

Risk-Reducing Salpingo-Oophorectomy in BRCA Mutation Carriers. A Prospective Multicentric Study

Del Vecchio Vittoria¹, Loizzi Vera¹, Cicinelli Ettore¹, Deromemaj Xheni¹, Kardhashi Anila², Paradiso Angelo³, Legge Francesco⁴, Natalicchio Maria Iole⁵, Resta Leonardo⁶, Resta Nicoletta⁷ and Cormio Gennaro^{1,2}

¹Obstetrics and Gynecology Unit, Department of Biomedical Sciences and Human Oncology, University of Bari, Italy

²Gynecology Unit, IRCCS Istituto Tumori "Giovanni Paolo II", Italy

³Institutional BioBank, Experimental Oncology and Biobank Management Unit, IRCCS Istituto Tumori "Giovanni Paolo II", Italy

⁴Gynecologic Oncology Unit, General Regional Hospital "F. Miulli" of Acquaviva delle Fonti, Italy

⁵Molecular Oncology and Pharmacogenomics laboratory, University of Foggia, Italy

⁶Department of Pathology, University of Bari, Italy

⁷Medical Genetics Unit, Department of Biomedical Sciences and Human Oncology, University of Bari, Italy

Abstract

BRCA1/2 are tumour-suppressor genes involved in DNA homologous recombination and ovarian cancer development.

Risk-reducing surgery (RRS) was performed in 100 patients carrying BRCA1 (aged between 30-73 years, median age was 51 years) and BRCA 2 mutation (aged between 36-70 years, median age was 53 years). 58 patients had previous history of breast cancer.

Between the 100 patients, 82 women (82 %) underwent risk-reducing salpingo-oophorectomy (RRSO) through a laparoscopic minimally invasive approach, 7 (7 %) underwent laparoscopic RRSO and contextual hysterectomy, 1 woman (1 %) underwent RRSO through a laparotomic approach and 10 women (10 %) laparotomic RRSO and hysterectomy. During 5 (5 %) laparoscopic RRSO, prophylactic bilateral mastectomy was also performed.

Early and late complication occurred in 3 patients (3 %). 2 patients (2 %) were found to have occult Serous Tubal Intraepithelial Carcinoma (STIC) and 3 patients (3 %) occult cancer.

RRSO is safe and feasible in BRCA mutation carriers. The procedure is effective for genetic prevention of ovarian cancer.

Keywords: BRCA, ovarian cancer, risk-reducing surgery

Introduction

Ovarian carcinoma is the leading cause of death among gynaecological malignancies. More than one-fifth of ovarian tumours have genetic predisposition and this genetic abnormality is related to a germline mutation in Breast Related-Cancer Genes (BRCA) 1 and 2 [1] in about 65–85% of cases. BRCA 1 and 2 are tumour suppressor-autosomal dominant inherited genes encoding proteins involved in homologous recombination [2].

Different studies evaluated the origin of early High Grade Serous Ovarian Cancer (HGSOC) in the distant portion of the fallopian tube and this discovery led to develop a risk-reducing strategy through a prophylactic bilateral salpingo-oophorectomy (BSO) in women with BRCA1/2 genes mutation [3].

The aim of this prospective study was to evaluate the feasibility, short-term morbidity, and incidence of occult disease in a large group of BRCA mutated women who underwent risk-reducing salpingo-oophorectomy.

Materials and Methods

All patients with a pathogenetic mutation of BRCA 1-2 genes referred between January 2016 and September 2019 to the three gynaecological institutions (University Hospital and National Cancer Institute in Bari and Miulli General Regional Hospital in Acquaviva delle Fonti) for risk reducing salpingo-oophorectomy were evaluated in this study.

All women were counselled about risks and benefits of surgical procedures, in particular the reduction rate of breast and ovarian cancer risk, the iatrogenic menopause (in fertile women) and the morbidity related to the surgery were discussed with the patients. Moreover, the chance to perform at the same time risk-reducing mastectomy was also offered.

