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Evidence of Stage Shift in Women Diagnosed With Ovarian Cancer During Phase II of the United Kingdom Familial Ovarian Cancer Screening Study

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This study reports about off-license use of cancer antigen 125 and sonography for screening for ovarian cancer in a registered clinical trial.

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A B S T R A C T

Purpose

To establish the performance of screening with serum cancer antigen 125 (CA-125), interpreted using the risk of ovarian cancer algorithm (ROCA), and transvaginal sonography (TVS) for women at high risk of ovarian cancer (OC) or fallopian tube cancer (FTC).

Patients and Methods

Women whose estimated lifetime risk of OC/FTC was $\geq 10\%$ were recruited at 42 centers in the United Kingdom and underwent ROCA screening every 4 months. TVS occurred annually if ROCA results were normal or within 2 months of an abnormal ROCA result. Risk-reducing salpingo-oophorectomy (RRSO) was encouraged throughout the study. Participants were observed via cancer registries, questionnaires, and notification by centers. Performance was calculated after censoring 365 days after prior screen, with modeling of occult cancers detected at RRSO.

Results

Between June 14, 2007, and May 15, 2012, 4,348 women underwent 13,728 women-years of screening. The median follow-up time was 4.8 years. Nineteen patients were diagnosed with invasive OC/FTC within 1 year of prior screening (13 diagnoses were screen-detected and six were occult at RRSO). No symptomatic interval cancers occurred. Ten (52.6%) of the total 19 diagnoses were stage I to II OC/FTC (CI, 28.9% to 75.6%). Of the 13 screen-detected cancers, five (38.5%) were stage I to II (CI, 13.9% to 68.4%). Of the six occult cancers, five (83.3%) were stage I to II (CI, 35.9% to 99.6%). Modeled sensitivity, positive predictive value, and negative predictive value for OC/FTC detection within 1 year were 94.7% (CI, 74.0% to 99.9%), 10.8% (6.5% to 16.5%), and 100% (CI, 100% to 100%), respectively. Seven (36.8%) of the 19 cancers diagnosed < 1 year after prior screen were stage IIIb to IV (CI, 16.3% to 61.6%) compared with 17 (94.4%) of 18 cancers diagnosed > 1 year after screening ended (CI, 72.7% to 99.9%; $P < .001$). Eighteen (94.8%) of 19 cancers diagnosed < 1 year after prior screen had zero residual disease (with lower surgical complexity, $P = .16$) (CI, 74.0% to 99.9%) compared with 13 (72.2%) of 18 cancers subsequently diagnosed (CI, 46.5% to 90.3%; $P = .09$).

Conclusion

ROCA-based screening is an option for women at high risk of OC/FTC who defer or decline RRSO, given its high sensitivity and significant stage shift. However, it remains unknown whether this strategy would improve survival in screened high-risk women.

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INTRODUCTION

Inherited mutations in *BRCA1* and *BRCA2* and Lynch syndrome (LS) account for a significant minority (15% to 25%) of ovarian cancers (OCs)^{1,2} and confer a high risk for OC: 11% to 37% by age

70 years in *BRCA2* carriers and 39% to 65% in *BRCA1* carriers.^{3,4} Other lower-penetrance homologous repair pathway genes have been implicated in familial OC.^{5,6}

Although medium-term survival with *BRCA*-associated OC exceeds that of sporadic OC,^{7,8} the long-term outlook remains poor.⁹ Risk-reducing

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salpingo-oophorectomy (RRSO) for women older than 35 years of age to prevent OC or fallopian tube cancer (FTC) and to detect occult neoplasia is recommended as the only proven mortality-reducing intervention.^{10,11} Although effective when used premenopausally,^{10,11} RRSO causes infertility and premature menopause, with associated cardiovascular risks,¹² osteoporosis,¹³ and neurologic risks¹⁴ (although premature menopause can be treated with hormone replacement therapy). Some women decline RRSO regardless of OC risk, and others prefer to defer it (eg, until menopause). Effective OC screening would be a welcome option for such women.

