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OPEN

## ORIGINAL STUDY

# The challenging screen detection of ovarian cancer in *BRCA* mutation carriers adhering to a 6-month follow-up program: results from a 6-years surveillance

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**Abstract**

***Objective:*** Approximately 25% of ovarian cancer (OC) cases are related to an inherited predisposition. Genetic mutations for the oncosuppressor genes *BRCA*1 and 2 have the best-known linkage to a higher incidence of OC and breast cancer, in approximately 70% to 80% of hereditary OC cases. To provide the first comprehensive clinical description of screen-detected (SD) OCs during a 6-years surveillance of a cohort of young *BRCA* carriers and carriers who refuse risk-reducing salpingo-oophorectomy.

***Methods:*** A prospective cohort study in a university hospital describing 191 women with *BRCA*1 and 2 mutations adhering continuously to our surveillance between 2015 and 2020, including a 6-monthly evaluation of cancer antigen 125 (CA 125) with concomitant transvaginal ultrasound (TVUS) performed by a dedicated specialist. Main outcomes were tumor's laterality, CA 125 at diagnosis, TVUS and computed tomography (CT) findings.

***Results:*** Risk-reducing salpingo-oophorectomy was performed in 58/191 (30.4%) of mutation carriers during the study period (one OC case identified). Nine SD-OCs and no interval OCs were found in the remaining 133 women. OCs (FIGO stage I or II: 88.9%) occur mainly in *BRCA 1* (77.8%), being bilateral in 85.7% *BRCA 1* and unilateral in 100% *BRCA 2*. No lesions involved only the tubes: left ovaries/tubes were more frequently involved. We have described three new possible scenarios regarding imaging: 1) *Evident cases* (33.3%, TVUS and CT obvious for OC, CA 125 sensitivity: 100%), 2) *Possible cases* (55.6%, TVUS and CT are in general accordance, documenting new TVUS signs: increased solid pattern of the ovary with peripheral cortical small cysts, hypoechoic circular mass near the ovary, intraparenchymal small hyperechoic foci), and 3) *Hidden cases* (11.1%, the smallest lesion but the highest stage (IIIA2), with CA 125 44.2 U/mL and concomitant endometrial hyperplasia).

***Conclusions:*** Different diagnostic tools must integrate to ensure early diagnosis of OC in *BRCA* mutation carriers adhering to a follow-up program.

***Key Words:*** CA 125 – Computed tomography – Early diagnosis – Surveillance – Ultrasound.

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Approximately 25% of ovarian cancer (OC) cases are related to an inherited predisposition.[1] Genetic mutations for the oncosuppressor genes *BRCA1* and *2* have the best-known linkage to a higher incidence of OC and breast cancer, in approximately 70% to 80% of hereditary OC (HOC) cases.[2] The lifetime risk of OC by the age of 70 in women with a confirmed *BRCA* mutation is very high, approximately 44% for *BRCA1* and 17% for *BRCA2* mutation carriers.[3]

Currently, there is no screening regimen effective in reducing OC mortality in *BRCA* mutation carriers. Risk-reducing salpingo-oophorectomy (RRSO) for prevention of OC and detection of occult neoplasia is recommended as the only proven mortality reducing intervention for women older than 35.[4] However, the National Comprehensive Cancer Network has advised multimodal screening, including cancer antigen 125 (or carbohydrate antigen 125 [CA 125]) assessment, and transvaginal ultrasound (TVUS) for OC early detection in young *BRCA* carriers and carriers who decline RRSO.[5] Nonetheless, the National Comprehensive Cancer Network emphasizes that this approach does not detect tumors at sufficiently early stages to influence prognosis and reduce mortality.[5] Concurrent TVUS and CA 125 determination should be considered every 6 months, starting at 35 years old, or 5-10 years before the first OC diagnosis in a susceptible family.[6]

The majority of *BRCA1*- and *BRCA2*-related OCs are still commonly diagnosed at advanced stages. In theory, the identification of OCs at early stages (The International Federation of Gynecology and Obstetrics [FIGO] I or II) would considerably improve the rate of optimal cytoreductive surgery and a woman's prognosis, also leading to significant cost savings for the community. Indeed, when OC is detected early enough and ideally in stage I, a woman's prognosis is usually excellent and the 5-year survival rate may exceed 90%.[7] The lack of specific symptoms at early stages means that most cases present late, hence the interest in presymptomatic screening is high.[8,9]

Since 1996, gynecological surveillance of young *BRCA* mutation carriers and carriers who refuse RRSO includes a 6-month evaluation of CA 125, with concomitant TVUS and a clinical gynecological examination by a dedicated specialist at our institution. This study is dedicated to a comprehensive prospective description of these screen-detected (SD) OC cases in *BRCA* mutation carriers adhering to our intense 6 months screening program and to describe the laterality of OC, CA 125 values, TVUS, and computed tomography (CT) in these always challenging diagnoses.

## METHODS

### Study design

A prospective mono-center cohort study was performed in the Modena Family Cancer Clinic of the Azienda Ospedaliero-Universitaria of Modena, between January 2015 and December 2020. In the Emilia Romagna region, women with a family history of breast and/or OC were invited for the first evaluation in a Spoke Center (Spoke and Hub Model).[10] According to the Tyrer-Cuzick evaluation, women at high risk were invited to involve the most representative living individuals of the family affected with breast cancer/OC for *BRCA* genetic testing.[10] Based on their lifetime breast cancer risk, they were offered to participate in a personalized surveillance program. After the first evaluation, some women were sent for a second evaluation in a Hub center. The Modena Family Cancer Clinic is one of four Hub centers, which identifies families with increased hereditary cancer risks. Since 1996, these centers offer genetic counselling and *BRCA* genetic testing to these families.