All patients provided written informed consent for data collection for research purpose.

Preoperative workup included pelvic examination, transvaginal ultrasound, PAP smear and hysteroscopy with endometrial biopsy

in order to rule out uterine pathology, electrocardiography examination, chest X-ray and CA125 dosage.

Laparoscopic approach was the surgical procedure chosen to perform the risk-reducing salpingoophorectomy, however, in presence of large uteri or previous multiple surgeries in the abdomen resulting in adhesions, a laparotomic approach was also used.

All surgical procedures on the adnexa were characterized by the resection of the tubes from their insertion into the uterine cornua to the fimbriated end and by the sectioning of the infundibolopelvic ligaments. Furthermore, peritoneal cytology and careful visual inspection of all abdominal and pelvic organs were provided in all patients.

Pathologic examination was performed according to the SEE-FIM (Sectioning and Extensively Examining the Fimbriated End) protocol [4].

Surgical data (operative time, length of hospital stay) and postoperative complications were prospectively recorded for all patients.

Results

One hundred and three patients were enrolled in the study. After counselling, two patients (1,9%) refused the procedure, whereas only one subject (1%) was not operated for anesthesiological contraindication (ASA 4) due to severe chronic pulmonary disease and aortic insufficiency.

Fifty-nine women had BRCA1 gene mutation (aged between 30-73 years) and forty-one had BRCA2 gene mutation (aged between 36-70 years).

Forty-nine women had familial predisposition for breast cancer and 30 for ovarian cancer. Moreover, among the 59 women who carried BRCA1 gene mutation, a personal history of breast cancer was present in 25 patients, whereas one had familial predisposition for pancreatic cancer, one for hepatic, gallbladder and pulmonary cancer, one for cervical cancer, two for gastric cancer and another one for thyroid cancer; among seven women

who carried BRCA2 gene mutation, a personal history of breast cancer was present in 16 patients, whereas three had familial predisposition for prostatic cancer, three for gastric cancer and one for colon cancer.

The younger patient with BRCA1 gene mutation was 30 years old, the older one was 73; the younger woman with BRCA2 gene mutation was 36 years old and the older one was 70. The median age of the performance of RRS was 51 years.

Among the 100 patients who underwent RRS, 82 women underwent RRSO through a laparoscopic minimally invasive approach, 7 underwent laparoscopic BSO and contextual hysterectomy, one underwent RRSO through a laparotomic approach and 10 laparotomic BSO and hysterectomy (Table 1). During five laparoscopic RRSO, prophylactic bilateral mastectomy was also performed.

Study population: N = 100 (Women who underwent RRS)	
Age (mean)	51 years
Personal history of breast cancer	58 (58 %)
Familial predisposition for breast cancer	49 (49 %)
Familial predisposition for ovarian cancer	30 (30 %)
Laparoscopic BSO	82 (82 %)
Laparotomic BSO	1 (1 %)
Laparoscopic Hysterectomy + BSO	7 (7 %)
Laparotomic Hysterectomy + BSO	10 (10 %)
Prophylactic bilateral mastectomy	5 (5 %)
BRCA1 mutation	59 (59 %)
BRCA2 mutation	41 (41 %)

Table 1. Characteristics of the study population

Patient	Age	BRCA Status	Previous Breast Cancer	Surgery	Diagnosis	Staging After Completion Surgery
CASE 1	49	BRCA1	YES	Laparoscopic RRSO	STIC	IA
CASE 2	56	BRCA2	NO	Laparoscopic RRSO	STIC	IA
CASE 3	46	BRCA1	YES	Laparoscopic RRSO	High-grade serous tubal carcinoma	IA
CASE 4	57	BRCA1	YES	Laparoscopic RRSO	High-grade serous tubal carcinoma	IA
CASE 5	52	BRCA1	YES	Laparoscopic RRSO	High-grade serous tubal and ovarian carcinoma	IA

Table 2. Characteristics of patients diagnosed with precancerous or cancerous conditions

All surgical procedures were well tolerated by all the patients; we registered only 3 intraoperative complications, which included bladder injuries in two patients and an intestinal perforation in one: these were intraoperatively successfully managed. The median operative time and length of hospital stay were 55 minutes and 1.2 days for patients undergoing laparoscopic BSO, 90 minutes and 2 days for patients undergoing laparoscopic hysterectomy and BSO, 116 minutes and 3.1 days for those undergoing laparotomic hysterectomy and BSO. The single laparotomic BSO lasted 130 minutes and the hospital stay lasted 3 days.

