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Risk-Reducing Salpingo-Oophorectomy: A Series of 90 BRCA1 and BRCA2 Mutation Carriers and Literature Review

Authors:
Vanesa Rodríguez-Fernández, MD[1,2;] Lucía Cameselle-Cortizo, Md[1]; Laura González Rodríguez, MD[2]; Elena Figueiredo-Alonso, MD[3]; María José Lamas González, MD[2,4]; Javier Valdés-Pons, MD, PhD[1,2]; Jorge F Cameselle-Teijeiro MD, PhD[1].

[1]Clinical Oncology Research Center ADICAM. Cangas (Spain).
[2]Service of Obstetrics and Gynecology.álvaro Cunqueiro Hospital. Vigo (Spain).
[3]Service of Obstetrics and Gynecology. Povisa Hospital. Vigo (Spain)
[4] Breast Pathology Unit. Meixoeiro Hospital. Vigo (Spain).

Corresponding Author:
Vanesa Rodríguez Fernández, MD.
Service of Obstetrics and Gynecology. Vigo University Hospital Complex, Álvaro Cunqueiro Hospital. Estrada Clara Campoamor Nº 341 - 36312 Vigo. Pontevedra (Spain).
Phone: 0034 986 825 130 – 0034 986 825 137

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Abstract
As long as we do not have an effective screening routine, risk-reducing salpingo-oophorectomy (RRSO) is considered the *gold standard* for ovarian, fallopian, and primary peritoneal cancer prevention in women with documented BRCA1/2 mutations or other mutations with increased risk of ovarian cancer. Our objective was to review the pathological findings of RRSO in BRCA mutations carriers in order to estimate the prevalence of occult ovarian/tubal carcinoma. We studied a series of 90 women BRCA1/2 mutation carriers, with or without previous breast cancer, who underwent RRSO in the hospitals of our health area of Vigo. In our series, 4 women (4.4%) were diagnosed with malignant lesions in the fallopian epithelium (all of them in early stages). The main predictor for detecting occult malignancy in women at high risk for ovarian cancer who are going to undergo RRSO is to adhere to the surgical-pathological protocol. However, we must always bear in mind that there will always be a residual risk of primary peritoneal carcinoma after RRSO (1.1% in our series). We emphasize the importance of performing a germ line testing for all women diagnosed with epithelial ovarian/fallopian/peritoneal cancer (NCCN Guidelines). Our data support the indication for RRSO in selected high-risk patients; and recall the importance of the identification of high-risk patients, in order to offer genetic counseling and preventive measures, both for patients and their families

Keywords: BRCA genes, Breast cancer, Fallopian cancer, Ovarian cancer, Primary peritoneal cancer, Risk-reducing salpingo-oophorectomy.

Vol. 5, No. 02; 2021

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Acronyms

Risk-reducing salpingo-oophorectomy	RRSO
Breast cancer	BC

Introduction

As long as we do not have an effective screening routine, risk-reducing salpingo-oophorectomy (RRSO) is considered the *gold standard* for ovarian, fallopian, and primary peritoneal cancer prevention in women with documented BRCA1 and BRCA2 (BRCA1/2) mutations or family history consistent with hereditary breast and ovarian cancer syndrome. It is necessary to improve the identification of high-risk women who are candidates for this prophylactic surgical technique. RRSO entails a series of consequences (sterility, surgical menopause, modifications in the sexual sphere, osteoporosis…) that we have to contrast with the related benefits (avoid the morbidity and mortality of ovarian, fallopian or primary peritoneal cancer). However, we have to bear in mind that there will always be a residual risk after RRSO of being diagnosed with a primary peritoneal carcinoma. More studies are needed to gauge the risks and benefits of RRSO.

The purposes of this article were to study the pathological findings of RRSO specimens performed on women carrying a mutation in the BRCA1/2 gene and to review the literature in this regard.

Material y Methods

We studied a series of women who underwent RRSO in the hospitals of the health area of southern Pontevedra (University Hospital Complex of Vigo, University Hospital Complex of Pontevedra, and Povisa Hospital of Vigo). We present the pathological findings of RRSO performed on women with documented BRCA1/2 mutations. Age at diagnosis, mutation detected, date of RRSO, and personal oncological history before and after the prophylactic surgery was also included. As a curiosity, we also include 4 patients with breast cancer (BC) who did not undergo RRSO and were later diagnosed with high-grade serous carcinomas of the ovary (at 49, 60, and 82 years) and a serous carcinoma of the endometrium (at 46 years). The medical records were studied retrospectively and prospectively. The data obtained in this study were entered into a computer database developed in the Microsoft Excel program.