At our institution, gynecological surveillance of *BRCA* mutation carriers includes a 6-month evaluation of CA 125,[11] with concomitant clinical gynecological examination and TVUS. Gynecological surveillance starts at 25 years of age. Since 2015, all procedures were performed by a dedicated specialist (G.G.) who counsels women over 35 years old about the importance of RRSO, the inefficacy of screening approaches in influencing prognoses and reducing mortality, and premature menopause management after RRSO. Women with altered clinical data, for example, CA 125 level above the threshold (>35 U/mL) in the absence of other possible explanations (endometriosis, adenomyosis, pelvic inflammatory disease, etc) or abnormal findings during TVUS imaging, are investigated by a second level CT scan.

In the final study group, we have included only *BRCA* mutation carriers without previous RRSO who have continuously adhered to our surveillance program between 2015 and 2020 (≥10 times out of a total of 12 visits requested in 6 y).

### Institutional review board approval

Ethical approval for this study was provided by the Ethics Committee Area Vasta Emilia Nord (Reference No. 515). All data were obtained from the electronic database and anonymized before analysis. All participants included in the study gave their written consent for the anonymous use of their clinical data for research purposes.

### Evaluated variables

All CA 125 measurements were performed in the same laboratory at Azienda Ospedaliero-Universitaria of Modena, with the same instrument using electrochemiluminescence technology (Model Cobas E 601, Roche Diagnostics, Basel, Switzerland). All the TVUS examinations for the ovarian and uterine evaluation have been performed by the same instrument (Voluson model E 6, General Electric HealthCare, Milan, Italy) equipped with an endovaginal probe (Model RIC, 5-9 MHz) by the same physician (G.G.). For TVUS categorization risk, we used the International Ovarian Tumor Analysis (IOTA) ADNEX model, which has four clinical variables (age [y], serum CA 125 level [U/mL], family history of ovarian cancer [yes/no], and type of center [oncology center versus other hospitals]), and six ultrasound variables (the maximum diameter of the lesion [mm], the proportion of solid tissue [the maximum diameter of the largest solid component divided by the maximum diameter of the lesion],

 

presence of more than ten cysts [yes/no], number of papillary projections [0, 1, 2, 3, >3], presence of acoustic shadows [yes/no], and presence of ascites [yes/no]).[12]

All CT scans were performed with a volume CT 64-slice scanner and subsequently 128-slice scanner (Lightspeed VCT, GE Medical Systems, Milwaukee, WI) with contrast enhancement administration (Iomeron 300) and bolus-tracking to obtain a multiphase examination (arterial, venous, and excretory phases) after an unenhanced scan. Multiplane image reconstruction was done with a 2.5 mm slice thickness and a 1.5 mm interval.

Histological analysis was performed by a single group of pathologists (Department of Pathology, Azienda Ospedaliera-Universitaria of Modena) for all the surgical samples. The FIGO OC staging system was first published in 1973 and was revised in 1988 in Rio de Janeiro.[13] Recent progress in understanding the origin, pathogenesis, and prognosis of different OC subtypes prompted a newer revision in 2014. The new staging system was reached by consensus of those participating in the FIGO meeting held in Rome, Italy, October 2012 and published in 2014. New categories (IC) were added to stage I tumors (IC1: surgical spill, IC2: capsule rupture before surgery or tumor on ovarian surface, and IC3: malignant cells in the ascites or peritoneal washings).

## RESULTS

### Features of OC cases

We prospectively followed ($n = 191$) *BRCA* mutation carriers (99/191 [51.8%] *BRCA 1*, 91/191 [47.6%] *BRCA 2*, 1/191 [0.5%] *BRCA* combined) (mean age at inclusion: $45.8 \pm 11.9$ years old [range 25-79]) with evaluations each 6 months from January 1, 2015 until December 31, 2020. An RRSO was performed in 58/191 (30.4%) during the study period: one serous OC case was found in these RRSO specimens (stage IA, three cases of serous tubal intraepithelial lesions [5.2%], and four of secretory cell outgrowth [6.9%]).

In the remaining women ($n = 133$), a total of nine cases of SD OC cases have been diagnosed by the same operator (G.G.) during the study period (6.7%). No interval cancers have been detected in the same period in this population.

All of the included OC cases ($n = 9$) remain alive with no relapse detection (censored in February 2021), with a total subsequent follow-up of 35.5 women/y. Two of these women (22.2%, case III and VII, see Table 1) were breast cancer survivors at the inclusion, whereas other 3 (33.3%, case I, II, and IV, see Table 1) were diagnosed with breast cancer in 2018, 2019, and 2020, respectively.

Seven out of 9 patients were *BRCA1* mutation carriers (77.8%), and 2 out of 9 were *BRCA2* mutation carriers (22.2%) (Table 1, ordered by age at diagnosis). The mean age at diagnosis was $57.5 \pm 11.1$ (range 41-79) years (Table 1); the oldest cases were both *BRCA2* mutation carriers. The mean time from the gynecological screening visit to diagnostic laparoscopic surgery was $27.3 \pm 8.0$ days (Table 1). All these laparoscopic surgeries, for the high grade of suspicion in these BRCA mutation carriers, have been performed by a gynecologic oncologist and the definitive cytoreductive surgical debulking treatment was performed immediately after the intraoperative diagnosis of OC after conversion to laparotomy.

The histologic types of OC found by the pathologist were mainly high-grade serous (7/9, 77.8%) and endometrioid (2/9, 22.2%). Concomitant endometrial hyperplasia was found in 3/9 (33.3%) cases. The mean lesion size was $3.9 \pm 2.4$ cm (range 0.7-6.8 cm). The FIGO stage at diagnosis was I or II in 8/9 of cases (88.9%), whereas in one case the stage at diagnosis was IIIA2. Positive retroperitoneal lymph nodes have not been found in any woman at surgical staging. The cancer was bilateral at diagnosis in 6/7 (85.7%) *BRCA1*, whereas unilateral in 2/2 (100%) *BRCA2*.