Histologic examination diagnosed 5 cases (5 %) of occult genital cancers using the SEE-FIM protocol. In particular, two patients had an incidental diagnosis of STIC; two had a high grade serous tubal carcinoma and the remaining one had a high grade tubal and ovarian serous carcinoma. Of the two cases of STIC, one was

RRS is defined as an operation performed in cases without lesions or absence of clinically significant lesions in order to remove organs at high risk of developing cancer, for the purpose of reducing the mortality risk from cancer or from the side effects of treatment. This article investigated feasibility, surgical complications and the risk of discovering occult genital malignancies at the time of RRS.

Previous studies have shown that women with BRCA1 germline mutation have a 40% to 60% risk of developing HGSO in their lifetime, whereas those with BRCA2 mutation have a 11% to 27% risk [5,6].

For this reason, since RRS could potentially prevent at least 90% of epithelial ovarian cancer and also 50% of breast cancer in women undergoing RRS before menopause, there is a strong indication to undergo prophylactic surgery in healthy women carrying BRCA1/2 genes mutation, and in those with a high-penetrance mutation in one of the other genes involved in gynaecological cancers with a strong family history of breast and/or ovarian cancer [7-10]. Women with occult ovarian cancer detected at the time of RRS have a 5-years survival rates higher than those of women with clinically detected ovarian cancer [2].

BRCA 1/2 mutation carriers who are not ready to undergo RRSO should be offered combined oral-contraceptive pills [11] and intensive surveillance with transvaginal ultrasound and CA125 blood test starting at age 30–35 years every six months [12].

Before undergoing risk-reducing surgery, all patients should be counselled about reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short-term Hormone Replacement Therapy (HRT) and about other related medical issues [13]. Clinical evidences showed a significant worsening of vasomotor symptoms after performing RRSO before natural menopause (hot flashes, night sweats and sweating) and a decline in sexual functioning that could significantly condition the quality of life of these patients and that could be improved by HRT to a recommended maximum age of natural menopause. However, women with a personal medical history of breast cancer that undergo RRS, are not eligible to HRT treatment [11].

Our preliminary analysis demonstrates that RRSO is feasible in BRCA mutated women because among the one hundred and three women only two refused the procedure. Our analysis showed that RRS was performed at 30 years in one woman carrying BRCA1 gene mutation and at 36 years in one carrying

49 years old with personal medical history of breast cancer and BRCA1 gene mutation and the other one was 56 years old with a strong familial predisposition for both ovarian and breast cancer and the BRCA2 gene mutation. Of the two cases of a high grade serous tubal carcinoma, one was 46 and the other 57 years and both of them had personal medical history of breast cancer and BRCA1 gene mutation. The remaining case with a high grade tubal and ovarian serous carcinoma was 52 years old with a personal medical history of breast cancer and BRCA1 gene mutation (Table 2).

All the 5 patients with diagnosis of occult cancer underwent completion surgery and the FIGO staging was IA for all of them.

At a median follow-up of 9 months after RRSO no patients experienced new cancer.

Discussion

BRCA2 gene mutation. These procedures were performed at this age because the first had a strong familial predisposition for breast and ovarian cancer and the second one had both a personal medical history of breast cancer and also a strong familial predisposition for breast and ovarian cancer. Both patients had no desire for preservation of their fertility because they had completed their childbearing.