Annual OC screening in the general population that uses a cutoff for the serum tumor marker cancer antigen 125 (CA-125) was associated with improved survival.¹⁵ In the high-risk population, we¹⁶ and others¹⁷⁻²⁰ have reported annual screening using a CA-125 cutoff and transvaginal sonography (TVS). Although we demonstrated high sensitivity (> 80%) and positive predictive value (PPV; 25%), two symptomatic interval cancers occurred, and 69% of detected cancers were stage III to IV.¹⁶ This annual screening interval has been associated with a poor 10-year survival rate of 36% in *BRCA1/2* carriers.²¹

Multimodal screening with the risk of ovarian cancer algorithm (ROCA) to interpret serial CA-125 results, and TVS as a second-line test, in the randomized general-population United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) achieved high sensitivity and specificity.^{22,23} Significantly more (40%) low-volume (stages I, II, or IIIa) invasive epithelial ovarian/peritoneal cancers were identified compared with unscreened controls (26%) on an intention-to-screen analysis, and the trial provided an encouraging, though not definitive, mortality benefit.²⁴

Random assignment to a nonscreening arm is thought to be unacceptable to high-risk women and clinicians.¹⁶ Even if ethical, it would likely be unfeasible, so research screening in this population is limited to prospective cohort studies. To our knowledge, this is the first published study to use ROCA-based screening to define sensitivity in the high-risk population.

PATIENTS AND METHODS

A prospective multicenter cohort screening study was undertaken within the United Kingdom (UK) National Health Service (NHS). Ethical approval was given by the Eastern Multicentre Research Ethics Committee (Reference No. 97/5/007). The protocol can be found online.²⁵

Entry Criteria

High-risk women at an estimated minimum 10% lifetime risk of OC were recruited; inclusion criteria (Data Supplement, online only) depended on family history or predisposing mutations. Documentation (death certificates and/or histopathology reports) of relevant cancers was required, and eligibility was confirmed by the coordinating center (CC). Clinical genetic testing was performed by accredited NHS laboratories. After screening ended, 45.2% of the study population underwent *BRCA1/2* next-generation sequencing research testing.²⁶

Recruitment

Participants were recruited at 42 centers in the UK by specialist nurses, clinical geneticists, or gynecologists. In December 2006, participants

in the UK Familial Ovarian Cancer Screening Study (UK FOCSS) Phase I (annual screening using a CA-125 cutoff and TVS)¹⁶ were invited to join this study—UK FOCSS Phase II. Other participants were recruited de novo. Women were counseled about RRSO and screening limitations. All participants provided written consent.

Screening

The trial database¹⁶ scheduled serum CA-125 tests every 4 months and TVS annually. Venipuncture packs were mailed to participants for use in primary care and blood samples returned to the CC laboratory for CA-125 assay.²³ Results were uploaded to the database, which calculated OC risk using the high-risk ROCA, which also incorporated the higher a priori risk in our population and different reference levels for risk stratification for postmenopausal compared with premenopausal women, because of the higher baseline CA-125 and variability in premenopausal women.²⁷ Menopausal status was determined by the database by using the age of participants and their responses to questions about gynecologic history and/or symptoms, which were returned with serum samples (Data Supplement).

Initial risk of ovarian cancer (ROC) was based on initial CA-125 level and estimated age-specific OC incidence. Subsequently, ROC was based on absolute CA-125 level and rate of change. Initially high or increasing CA-125 levels (even < 30 iU/ml) generated a high ROC, whereas initially low, stable-high (even > 30 iU/ml), or decreasing levels generated low ROCs. ROCA results were used for triage, including expedition of repeat CA-125 tests and/or TVS after abnormal results (Data Supplement).

Collaborating centers performed scans and completed proformas (Data Supplement), which were classified by the database according to predetermined criteria (Data Supplement).¹⁶ When indicated, women were referred to a gynecologist for clinical assessment, with a view to surgical removal of the fallopian tubes and ovaries. The final decision about surgery was made after additional investigation and discussion with the patient.

Follow-Up

Participants were flagged (by their unique NHS number) with relevant cancer registries, which provided cancer and/or death data.¹⁶ Collaborators notified the CC when women withdrew before routine screening ended (June 30, 2011). Women were observed through cancer registries with censorship that was based on date of death, last notification from the registry, or last contact if they were lost to registry follow-up. Participants were sent health questionnaires in January 2011 and April 2013 specifically asking about surgery that involved removal of fallopian tubes/ovaries and cancer diagnosis.

