The reduction of CA 125 serum levels in BRCA 1/2 mutation carriers after risk-reducing salpingo-oophorectomy is only partially associated with surgery: a prospective cohort, other biomarker controlled, study

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Objectives **A significant reduction in CA 125 postoperative serum levels was observed after risk-reducing salpingo-oophorectomy (RRSO) in BRCA mutation carriers. In contrast to previous studies, where control groups were absent, we conducted a prospective study including also a screening only group (RSSO refusal) and a group having previously undergone RRSO.**
Methods **Consecutive BRCA1 and BRCA2 mutation carriers, not hysterectomised, >35 years old and with completed childbearing, were recruited. Some women had previously undergone RRSO (previous RRSO group). The others, who had either chosen RRSO (actual RRSO group) or screening only (screening only group), were enrolled (patient-preference trial). A prospective evaluation (basal and 6-month) of CA 125 and CEA (control biomarker) was performed.**
Results **The study consisted of 116 women, 44.8% BRCA1 and 55.2% BRCA2 mutation carriers (n = 25 in the previous RRSO group, n = 29 in the actual RRSO group, n = 62 in the screening only group). For all subjects, we observed a 6-month decrease in CA 125 (−7.8%, *P* = 0.003), which was significantly linked only to endometriosis history (odds ratio 1.4; 95% confidence interval 1.1–1.8; *P* = 0.002). Between different groups, we recorded a non-significantly different decrease in CA 125. CEA showed a 6 months significant increase (+15.4%, *P* < 0.0001), which was similar between groups.**
Conclusion **The decrease in CA 125 in BRCA mutation carriers after RRSO was only partially associated with surgery, depending also on a physiological decline: this is extremely important in their longitudinal monitoring for the prevention of ovarian cancer.** ***European Journal of Cancer Prevention*** **29: 350–356**

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Introduction

The lifetime risk of ovarian cancer (OC) by the age of 70 in women with a confirmed breast related cancer antigens (BRCA) mutation is very high, approximately 40% of BRCA1 and 18% of BRCA2 mutation carriers (Antoniou *et al.*, 2003). Currently, there is no screening regimen effective in reducing OC mortality in high-risk populations, in particular for BRCA mutation carriers. Risk-reducing salpingo-oophorectomy (RRSO) for women older than 35, in preventing OC or fallopian tube cancer and detecting occult neoplasia, is recommended as the only proven mortality reducing intervention (Toss *et al.*, 2019).

However, the National Comprehensive Cancer Network (NCCN) has advised multimodal screening, including Cancer Antigen 125 [or Carbohydrate Antigen 125 (CA 125)] assessment, and transvaginal ultrasound (TVUS) for OC prevention in BRCA carriers who refuse RRSO (National Comprehensive Cancer Network, 2019). The NCCN emphasises that this approach does not detect tumours at sufficiently early stages to influence prognosis, thereby reducing mortality (National Comprehensive Cancer Network, 2019). 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 (Cortesi *et al.*, 2017). CA 125, first described by Bast *et al.* (1981), has long been considered an accurate serum biomarker for OC. However, its metabolic elevation can be non-specific. For example, peritoneal irritation can increase CA 125 levels. For this reason, endometriosis is a common cause of CA 125 elevation in premenopausal women (Mol *et al.*, 1998), in particular those with ovarian endometriomas

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(Kitawaki *et al.*, 2005). Other causes of CA 125 elevation in premenopause could be pelvic inflammatory disease, in particular in the presence of pelvic abscesses, the menstrual phase of the cycle and during the first trimester of pregnancy (Granato *et al.*, 2015).

The CA 125 antigen can be detected in derivatives of coelomic epithelium, the endometrium, the uterine cervix and fallopian tubes. With respect to female organ influence on CA 125 levels, hysterectomies were found to influence these levels (Pauler *et al.*, 2001): women, after uterine removal, present lower CA 125 levels. However, the role of the ovaries and fallopian tubes in CA 125 metabolism is unclear: ovary removal may cause changes in CA 125 levels and therefore, there is a requirement for new reference serum levels which may improve the care for BRCA patients after RRSO. Unilateral oophorectomy is not linked to CA 125 concentrations (Pauler *et al.*, 2001). However, for bilateral RRSO, significant reductions in CA 125 postoperative levels were observed in the literature, specifically in two retrospective studies: in Chen *et al.* (2014), the reductions were evident only in BRCA1 but not in BRCA2 mutation carriers, while in van Altena *et al.* (2011), a relative decrease of 18% was recorded for CA 125 levels after RRSO in BRCA1 and BRCA2 mutation carriers. Curiously, for both retrospective studies, a control group – that is, those not having undergone RRSO – was absent. For this reason, the aim of this study was to prospectively evaluate CA 125 trends in relation to RRSO, in comparison to a screening only group (refused RRSO), and a group having previously undergone RRSO. We used the carcinoembryonic antigen (CEA) as a control biomarker.