Surgery in our series may be accomplished through a minimally invasive approach in 82 % of cases as previously reported in other series. In our study, 17 % of the patients had also hysterectomy at the time of RRSO and recent studies showed that the association of BSO to total hysterectomy could further reduce the incidence of both ovarian and endometrial cancer since BRCA1 mutation carriers could also give rise to serous/serous like endometrial carcinoma [3]. This procedure should be discussed with the patient in particular in case of uterine disease (e.g. symptomatic or atypical hyperplasia, leiomyoma and/or adenomyosis) or in case of hormonal treatment (i.e. tamoxifen) for breast cancer.

In this study, the 5 % of women had a diagnosis of occult precancerous or cancerous condition. We found two cases (2 %) of occult precancerous condition (STIC) and three cases (3 %) of high grade genital cancer. Women with BRCA mutations who present with an asymptomatic STIC carry only an approximate 5% of ever developing a metastatic serous cancer [14]. Among these five cases of occult genital malignancy, four cases were related to BRCA1 gene mutation. All of these aspects suggest the possible faster occurrence and unfavourable prognosis in women carrying BRCA1 mutation. Moreover, women with BRCA1 compared to BRCA2 mutations tend to be diagnosed with ovarian cancer approximately a decade younger than women with ovarian cancer without an identifiable genetic mutation. However, regardless the type of mutation involved (BRCA1/2), Current National Comprehensive Cancer Network (NCCN) guidelines [13] recommend risk-reducing salpingo-oophorectomy at age 35-45 years and after completion of childbearing [15]. In particular, RRS should be performed at age 35-40 years for BRCA1 carriers and 40-45 years for BRCA2 carriers. Results from a clinical trial carried on by Gynaecologic Oncology Group, showed the detection of invasive or intraepithelial ovarian/tubal/peritoneal neoplasms in 25 (2.6%) of 966 RRSOs: the BRCA1 mutation carriers were 4.6%, the BRCA2 mutation carriers 3.5% and the noncarriers ones 0.5% ($p=0.001$) [16].

The higher proportion of occult cancer detected in our series as compared to previously reported series might be related to a selection bias as a large proportion of women in our study had already developed breast cancer.

In the 100 surgical procedures performed described in this study, no severe complications were registered. Only two bladder and one colon injuries occurred and they were promptly managed and resolved. All the risk-reducing surgical procedures were safe and well tolerated. The majority of the RRSO were performed with a minimally invasive approach characterized by the advantage of lower operative time and hospital stay. Although the short follow-up does not permit definitive conclusion, none of the patients enrolled in our study presented a new cancer.

Despite a small (3.9 % for BRCA1 and 1.9% for BRCA2 mutation carriers) residual lifetime risk of primary peritoneal cancer in the 20 years after RRSO [17], we believe that the widespread application of genetic testing will result in a progressive increase of RRSO [11] and in a decrease of invasive cancer.

Conclusions

Despite the small sample size of population of this study, we highlighted the importance of RRSO as an effective procedure in women at high risk of developing epithelial ovarian carcinoma. More data are needed to strengthen our results and to underline the importance of a “genetical screening” to counteract and prevent gynaecological malignancies.