Diagnostic Documentation

Whenever women underwent salpingo-oophorectomy, the CC obtained documentation of indication, operation notes, and histopathology/cytopathology reports. These were reviewed by a gynecologic oncologist (A.N.R.) and pathologist (E.B./N.S.) and were classified according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). Trial surgery was defined as either screen-positive or screen-related (nonconcerning abnormal results, such as simple cysts and/or transient/stable abnormal ROC results that contributed to the participant's decision to undergo surgery).¹⁵ Centers were provided with an RRSO protocol, which advocated serial sectioning of fallopian tubes/ovaries (Data Supplement). A surgical complexity score was assigned using recognized criteria (Data Supplement).²⁸

Statistical Analysis

For performance analyses, data were censored 365 days after the last UK FOCSS screen. Invasive OC, FTC, or primary peritoneal cancer (PPC) diagnosed < 365 days after the last screen were included. Cancers that occurred after censoring and diagnosed before February 28, 2016 were

reported but not included in the performance analyses. The study was powered to estimate sensitivity within 10% (expected 95% CI), given an annual OC incidence of 0.5%. Analyses were done with Stata (version 14; STATA, College Station, TX).

Compliance with blood tests and scans was defined as the proportion of requested tests received by the CC. These were analyzed separately and according to screen type (eg, routine, protocol-indicated repeat).

Women who underwent salpingo-oophorectomy were only classified as having undergone RRSO if they were asymptomatic, they had normal results at prior screen, and the recruiting center indicated RRSO as the reason for withdrawal. Cases in which abnormal results prompted surgery were true positive (TP) if invasive epithelial OC/FTC was diagnosed. All other diagnoses (including borderline/benign tumors) that resulted from surgery that was prompted by abnormal results were false positive (FP). Cases in which nonconcerning test results (simple cysts/transiently elevated CA-125) contributed to the decision for surgery were classified as

screen-related surgery, to provide estimates of likely additional surgeries in any future screening program. True-negative (TN) designations were for those patients in whom the last screen was normal and no OC/FTC was diagnosed < 365 days. Patients who presented with clinically diagnosed interval cancers between screens or < 365 days after the final screen were considered false negative (FN). Prevalent cases were those diagnosed at first screen. Incident cases were those diagnosed subsequently. For women who transferred from Phase I (annual CA-125 cutoff and scan) to Phase II (ROCA every 4 months and annual TVS), their first Phase II screen was classified as incident.

We reported performance according to whether occult cancers diagnosed < 365 days after a prior screen were classified as FN or TP.¹⁶ In an attempt to estimate true sensitivity, we assumed that the proportion of occult cancers identified at RRSO, which would have been screen detected had women not undergone surgery, would be identical to that observed in those who continued screening. We then used the lower confidence limit of

Fig 1. CONSORT diagram. Percentages refer to the proportion of the total in preceding box. (*)Ineligible due to new information about family cancer history, tested negative for family mutation, or already undergoing investigation for abnormal screening results during UK Familial Ovarian Cancer Screening Study Phase I. (†)Unable to establish current whereabouts or nonresponder despite correct address. (‡)Defined as either screen-positive or screen-related (nonconcerning abnormal results, such as simple cysts and/or transient/stable abnormal ROC results that contributed to the participant's decision to undergo surgery). Includes volunteers who underwent unilateral salpingo-oophorectomy or diagnostic laparoscopy only who returned to screening. (§)Insufficient data to determine indication (all had normal final screen results, none had cancer). RRSO, risk-reducing salpingo-oophorectomy.

observed sensitivity in women who did not undergo RRSO as a conservative estimate of occult cancer detection sensitivity, and we rounded the predicted number of occult cancers detected to the nearest integer.

Because the protocol required parallel CA-125 and TVS, the results of which influenced each other's timing, it was not possible to calculate performance characteristics per test. Therefore, we calculated these metrics per woman-screen year (WSY) for the protocol overall.

To allocate WSYs to correct outcomes we applied the following rules; for TP and FP detection screens, the WSY that commenced with that screen was classified as TP or FP, respectively. WSYs before the detection screen were TN. For occult cancers diagnosed < 365 days after prior screen, the WSY that commenced with that screen was classified as FN or TP (dependent on analysis type), and prior WSYs were TN. For TN cases, all WSYs were classified TN.