Results

We present the pathological findings of RRSO performed on 90 women with documented BRCA1/2 mutations: 52 had previously a BC and 38 women without this oncological history (although 5 of them were subsequently diagnosed with BC) (Table 1).

It is striking that in up to 4 women (4.4%) malignant lesions were diagnosed at the level of the tubal epithelium. One of them was a healthy woman with a BRCA1 mutation (known since 2006) who was diagnosed ten years later with serous tubal infiltrating carcinoma (pT1a) at the time of RRSO. Another healthy woman with a BRCA1 mutation (known since 2015) underwent

Vol. 5, No. 02; 2021

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RRSO four years later, finding a serous tubal intraepithelial carcinoma. Among the group of BC patients, one of them was diagnosed with BC at age 46 (2011) and the BRCA1 mutation was identified in 2016; this patient underwent RRSO and was diagnosed with serous tubal intraepithelial lesion. Among the group of patients with BRCA2-positive BC, a woman was diagnosed at 47 years (2017) with BC and the mutation was identified in 2018; RRSO was performed in 2019 and she was diagnosed in the surgical piece of a serous tubal intraepithelial carcinoma with micro-invasion foci. All four women are healthy and disease-free at present.

Table 1. Pathological findings of RRSO performed in BRCA mutation carriers with and without previous breast cancer.

	RISK-REDUCING SALPINGO-OOPHORECTOMY ANATOMOPATHOLOGICAL FINDINGS		
	WITHOUT PATHOLOGICAL FINDINGS	BENIGN FINDINGS	MALIGNANT FINDINGS
BRCA1 + With Previous BC n = 23	n = 21	**Ovary: Endometriosis** (n = 1)	**Serous Tubal Intraepithelial Lesion** (n = 1)
BRCA1 + Without Previous BC n = 19	n = 16	**Ovary: Serous Cystadenoma** (n = 1)	**Serous Tubal Carcinoma (pT1a)** (n = 1) **Serous Tubal Intraepithelial Carcinoma** (n = 1)
BRCA2 + With Previous BC n = 29	n = 23	**Peritubal tissue: Endometriosis** (n = 1) **Ovary: Germ Cysts and Teak Lutein Cysts** (n = 1) **Ovary: Epithelial Inclusion Cysts** (n = 2) **Ovary: Capillary Hemagioma and Fibroma** (n = 1)	**Serous Tubal Intraepithelial Carcinoma with micro-invasion foci** (n = 1)
BRCA2 + Without Previous BC n = 19	n = 15	**Ovary: Epithelial Inclusion Cysts** (n = 1) **Ovary: Germ Inclusion Cysts** (n = 1) **Ovary: Endometriosis** (n = 1) **Ovary: Serous Cystadenoma** (n = 1)	

Vol. 5, No. 02; 2021

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In Tables 2 and 3 we show the chronology of events in more detail: age of cancer, genetic diagnosis, and date of RRSO. We also included in Table 2 three patients diagnosed with BC, they were BRCA1 mutation carriers who did not benefit from a RRSO and ended up being diagnosed with high-grade serous carcinoma of the ovary. A fourth patient diagnosed in 2011 with BC at age 40, also a BRCA1 mutation carrier (known since 2017), was diagnosed with serous endometrial carcinoma when a prophylactic hysterectomy with bilateral salpingo-oophorectomy was performed in 2017.

Table 2. Pathological findings of RRSO performed in BRCA1/2-positive BC patients.

