	1 (0.8%)	-	3 (5%) (1.7 % TOC)	2 (3.3%) (1.6 % TOC)	8 (1.9%) (1% TOC)
Tubal CA	1	-	-	-	1	1
Ovarian CA	1	-	-	1	-	2
Metastatic BC	-	1	-	1	-	2
Endometrial endometrioid CA	-	-	-	1	1	2
STIC	7 (4.5%)	-	-	-	-	7 (1.7%)
STIL	4 (2.5%)	4 (3.4%)	-	5 (8.3%)	3 (4.9%)	16 (3.9%)

RRSO: Risk-reducing salpingo-oophorectomy; BRCA: breast related cancer antigens; TOC: Tubo-Ovarian cancer; CA: cancer; BC: breast cancer; STIC: Serous tubal intraepithelial Cancer; STIL: serous tubal intraepithelial lesion.

family history was observed in 381 women, it was not available in 3 cases (having a *BRCA2* mutation). A total of 29 women had a negative family history for cancer: 8 carrying a *BRCA1* mutation, 6 with *BRCA2* mutations, 1 *BRCA1-2*, 4 *BRCA*-negative and 8 *BRCA* unknown (Table II).

Median age at RRSO was 47.0. A total of 309 (75.2%) women had previously been diagnosed with breast cancer (BC). Median age at first BC was 40: 38 for *BRCA1*, 40 for *BRCA2*, 43 and 43.5 respectively for *BRCA*-negative and *BRCA* unknown, 42 for *BRCA1-2* (Table II). RRSO was performed in all patients. Concurrent hysterectomy was performed in 93 women (22.6%): 84 by minimally-invasive approaches (54 lps and 30 robot-assisted laparoscopy) whereas 9 underwent laparotomy. Peritoneal washing was not available in two cases (one *BRCA* negative and one *BRCA* unknown), five specimens were inadequate. Atypical cells were detected in one *BRCA2* and in one *BRCA*-negative woman whose histology was negative. Malignant cells were retrieved in a *BRCA* negative patient who had invasive OC. Fifteen (3.7%) occult carcinomas were diagnosed (Table III). These included 4 tubo-ovarian cancers and 2 endometrial endometrioid cancers (detected by Pipelle biopsy during RRSO), 2 BC metastatic to the adnexa, 7 STICs. Median age of occult carcinomas patients at RRSO was 54 (range=37-70). Sixteen patients were diagnosed with STIL (3.9%) (Table III), with a mean follow-up of 3 years (range=0-15 years) none of them developed peritoneal cancer. All 7 STICs occurred among women carrying a *BRCA1* mutation, all but one with a positive family history for TOC. Median age at RRSO was 54 years (range=43-67 years). One was premenopausal, six postmenopausal. Six women had a positive personal history of BC. Preoperative CA125 was negative for all of them. Peritoneal washing was negative. Four patients underwent a restaging procedure, that was negative, while the other 3 were followed closely; none of them received adjuvant chemotherapy and with a median follow-up of 30 months

Table IV. *Tubo-ovarian invasive cancers at RRSO*.

Patient	Age at RRSO	Mutational status	BC history	Preop CA125	US stage	Pathology	Cytology	Staging	FIGO	CHT	Recurrence	Status	DFS	OS
1	37	*BRCA1*	Negative (at 42 diagnosis of triple negative BC)	36	Negative	0.4 cm HGSOC OSE. FT: negative	Negative	Robot-assisted hysterectomy, omentectomy, peritoneal biopsies, pelvic and paraortic lymphade-nectomy	IC	6 cycles CBDCA	-	NED		71
2	59	*BRCA1*	At 37 triple negative BC	8	Negative	right FT: HGSTC. Left FT: STIC	Negative	Robot-assisted hysterectomy, omentectomy, peritoneal biopsies, pelvic and paraortic lympha-denectomy	IA	6 cycles CBDCA	-	NED		81
3	62	*BRCA*-negative, positive FH *BRCA2* daughter	Luminal B BC at 60	51	Negative	HGSOC. FT: negative	Positive	Laparoscopic hysterectomy, omentectomy, peritoneal biopsies	IIIC	6 cycles CBDCA+ PTX	-	AWD (BC metastatic to the bone)		11
4	67	*BRCA*-unknown	-	121	Salpingitis	HGSTC metastatic to the greater omentum and pelvic and aortic nodes	Negative	Conversion to laparotomy: omentectomy and pelvic and paraortic lymphadenectomy (previous benign hysterectomy)	IIIC (node positive)	6 cycles CBDCA+ PTX+ BEVACI ZUMAB (furthered as maintenance until 22 cycles)	-	NED		27

