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Evaluation of Transvaginal Ultrasound plus CA-125 Measurement and Prophylactic Salpingo-Oophorectomy in Women at Different Risk Levels of Ovarian Cancer: The Modena Study Group Cohort Study

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Keywords

BRCA1 · *BRCA2* · Salpingo-oophorectomy · Surveillance · CA-125 measurement · High risk

Abstract

Objective: To evaluate the effectiveness of transvaginal ultrasound (TVU) and serum CA-125 measurement in women at different risk of developing ovarian cancer/fallopian tube cancer (OC/FTC) and the incidence of primary peritoneal cancer (PPC) after risk-reducing salpingo-oophorectomy (RRSO). ***Methods:*** Between 2002 and 2014, 661 women at different risk of OC/FTC/PPC due to a family history or *BRCA1/2* gene mutation were offered TVU and CA-125 measurement or RRSO as prevention strategies. The detection rate of OC/FTC/PPC was evaluated, and the sensitivity and specificity for CA-125 measurement and TVU were calculated. Survival and event analysis was performed for diagnosed patients. ***Results:*** After a median follow-up of 112 months, 12 OC/FTC/PPC cases were detected (2.6/1,000 persons/year). The screening sensitivity was 70%, with 73% for *BRCA* carriers. Six (50%) of 12 cancers were stage I or II. Among 41 women who underwent RRSO, 2 *BRCA1* carriers developed a PPC (4.9%). At 61-month follow-up, overall and event-free survival were 75 and 64%, respectively. ***Conclusions:*** The cancer detection rate in women with *BRCA* mutation or a strong family history supports the effectiveness of our surveillance program for early diagnosis. Screening for women at lower risk of OC/FTC is not recommended. A residual risk of PPC after RRSO remains for *BRCA1* carriers.

Introduction

More than one-fifth (about 23%) of ovarian cancer (OC) cases have been related to hereditary conditions [1]. The most frequent genetic abnormality is a germline mutation in the *BRCA* genes. *BRCA1* and *BRCA2* mutation carriers have an increased lifetime risk of developing breast cancer (BC) and OC (up to 85% for BC and up to 54% for OC) [2–5]. Nevertheless, several other suppressor genes and oncogenes have been associated with hereditary OC (i.e., *TP53*, *BARD1*, *CHEK2*, *RAD51*, and *PALB2*) [1, 6–8].

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Nowadays, women at high risk of OC, fallopian tube cancer (FTC), and primary peritoneal cancer (PPC) can receive, as a primary option to decrease the possibility of developing these cancers, risk-reducing salpingo-oophorectomy (RRSO) [9, 10]. A recent systematic review showed that RRSO not only reduces the risk of OC and BC, but also provides an advantage in overall survival, ranging between 60 and 69% [11].

Alternatively, intensive surveillance by annual or semiannual concurrent transvaginal ultrasound (TVU) and serum CA-125 measurement can be offered to women who decline RRSO [12]. However, many studies reported that an annual TVU and CA-125 measurement performed in *BRCA1/2* mutation carriers could not prevent the diagnosis of advanced OC [13–15]. In 2009, the first prospective study of TVU and CA-125 measurement was completed, with survival as the primary outcome, suggesting that annual surveillance by TVU and CA-125 measurement could detect tumors at an early stage, influencing survival [16].

Recently, a phase II study highlighted that screening more frequently than annually with prompt surgical intervention seems to offer a better chance of early-stage detection in high-risk women [17].

The objective of this study was to assess the sensitivity of TVU plus CA-125 measurement as a screening test for OC/FTC/PPC in high-risk women and *BRCA1/2* mutation carriers, also considering the rate of early-stage diagnosis. Furthermore, another objective was to evaluate the residual risk of PPC in women at genetic risk who have undergone RRSO.

Patients and Methods

Study Design and Characteristics of the Study Population

A nonrandomized prospective cohort study was approved by the Ethics Committee of Modena, Italy, to evaluate the outcomes of women in a surveillance program or of women who underwent RRSO. Carriers of *BRCA1* or *BRCA2*, *TP53*, *MLH1*, or *MSH2* mutations or subjects at risk according to our previously described criteria [18] at least 18 years of age were eligible.

Since 2002, with the aim to identify individuals at risk of BC, women referred to the mammographic screening program or to general practitioners or specialists compiled a record card on family history. In case of a family history of BC, OC, or both, genetic counseling was proposed to the Modena Study Group for Familial Breast and Ovarian Cancer. Among 17,460 women at risk, 4,889 (28%) accepted to undergo genetic counseling, during which the genealogic tree was drawn.