Methods

Study design

A prospective mono-centre cohort study was performed in the Modena Family Cancer Clinic (MFCC) of the Azienda Ospedaliero-Universitaria of Modena, between January 2017 and August 2019. In the Emilia Romagna region, women with a family history of breast cancer or OC or both were invited for a first evaluation in one of 13 Spoke Centres (Spoke and Hub Model). On the basis of their lifetime breast cancer risk, they were offered participation in a personalised surveillance program. After the first evaluation, some women were sent for a second evaluation in a Hub Centre. The MFCC is one of four Hub centres, which identifies families with increased hereditary cancer risks. Since 1996, these centres have offered BRCA genetic testing to these families.

At our Institution, gynaecological surveillance of BRCA mutation carriers includes a 6-monthly evaluation of CA 125, with concomitant TVUS and clinical exams. During these procedures, a dedicated specialist (G.G.) counsels women over 35 years old on the importance of RRSO, the inefficacy of screening approaches in influencing prognoses, and reducing mortality and premature menopause management after RRSO. Patients eligible for the study were enrolled during these preliminary visits and were asked to sign the informed consent sheets, with a prospective follow-up visit at 6 months. We added CEA as a control biomarker as we commonly use it in our oncology clinic.

Research methods

All consecutive BRCA1 and BRCA2 confirmed mutation carriers, non-hysterectomised women over 35 years old, with completed childbearing and not using hormonal contraceptives were recruited. Exclusion criteria involved a previous history of OC, or malignant uterine lesions, or CA 125 levels in the upper limits (>35 U/ml) at first visit.

Some women had just undergone RRSO in the past (previous RRSO group) in our or other Institutions. The remaining were similarly educated on the possible risks and benefits of RRSO, or the sole screening follow-up modality in relation to the specific age by the same physician (G.G.). Women who spontaneously chose either RRSO (actual RRSO group) or screening (screening only group) were enrolled into the study. Considering the non-random allocation to study groups, this prospective study was considered a patient-preference trial.

Ethical approval and consent

Ethical approval for this study was provided by the Ethics Committee Area Vasta Emilia Nord (Reference No. 515, 2019). A specific informed consent was obtained from each woman for the use of her sensitive data in research analysis.

Evaluated variables

All CA 125 and CEA 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).

Oncological and gynaecological histories were obtained from subjects in the first visit; these included, parity, menopausal status (based on amenorrhoea longer than 12 months), breast cancer history and eventual hormone treatments for breast cancer use (gonadotropin realising hormone analogues, tamoxifen or aromatase inhibitors) and history of endometriosis (previous surgeries with a histological diagnosis).

Study endpoints

The primary outcome was:

(1) to evaluate CA 125 trends in BRCA1 or 2 females prior to and after a 6-month follow-up in three different groups (actual RRSO, previous RRSO and screening only group).

The secondary outcomes were:

(1) to evaluate CEA trends in BRCA1 or 2 women prior to and after a 6 month follow-up in three different groups (actual RRSO, previous RRSO and screening only group);
(2) to evaluate variations in CA 125 and CEA levels in relation to other confounding factors such as BRCA type, parity, menopausal status at visit 1, previous breast cancer status, hormonal treatments for breast cancer and endometriosis history.

Statistical analysis

Statistical analyses were performed using the statistical package StatView (version 5.01.98; SAS Institute Inc, Cary, North Carolina, USA). Within-group and intragroup comparisons were performed using *t*-tests for paired data and Wilcoxon signed-rank tests for normal and non-normal data distributions, respectively. Possible features related to biomarker (CA 125 and CEA) trends were evaluated using independent factors defined by logistic regression analysis for categorical variables (dependent variable: biomarker variation between visit 1 and 2). For multivariate analysis, categorical data were entered as dummy variables. BRCA type, nulliparity yes/no, previous C section yes/no, actual menopausal status yes/no, previous breast cancer diagnosis yes/no and history of endometriosis yes/no were entered as single dummy variables.