The results for the affected lateral site (left ovary and/or tube, right ovary, and/or tube) are reported in Table 2 for all

**TABLE 1.** *Features of ovarian/primary fallopian tube carcinoma in BRCA mutation carriers included in the study (ordered by age at diagnosis)*

| Patient # | Age | *BRCA* | Time to surgery (d) | Histology | Added endometrial findings | Mean lesion size at histology (cm) | FIGO stage | Uni or bilateral | Time of diagnosis during follow-up/CA 125 levels/US findings/type of case |
|---|---|---|---|---|---|---|---|---|---|
| I | 41 | 1 | 19 | Endometrioid | Hyperplasia | 6 | IIA | Bilateral | After 36 mo/CA 125 elevated/US abnormal findings/Evident case |
| II | 47 | 1 | 27 | Serous | | 2.8 | IC3 | Bilateral | After 28 mo/CA 125 normal/US suspicious findings/Possible case |
| III | 49 | 1 | 19 | Serous | | 1.9 | IIA | Bilateral | After 12 mo/CA 125 elevated/US suspicious findings /Possible case |
| IV | 53 | 1 | 26 | Serous | | 5 | IIB | Bilateral | After 12 mo/CA 125 elevated/US abnormal findings/Evident case |
| V | 57 | 1 | 28 | Serous | | 1.2 | IC2 | Unilateral | After 18 mo/CA 125 elevated/US suspicious findings/Possible case |
| VI | 59 | 1 | 26 | Serous | Hyperplasia | 0.7 | IIIA2 | Bilateral | After 18 mo/CA 125 elevated/US normal findings/Hidden case |
| VII | 60 | 1 | 41 | Endometrioid, 30% undifferentiated | Hyperplasia | 6.8 | IIA | Bilateral | After 30 mo/CA 125 normal/US suspicious findings/Possible case |
| VIII | 62 | 2 | 22 | Serous | | 6 | IIB | Unilateral | After 24 mo/CA 125 normal/US suspicious/Possible case |
| IX | 79 | 2 | 37 | Serous | | 4 | IIB | Unilateral | After 18 mo/CA 125 and US abnormal findings/Evident case |

CA, cancer antigen.

**TABLE 2.** *Affected site (left ovary and/or tube, right ovary and/or tube) for all the histological specimens analysed in the 9 patients included (X: affected) (cases ordered by age at diagnosis, see Table 1)*

| | Case I | Case II | Case III | Case IV | Case V | Case VI | Case VII | Case VIII | Case IX |
|---|---|---|---|---|---|---|---|---|---|
| Right ovary | X | X | X | X | | X | X | | |
| Right tube | | X | | | | X | | | |
| Left tube | X | | X | X | | | | X | X |
| Left ovary | X | X | X | X | X | X | X | X | X |

the specimens analyzed: we have noted a left predominance. No lesions (0%) involved only the tubes. In particular, in all specimens, the left ovary was always involved in 9/9 (100%), whereas the right ovary was involved in 6/9 (66.7%) of the cases. Similarly, the left tube was more frequently involved than the right one (5/9 [55.6%] vs 2/9 [22.2%] of the cases) (Table 2).

### CA 125 at diagnosis

The mean value of CA 125 at diagnosis was 194.3 ± 335.3 (range 20.4-877.3) U/mL. Only 3/9 (33.3%) cases were diagnosed with a CA 125 level lower than our diagnostic threshold (35 U/mL) (Fig. 1). Despite our intense 6-month follow-up, two participants were found with CA 125 levels above 600 U/mL (case I: 877.3 U/mL [6 mo before 7.8 U/mL) and case IV: 650 U/mL (6 mo before: 10.7 U/mL)]. The trend of this biomarker of the other seven cases (up to 24 months before and at diagnosis) is reported in Figure 1.

### *Transvaginal ultrasound findings*

The IOTA ADNEX model has not been helpful in our clinical practice for this screening population. Only 3/9 (33.3%) patients were eligible for IOTA ADNEX model because they presented with at least one adnexal mass (ovarian, para-ovarian, or tubal). In essence, these cases scored more than 75% for risk of malignancy according to IOTA ADNEX Model, but they were all women with high CA 125 levels and of advanced age (case I, IV, IX).

The other 6/9 (66.7%) women were not eligible for IOTA ADNEX model because they did not present with an adnexal mass at the first evaluation. Case VII presented a solid left ovary (measures: 44×31×25 mm) with four cortical small anechoic cysts of 17 mm, 17 mm, 16 mm, and 13 mm with Doppler color score 1 (Fig. 2). This score was associated with a postmenopausal asymptomatic endometrial thickening (histological diagnosis: endometrial hyperplasia without atypia), not present six months before (Fig. 2). Case III had a right ovary (measures: 47×29×35 mm) with a solid lesion of 13 mm with a papillation of 4 mm (color score 1) (Fig. 3). The left ovary seemed normal for age (Fig. 3). A similar situation was found in case II, with a solid lesion of 29×24 mm with Doppler color score 1 in the right ovary (Fig. 4) and an apparently normal left ovary (Fig. 4).

Two other cases, V and VIII, presented with a solid circular not vascularized mass near the left ovary of 10 mm and 28 mm, respectively (''hypoechoic circular mass'', Fig. 5). All these women (III, V, VII, and VIII) were re-evaluated after 2-3 weeks during which the dimensions of the mass were noted to increase (Fig. 2). The majority of the lesions (7/9, 77.8%) were noted on the left side.