BC Patients (BRCA1+)		**BC Patients (BRCA2+)**	
Bilateral BC 37 & 37 (2004)	BRCA1 **2007:**Without pathological findings	BC 50 (2007) & Basal cell carcinoma	BRCA2 (2010) 2011 (HT+ Bilateral SO): Without pathological findings
BC 63 (1991) & CRC 79 (2008) & Ovarian cancer 82 (2011)	BRCA1: 2013 **RRSO was not performed** **2011: Ovarian cancer** (82) after BC and CRC	Bilateral BC 40 (2003) & 47 (2010)	BRCA2: 2012 **2012: Endometriosis in the peritubal tissue**
Bilateral BC 28 (1990) & 33 (1996)	BRCA1: 2008 2012 (HT + Bilateral SO): Without pathological findings	BC 44 (2008)	BRCA2 2013: Without pathological findings
BC 40 (1990)	BRCA1: 2013 2013: Without pathological findings	Bilateral BC 36 (1999) & 49 (2012)	BRCA2: 2012 2014: Without pathological findings
Bilateral BC 49 & 49 (2012)	BRCA1: 2013 2014: Without pathological findings	BC 38 (2008)	BRCA2: 2014 2014: Without pathological findings
Bilateral BC 36 (2003) & 47 (2014)	BRCA1: 2014 2015: Without pathological findings	BC 33 (2013)	BRCA2 2014: Without pathological findings
BC 48 (2013)	BRCA1: 2013 2015: Without pathological findings	BC 45 (2014) Basal cell carcinoma	BRCA2: 2014 2015: Without pathological findings
Bilateral BC 32 (1986) & 55 (2009)	BRCA1: 2015 2015: Without pathological findings	BC 27 (1999)	BRCA2: 2014 2015: Without pathological findings
BC 45 (2012)	BRCA1: 2014 2015: Without pathological findings	BC 27 (1999)	BRCA2: 2014 2015: Without pathological findings
BC 45 (1998) & Ovarian cancer 60 (2015)	BRCA1: 2016 **RRSO was not performed** **2015: Ovarian cancer** (60)	BC 56 (2010)	BRCA2: 2014 2015: Without pathological findings
BC 35 (2016)	BRCA1: 2016 2016: Without pathological findings	BC 34 (2004)	BRCA2:2011 **2015: Ovarian Germ Cysts, Teak Lutein Cysts**
Bilateral BC 45 (1997) & 63 (2015)	BRCA1: 2015 2016: Without pathological findings	BC 59 (2013)	BRCA2: 2014 2015: Without pathological findings
BC 43 (2011)	BRCA1: 2016 2016: Without pathological findings	BC 44 (2016)	BRCA2 (2016) 2016: Without pathological findings

BC 27 (2015)	BRCA1 2017: Without pathological findings	Bilateral BC 39 (2008) & 44 (2014)	BRCA2:2020 **2016:Ovary with Epithelial Inclusion Cysts**
Bilateral BC 42 (2000) &53 (2011)	BRCA1 2017: Without pathological findings	BC 53 (2013)	BRCA2: 2015 **2016:Ovary with Epithelial Inclusion Cysts**
Bilateral BC 58 (2008) & 62 (2012)	BRCA1: 2017 2017: Without pathological findings	BC 44 (1991)	BRCA2: 2013 **2016:**Without pathological findings Later: Pancreatic Cancer
BC 40 (2001)	BRCA1: 2016 2017: Without pathological findings	BC 52 (2002)	BRCA2: 2011 2016: Without pathological findings
BC 47 (2005)	BRCA1:2014 2017: Without pathological findings	Bilateral BC 40 (1995) &47 (2002)	BRCA2: 2015 2017: Without pathological findings
BC 46 (2011)	BRCA1:2016 **2017: Serous Tubal Intraepithelial Lesion**	Bilateral BC 42 (2006) & 53 (2017)	BRCA2: 2012 2017: Without pathological findings
BC 33 (2011)	BRCA1:2011 2017: Without pathological findings	BC 42 (2011)	BRCA2: 2016 2017: Without pathological findings
BC 40 (2017)	BRCA1:2017 **2017: Ovary with Endometriotic Cysts**	BC 36 (1998)	BRCA2: 2016 2017: Without pathological findings
BC 40 (2011) & Endometrial cancer 46 (2017)	BRCA1: 2017 **2017** (HT + Bilateral SO): **Endometrial Serous Carcinoma**	Bilateral BC 43 (1989) & 65 (2011)	BRCA2:2017 **2018: Ovarian capillary hemangioma and Ovarian fibroma**
BC 37 (1987)	BRCA1: 2019 2017: v	BC 47 (2017)	BRCA2: 2018 2019: Without pathological findings
BC 49 (2012)	BRCA1: 2018 2018: Without pathological findings	BC 47 (2017)	BRCA2: 2018 **2019:Serous Tubal Intraepithelial Carcinoma with micro-invasion foci**
BC 33 (2003) & Ovarian cancer 49 (2018)	BRCA1: 2019 **RRSO was not performed** **2018: Ovarian cancer** (49), after BC	BC 62 (2005) & CRC & Papillary Thyroid Carcinoma	BRCA2: 2017 2019: Without pathological findings
BC 33 (2012)	BRCA1: 2013 2020: Without pathological findings	BC 64 (2018) & Basal cell carcinoma	BRCA2:2018 2019: Without pathological findings
BC 29 (2007)	BRCA1: 2019 2020: Without pathological findings	BC 35 (2017)	BRCA2: 2017 2018: Criopreservación de ovocitos 2019: Without pathological findings
		BC 30 (2004)	BRCA2: 2014 2019: Without pathological findings
		Bilateral BC 41 (2003) & 57 (2019)	BRCA2: 2019 2020: Without pathological findings