For all analyses, the null hypothesis was rejected at a two-tailed *P*-value <0.05. Results were expressed as the mean ± standard error if parametric or the median if the distribution was not normal.

Results

Patients and groups

In total, 125 consecutive women were recruited. Of these women, eight were lost to follow-up as they did not attend for the second evaluation at 6 months (n = 4 breast cancer first diagnosis/recurrence, n = 4 withdrew consent). Another woman was included in the first visit, in the actual RRSO group, but was excluded for a diagnosis of inoperative serous tubal intraepithelial carcinoma during RRSO.

The remaining women (n = 116), with the following BRCA characteristics; 52 (44.8%) BRCA1 and 64 (55.2%) BRCA2 mutations, were included in the final study group. Specifically, n = 25 subjects (21.6%) had just undergone RRSO (previous RRSO group), on average 3.9 ± 3.2 years before the first study visit. Twenty-nine women (25.0%) decided to undergo RRSO between visit 1 and 2 (actual RRSO group), on average 0.2 ± 0.1 years after visit 1, while the remaining 62 (53.4%) women adhered to the screening program (screening only group). We did not observe altered pathological results in the women from the actual RRSO group, nor any endometriosis cases.

Basal features between the three groups were similar (Table 1), if age at RRSO was excluded (at a younger age in the previous RRSO group in comparison to actual RRSO group, $P = 0.02$).

CA 125 levels and trends

Basal CA 125 levels were lower in postmenopausal women (9.2 vs. 11.5 U/ml, $P = 0.04$) but not dependent on BRCA type, parity, previous C section, history of endometriosis, previous breast cancer diagnosis and actual/past use of hormone modulation for breast cancer ($P > 0.05$).

In the entire group (n = 116), we observed a significant decrease in CA 125 levels (median from 10.3 to 9.5 U/ml, –7.8%, $P = 0.003$) (Fig. 1), over the 6 months.

For multivariate analysis, including BRCA type, nulliparity yes/no, previous C section yes/no, actual menopausal status yes/no, previous breast cancer diagnosis yes/no and history of endometriosis yes/no, the CA 125 decrease was significantly linked only to endometriosis history [odds ratio (OR) 1.4; 95% confidence interval (CI) 1.1–1.8; $P = 0.002$] (Table 2).

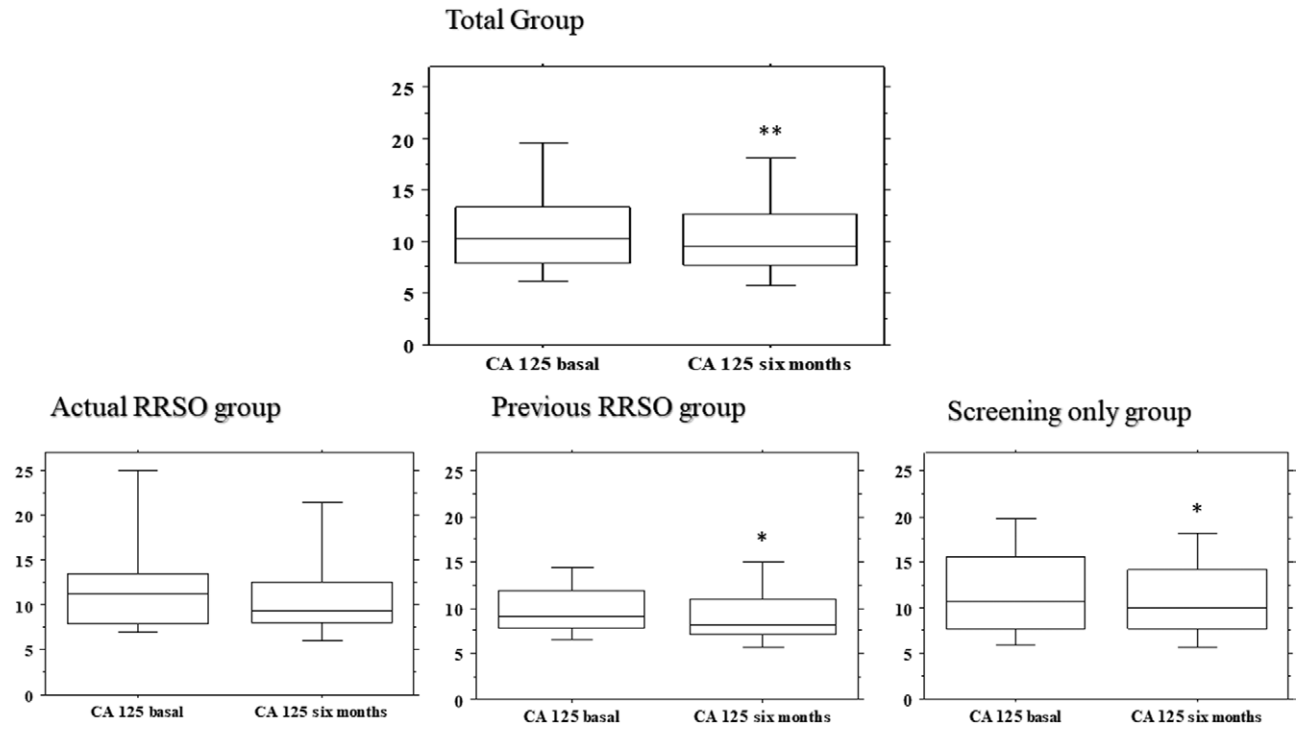
For the three groups (actual RRSO, previous RRSO and screening only group), we recorded a non-significantly different decrease in CA 125 levels across all groups [actual RRSO: –1.6 U/ml (–17.4%), previous RRSO: –1.0 U/ml (–10.8%), screening only group: –0.8 U/ml (–7.3%), $P = 0.46$ between groups] (Fig. 1).