We have not found previously recognized US signs for ovarian diagnostics in case VI; indeed, the ovaries had normal morphology for menopausal status (Fig. 6A, B). In this case, the only found sign was a hyperechoic parenchymal spot of 3 mm (Fig. 6B) in the left ovary, that we named ''small hyperechoic foci.'' A similar sign was also found in case II (Fig. 4).

For these reasons, the TVUS signs for early-stage SD OC in *BRCA* mutation carriers that we have documented are:

- The increased solid pattern of the ovary with peripheral cortical small anechoic cysts (Fig. 2)

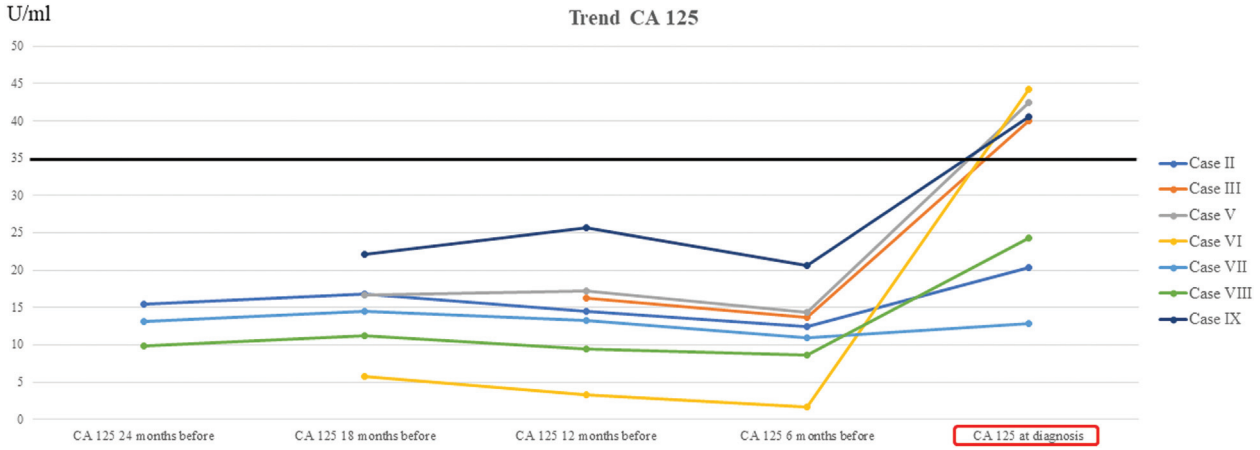


**FIG. 1.** Semestral trend of CA 125 of seven cases (#II, III, V, VI, VII, VIII, IX) up to 24 months before and at diagnosis. CA, cancer antigen.