Family histories of BC and/or OC were classified according to the following criteria, as already published [18]: (1) at least three relatives diagnosed with BC or OC in two different generations; (2) at least one of the three relatives must be a first-degree relative of one of the other two; in the case of male interposition, a relationship of different degree is allowed; (3) at least one BC must be diagnosed before the age of 40 years or be bilateral; (4) at least one BC diagnosed at age ≤35 years, regardless of family history; (5) at least one BC and one OC diagnosed in the same woman, regardless of family history; (6) at least one male BC, regardless of family history; (7) one sporadic BC or OC. Applying these criteria, subjects were classified at high, intermediate, or slightly increased risk as described in Table 1. When the first five, or first and second, or first and third criteria were fulfilled, the family was classified at high risk; in case of first or sixth criterion, or the second together with the third criterion, families were considered at intermediate risk; the second or the third or the last criterion defined families at slightly increased risk. Finally, a group classified at genetic risk was defined as having a *BRCA1* or *BRCA2* gene mutation.

Among the 4,889 women who underwent genetic counseling, 3,981 resulted at different increased risk as follows: 2,442 subjects were at high risk, 829 at intermediate risk, 572 at slightly increased risk, and 138 were germline genetic mutation carriers. Patients who had a personal history of OC were excluded, whereas among women classified as high, intermediate, or slightly increased risk, only those with OC reported in the family were considered for the study. Only 2 cases with mutations in the mismatch repair genes and 1 patient harboring a *TP53* mutation entered the study. One hundred and twenty-four patients already affected by BC were included as well, 47 of whom were *BRCA1/2* mutated and 1 harbored a *TP53* germline mutation, whereas 60 belonged to the high-risk group, 15 to the intermediate-risk group, and 1 to the slightly-increased-risk group.

In December 2014, 661 women were eligible for our study: 127 were *BRCA1/2* carriers (71 *BRCA1* and 56 *BRCA2*, respectively), 2 had Lynch syndrome, 1 carried a germline *TP53* mutation, 334 were at high risk, 144 were at intermediate risk, and 53 were at slightly increased risk (Fig. 1). All women characterized by ascertained predisposing gene mutations were offered RRSO along the post-test oncogenetic counseling session. RRSO was proposed after 35 years of age and when childbearing decisions were complete. Rarely, also women without gene mutations but with an important family history of OC could ask for RRSO and after accurate counseling could undergo prophylactic surgery.

Surveillance was offered starting at 25 years of age with 6-monthly serum CA-125 measurement and TVU to *BRCA1/2*, *MLH1*, *MSH2*, and *TP53* mutation carriers and annual to the high-, intermediate-, and slightly-increased-risk group. Every patient received CA-125 measurement and TVU at the same center. Serum CA-125 levels were measured by the radioimmunoassay FDI CA 125 II (Fujirebio Diagnostics, Göteborg, Sweden) that considers the cutoff of 35 U/mL as distinguishing between normal and abnormal results.

Ultrasound evaluation was carried out with three-dimensional gray-scale ultrasonography. The three-dimensional studies were performed with the Kretz Voluson 530D using a mechanized transvaginal probe. Surface rendering and power Doppler imaging were performed by the same gynecologic sonographer and reassigned to one of four echo patterns: cystic, multicystic, complex, or solid. The sonographic criteria used for diagnosing OC were based on a system that included morphological characteristics, histological prediction, and power Doppler imaging. The ultrasound features for predicting malignant lesions were the following: in-

Table 1. Modena criteria

			Pedigree classification	
High risk				
(I) At least 3 relatives diagnosed with BC (or OC) in 2 different generations	(II) One BC/OC case is a first-degree relative of the other 2 (of the other 1 if the first criterion is not fulfilled)[a]	(III) At least 1 case has been diagnosed at the age ≤40 or with bilateral BC		
✓	✓	✓	hereditary	HBC/HBOC[b]
✓	✓		suspected hereditary	SHBC/SHBOC
✓		✓	suspected hereditary	SHBC/SHBOC
BC diagnosed at age ≤35, regardless of family history			early onset	EOBC
BC and OC in the same woman, regardless of family history			breast/ovarian cancer	BOC
Intermediate risk				
✓			familial	FBC/FBOC
	✓	✓	strongly suspected familial	SFBC+[c] SFBOC+[c]
Male BC, regardless of family history			male BC	MBC
Slightly increased risk				
	✓		suspected familial	SFBC[c]/SFBOC[c]
		✓	suspected familial	SFBC[c]/SFBOC[c]
BC/OC without any of the described criteria			sporadic BC	SpBC/SpOC

BC, breast cancer; BOC, breast/ovarian cancer; EOBC, early-onset breast cancer; FBC, familial breast cancer; FBOC, familial breast/ovarian cancer; HBC, hereditary breast cancer; HBOC, hereditary breast/ovarian cancer; MBC, male breast cancer; OC, ovarian cancer; SFBC, weakly suspected familial breast cancer; SFBC+, strongly suspected familial breast cancer; SFBOC, weakly suspected familial breast/ovarian cancer; SFBOC+, strongly suspected familial breast/ovarian cancer; SHBC, suspected hereditary breast cancer; SHBOC, suspected hereditary breast/ovarian cancer; SpBC, sporadic breast cancer; SpOC, sporadic ovarian cancer.