Table 1 Basal features of study groups [previous risk-reducing salpingo-oophorectomy group (n = 25), actual risk-reducing salpingo-oophorectomy group (n = 29), screening only group (n = 62)]

	Previous RRSO group (n = 25)	Actual RRSO group (n = 29)	Screening only group (n = 62)	*P* value
Age (years)	53.1 ± 1.5	53.4 ± 1.3	53.2 ± 1.3	0.99
BRCA1 (%)	14 (56.0%)	15 (51.7%)	23 (37.1%)	0.19
Age at RRSO (years)	49.2 ± 1.5	53.8 ± 1.3	–	0.02
Parity (n)	1.3 ± 0.1	1.7 ± 0.2	1.5 ± 0.1	0.37
Previous C sections (%)	7 (28.0%)	7 (24.1%)	14 (22.6%)	0.75
History of endometriosis (n)	1 (4%)	2 (7%)	2 (3.2%)	0.72
Breast cancer survivors (n)	14 (56.0%)	16 (55.2%)	37 (59.7%)	0.90
Median CA 125 basal value (U/ml)	9.2 (5.3–27.0)	10.9 (5.6–30.7)	10.9 (1.9–31.7)	0.39
Median CEA basal value (ng/ml)	1.2 (0.6–3.0)	1.5 (0.4–5.2)	1.3 (0.3–5.7)	0.49

BRCA, breast related cancer antigens 1; RRSO, risk-reducing salpingo-oophorectomy.

Fig. 1



Box plots with medians of serum CA 125 levels before and after 6 months follow up in the total group and in the different study groups [actual RRSO group (n = 29), previous RRSO group (n = 25), screening only group (n = 62)]. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. RRSO, risk-reducing salpingo-oophorectomy.

Table 2 Multivariate logistic regression

	OR of CA 125 decrease	OR of CEA increase
BRCA type (1 vs. 2)	NS	2.1 (1.1–7.2), $P = 0.02$
Nulliparity (yes vs. no)	NS	2.7 (1.7–27.4), $P = 0.006$
Previous C section (yes vs. no)	NS	NS
Actual menopausal status (yes vs. no)	NS	NS
Previous breast cancer (yes vs. no)	NS	NS
Endometriosis history (yes vs. no)	1.4 (1.1–1.8), $P = 0.002$	NS

Results from multivariate analyses evaluating the association between CA 125 decrease in U/ml and CEA increase in ng/ml, respectively (dependent variable: biomarker variation between visit 1 and 2), and BRCA type, nulliparity yes/no, previous C section yes/no, actual menopausal status yes/no, previous breast cancer diagnosis yes/no and history of endometriosis yes/no.
BRCA, breast related cancer antigens; CEA, carcinoembryonic antigen; OR, odds ratio.