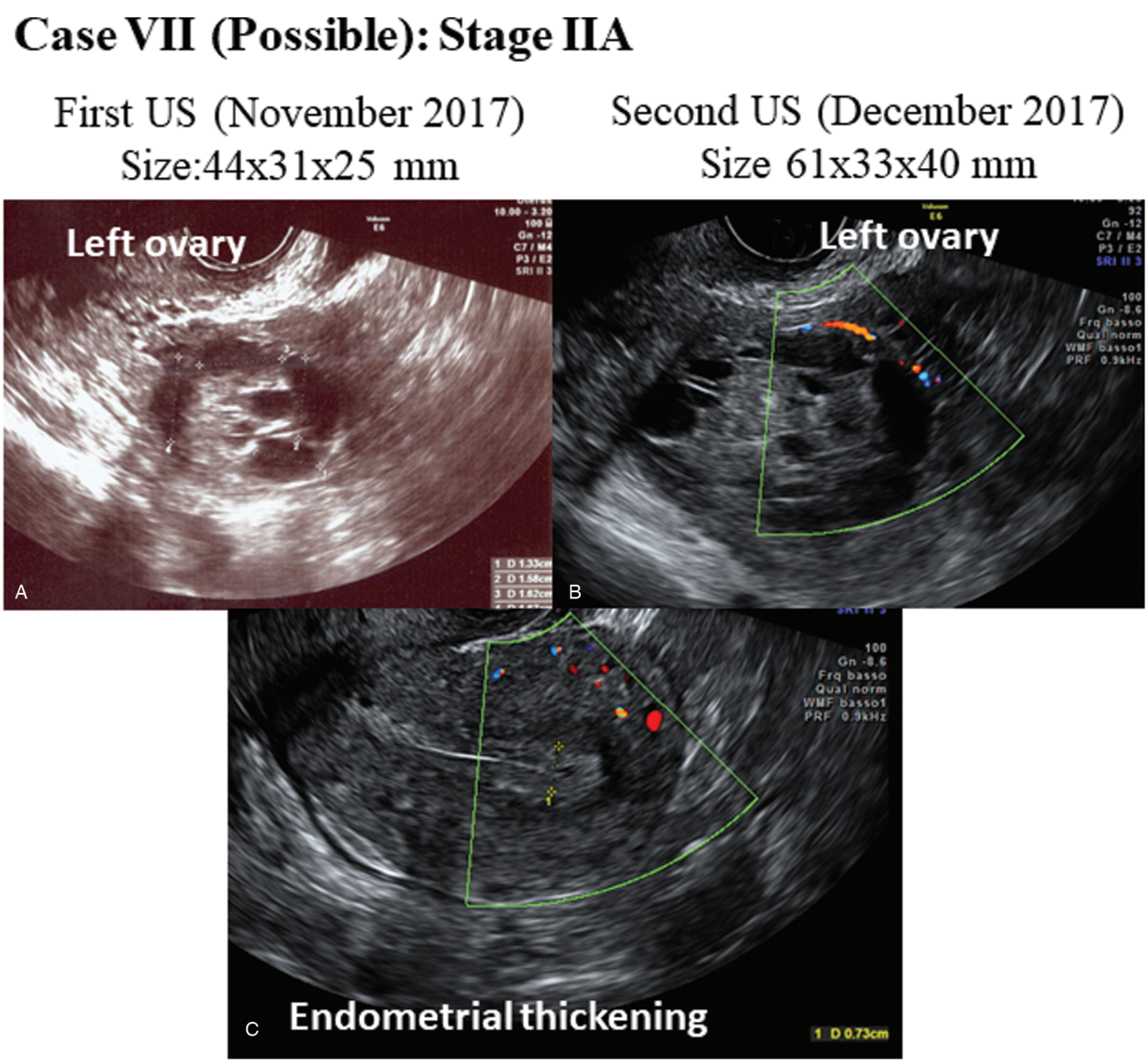


**FIG. 2.** Case VII (possible case): Stage IIA. TVUS findings first US **(A)** and second US **(B)** evolutive pattern from November to December 2017. **(C)** asymptomatic endometrial thickening associated (7 mm, histology: endometrial hyperplasia without atypia). TVUS, transvaginal ultrasound.

- Solid circular mass near the ovary (''hypoechoic circular mass'') (Fig. 5)
- Intraparenchymal ''small hyperechoic foci'' (Figs. 4 and 6B)

We want to propose additional TVUS suggestions for early diagnosis:
- Evolutive pattern (in 2-3 weeks) (Fig. 2)
- Associated endometrial thickening (Fig. 2)

### Computed tomography

An independent radiologist (F.F.) reanalyzed images from all CT scans, giving independent scores of 0 (no signs of disease), 1 (possible signs of disease), and 2 (a clear sign of disease). In one case (VI) (1/9, 11.1%), no signs of disease were detected, as happened for TVUS (Fig. 6C, D): ovaries were normal for morphology (size and density) and location. In all the other cases (7/9, 77.8%) lesions were found on the left side and in some cases (3/9, 33.3%) minor alterations in morphology and density were found on the right side. In particular, in 5/9 (55.6%), the assigned score was 1 (cases II, III, V, VII, and VIII) (Fig. 3), whereas in the other 3/9 (33.3%) the score was 2 (cases I, IV, IX) (Fig. 7B-D). When the lesion was found, the pattern was predominantly solid in 7/8 cases (87.5%), except in case III, with higher density both at basal and contrast-enhanced scans (relative to the increased enhancement of the solid component).

No calcifications, significant alteration of ovary boundaries, lymph-nodes, or pelvic fluid were found in any woman.