[a] Male relatives excluded when calculating the degree of relationship. [b] If at least two of the malignancies are OC, the pedigree must be classified as HBOC even if the third criterion is not fulfilled. [c] At least 2 cancer cases are required.

creased size of adnexa, irregular solid tumor, or multilocular solid cyst with at least one papillary projection, and multicystic lesion with at least score 2 of blood flow into the septa by color Doppler examination. A solid "sausage-like" or fibroma-like perfused structure near the ovary, or in cases of hydrosalpinx containing a solid area with rich vascularity, could be considered suspicious for tubal cancer [19, 20]. The gynecologist who performed surveillance by TVU was informed about the mutation status and the risk category.

Prophylactic RRSO was performed by laparoscopy, after a previous examination of abdominal and pelvic units, considering liver, omentum, and peritoneum surface. Any suspected lesion was biopsied and peritoneal washing was always carried out for cytological analysis. Ovaries and fallopian tubes were completely removed after dissection of ovarian and fallopian meso- and uterine-ovarian ligamentum. Discharge was performed with an endobag to avoid endoperitoneal dissemination of possible lesions. Uterine removal was performed only in specific cases, particularly when endometrial or myometrial lesions were diagnosed by TVU.

Data Collection and Statistics

A database was set up at our institution, which consisted in collecting family and individual characteristics, surveillance and follow-up data, additional investigations, and outcome of each examination. We used a 10000 Monte Carlo simulation model to integrate these data to estimate survival probability for women with a *BRCA1* or *BRCA2* mutation. With a post hoc power analysis of 80% and a survival rate >70%, we considered the study effective, according to other survival estimates for *BRCA1/2* carriers [21]. We calculated person-years of follow-up in age and calendar period categories from 2002 to 2014. We then computed the detection rate of OC/FTC/PPC found in both groups at the first screening visit or subsequent examination as well as the rates of cancers occurring in the interval between two examination rounds, so-