Carcinoembryonic antigen levels and trends

CEA basal levels were higher in women with a previous breast cancer diagnosis (1.8 vs. 1.1 ng/ml, $P = 0.001$) and in postmenopausal women (1.4 vs. 1.1 ng/ml, $P = 0.01$), but were not dependent on BRCA type, parity, previous C section, actual/past use of hormone modulation for breast cancer or history of endometriosis ($P > 0.05$).

In contrast to CA 125 levels, for the whole group we observed a 6 months significant increase in CEA levels (median from 1.3 to 1.5 ng/ml, +15.4%, $P < 0.0001$) (Fig. 2).

In multivariate analysis, including BRCA type, nulliparity yes/no, previous C section yes/no, actual menopausal status yes/no, previous breast cancer diagnosis yes/no and history of endometriosis yes/no, the CEA increase was significantly linked to nulliparity (OR 2.7; 95% CI 1.7–27.4; $P = 0.006$) and the BRCA1 mutation (OR 2.1; 95% CI 1.1–7.2; $P = 0.02$) (Table 2).

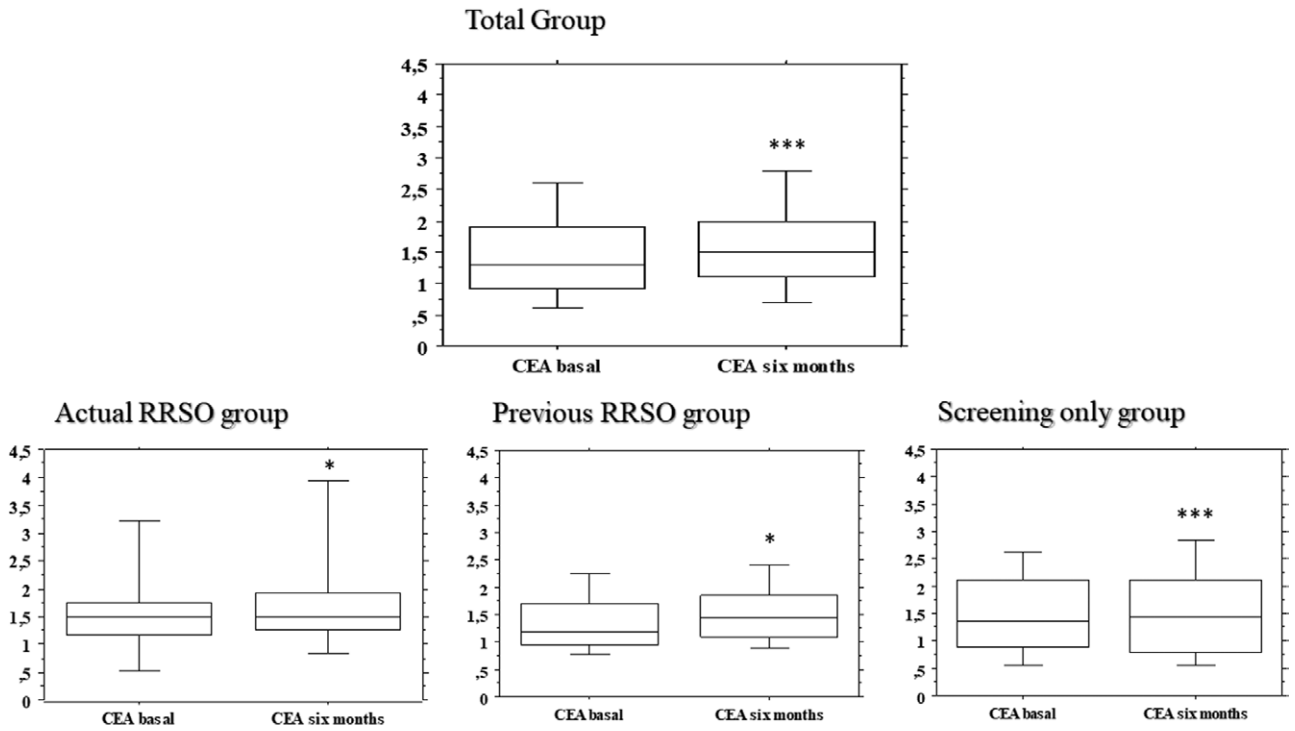
For the three groups (actual RRSO, previous RRSO and only screening group), we recorded a non-significant increase across all groups [actual RRSO: +0.1 ng/ml (+6.7%), previous RRSO: +0.2 ng/ml (+16.7%), screening only group: +0.2 ng/ml (+15.4%), $P = 0.55$ between groups] (Fig. 2).