Notes: CRC: colorectal carcinoma; HT: Hysterectomy; SO: salpingo-oophorectomy

Vol. 5, No. 02; 2021

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Table 3. Pathological findings of RRSO performed in healthy BRCA1/2 mutation carriers.

BRCA1-Positive Women (without BC)		**BRCA2-Positive Women (without BC)**	
BRCA1:2006	**2016:Serous Tubal Carcinoma(pT1a)**	BRCA2: 2010	**2016: Ovary with Epithelial Inclusion Cysts**
BRCA1: 2009	2010: Without pathological findings	BRCA2: 2010	2014: Without pathological findings 2015: Thymoma
BRCA1: 2009	2011: Without pathological findings	BRCA2: 2011	2016: Without pathological findings
BRCA1: 2009	2011: Without pathological findings	BRCA2: 2014	2014: Without pathological findings
BRCA1: 2011	2013: Without pathological findings	BRCA2: 2014	2014: Without pathological findings
BRCA1: 2011	2014: Without pathological findings **2020:Serous Peritoneum Carcinoma**	BRCA2: 2014	2014: Without pathological findings
BRCA1: 2011	2016 (HT + Bilateral SO)Without pathological findings 2018: sarcomatoid carcinoma of the bladder	BRCA2: 2014	2014: Withouth pathological findings
BRCA1: 2013	2014: Without pathological findings 2019: Lung adenocarcinoma	BRCA2: 2014	2014: Withouth pathological findings
BRCA1: 2013	2014: Without pathological findings	BRCA2: 2014	**2015: Serous Cystadenoma of the Ovary**
BRCA1: 2014	2016: Without pathological findings	BRCA2: 2014	2014: Without pathological findings 2015: In Situ BC
BRCA1: 2015	2016: Without pathological findings	BRCA2: 2014	2014: Without pathological findings 2016: Infiltrating BC
BRCA1: 2015	2019: Prophylactic Mastectomy **2019: Serous Tubal Intraepithelial Carcinoam**	BRCA2: 2014	2014: Without pathological findings 2016: Infiltrating BC
BRCA1: 2017	2018: Without pathological findings	BRCA2: 2014	2015: Without pathological findings Previous: Melanoma (1998)
BRCA1: 2018	2020: Without pathological findings	BRCA2: 2014	**2016: Ovary with Germ Inclusion Cysts**
BRCA1: 2019	2020: Without pathological findings	BRCA2: 2015	2015: Without pathological findings
BRCA1: 2019	2020: Without pathological findings	BRCA2: 2015	2016: Without pathological findings 2018: Infiltrating BC
BRCA1	2016 (HT + Bilateral SO): Without pathological findings	BRCA2: 2017	**2018: Ovarian Endometriosis**
BRCA1	**2018:Ovary: Serous Cystadenoma**	BRCA2: 2019	2020: Without pathological findings
BRCA1: 2017	2020: Without pathological findings 2020: Infiltrating BC(38)	BRCA2: 2019	2020: Without pathological findings

Notes: HT: Hysterectomy; SO: salpingo-oophorectomy.

Vol. 5, No. 02; 2021

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One healthy BRCA1 mutation carrier (known since 2011) underwent a RRSO in 2014 without pathological findings, and presented six years later (2020) with a serous peritoneal carcinoma. Serous tubal carcinomas were found in two of the 19 (10.5%) healthy BRCA1 mutation carriers who underwent RRSO: one infiltrating serous tubal carcinoma (pT1a) and another serous tubal intraepithelial carcinoma. No malignant neoplasms were found in RRSO performed in healthy BRCA2 mutation carriers.

Discussion

Ovarian cancer is a heterogeneous disease. More than 90% of ovarian cancers are epithelial: they can arise from the epithelium of the ovarian surface, but also from the fallopian tubes, foci of endometriosis, or in the peritoneum [1]. Four main types are distinguished within epithelial ovarian cancer: serous, endometrioid, mucinous, and clear cell. Each of them shows gene expression patterns that correlate with their morphological counterparts in normal tissues: serous tumors were correlated with the fallopian tubes, mucinous tumors with the colonic mucosa, and endometrioid and clear cells with the endometrium [2].