RRSO: Risk-reducing salpingo-oophorectomy; BC: breast cancer; CA125: carbohydrate antigen 125; US: ultrasound findings; FIGO: International Federation of Gynecology and Obstetrics; CHT: chemotherapy; DFS: disease free survival; OS: overall survival; BRCA: breast related cancer antigens; STIC: serous tubal intraepithelial cancer; HGSOC: high grade serous ovarian cancer; OSE: ovarian surface epithelium; FT: fallopian tube; CBDCA: carboplatin; PTX: paclitaxel; HGSTC: high-grade serous tubal carcinoma; FH: familial history; NED: no evident disease; AWD: alive with disease.

(range=9-84 months) none of them developed peritoneal cancer. As shown in Table III invasive cancers were detected in eight patients. Median age at RRSO was 52.5 years (range=37-70 years). The 2 endometrial endometrioid cancers were diagnosed in the *BRCA*-negative/unknown group, with a median age at diagnosis of 60. Details about FIGO stage, management and disease status of the 4 patients diagnosed with TOC are summarized in Table IV. Their median age at RRSO was 60.5 years (range=37-67 years). At a median FUP of 49 months (range=11-81 months) 3 patients are NED, whereas 1 is alive with BC metastatic to the bone. One *BRCA2* woman with negative pathology at RRSO (performed at 51 years of age) developed PPC STAGE FIGUREO IIIC at 15 months diagnosed by a raise in CA125. She received one line chemotherapy with CBDCA and PTX and she is presently NED at 46 months.

Discussion

Our study, based on one of the largest single-center series of tested subjects to date, showed a low prevalence of occult invasive cancer (1.9%) and STIC (1.7%) in high-risk women. Among those with invasive cancer two women had elevated preoperative CA125 (51 and 121 U/ml respectively) and therefore they should not have met the criteria for the definition of “true occult” cancer but nevertheless they were referred to us seeking prophylactic surgery. Both cases displayed extra-adnexal spread.

Excluding those cases of EC and BC the rate of occult TOC in the entire study population drops to 1% that might be even a more realistic percentage, as it properly pictures the risk of occult cancers in this group of higher risk patients. The main strengths of our study are: the inclusion of consecutive and uniform series of asymptomatic, screen-negative high-risk women, the large sample-size, and the long duration of follow-up. Moreover, added values are the independent histopathological review by two expert gynecologic pathologists, and the clear separation between *BRCA*-positive, *BRCA*-negative and *BRCA*-unknown cases, since most studies report on proven *BRCA* carriers only. Furthermore, the fact that endometrial biopsy and peritoneal washing were routinely performed makes our results unique compared to those available in the literature. Moreover, this is the first report on the impact of RRSO on HBOC in Italy, accomplished in a leading nationwide cancer center.

Potential weaknesses may be the single-center nature of the study and the fact that the ethnicity of the population enrolled is mostly Caucasian white of southern European origin.

In light of upcoming new evidences of a more complex picture in the genetic risk of cancer and of the recently acquired knowledge that more genes are involved, even in the same pathway, our data might be useful as a basic background for future research and further understanding in the field of genetic cancer prevention (19).

We found a prevalence of occult cancer at RRSO of 5.7% in *BRCA*-carriers. Conversely, the prevalence in the *BRCA*-negative/unknown was 4.1%, corrected to 2.5% when the 2 uterine endometrial endometrioid cancers, detected in this subgroup, were excluded.

In the literature, the prevalence of occult cancer in *BRCA*-carriers and high-risk women varies considerably, from 2-3% in large, mainly multicenter series to 7-12% in smaller, mostly single-center series. The lower prevalence of occult cancer in our series may be explained by the rigorous patient selection, the younger age at RRSO, the homogeneity and the significant size of the sample.