To investigate potentially avoidable delays, we analyzed screening and screen-to-surgery intervals.¹⁶ Detection screens were defined as an abnormal TVS and/or abnormal ROC that led to a surgery/biopsy that diagnosed OC/FTC. Delayed screens were defined as any detection screen performed after the protocol-indicated date. Delay was calculated as the detection screen date minus the protocol-indicated date. The interval from screen date to diagnosis was calculated to the date of surgery/biopsy. We compared International Federation of Gynecology and Obstetrics stage and postsurgery zero residual disease rates in OC/FTC diagnosed during and < 365 days from the end of UK FOCSS screening with those diagnosed > 365 days after screening ended. We also compared stage-distribution and zero residual disease rates in incident screen-detected cancers in Phases I and II of the study. No survival analysis was performed because of the low number of events observed.

RESULTS

Between June 14, 2007, and May 15, 2012, 4,531 women were recruited. This included 2,362 (66.3%) of 3,563 eligible women from UK FOCSS Phase I (Fig 1). Table 1 lists inclusion indications. A total of 183 (4.0%) women withdrew before screening (Fig 1). The outcome of the remaining 4,348 women (96.0%) were analyzed. The median age at recruitment was 45.5 years (range, 34.2 to 84.8 years). Of the eligible women, 1,278 women (29.4% of participants) underwent mutation testing, and 1,965 (45.2%) subsequently underwent next-generation sequencing.²⁴ Overall, 924 (21.3%) women were known mutation carriers (further demographics in Data Supplement).

The last cancer notifications from NHS Digital were received on February 28, 2016 (England/Wales), May 15, 2016 (Scotland), and April 19, 2016 (Northern Ireland); the last death notifications were received on March 14, 2016 (all countries). Follow-up was possible for 4,046 women (93.1%). Median follow-up beyond last screen/withdrawal was 4.7 years (range, 0 to 8.7 years).

Screening/Compliance

The 4,348 screened participants underwent 13,728 WSY (median, 3.26 screen-years per woman; range, 1.00 to 5.94 screen-years per woman). A total of 189 women (4.3%) ceased screening by choice. Five hundred fifty-eight (12.8%) ceased because of surgical removal of both fallopian tubes/ovaries for RRSO (n = 534) or indeterminate reasons (n = 24). A total of 377 women (8.7%) whose last screen was abnormal continued screening until May 15, 2012, by which time 315 had normal results and did not

Table 1. Inclusion Criteria and Mutation Status in Screened Participants (N = 4,348)

Indication for Inclusion	No. of Patients (%)
Known mutation in family and/or proband	975 (22.4)
Breast/ovarian cancer in family; no known mutation	1,761 (40.5)
Ovarian cancer only in family; no known mutation	1,034 (23.8)
Lynch's syndrome in family; no known mutation	77 (1.8)
Did not fit standard inclusion criteria but deemed high risk by recruiting center and study clinical geneticist (J.M.)	501 (11.5)
Mutation status of proband from clinical genetics testing	
Total no. who underwent clinical genetics testing	1,278 (29.4)
Tested positive	854 (19.6)
Tested negative	381 (8.8)
Result unavailable	43 (1.0)
Untested	3,070 (70.6)
<i>BRCA1</i> or <i>BRCA2</i> mutation carrier	734 (16.9)
<i>BRCA1</i>	377 (8.7)
<i>BRCA2</i>	352 (8.1)
<i>BRCA1/2</i>	5 (0.1)
MMR gene mutation carrier	120 (2.8)
<i>MLH1</i>	40 (0.9)
<i>MSH2</i>	52 (1.2)
<i>MSH6</i>	12 (0.3)
<i>PMS2</i>	2 (0.05)
MMR gene mutation (gene not specified)	14 (0.3)
Total no. who underwent research NGS testing	1,965 (45.2)
<i>BRCA1</i> mutation by NGS	40 (0.9)
<i>BRCA2</i> mutation by NGS	30 (0.7)
Total tested by clinical genetics or NGS	3,243 (74.6)
Total <i>BRCA1/2</i> mutation carriers	804 (18.5)
Total <i>BRCA1/2</i> and MMR mutation carriers	924 (21.3)

NOTE. Documentation (death certificates or histopathology reports) of relevant cancers in the family was required. This was available for 2,226 (66.0%) of 3,373 women who were included for reasons other than a predisposing mutation in themselves or a first-degree relative.

Abbreviations: MMR, mismatch repair; NGS, next generation sequencing.

undergo surgery. Care was transferred to local gynecologists for the 62 women who still had abnormal results. Three of these 62 women underwent surgery; none had cancer.