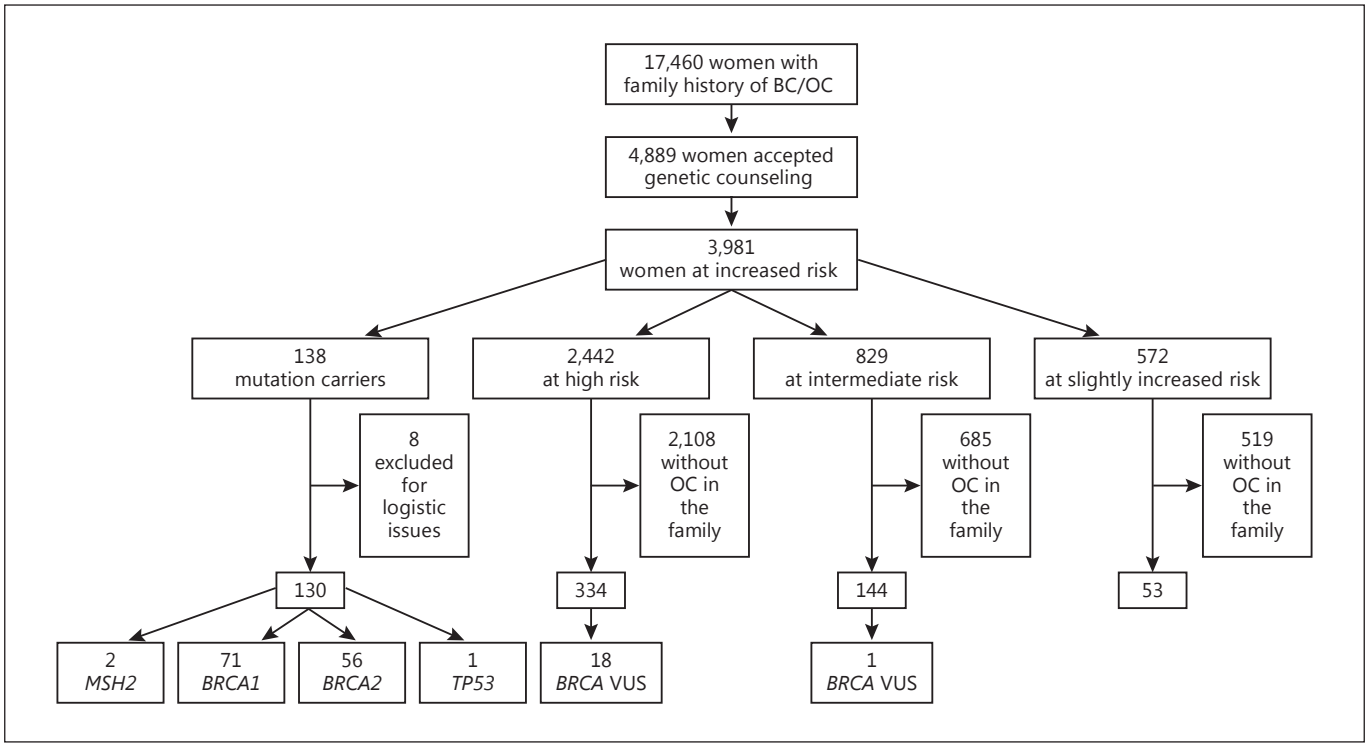

Fig. 1. CONSORT diagram of the study. BC, breast cancer; OC, ovarian cancer; VUS, variant of unknown significance.

called interval cancers. The interval cancer ranged within 6 months in the germline mutation carriers setting and within 1 year in the other risk groups. Person-years of risk were calculated from the date of the baseline visit, at which the women were evaluated for their risk and subsequent screening visits were scheduled, to the endpoint of interest: the date of cancer detection (at surveillance or in the interval between two examinations) or the end of the study period. The sensitivity of the screening test was calculated as the ratio between true-positive and true-positive plus false-negative or interval cancer. False negatives or interval cancers were those presenting clinically <183 days after the last screening for mutation gene carriers or <365 days after the last screening for women not harboring gene mutations. The specificity of the screening was calculated as the ratio between true-negative and true-negative plus false-positive. False positives were considered patients with a suspicion of cancer that was not confirmed by histology at the time of surgery. The χ^2 test was used to calculate p values for categorical variables; for continuous variables the Mann-Whitney test was utilized. All statistical tests were two-sided.

Results

Patients and Clinical Characteristics

The characteristics of the study population are shown in Table 2. Among all 661 women, 41 underwent RRSO, whereas the remaining 620 chose to follow a surveillance program of TVU and serum CA-125 measurement, according to the risk category. The median age of the RRSO group was 47 years compared with 50 years for the surveillance group ($p = 0.87$). The adherence rate to the surveillance program was 65%, with 35% of women lost to follow-up compared with 21% in the RRSO group ($p = 0.01$). No women harboring *MSH2* or *TP53* mutations underwent RRSO. Among the 127 *BRCA* mutation carriers, 26 (20.5%) chose RRSO, whereas 15 women (2.4%) in the nonmutated group asked to undergo prophylactic surgery. Nine women in the mutated group (6%) were too young at the time of analysis to undergo RRSO. All women undergoing RRSO, except for 2 patients already affected by BC before 35 years who chose RRSO at the time of breast surgery, had completed childbearing decisions. No differences were shown between the two treatment groups in terms of *BRCA1* and *BRCA2* mutation frequency. The same rate of previous pregnancies was seen for both groups (72 and 73% for surveillance and RRSO, respectively). A statistically significant difference was seen for the rate of previous BC, with the higher rate (49%) in the RRSO group compared with 18% in the surveillance group ($p < 0.001$). A total of 20 patients were found to be affected by BC in the RRSO group compared

Table 2. Characteristics of the study population

	Surveillance group (n = 620)	RRSO group (n = 41)	p value	Total (n = 661)
Median age, years	50 (range 25–85)	47 (range 33–61)	ns	
Age <50 years	358 (58%) [38–69]	25 (61%) [43–70]	ns	383
Median follow-up, months	112 (range 1–263)	119 (range 9–660)	ns	
Lost to follow-up	217 (35%) [22–40]	9 (21%) [9–40]	0.01	226
BRCA1/2	101 (16%) [11–21]	26 (64%) [44–71]	<0.001	127
HNPCC/p53	3 (0.5%) [0–1.4]	–	–	3
High risk	324 (52%) [48–56]	10 (24%) [15–33]	<0.001	334
Intermediate risk	139 (23%) [20–26]	5 (12%) [5–26]	<0.001	144
Slightly increased risk	53 (8.5%) [7–11]	–	–	53
Type of mutation				
BRCA1 pathogenic	57 (49%) [40–58]	14 (48%) [29–67]	ns	71
BRCA2 pathogenic	44 (38%) [26–44]	12 (41%) [24–61]	ns	56
VUS	16 (13%) [8–21]	3 (11%) [2–27]	ns	19
HNPCC/p53	3 (100%)	–	–	3
Previous pregnancy	444 (72%) [66–74]	30 (73%) [57–86]	ns	474
Previous breast cancer	104 (17%) [15–21]	20 (49%) [33–85]	<0.001	124

Figures in parentheses are percentages or ranges and figures in brackets 95% confidence intervals. HNPCC, hereditary nonpolyposis colorectal cancer; ns, not significant; RRSO, risk-reducing salpingo-oophorectomy; VUS, variant of unknown significance.

with 104 in the surveillance group. Among the 20 patients affected by BC in the RRSO group, 18 (90%) were *BRCA1/2* mutated.