References

1. Toss A, Tomasello C, Razzaboni E, Contu G, Grandi G, et al. Hereditary Ovarian Cancer: Not Only BRCA 1 and 2 Genes. *Biomed Res Int*. 2015; 341723.
2. Temkin SM, Bergstrom J, Samimi G, Minasian L. Ovarian Cancer Prevention in High-risk Women., *Clin Obstet Gynecol*. 2017; 60: 738-757.
3. Bogani G, Tagliabue E, Signorelli M, Chiappa V, Carcangiu ML, et al., Assessing the Risk of Occult Cancer and 30-day Morbidity in Women Undergoing Risk-reducing Surgery: A Prospective Experience., *J Minim Invasive Gynecol*. 2017; 24: 837-842.
4. Mallen A, Soong TR, Townsend MK, Wenham RM, Crum CP, Tworoger SS., Surgical prevention strategies in ovarian cancer. *Gynecol Oncol*. 2018; 151: 166-175.
5. Lee YJ, Lee SW, Kim KR, Jung KH, Lee JW, et al. Pathologic findings at risk-reducing salpingo-oophorectomy (RRSO) in germline BRCA mutation carriers with breast cancer: significance of bilateral RRSO at the optimal age in germline BRCA mutation carriers. *J Gynecol Oncol*. 2017; 28: e3.
6. Loizzi V, Cicinelli E, Santamaria F, Murgia F, Minicucci V, et al. BRCAmut and "founder effect": a prospective study in a single academic institution. *Oncotarget*. 2018; 9: 22353-22358.
7. Mau C, Untch M. Prophylactic Surgery: For Whom, When and How? *Breast Care (Basel)*. 2017; 12: 379-384.
8. Heemskerk-Gerritsen BA, Seynaeve C, van Asperen CJ, Ausems MG, Collée JM, et al. Hereditary Breast and Ovarian Cancer Research Group Netherlands., Breast cancer risk after salpingo-oophorectomy in healthy BRCA1/2 mutation carriers: revisiting the evidence for risk reduction. *J Natl Cancer Inst*. 2015; 107: djv033.
9. Nasim Mavaddat, Pharoah PDP, Michailidou K, Tyrer J, Brook MN, et al. Prediction of Breast Cancer Risk Based on Profiling with Common Genetic Variants. *J Natl Cancer Inst*. 2015; 107: djv036.
10. Rebbeck TR, Mitra N, Wan F, Sinilnikova OM, Healey S, McGuffog L, et al, Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. *JAMA*. 2015; 313: 1347-1361.
11. Walker JL, Powell CB, Chen LM, Carter J, Bae Jump VL, et al. Society of Gynecologic Oncology recommendations for the prevention of ovarian cancer. *Cancer*. 2015; 121: 2108-2120.
12. Finch A, Chiang JK, Elit L, McLaughlin J, Springate C, et al. The impact of prophylactic salpingo-oophorectomy on menopausal symptoms and sexual function in women who carry a BRCA mutation. *Gynecol Oncol*. 2011; 121: 163-168.
13. NCCN Guidelines Version 3.2019, BRCA-Related Breast and/or Ovarian Cancer Syndrome.
14. Soong TR, Kolin DL, Teschan NJ, Crum CP. Back to the Future? The Fallopian Tube, Precursor Escape and a Dualistic Model of High-Grade Serous Carcinogenesis. *Cancers (Basel)*. 2018; 10: E468.
15. Lee EG, Kang HJ, Lim MC, Park B, Park SJ, et al. Different Patterns of Risk Reducing Decisions in Affected or Unaffected BRCA Pathogenic Variant Carriers, *Cancer Res Treat*. 2019; 51: 280-288.
16. Sherman ME, Piedmonte M, Mai PL, Ioffe OB, Ronnett BM, et al. Pathologic Findings at Risk-Reducing Salpingo-Oophorectomy: Primary Results From Gynecologic Oncology Group Trial GOG-0199. *J Clin Oncol*. 2014; 32: 3275-3283.
17. Finch APM, Lubinski J, Møller P, Singer CF, Karlan B, et al. Impact of Oophorectomy on Cancer Incidence and Mortality in Women with a BRCA1 or BRCA2 Mutation. *J Clin Oncol*. 2014; 32: 1547-1553.

***Correspondence:** Vittoria Del Vecchio, MD, Department of Biomedical Science and Human Oncology, Obstetrics and Gynecology Unit, University of Bari, Piazza Giulio Cesare 11, 70124 Bari, Italy, Tel: ++39 080 5592232, E-mail: vittoria.delvecchio.md@gmail.com

Rec: Apr 15, 2020; Acc: May 06, 2020; Pub: May 09, 2020

Arch Obs Gyn. 2020;1(2):111

DOI: 10.36879/AOG.20.000111

Copyright © 2020 The Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC-BY).