Discussion

Principal findings

Our study is the first longitudinal prospective evaluation of CA 125 levels in BRCA mutation carriers, without a

Fig. 2



Box plots with medians of serum CEA levels before and after 6 months follow-up in the total group and in the different study groups [actual RRSO group (n = 29), previous RRSO group (n = 25), screening only group (n = 62)]. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. CEA, carcinoembryonic antigen; RRSO, risk-reducing salpingo-oophorectomy.

history of OC, undergoing actual or previous RRSO, when compared to controls – that is, not undergoing RRSO. We found that decreases in CA 125 levels were common during the 6 months follow-up of BRCA1 and BRCA2 mutation carriers, and probably not completely associated with RRSO as proposed by other authors, depending also on a physiological decline. These data confirmed that the contribution of ovaries and fallopian tubes to CA 125 levels appears to be low, because the surface epithelium of these organs do not express the CA 125 antigen, except in inclusion cysts, areas of metaplasia and papillary excrescences (Kabawat *et al.*, 1983). Our study also suggests that CA 125 serum reference levels in BRCA gene mutation carriers, should always be adjusted according to patient age (considering a semestral 7–8% 'physiological' decline) and previous RRSO status. Our results were reinforced by the concomitant evaluation of CEA levels, showing an opposite behaviour in the same cohort. Unfortunately, the limited numbers in this study did not allow us to extrapolate new reference levels for CA 125, adjusted for age and RRSO status.

Interpretation of main findings

A significant reduction in CA 125 postoperative levels, after RRSO was recorded in two retrospective studies. Chen *et al.* (2014) determined significant reductions in CA 125 levels after RRSO in 48 BRCA1 mutation carriers, but no significant differences in 40 BRCA2 mutation carriers. Alternatively, van Altena *et al.* (2011) detected a relative decrease of CA 125 levels in 60 BRCA mutation carriers. In this study, it was not specified if the same decreases occurred for both BRCA1 and BRCA2 mutation carriers. They found similar quantitative decreases of CA 125 in comparison with our data (18% vs. 17.4%), although it was a longer interval between surgical procedures and the second blood sample collection (12 in comparison to 6 months). In contrast to van Altena *et al.* (2011), we did not find that CA 125 decreases were dependent on menopausal status: in our study, this decline was similar in premenopausal and postmenopausal women at the time of inclusion. In our study, the menopausal status at the time of inclusion (amenorrhoea longer than 12 months) was prospectively evaluated and was not obtained from women's records as in van Altena *et al.* (2011). Moreover, we excluded women with adnexal dysplasia at RRSO.

The significance of our study is its prospective design and the vital presence of two other study groups; women with previous RRSO and women that refused RRSO in the screening only group. We found a non-statistical reduction of CA 125 levels in women with an actual RRSO, when compared to the other groups. In reality, this decline appears higher in the actual RRSO group

(17.4%), but it happens significantly also in the larger group of sole screening group (7.3%). For this reason, decreases in CA 125 levels in BRCA1 and BRCA2 mutation carriers after RRSO appear to be partially related to surgery, depending also on a physiological decline.