After a median follow-up of 112 months (range 1–263) for women who underwent surveillance and of 119 months (range 9–660) for women who underwent RRSO, 10 gynecologic tumors composed by serous OC, FTC, and PPC were found in the surveillance group and 2 PPCs in the RRSO one. Among the 104 germline mutation carriers and 516 nonmutated women who were surveilled, 9 *BRCA* carriers (8.7%) and 1 patient belonging to the high-risk group (0.3%) developed a gynecologic cancer, whereas among the 26 *BRCA*-mutated patients who underwent RRSO, 2 (7.7%) developed PPC. Particularly, in the surveillance group, 6 serous OCs, 2 fallopian serous carcinomas, and 1 PPC arose in the *BRCA*-mutated patients, and 1 serous OC in the high-risk group. All cancers were classified as high-grade serous carcinomas according to the two-tier Malpica classification [22]. No women belonging to intermediate-risk or slightly-increased-risk groups were found to be affected by gynecologic cancer. As incidental findings, 2 endometrial and 1 granulosa cell tumors were identified in the surveillance group. At the time of diagnosis, 9 patients underwent surgery with hysterectomy plus oophorectomy; 1 patient affected by PPC, aged 82 years, received only an ultrasound-guided peritoneal biopsy. Two patients with a previous RRSO received an omentectomy plus peritoneal biopsy.

With regards to staging, in the surveillance group, 1 patient affected by serous OC was diagnosed in stage I (10%), 5 in stage II (50%), 3 (one of which was PPC) in stage III (30%), and 1 in stage IV (10%). Within the RRSO group, both PPCs were diagnosed in stage III (100%). The characteristics of patients who developed cancers are shown in Table 3. All affected patients received platinum-based chemotherapy.

Efficacy of Screening

With the total number of follow-up years being 4,521, the OC/FTC/PPC detection rate was 2.6 per 1,000 person-years. With regards to 127 *BRCA1/2* pathogenic mutation carriers, the number of follow-up years was 1,094, with a cancer detection rate equal to 10.5 per 1,000 person-years.

Out of the 12 patients affected by OC/FTC/PPC, we had 3 (25%) symptomatic and 9 (75%) asymptomatic tumors; excluding 1 case arising in a nonmutated patient, the rate of symptomatic cancer increased to 27%. Nine of the 12 tumors were detected at screening (2 at the first round and 7 at a subsequent round), so the total rate of screening-detected cancers was 2.0 per 1,000, whereas the rate of screening-detected BRCA-related cancer was 7.3

Table 3. Characteristics of the patients who developed gynecologic cancer

Patient No.	Last screening TVU	Last CA-125 screening	Round	Detection	Age at Dx	Type	FIGO stage	Grading	Surgery	CT	OS	BC/age at Dx	Family history of OC
Screened women													
1	abnormal	abnormal	V	screen-detected	57	OC	IIa	HGSC	yes	yes	alive	no	HBOC
2	normal	normal	III	interval	60	OC	IIIc	HGSC	yes	yes	alive	yes/55	*BRCA1*
3	abnormal	abnormal	II	screen-detected	45	OC	IIc	HGSC	yes	yes	dead	no	*BRCA1*
4	normal	abnormal	V	screen-detected	56	OC	IIc	HGSC	yes	yes	alive	no	*BRCA2*
5	abnormal	abnormal	XVIII	screen-detected	50	FTC	Ia	HGSC	yes	yes	alive	yes/33	*BRCA1*
6	normal	normal	VI	interval	36	OC	IIIc	HGSC	yes	yes	alive	no	*BRCA1*
7	normal	abnormal	I	screen-detected	83	PPC	IIIC	HGSC	no	yes	alive	yes/50	*BRCA1*
8	abnormal	abnormal	I	screen-detected	54	OC	IIC	HGSC	yes	yes	alive	no	*BRCA1*
9	normal	normal	XII	interval	79	FTC	IV	HGSC	yes	yes	alive	no	*BRCA2*
10	abnormal	abnormal	VIII	screen-detected	46	OC	IIC	HGSC	yes	yes	dead	no	*BRCA1*
Patient No.	Age at RRSO	Last CA-125 screening	Round	Detection by CA-125	Age at Dx	Type	FIGO stage	Grading	Surgery	CT	OS	BC/age at Dx	Family history of OC
Women undergoing RRSO													
11	58	abnormal	XI	screen-detected	64	PPC	IIIC	HGSC	yes	yes	alive	yes/64	*BRCA1*
12	47	abnormal	IV	screen-detected	50	PPC	IIIC	HGSC	yes	yes	dead	yes/45	*BRCA1*