Theories of carcinogenesis indicate that serous ovarian cancers derive from the epithelium of the fallopian tube and affect the ovary secondarily, highlighting two hypotheses for their pathogenesis. According to the first, the precursors of ovarian cancer develop in the fimbriae from an occult serous tubal intraepithelial carcinoma (STIC –*serous tubal intraepithelial carcinoma*-), subsequently involving the ovary. The second theory supports the implantation of normal fimbrial epithelium on the ovarian surface during ovulation, resulting in a cortical inclusion cyst where malignant transformation can arise [3, 4].

Between 15-20% of patients with ovarian cancer are BRCA1/2 mutation carriers. Although a family history of breast and ovarian cancer is strongly correlated with the detection of a BRCA1/2 mutation, up to 50% of women with BRCA-positive ovarian cancer have no family history of cancer. This supports the importance and indication of genetic testing for all women with a personal diagnosis of epithelial ovarian cancer (including fallopian and peritoneal cancer), regardless of age at diagnosis and family history [5]. Carriers of these mutations are more likely to be diagnosed with high-grade serous ovarian cancer than other histologic subtypes.

Therefore, the increased risk of ovarian and fallopian tube cancer in BRCA1/2 positive women is well documented. For this reason and since there is no effective screening for this type of cancer, RRSO is the surgery of choice in women carrying BRCA mutation who have completed their birth desire.

RRSO is recommended from 35-40 years for BRCA1-positive and from 40-45 years for BRCA2-positive women, although the age of the youngest affected person in the family should always be considered [6]. This age difference is established because BRCA1 mutation carriers tend to develop ovarian cancer at younger ages [7].

Vol. 5, No. 02; 2021

ISSN: 2581-3366

RRSO has been shown to decrease the risk of primary ovarian, tubal, and peritoneal cancer by 80% in BRCA1/2 carriers [8]. A residual risk of 1-4.3% of primary peritoneal carcinoma has been reported [8, 9]. In our series, we have also been able to confirm that 1.1% of women with a previous RRSO (1 of 90) without presenting relevant pathological findings, were diagnosed six years later with peritoneal serous carcinoma. RRSO is estimated to confer a 77% reduction in all-cause mortality [10].

Regarding the reduction in the risk of BC associated with RRSO, the current data are controversial: initial studies showed a risk reduction in BRCA1/2 mutation carriers of 56% and 43% respectively [11], several studies corroborate this risk reduction of 51% [8], but more recent ones did not validate this protective effect [12, 13]. A study of the year 2020 showed that RRSO in premenopause decreased the risk of BC in BRCA1 but not in BRCA2 mutation carriers [14].

Occult ovarian and fallopian cancers removed prophylactically have been reported in women carrying a BRCA mutation, ranging from 2-12% [15-18]. For this reason, a standardized surgical protocol is important as well as a detailed and protocolzed histological study of the surgical pieces. In our study, in four of the 90 RRSOs performed (4.4%), malignant lesions were found at the level of the fallopian tube (serous carcinomas): one of the cases was infiltrating (pT1a), another was intraepithelial with foci of micro-invasion and in the remaining two, the lesion was exclusively intraepithelial.

RRSO has a specific surgical protocol, that we must follow [19]: minimally invasive laparoscopic approach, survey of the abdominopelvic cavity (upper abdomen, bowel surfaces, omentum, appendix, and pelvic organs), biopsy of any abnormal peritoneal finding, pelvic washing for cytology (50 cc of normal saline instilled and aspirated immediately), bilateral salpingo-oophorectomy (including: 2 cm of infundibulopelvic ligament, all of the fallopian tubes from the uterine horn and especially the peritoneum surrounding the ovaries and fallopian tubes, as well as areas of underlying adhesions between the tube/ovary, and pelvic wall), minimize fallopian tube/ovarian manipulation to avoid traumatic exfoliation, place the ovaries and tubes in an endo bag for retrieval from the pelvis. Interval salpingectomy and deferral of oophorectomy are not indicated.

Serial sectioning and careful microscopic examination of the bilateral salpingo-oophorectomy specimen is a well-established practice. This is done using the protocol SEE-FIM (*Sectioning and Extensively Examining the Fimbriated End*), which involves pathological revision of the entire sample in 2 to 3 mm sections, as well as the longitudinal section of the fimbria [20, 21] (Figure 1). The main predictor for detecting hidden malignancy in women at high risk for ovarian cancer who are going to undergo RRSO is to adhere to the surgical-pathological protocol. It is important because following a standardized protocol is associated with higher rates of diagnosis.