Compliance with requested routine CA-125 tests and scans were 92.1% (27,138 of 29,450 CA-125 tests) and 94.6% (9,100 of 9,619 scans), respectively (Data Supplement). Compliance for scans was based on reports received, not scans undertaken, so it is likely an underestimate. Protocol-indicated repeat test compliance was higher: 97.4% (4,716 of 4,834) of blood tests, and 98.8% (2,792 of 2,825) of scans requested were received.

Of the 32,587 blood samples received, routine tests comprised 83.3% (27,138 of 32,587), protocol-triggered repeats comprised 14.5% (4,716 of 32,587), and 2.2% (733 of 32,587) were requested by study clinicians (eg, because CA-125 levels had increased by $\geq 50\%$, despite a normal ROC). A total of 2,233 (6.9%) of 32,587 blood samples were discarded because they arrived more than 56 hours after venipuncture. Of the 12,038 scan results, 75.6% (9,100 of 12,038) were annual, 23.2% (2,792 of 12,038) were triggered early by abnormal ROC results and/or previous abnormal scans, and 1.2% (146 of 12,038) were repeated because of a poor view of the ovaries.

Overall, 162 (3.7%) of 4,348 women underwent screen-positive trial surgery. Thirteen of these 162 women had screen-detected cancers. The remaining 149 (3.4%) of the 4,348 women underwent

false-positive surgery prompted by abnormal results (Table 2). Of these 149 women who underwent false-positive surgery, 46 (30.9%) had an abnormal ROC alone, 62 (41.6%) had an abnormal scan alone, and 41 (27.5%) had abnormal results for both tests. Overall, 95 (63.8%) of the 149 women who underwent false-positive surgery had benign ovarian pathology, two (1.3%) had borderline ovarian tumors, and 52 (35.0%) had other/no pathology identified. An additional 37 (0.9%) of the 4,348 women underwent screen-related trial surgery.

Invasive OC/FTC/PPC

Thirty-seven women were diagnosed with invasive cancer before February 28, 2016 (Table 3); nineteen occurred during 13,728 WSY < 365 days after prior screen and/or withdrawal (annual incidence 0.14%). In addition, 18 women were diagnosed > 365 days after their last UK FOCSS screen (median, 666 days; range, 400 to 2,159 days). The median age at diagnosis in the 37 women diagnosed with OC/FTC/PPC was 50 years (range, 37 to 79 years). All diagnoses occurred in families with hereditary breast-ovarian cancer. Thirty-four (91.2%) of the 37 women were diagnosed with high-grade serous carcinoma. Cancers in 31 (83.8%) of the 37 women occurred in mutation carriers—24 (64.9%) were *BRCA1* carriers and seven (18.9%) were *BRCA2* carriers. Three (8.1%) of the 37 women were *BRCA1/2* negative; one (2.7%) of the 37 women had a *BRCA2* variant of unknown significance; two (5.4%) of the 37 women were untested. Of the 37 women diagnosed with OC/FT/PPC, 23 (62.2%) knew they carried pathogenic mutations and 14 (37.8%) had a history of breast cancer. No OC occurred in women with a family history of LS or those who were mutation carriers for the syndrome (n = 192; 558 WSY).

The 19 invasive OC/FTCs diagnosed within 365 days of prior screen included one prevalent screen-positive OC (International Federation of Gynecology and Obstetrics stage IIIC) and 18 incident cancers. Twelve of the 18 incident OC/FTCs were screen detected and six were occult cancers identified at RRSO. Of the 12 patients with incident screen-detected cancer, 11 (91.7%) had

an abnormal ROC and 5 (41.7%) had a normal TVS at detection (compared with zero of 13 patients who had normal TVS at detection in UK FOCSS Phase I; $P = .015$). The median CA-125 level at detection was 53.8 iU/ml (range, 11.7 to 219.2 iU/ml) in UK FOCSS Phase II (< 30 iU/ml in four of 12 patients) compared with 73 iU/ml (range, 4 to 3,874 iU/ml) in Phase I, which did not mandate assay type and recommended premenopausal and postmenopausal cutoffs of 35 and 30 iU/ml, respectively, rather than according to the ROCA. Five (38.5%) of the 13 screen-detected OC/FTCs (CI, 13.9% to 68.4%) and 5 (83.3%) of the six occult OC/FTCs (CI, 35.9% to 99.6%) were stage I to II. Overall, 10 (52.6%) of the 19 cancers diagnosed within 365 days of prior screen were stage I to II (CI, 28.9% to 75.6%).