BC, breast cancer; CT, chemotherapy; Dx, diagnosis; FIGO, International Federation of Gynecology and Obstetrics; FTC, fallopian tube cancer; HBOC, hereditary breast/ovarian cancer; HGSC, high-grade serous carcinoma; OC, ovarian cancer; OS, overall survival; PPC, primary peritoneal cancer; RRSO, risk-reducing salpingo-oophorectomy; TVU, transvaginal ultrasound.

per 1,000. Among the 9 screening-detected cancers, 1 was symptomatic and was diagnosed by pelvic ultrasound and CA-125 increase, and 8 were asymptomatic cancers. However, 3 cancers (2 appearing with ascites and 1 accidentally shown at abdominal ultrasound) were diagnosed in the 6-month interval between screenings (total interval cancer rate 0.6 per 1,000 and *BRCA* interval cancer rate 2.7 per 1,000). The diagnosis was made only by abdominal ultrasound plus cytological examination on ascites in 2 cases and by CA-125 increase plus pelvic ultrasound in 1 case. The time interval from the last negative screening until diagnosis ranged from 2 to 3 months.

The cutoff point for initial CA-125 measurement increased by >50 U/mL – in the absence of malignant disease – in only 7 out of 358 premenopausal women, making the false-positive rate equal to 1.9%. Three of them belonged to the group of 71 premenopausal *BRCA*-mutated patients (4.2%). On the other hand, in the postmenopausal age where a CA-125 level ≥35 U/mL is suspicious for malignant disease, only 3 women (1%) had a false-positive value, 1 of whom (2.1%) was in the *BRCA*-mutated group.

The sensitivities of TVU, CA-125, and both are shown in Table 4. TVU was excluded in case of previous RRSO. Among 12 cancers, 9 (75%) were diagnosed with CA-125 measurement, 5 with TVU (50%), and 7 with one or the other of two examinations (70%), excluding 2 PPCs arising in previous RRSO. Considering the total screening sensitivity, it increased with age, moving from a low rate in the age group <50 years (50%) to 70% in the oldest age group. Similarly, in the *BRCA1/2*-mutated patients, the highest sensitivity (73%) was reached by CA-125, whereas in case of high-risk women, CA-125 and TVU were able to detect 100% of cancers, even if only one cancer was diagnosed.

Specificity ranged between 81% in the high-risk group and 100% for women with previous RRSO for CA-125. Both techniques reached a specificity of 91–99% in the high-risk group and *BRCA*-mutated women, respectively.

Survival and Event Analysis

With a post hoc power analysis >80%, after a median follow-up of 61 months, the efficacy criteria were met with 3 deaths observed (total overall survival of 75%, equal to 73% in the *BRCA*-mutated patients). In addition

Table 4. Diagnostic sensitivities for the different imaging modalities for the 12 gynecologic cancers

	CA-125				TVU[a]				CA-125/TVU[a]			
	sensitivity		specificity		sensitivity		specificity		sensitivity		specificity	
All women (n = 661)	75% (28–92)	TP 9 FN 3	89% (50–92)	TN 583 FP 66	–	–	–	–	–	–	–	–
RRSO (n = 41[a])	100%	TP 2 FN 0	100%	TN 39 FP 0	–	–	–	–	–	–	–	–
Surveillance (n = 620)	70% (35–95)	TP 7 FN 3	89% (48–93)	TN 544 FP 66	50% (20–78)	TP 5 FN 5	95% (60–98)	TN 577 FP 33	70% (42–91)	TP 7 FN 3	91% (63–98)	TN 558 FP 52
<50 years (n = 383)	50% (5–75)	TP 1 FN 1	87% (44–90)	TN 335 FP 46	50% (9–99)	TP 1 FN 1	93% (50–96)	TN 357 FP 24	50% (9–99)	TP 1 FN 1	95% (70–99)	TN 362 FP 19
≥50 years (n = 278)	70% (40–95)	TP 7 FN 3	92% (55–95)	TN 248 FP 20	43% (15–70)	TP 3 FN 7	96% (62–99)	TN 257 FP 11	70% (55–99)	TP 7 FN 3	94% (73–97)	TN 260 FP 8
BRCA+ (n = 127)	73% (39–94)	TP 8 FN 3	99% (70–99)	TN 115 FP 1	44% (14–78)	TP 4 FN 5	92% (53–93)	TN 108 FP 10	73% (30–92)	TP 8 FN 3	99% (70–99)	TN 115 FP 1
High risk (n = 334)	100%	TP 1 FN 0	81% (50–96)	TN 269 FP 64	100%	TP 1 FN 0	95% (54–96)	TN 315 FP 18	100%	TP 1 FN 0	91% (53–97)	TN 303 FP 31

Values for sensitivity and specificity are given as percentages with exact 95% confidence intervals from binomial distribution in parentheses. Sensitivity was defined as the percentage of cancers detected (with a specific modality) among all cancers detected with any modality: TP / (TP + FN), where TP is true-positive at the histological examination and FN is false-negative as cancer diagnosed within the last negative screening. Specificity was defined as the percentage of healthy people among all patients evaluated: TN / (TN + FP), where TN is true-negative for cancer and FP is false-positive at the histological examination. RRSO, risk-reducing salpingo-oophorectomy; TVU, transvaginal ultrasound.