The detection of a true occult invasive cancer in a woman carrying a *BRCA1* mutationat the age of 37 is in agreement with data from the literature that underline the importance of anticipating a prophylactic surgical procedure in this subgroup of patient. This patient had no proven tubal lesion, despite performing multiple sections of the specimens and pathology revision. Although the fallopian tube is suggested to be the primary origin of tumorigenesis in *BRCA*-carriers, the ovary seems to be the favorite site for tumor growth beyond the microscopic stage (20-26).

Opportunistic salpingectomy, at the time of other benign gynecologic surgery as a primary preventive strategy, has been recommended for low risk women, as some studies have shown a risk reduction of ovarian cancer rate in women after bilateral prophylactic salpingectomy (27, 28).

Therefore, bilateral salpingectomy has been recently recommended as a temporary risk-reducing surgical procedure for *BRCA*-carriers as well, in order to avoid the menopausal symptoms deriving from oophorectomy. Many Authors (29, 30) seem to favor prophylactic salpingectomy around the age of 40 delaying oophorectomy at the age of 45. The need of gathering more data, better if within a clinical trial, and the results of our current study would suggest a careful implementation into clinical practice of such a conservative approach.

In the present study, we describe a subgroup of women that has not yet been described to our knowledge in the available literature to date, it includes 14 women (3.4%) who had a germinal pathogenic mutation in both BRCA 1 and 2 genes, whose clinical significance is still unclear. Two patients had a positive family history of cancers in the HBOC spectrum in both paternal and maternal line. Eleven out of fourteen (78.6%) women had a previous history of BC: seven were triple negative, three luminal B and one luminal Her-2 tumors. Age at BC onset ranged from 30 to 50 years. Specimens collected at RRSO including peritoneal washing and endometrial biopsy were all negative.

All STICs were detected among *BRCA1*-carriers, with a prevalence of 4.5%, which makes 1.7% of our entire higher risk population. In the literature STIC has been reported in 1-12% of the prophylactically removed ovaries and fallopian tubes in *BRCA*-carriers, mostly in the fimbrial end of the tube (7, 9-17). If we consider all *BRCA*-carriers in our population, percentage would be 2.4%.

Invasive cancer and evidence of distant metastasis were not noted at the time of STIC surgical staging. It is still unclear how to properly manage these cases. In our study, peritoneal washing performed at the time of RRSO was negative, 4 patients were restaged whereas 3 were not. None of them received adjuvant treatment and with a median follow-up of 30 months (9-84), oncologic outcomes were equal. Therefore, even though the number is small, it seems that clinical follow-up without staging surgery or adjuvant treatment may be a reasonable option for this subgroup of patients (31).

The chance of developing peritoneal cancer after RRSO is been reported to be up to 4.3% in selected studies. In our series so far none of those patients who were diagnosed with STIC developed a peritoneal cancer. It is interesting to notice that a PPC was detected after 15 months in a patient with completely negative pathology findings at the time of RRSO. This finding highlights the importance of adopting a standardized and strict follow-up (32).

Sixteen atypical hyperplastic lesions (3.9%) were detected, eight of them among *BRCA*-carriers (2.8%), and none developed cancer. However, the clinical significance of atypical hyperplasia with cytological anomalies is still unclear; though, interestingly, the highest rate of STIL (8.3%) was detected among *BRCA*-negative women.

Our study, covering an 18-year period, shows a substantial low risk of diagnosing occult cancer among a high-risk population of women undergoing RRSO. Such a low detection rate might be due to the strict criteria for patients' selection, which include younger age at RRSO (particularly in women carrying a *BRCA* mutation) and a negative screening prior to surgery.

In conclusion, our data support the indication for RRSO in selected high-risk patients. A thorough follow-up is mandatory and we also believe that an endometrial biopsy should be routinely obtained as it raises the chances of detecting occult endometrial cancers that may be otherwise missed.

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Received July 4, 2017
Revised July 24, 2017
Accepted August 2, 2017