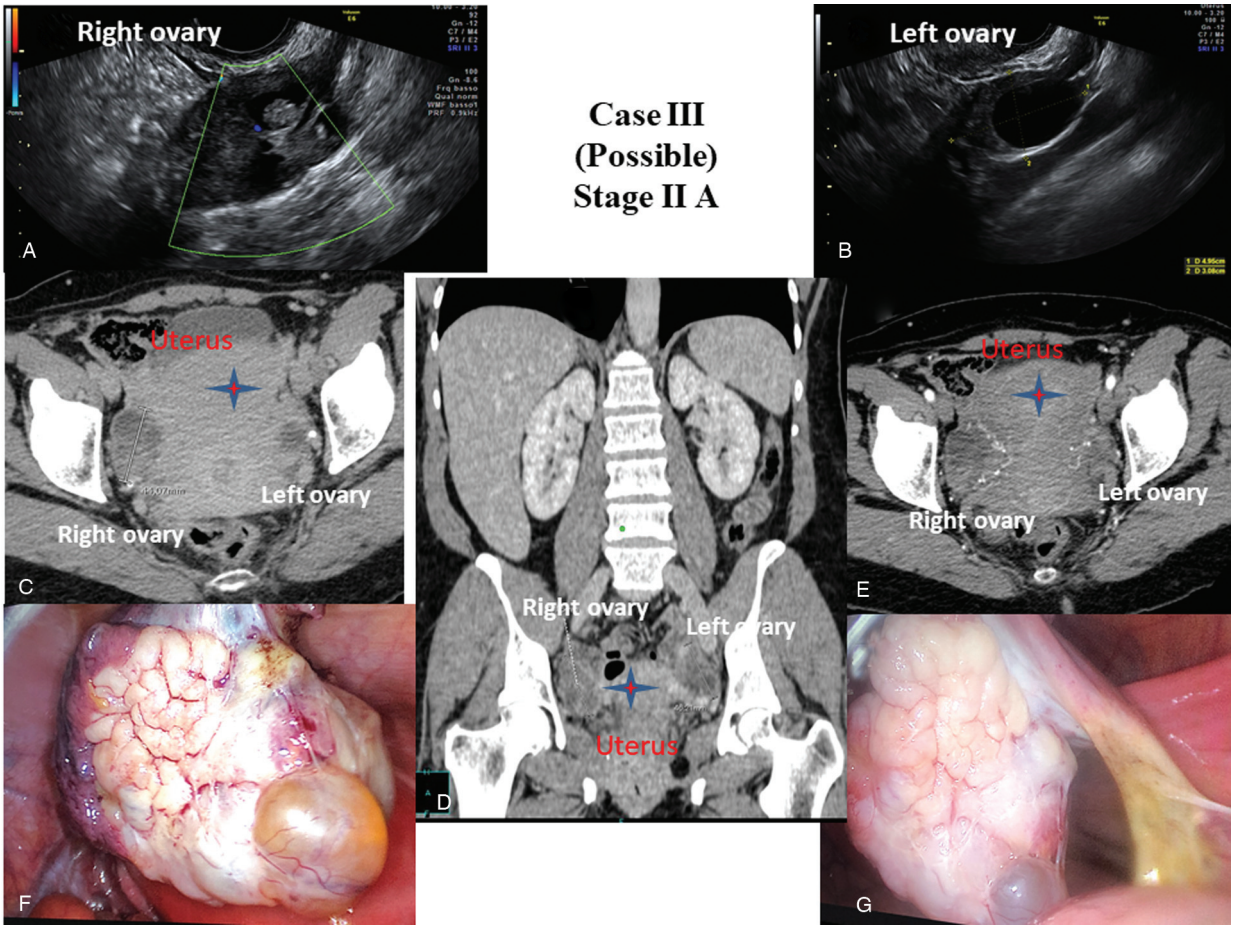


**FIG. 3.** Case III (possible case): Stage IIA. **(A)** TVUS right ovary, **(B)** TVUS left ovary, **(C-E)** CT images, laparoscopic findings of right **(F)** and left **(G)** ovary. TVUS, transvaginal ultrasound.

## Explanation

### *Evident cases (Fig. 7)*

These cases are evident when TVUS and CT clearly suggest the disease. CT images show a dislocated left ovary with increased solid component and loss of typical morphology. We found this pattern in 3/9 cases (33.3%) (I, IV, and IX). CA 125 sensitivity was 100% in this group.

### *Possible cases (imaging with suspected signs) (Figs. 2-5)*

We found this pattern in five cases (55.6%) (patient II, III, V, VII, and VIII). TVUS (with our proposed early signs) and CT (risk 1) are in general accordance. In 3 of them (60%) (case II, VI, and VII), CA 125 was negative, and one of them (case VII) (20%) presented with endometrial hyperplasia (Figs. 2-5).


**FIG. 4.** Case II (possible case): Stage IC3. **(A)** TVUS right ovary, **(B)** TVUS right ovary with small hyperechoic foci, **(C)** TVUS left ovary. TVUS, transvaginal ultrasound.

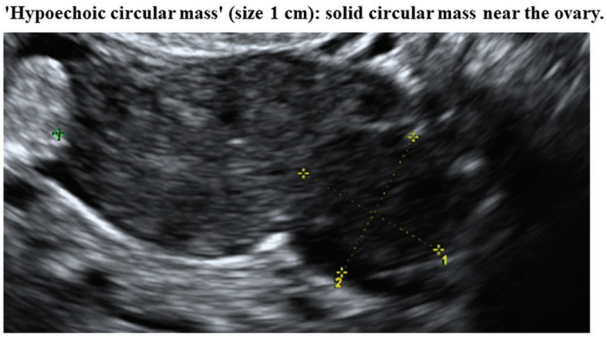


**FIG. 5.** Case (possible case). ''Hypoechoic circular mass'' (size 1 cm): solid circular mass near the left ovary.

### *Hidden cases (no imaging signs) (Fig. 6)*

We found this pattern in 1/9 (11.1%) case (VI), a *BRCA* 1 mutation carrier, unfortunately with the smallest local lesion (0.7 cm) but the highest stage at diagnosis (stage IIIA2). CT images show normal ovaries at both sides with no signs of possible disease. The CA 125 level was positive (44.2 U/mL), and we found a concomitant asymptomatic endometrial hyperplasia.

## DISCUSSION

### Principal findings

Our research opens many new issues about early diagnosis of OC in *BRCA* mutation carriers adhering to a 6-month screening. In particular, cancers occur mainly in *BRCA1* mutation carriers, at a younger age in comparison to *BRCA2*. The negativity of CA 125 should not stop us from further investigation, because in early stages, CA 125 may not rise in about 33.3% of the cases. All the cancers found involved the ovaries already in the early stages, questioning the role of prophylactic salpingectomy.

Considering imaging techniques (TVUS and CT), we have described three new possible scenarios:

1) Evident cases;
2) Possible cases, in which TVUS and CT are in general accordance (for these cases we have documented TVUS based early signs); and
3) Hidden cases, the smallest lesion (in our case with a size of only 7 mm) but the highest tumor stage (IIIA2), associated with CA 125: 44.2 U/mL and endometrial hyperplasia. Therefore, despite the advancement of the technique, there are still some OC cases that, unfortunately, can escape our diagnostic imaging.