[a] In patients with previous RRSO, TVU was not performed.

to these patients one more, belonging to the group of interval cancers, had a relapse 2 years after diagnosis and is now receiving platinum-based therapy, making the rate of event-free survival 64%.

However, among all interval cancers (3 cases), no deaths were registered, with a median survival period of 6 years. By comparing patients diagnosed in the surveillance program and those who developed cancer after RRSO, a better survival (80%) was seen in the screening group than in the preventive surgery group (50%). Among all patients deceased only 1, belonging to the RRSO group, was previously affected by BC, but the death was related to the gynecologic cancer.

Discussion

Main Findings

The OC/FTC/PPC detection rate was 2.6 per 1,000 person-years, with a cancer detection rate of 10.5 per 1,000 person-years in *BRCA1/2* mutation carriers. No women belonging to the intermediate-risk or the slightly-increased-risk groups were found to be affected by OC/FTC/PPC.

In our surveillance program, the rate of early-stage OC/FTC/PPC, including stages I and II, was equal to 60%. Our total screening sensitivity was 70%, whereas the specific *BRCA1/2* sensitivity slightly increased, reaching 73%. The 5-year survival rate was 75 and 73% for total and *BRCA* patients, respectively, with a 64% event-free survival. Finally, we found 7.7% of *BRCA* patients who developed a PPC after RRSO, all arising in *BRCA1* mutation carriers.

Strengths and Limitations

To our knowledge, this is the first study to consider a prevention program for women at different risk of developing OC/FTC/PPC. Although the data cannot be considered conclusive, our results show that in the intermediate-risk and slightly-increased-risk groups, the surveillance program is not recommended. Totally, among 516 nonmutated patients, only 0.3% developed a cancer. The strengths of this study are the long follow-up period and the high survival rate found in patients diagnosed by the screening program. The most important limits of our study are the small number of cases diagnosed by the screening and the lack of a randomized prospective study. Furthermore, a low rate of RRSO acceptance was regis-

tered in our series, probably because women did not receive adequate counseling by the gynecologic oncologist at the time of gene testing result release. As a matter of fact, this professional figure may well provide knowledge related to OC, such as the lack of early symptoms, the limited role of screening strategies, and recent updates on minimally invasive surgical approaches including single-port laparoscopic surgery. Moreover, the gynecologic oncologist may adequately discuss the effects and management options of early menopause, including the advantages or disadvantages and risks of hormone replacement therapy. As a consequence, in the last 2 years, during which the gynecologic oncologist was routinely introduced into the genetic counseling for *BRCA1/2* mutation carriers, the rate of RRSO has increased by 50%. Another bias of the study could be the fact that gynecologists were informed about the BRCA status of every woman before TVU was performed; that could have led the sonographer to better explore adnexa and prescribe more recalls or laparoscopies. In order to better evaluate the real benefit of RRSO in our population, the median age for this intervention, which is 47 years at present, should be reduced to a maximum of 40 years, particularly in the *BRCA1* mutation carriers where the risk of OC/FTC/PPC starts in the fourth decade.

Interpretation

The early-stage diagnosis in our study, also considering PPCs arisen after RRSO, was higher than that reported in an age-matched population not considered at increased risk (50 vs. 35%, respectively) [23], whereas the total rate of advanced stages was lower than that found in *BRCA1/2* carriers at diagnosis, as reported in a recent meta-analysis (54 vs. 62%, respectively) [24]. In a previous multicenter, observational, follow-up study where 888 *BRCA1/2* mutation carriers performed an annual TVU plus CA-125 serum screening, among 10 incident cancers, the rate of advanced stages (III/IV) was equal to 80% [13]. Furthermore, also the rate of interval cancer was higher (50 vs. 25%) in this study. The possible explanation of this difference could have different reasons: the first one could be the inclusion in our analysis of women at lower risk, although a low rate of advanced stage was seen in the *BRCA1/2* risk group. It could further depend on the 6-monthly screening, which reduces the period between two examinations, and on a better attitude to explore fallopian tubes than in the past, after the theory of STIC was introduced.