Eighteen cancers were diagnosed > 365 days after the end of UK FOCSS screening. Two occult cancers were detected at RRSO, three cancers were detected at annual screening performed locally, and 13 were detected when women presented with symptoms. Only one (5.6%) of the 18 cancers was diagnosed at stage I to II (CI, 0.2% to 27.3%).

Women were significantly less likely to be diagnosed with stage IIIB to IV OC during UK FOCSS Phase II screening (seven [36.8%] of 19; CI, 16.3% to 61.6%) compared with those diagnosed subsequently (17 [94.4%] of 18; CI, 72.7% to 99.9%; $P < .001$). Twelve (92.3%) of 13 women who had screen-detected cancers had zero postsurgical residual disease (CI, 64.0% to 99.8%). Overall, 18 (94.8%) of 19 women diagnosed with OC during UK FOCSS had zero postsurgical residual (CI, 74.0% to 99.9%) compared with 13 (72.2%) of 18 women who were diagnosed subsequently (CI, 46.5% to 90.3%; $P = .09$). None of the women diagnosed during UK FOCSS required complex surgery, one had interval surgery. Three of the subsequently diagnosed women required complex surgery, seven had interval surgery, and two had no debulking (Table 3). The proportion of women diagnosed with OC during UK FOCSS who had neoadjuvant chemotherapy (1 [5.3%] of 19 women; CI, 0.1% to 26.0%) was significantly lower than in the women diagnosed subsequently

Table 2. Diagnoses in Women Who Underwent False-Positive Surgery to Rule Out Ovarian Cancer As a Result of Abnormal Screening Tests (n = 149)

Histopathologic Diagnosis	No. With Only Scan Abnormal (n = 62)	No. With Only ROCA Abnormal (n = 46)	No. With Both Scan and ROCA Abnormal (n = 41)	Total No. (%) With Abnormalities (n = 149)*
Benign ovarian pathology				
Benign ovarian tumor	37	17	22	76 (51.0)
Endometriosis	9	3	7	19 (12.8)
Borderline ovarian tumor				
Serous borderline ovarian tumor	0	1	1	2 (1.3)
Nonovarian malignancy				
Metastatic breast cancer	0	0	1	1 (0.7)
Benign tubal pathology				
Fimbrial/paratubal cyst	3	5	3	11 (7.4)
Hydrosalpinx	2	0	2	4 (2.7)
STIC lesion	2	1	0	3 (2.0)
Uterine/cervical pathology				
Fibroids	5	1	1	7 (4.7)
Complex atypical endometrial hyperplasia	1	2	1	4 (2.7)
Endometrial polyp	0	3	1	4 (2.7)
CIN	2	0	0	2 (1.3)
No pathology reported	5	16	5	26 (17.4)

Abbreviations: CIN, cervical intraepithelial neoplasia; ROCA, risk of ovarian cancer algorithm; STIC, serous tubal intraepithelial carcinoma.

*Total of 159 diagnoses in 149 women, because some women had more than one diagnosis.

Table 3. Invasive Ovarian, Tubal, and Peritoneal Cancers That Occurred During Screening and Follow-Up