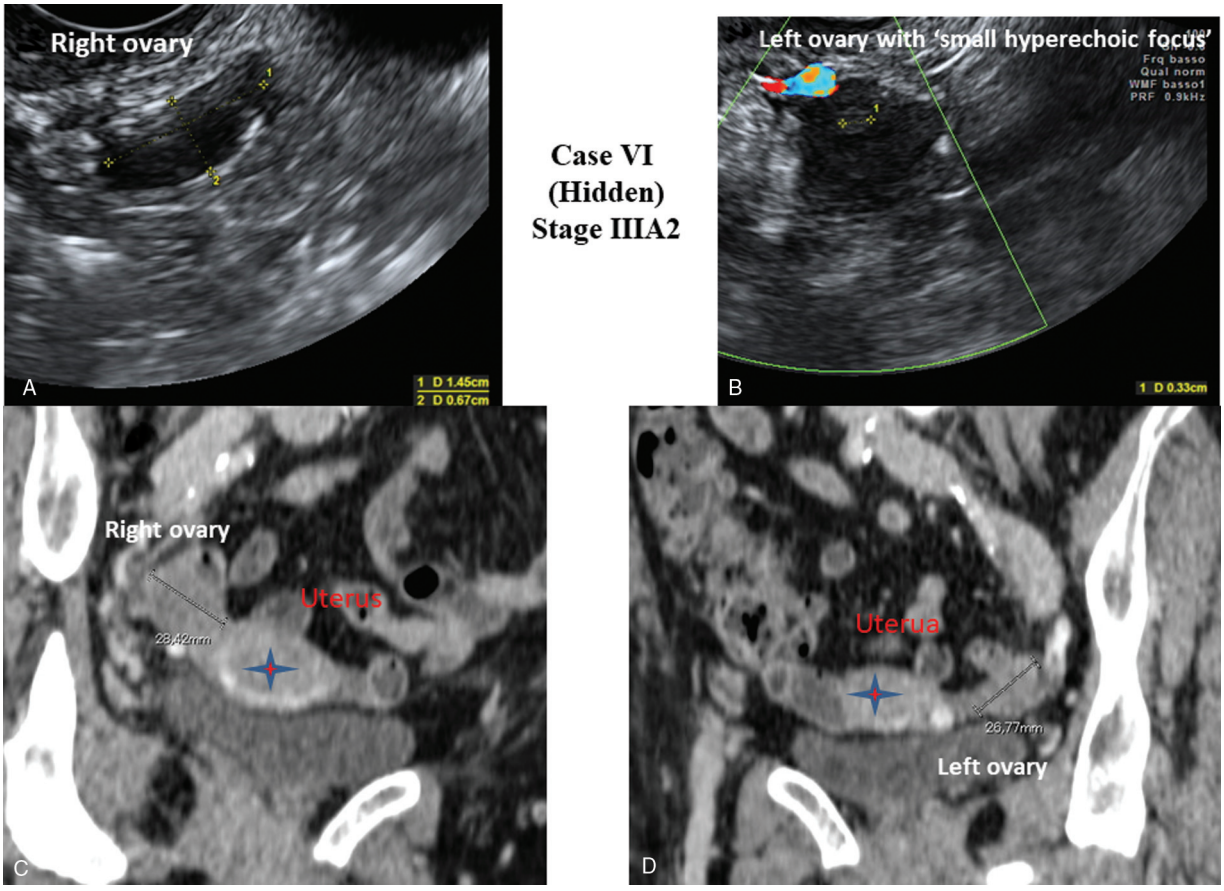


**FIG. 6.** Case VI (hidden case): Stage IIIA2. **(A)** TVUS right ovary, **(B)** TVUS left ovary with the intraparenchymal ''small hyperechoic foci'' of 3.3 mm, **(C)** CT right ovary, **(D)** CT left ovary. CT, computed tomography; TVUS, transvaginal ultrasound.

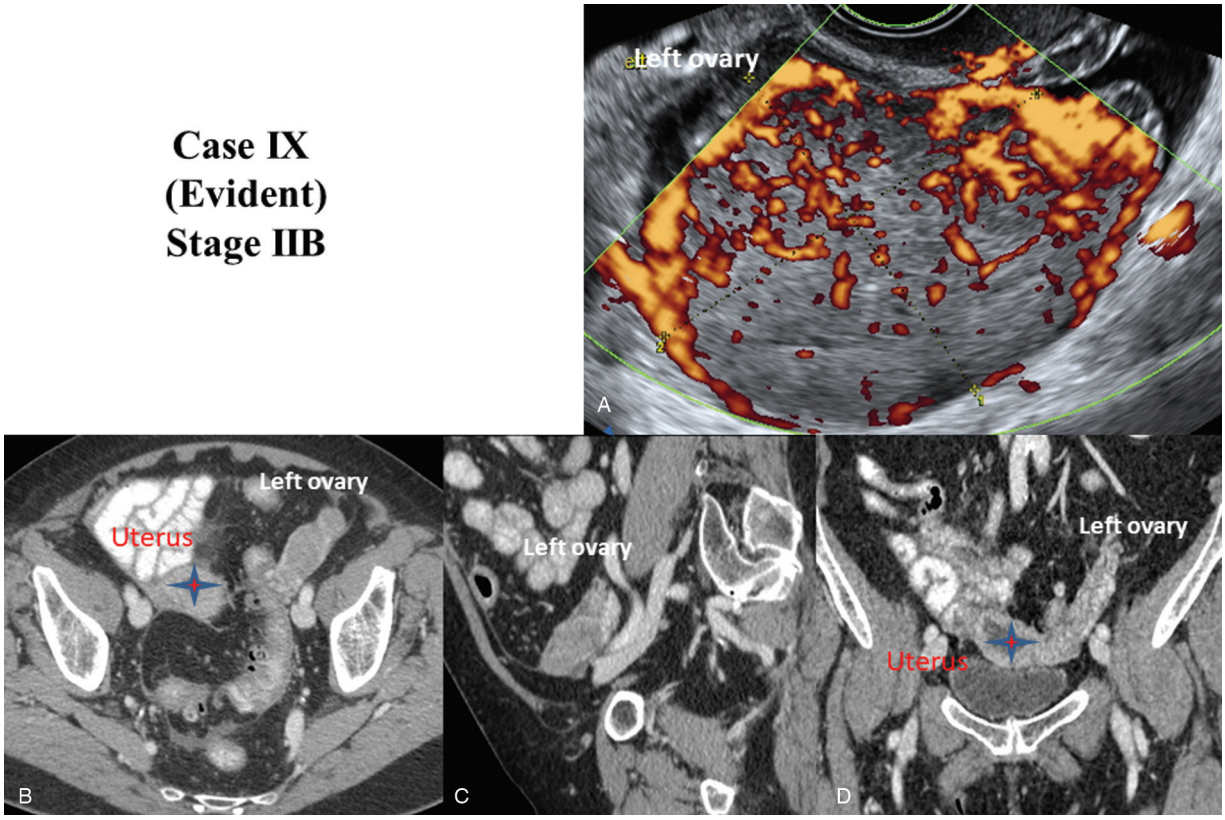


**FIG. 7.** Case IX (evident case): Stage IIB. **(A)** TVUS: solid cyst with high vascularization (color score 4) of 60 mm of the left ovary. **(B-D)** CT images. CT, computed tomography; TVUS, transvaginal ultrasound.