Among all cancer diagnosed, 25% of cases (3/12) were PPCs, which raises the issue of the reliability of TVU for this kind of tumor, particularly in *BRCA*-mutated patients, even if Savelli et al. [25] underline the good sensitivity of power Doppler sonography in diagnosing hypoechoic nodules attached to the peritoneum (88%) and the presence of blood vessels (91%). In our series, patients who received RRSO and further developed PPC had an interval time between surgery and cancer onset of 4.5 years, in line with data in the literature. However, as was recently pointed out, there is a lack of follow-up protocols in the current literature for women undergone RRSO [26].

Our results are similar to those shown in the Japanese Shizuoka Cohort Study of Ovarian Cancer Screening in which postmenopausal average-risk women were more likely detected at an early stage (63%) as compared to the control arm (38%) [27]. Also, the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) study [28], in which ultrasound plus CA-125 measurement reached a sensitivity of 89.4%, was related to postmenopausal average-risk women, whereas the median age of our screened women was 50 years.

Regarding mortality data, our study compared well with the Kentucky Screening Study, a single-arm annual ultrasound screening study of 25,327 women [29]. This high survival rate being mostly attributable to *BRCA1/2* mutation carriers, it could be hypothesized that specific therapies, such as PARP inhibitors, improved the prognosis of these patients. Since in Italy, olaparib was approved for second-line therapy last year, no one affected by OC/FTC/PPC during the study was treated with this PARP inhibitor, rendering our survival data imputable to early diagnosis.

Recently, the UKCTOCS trial has shown a significant decrease in mortality with multimodality screening by CA-125 interpreted with use of the risk of ovarian cancer algorithm (ROCA) for subsequent TVU, from the 7th to 14th year [30], in contrast with the randomized prospective Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial that found no reduction in mortality with the annual use of combined TVU and CA-125 in screening asymptomatic postmenopausal women at general-population risk of OC [31].

Our rate of increased cutoff point for initial CA-125 in young women in the absence of malignant lesions was consistent with the 2% false-positive rate found in the NCT00039559 study [32]. On the other hand, in the postmenopausal group, the slightly increased level of CA-125 at entry (>35) registered the rate of about 1% of false-positives. Furthermore, the ROCA model would not seem feasible in the *BRCA*-mutated population, since in our series diagnosis of OC was performed at the first increase

of CA-125 in all patients except for one, drawing a blood sample every 6 months.

PPC onset after RRSO was already reported by Finch et al. [33] and could be related to the lack of pathology protocols for RRSO specimens, which possibly explains the absence of occult cancer at surgery. In our experience, no PPC was found in *BRCA2* carriers, underlying the safety of RRSO in this group of patients, differently from Finch et al. [34], who found a 1.9% rate for this population.

With regards to the low number of cancer detected, these data suffer of a limited accrual of people at different risk of OC/FTC/PPC, since only 28% of women with a family history of BC/OC accepted to undergo genetic counseling. Furthermore, 35% of the people in the study was lost to follow-up, even if the rate of surveillance abandonment was in line with a recent German study that investigated the adherence to BC screening program in *BRCA1/2* mutation carriers [35], where 41% of women left the program; predictors of adhesion were the high perception of risk, the concern for cancer, and having young children.

Our study sample is characterized by different factors between the two groups of patients who underwent screening and RRSO, in particular, there were more *BRCA1/2* carriers in the RRSO group. This could show that the low number of cancers diagnosed in the surveillance group is really due to the high rate of RRSO in the *BRCA1/2* patients. The higher rate of BC found in the RRSO group in comparison with the surveillance one reflects the incidence of this disease in *BRCA1/2* carriers, which are the most represented patients in the prophylactic surgery category, but it is not considered the cause of death. Also, the prolonged period of follow-up for RRSO in comparison with the surveillance patients did not impact the survival data, since no significant difference was found between the two groups of women.

Conclusions

Women at high risk according to *BRCA* status or strong family history can be diagnosed, in 60% of cases, at an early stage by TVU plus CA-125 measurement, also providing an increased overall survival for OC/FTC/PPC, whereas this screening is not recommended in the intermediate-risk and slightly-increased-risk groups. Concerns about residual risk of PPC after RRSO remain for *BRCA1* carriers.

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Statement of Ethics

The ethics committee of University Hospital Azienda Ospedaliero-Universitaria Policlinico di Modena approved the study on September 20, 2016 (209/16).

Disclosure Statement

The authors declare that they have no financial disclosure or conflict of interests.

Author Contributions

L. Cortesi and M. Federico planned the study. G. Contu, A. Xholli, and G. Grandi performed the TVUs. V. Medici performed genetic testing. A. Xholli, G. Grandi, and A. Cagnacci performed RRSO. I. Marchi collected the data. L. Cortesi, E. De Matteis, A. Toss, and I. Marchi analyzed data. L. Cortesi and E. De Matteis wrote the paper. A. Toss and M. Federico revised the paper.

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