Mutation status by detection type	Age at Diagnosis (years)	Cancer Site, Histotype	FIGO Stage, Grade	CA-125 at Detection or Final Screen (IU/ml)	ROCA Score at Detection Screen or Final Screen	Ultrasound Scan Result at Detection or Final Screen	Interval in Screen-Positive Women Between Abnormal Test and Diagnosis (days)	Interval in Screen-Negative Women Between Last Screen and Diagnosis (days)	Debulking: Optimal (o) or Complete (c)	Surgical Complexity Score ^a	Year of Diagnosis	Alive on Death Censor Date, March 14, 2016
Prevalent screen-detected cancers (n = 1)^a												
<i>BRCA1</i> positive	53	C56, serous/endometrioid	IIc, high grade	341.2	High intermediate	Normal	80	NA	C	5	2010	Y
Incident screen-detected cancers (n = 12)^a												
Unstested (mother negative)	52	C56, clear cell	Ia, high grade	11.7	Normal	Abnormal	9	NA	C	3	2010	Y
<i>BRCA1</i> positive	64	C57, serous	Ic, high grade	28.0	Elevated	Normal	56	NA	C	2	2010	Y
<i>BRCA1</i> positive	45	C56 and C54.1, endometrioid (synchronous)	IIb, G2 ovarian and Ia, G2 endometrioid	56.3	High intermediate	Abnormal	49 (CA-125) 63 (scan)	NA	C	4	2010	Y
<i>BRCA1</i> positive	46	C56, serous	IIc, high grade	24.2	Low intermediate	Abnormal	3 (CA-125) 49 (scan)	NA	C	3	2010	Y
<i>BRCA1</i> negative	49	C56, serous	IIc, high grade	23.8	High intermediate	Normal	100	NA	C	3	2011	Y
Unstested	50	C56, serous	IIla, high grade	33.8	High intermediate	Normal	147 ^b	NA	C	2	2011	Y
<i>BRCA1</i> positive	39	C56, serous	IIlb, high grade	90.3	High intermediate	Normal	178 ^c	NA	C	3	2011	Y
<i>BRCA1</i> positive	37	C56, serous	IIlb, high grade	79.8	High intermediate	Abnormal	209 (CA-125) ^d 200 (scan)	NA	C	4	2010	Y
<i>BRCA1</i> positive	54	C56, serous	IIlc, high grade	79.4	High intermediate	Abnormal	64 (CA-125) 48 (scan)	NA	C	4	2010	Y
<i>BRCA1</i> positive	46	C56, endometrioid/serous	IIlc, high grade	219.2	High intermediate	Abnormal	43 (CA-125) 29 (scan)	NA	O	2	2011	Y
<i>BRCA1</i> negative	48	C56, serous	IIlc, high grade	51.2	Intermediate	Abnormal	115 (CA-125) 60 (scan)	NA	C (at IDS)	3	2009	N
<i>BRCA1</i> positive	39	C56, serous	IIlc, high grade	96.9	Intermediate	Normal	125 ^e	NA	C	2	2009	N
Oculta cancers diagnosed within 365 days of prior screen (n = 6)^f												
<i>BRCA2</i> positive	66	C57, serous	Ia, high grade	13.3	Normal	Normal	NA as occult	168 (CA-125) 334 (scan)	C	2	2011	Y
<i>BRCA1</i> positive	42	C57, serous	Ia, high grade	7.9	Normal	Normal	NA as occult	34 (CA-125) 267 (scan)	C	2	2010	Y
<i>BRCA2</i> positive	52	C57, endometrioid	Ia, G2	36.5	Normal	Normal	NA as occult	2 (CA-125) 255 (scan)	C	2	2011	Y
<i>BRCA2</i> VUS	47	C56, serous	Ic ^g , high grade	8.8	Normal	Normal	NA as occult	121 (CA-125) 77 (scan)	C	3	2011	Y
<i>BRCA2</i> positive	57	C57, serous	IIa, high grade	28.1	Intermediate ^g	Normal	NA as occult	131 (CA-125) 144 (scan)	C	3	2009	N
<i>BRCA1</i> positive	55	C56, serous	IIla, high grade	7.7	Normal	Normal	NA as occult	24 (CA-125) 81 (scan)	C	2	2010	Y
Diagnosed > 1 year after end of screening on UK FOCSS (n = 18)ⁱ												
<i>BRCA1</i> positive	51	C56, serous	Ic, high grade	12.7	Normal	Normal	NA as occult	654 (CA-125) 815 (scan)	C	2	2013	Y
<i>BRCA1</i> positive	43	C56, serous	IIlb, high grade	No sample provided	NA	Normal	NA as occult	400 (scan only)	C	5	2012	Y
<i>BRCA1</i> positive	50	C57, serous	IIlc, high grade	6.6	Normal	Normal	NA as presented with postmenopausal bleed	531 (CA-125) 1,966 (scan)	C	4	2013	Y
<i>BRCA1</i> positive	53	C56, serous	IIlc, high grade	14.1	Normal	Normal	Detected on annual screening post study end ^j	1,020 (CA-125) 1,173 (scan)	C	10	2014	Y
<i>BRCA1</i> positive	39	C57, serous	IIlc, high grade	31.2	Normal	Never had UK FOCSS scan	Detected on annual screening post study end ^k	726 (CA-125) only	O	3	2013	Y

(continued on following page)

Table 3. Invasive Ovarian, Tubal, and Peritoneal Cancers That Occurred During Screening and Follow-Up (continued)