**Results in the context of what is known**

Most OCs that occur in *BRCA* women are high-grade serous cancers, and these are infrequently SD at an early stage. The clinic-pathologic features of SD OCs suggest that screening may not reduce mortality in these women.[14] The majority of the published prospective screening studies did not show a reduction of the OC mortality in the general population[15] nor the potential to diagnose OC at an enough early stage in high-risk women.[16-18] Surveillance by TVUS and serum CA 125 measurement in women at increased familial risk of OC was judged ineffective in detecting OCs at a sufficiently early stage to influence prognosis; it is also not a reasonable substitute for RRSO. However, screening more frequently than annually with prompt surgical staging and treatment (in our study after a mean of 27.3 d) seems to offer a better chance of early-stage detection.[19] Thus, for young women or for those who refuse RRSO, concurrent TVUS and CA 125 determination every six months has been proposed. In this view, our data, based on the same dedicated specialist using a modern TVUS instrument over the last 6 years, are more reassuring, and they confirm our previous report.[6] No interval OCs were detected. The nine SD OCs are all in the early stages (I or II) and are still OC-free today except for one case (diagnosed at stage III A2) that, due to its microscopic spread, it would never have been identifiable, except for the rise in CA 125 and the concomitant endometrial hyperplasia (Hidden Case). For these reasons, for young women carrying *BRCA* mutations and declining RRSO, TVUS using up to date equipment and read by a physician with expertise in gynecologic imaging along with CA 125 assessment performed every 6 months could improve outcomes.

Our data indicate that the ovary may be the preferred site for cancer growth in *BRCA*1/2 mutation carriers, especially the left ovary. Although early-stage cancers in *BRCA* mutation carriers are rarely reported in detail, our observation is also confirmed in other previous reports,[20,21] with cancers found mainly in the ovaries of *BRCA*1 mutation carriers. These findings imply that the ovarian microenvironment provides a permissive environment for an early step of carcinogenesis: this idea has implications for current clinical management strategies. In recent years, much interest has gathered behind the idea that the fallopian tube is the singular site of origin for OC, mainly from the data of RRSO specimens in *BRCA* women.[22] A bilateral salpingectomy per se has recently been put forward as a temporary risk-reducing surgical procedure for *BRCA* mutation carriers.[23]

However, caution is needed with translating the tubal hypothesis into clinical practice before it is proven.[24] Besides, even if fallopian tubes are removed, initiated cells may spread to the ovary at a very early point.[20,22]

The preferred left side has never been reported for OC origin in *BRCA* mutation carriers, herein verified for both ovary and tube locations. It has been reported that

 

endometrioid OC can arise more frequently on the left than the right adnexa,[25] probably due to the link with endometriomas, that are more frequently diagnosed on the left side.[26] A left lateral predisposition for serous histotype has never been previously described either in the general population or in *BRCA* mutation carriers. If confirmed, it is an important issue for early diagnosis.

### Clinical and research implications

Macroscopical features of OC usually include multiple loculations and vascular solid papillary tissue with the cyst cavity. The solid part is white and contains extensive necrosis and hemorrhage.[27] The IOTA study aimed to develop diagnostic TVUS algorithms to assist clinicians in characterizing adnexal pathology, irrespective of their level of expertise.[12] However, this tool is largely useless in our screening program because patients were eligible for IOTA if they presented with at least one adnexal mass (ovarian, para-ovarian, or tubal), whereas in our cases the majority of cases (6/9, 66.6%) did not have an adnexal mass at first evaluation. Indeed, this tool has been validated only in a nonscreening population, and not in high-risk women similar to our population.[28] In the previous studies, the vast majority of serous OC was defined as multilocular-solid or solid masses, with papillary projections in only 7% of cases, and a high vascularization in more than 95% of the case.[29] However, these features were not widely applicable to our screening population. For these reasons, we have documented new TVUS-based early signs, as the increased solid pattern of the ovary with peripheral cortical small cysts, the presence of a solid circular mass near the ovary (''hypoechoic circular mass''), and the intraparenchymal ''small hyperechoic foci.'' They have to be validated in future studies on larger *BRCA* mutation carrier populations. Additional suggestions have also been proposed: the importance to think to the left side, the associated endometrial thickening, and the evolutive pattern (in 2-3 weeks). In the case of equivocal imaging findings, short-term follow-up in several weeks seems appropriate. Serial TVUS can be a longitudinal biomarker, which permits the lesions that are destined to resolve over time to undergo conservative management versus those with aggressive growth patterns.[30]

### Strengths and limitations

The number of cancer cases included in this study is low, 9 in 6 years of screening: however, we did not find many published studies reporting this number of SD cancers in *BRCA* mutation carriers enrolled in a screening program. There is only 1 case reported in Oei et al[17] and van der Velde et al[18] 3 cases in Olivier et al,[16] and at most 13 cases in Rosenthal et al.[19] Considering a reported OC incidence of 10.5 cases per 1,000 person-years in *BRCA* mutation carriers,[6] this relatively low number ($n = 9$) has to be expected for about 200 women followed for 6 years (also considering the concomitant RRSO rate). Moreover, we have not found any previously published papers that clearly describe these cases from the clinical point of view. Therefore, all our results must be considered absolutely preliminary before other independent studies will show any overlap.

## CONCLUSIONS

The screen detection of OCs in *BRCA* mutation carriers adhering to a follow-up program represents a challenge even today, where the different diagnostic tools must integrate to ensure an early diagnosis. Further multicenter studies are needed to evaluate how new diagnostic tools can help us overcome this challenge.

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