Vol. 5, No. 02; 2021

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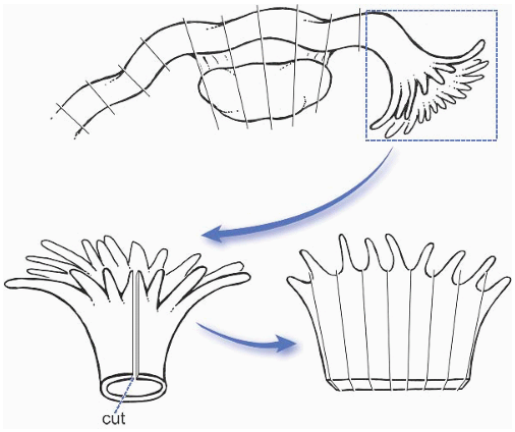

Figure 1. Serial section of the fallopian tube and ovary, from a sample of RRSO (SEE-FIM protocol). The fimbriated end should be amputated from the rest of the tube and sectioned serially at 2 mm intervals along the long axis. The remainder of the fallopian tube as well as the ovary should be cut perpendicular to the long axis at 2 mm intervals.

For the non-BRCA genes (BRCAX), various studies show that carriers of BRIP1, RAD51C, and RAD51D have a moderate risk of ovarian cancer, so RRSO is recommended; although there is no evidence of at what age it is recommended to perform RRSO (the guidelines recommend its consideration in peri/menopause: 45-50 years) [6]. The cumulative risk of ovarian cancer for Lynch syndrome carriers is 60%, therefore RRSO is also recommended in these patients. In general, risk-reducing surgery (hysterectomy + bilateral salpingo-oophorectomy) is recommended in women with Lynch syndrome at similar ages to BRCA2 carriers (around 40-45 years) [22, 23], although guidelines such as those of the National Comprehensive Cancer Network (NCCN) do not specify age [24] because there is variability according to the type of mutation and family history [25]. For the PALB2, ATM, CHEK2, or NBN genes, it is recommended to consider RRSO based on family history.

The benefits and side effects associated with RRSO and subsequent surgical menopause need to be weighed. In premenopausal women, oophorectomy increases the risk of cardiovascular morbidity, osteoporosis, and associated endocrine symptoms including hot flashes and impaired sexual function. Fear of these symptoms can influence the decision to undergo this procedure. In general, for BRCA1/2 mutation carriers, the impact on the quality of life-related to surgical menopause is outweighed by the reduction in cancer risk [26, 27]. It is recommended that a gynecologist-oncologist explain the risks/benefits and help patients who are considering RRSO to understand how it can affect the quality of life and assess treatment options, if necessary. The role of hormone replacement therapy in BRCA1/2 mutation carriers submitted to RRSO has been controversial. Although the evidence is limited, hormone therapy has a number of reported benefits and does not appear to affect BC risk [28].

Vol. 5, No. 02; 2021

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Conclusion

In our series of 90 RRSOs performed on women carrying BRCA1/2 mutations, with and without previous breast cancer, 4 women (4.4%) were diagnosed with malignant lesions in the fallopian epithelium (all of them in early stages).In the absence of new imaging techniques or new serum markers to predictably identify early-stage ovarian and fallopian cancer, RRSO remains the best option for women at high risk of developing ovarian and fallopian cancer. The main predictor for detecting hidden malignancy in women at high risk for ovarian cancer who are going to undergo RRSO is to adhere to the surgical-pathological protocol. However, we must always bear in mind that there will always be a residual risk of primary peritoneal carcinoma after RRSO (1.1% in our series).

We emphasize the importance of performing a germline testing for all women diagnosed with epithelial ovarian cancer (including fallopian and peritoneal cancer), regardless of age at diagnosis (NCCN Guidelines). We also recall the importance of trying to identify all women with hereditary breast and ovarian cancer syndrome (BRCA1/2 mutation carriers) and those carriers of other mutations with increased risk of ovarian cancer.

Our data support the indication for RRSO in selected high-risk patients; and recall the importance of the identification of high-risk patients, in order to offer genetic counseling and preventive measures, both for patients and their families.

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Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Vol. 5, No. 02; 2021

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Vol. 5, No. 02; 2021

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