Longitudinal evaluation of biomarkers provides information that cannot be represented by single values or characteristics. It would have been beneficial to have developed a model that accounted for all longitudinal measurements, providing clear indications of patient-specific CA 125 profiles for the analysis of associations with OC risk. Longitudinal evaluation studies of CA 125 levels over time have been reported in high-risk women, in particular the risk of OC algorithm (ROCA) (Skates *et al.*, 1995; Menon *et al.*, 2005; Menon *et al.*, 2009; Skates *et al.*, 2011; Lu *et al.*, 2013; Skates *et al.*, 2017). Longitudinal CA 125 data indicate that a woman's baseline CA 125 level is unique (Skates *et al.*, 1995; Menon *et al.*, 2005; Menon *et al.*, 2009; Skates *et al.*, 2011; Lu *et al.*, 2013; Skates *et al.*, 2017), though similar as determined in our study groups (actual RRSO, previous RRSO and screening only group). ROCA studies have identified significant biomarker increases above each individual's baseline, personalising tests, and increasing the likelihood of earlier detection of OC, ideally before reaching the 35 U/ml threshold. The trend before a possible elevation of CA 125 from the numerous and large ROCA studies results was never clearly reported from their results, but it seems to confirm the trend herein demonstrated: a slight decrease, in our sample this decrease is of about 7.3% after a semestral evaluation. This was observed from the slight decrease in CA 125 levels as shown in Figure 2 of Lu *et al.* (2013) and Figure 1 of Skates *et al.* (2017); moreover, it was suggested in Skates *et al.* (1995), that 'the level of CA 125 either falls or remains constant over time' in women, but this trend was not clearly reported in the discussion part to date. This longitudinal result for CA 125 trends was confirmed for OC survivors, to predict overall survival in patients (Chiang *et al.*, 2014; Cao *et al.*, 2018): it can be seen in Figures 1 and 3 of Chiang *et al.* (2014), where it showed a slight longitudinal decrease.

Validity of results

This issue is an important result as it suggests that cut-offs should be updated, and decreased from year to year of age. This is confirmed by our data and other studies demonstrating that postmenopausal women have lower CA 125 levels (Skates *et al.*, 2011; van Altena *et al.*, 2011). These results have also been confirmed by other studies evaluating the impact of age on CA 125 levels, that is, significant, though small decreases in CA 125 with age (Zurawski *et al.*, 1990; Pauler *et al.*, 2001).

It is plausible that cut-offs could drop by about 14.6% per year (7.3% every 6 months as herein shown), for example, 35 U/ml (Skates *et al.*, 2011) at 53 years old (average age of our patients) could become 30.1 U/ml at 54 years old. However, it is not possible that this marked drop could be constant throughout life, from premenopausal to postmenopausal period. Understanding this different variation deltas and creating the customs thresholds for the different phases of life in BRCA patients will be the outcomes of the next studies.

There is much debate on the role of CA 125 levels after RRSO for BRCA mutation carriers, in terms of risk of peritoneal serous papillary carcinoma (Harmsen *et al.*, 2018): this screening must take similarly in account the impact of RRSO and age on CA 125 values.

Endometriosis is a well-known cause of increased CA 125 levels. In our study, the medical history of this disease was the only factor that influenced declines in CA 125, higher in the endometriotic subjects, opposite to van Altena *et al.* (2011): in none of our women was other evidence for endometriosis found during RRSO.

Our results are reinforced by opposite CEA trends, when compared to CA 125. This marker is an oncofetal glycoprotein normally expressed by mucosal cells. Although most commonly associated with colorectal cancer, CEA is elevated in other malignancies such as breast, liver, stomach and pancreatic cancer (Hammarström, 1999). However, a number of benign conditions may lead to elevations in serum CEA levels, including smoking, pancreatitis, biliary obstruction, peptic ulcer disease and hypothyroidism. In our population, this marker was increased in breast cancer survivors and postmenopausal women. Our data, showing longitudinal increases of CEA in BRCA mutation carriers, especially in BRCA1 and nulliparous women, deserves further investigation, that is, to improve screening policies.

Strengths and limitations of the study

The non-random allocation to treatments was a drawback in the study design, although a randomised trial is not feasible in this setting (RRSO is an optional surgery). The rate of RRSO acceptance in our sample was high (31.9%), since a gynaecologic oncologist was introduced to genetic counselling for BRCA1/2 mutation carriers in 2016: since then, the RRSO acceptance rate has increased by 400% in our Institution. Even though the small sample size limits the strength of our results. In enlarging the study population, CA 125 and CEA trends may not change, but more precise values for the different groups may be determined. The next step from this study will be to prospectively validate these combined trends in our BRCA screening services for OC prevention.

Conclusion

The decrease in CA 125 levels in BRCA 1/2 mutation carriers after RRSO was related only partially to surgery, depending also on a physiological decline. Our study suggests that reference levels of serum CA 125 in BRCA

gene mutation carriers should always be adjusted according to patient age and previous RRSO status. This is extremely important in their longitudinal monitoring for the prevention of OC.

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Conflicts of interest

There are no conflicts of interest.

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