Mutation status by detection type	Age at Diagnosis (years)	Cancer Site, Histotype	FIGO Stage, Grade	CA-125 at Detection or Final Screen (U/ml)	ROCA Score at Detection Screen or Final Screen	Ultrasound Scan Result at Detection or Final Screen	Interval in Screen-Positive Women Between Abnormal Test and Diagnosis (days)	Interval in Screen-Negative Women Between Last Screen and Diagnosis (days)	Debulking: Optimal (o) or Complete (c)	Surgical Complexity Score ^e	Year of Diagnosis	Alive on Death Censor Date, March 14, 2016
<i>BRCA1</i> positive	47	C56, serous	IIc, high grade	58.9	Low intermediate ⁱ	Normal	NA; presented with heavy menstrual bleeding ^m	511 (CA-125) 604 (scan)	O	3	2012	Y
<i>BRCA1</i> positive	44	C56, serous	IIc, high grade	10.1	Normal	Normal	NA; presented with abdominal pain/bloating ⁿ	759 (CA-125) 772 (scan)	C (at IDS)	3	2013	Y
<i>BRCA1</i> positive	59	C48.1, serous	IIc, high grade	6.4	Low intermediate ^o	Normal	NA; presented with constipation/ bloating 30 months post-RRSO ^p	980 (CA-125) 987 (scan)	C (at IDS)	2	2013	Y
<i>BRCA</i> negative	72	C56, serous	IIc, high grade	10.8	High intermediate	Normal	Detected on annual screening post study end ^q	677 (CA-125) 708 (scan)	No debulking surgery done ^s	NA	2013	Y
<i>BRCA1</i> positive	47	C57, serous	IIc, high grade	35.2	Normal	Normal	NA; presented with pelvic pain	1,176 (CA-125) 1,388 (scan)	C	9	2014	Y
<i>BRCA1</i> positive	54	C57, serous	IIc, high grade	11.8	Normal	Normal	NA; suspicious left adnexal mass on TVS done as preoperative screen before planned RRSO	399 (CA-125) 663 (scan)	C	9	2012	N
<i>BRCA1</i> positive	52	C56, serous	IIc, high grade	4.5	Normal	Normal	NA; presented with abdominal pain/distension	2,159 (CA-125) 2638 (scan)	C (at IDS)	2	2014	Y
<i>BRCA1</i> positive	52	C57, serous	IIc, high grade	15.6	Normal	Normal	NA; presented with unexpected stage IIc disease found at RRSO	1,197 (CA-125) 1,157 (scan)	C	4	2013	Y
<i>BRCA2</i> positive	79	C56/C57, serous	IIc, high grade	7.9	Normal	Normal	NA; presented with bowel obstruction after screening ended	1,430 (CA-125) 1,535 (scan)	Debulking surgery not possible ^a	NA	2015	N
<i>BRCA2</i> positive	68	C56, serous	IIc, high grade	25.9	Normal	Normal	NA; presented with abdominal pain/distension	869 (CA-125) 1,314 (scan)	O (at IDS)	3	2014	Y
<i>BRCA2</i> positive	63	C56, serous	IV, high grade	14.0	Normal	Normal	NA; presented with shortness of breath/abdominal distension	1,288 (CA-125) 1,197 (scan)	C (at IDS)	4	2015	Y
<i>BRCA1</i> positive	50	C56, serous	IV, high grade	8.5	Normal	Normal	NA; presented with malignant pleural effusion	1,157 (CA-125) 1,402 (scan)	C (at IDS)	2	2014	Y
<i>BRCA2</i> positive	43	C57, serous	IV, high grade	11.1	Normal	Normal	NA; presented with malignant pleural effusion	541 (CA-125) 726 (scan)	C (at IDS)	3	2012	Y

Abbreviations: C48.1, primary peritoneal cancer; C54.1, endometrial cancer; C56, ovarian cancer (excluding borderline ovarian tumors in this table); C57, fallopian tube cancer; FIGO, International Federation of Gynecology and Obstetrics; G, grade; IDS, interval debulking surgery; NA, not applicable; ROC, risk of ovarian cancer; ROCA, risk of ovarian cancer algorithm; RRSO, risk-reducing salpingo-oophorectomy; TVS, transvaginal sonography; UK FOCSS, United Kingdom Familial Ovarian Cancer Screening Study; VUS, variant of unknown significance.

^aFor these cases, ultrasound scan result is at time of referral.

^bReluctant to have surgery. Computed tomography scan done and reported as normal; underwent surgery when CA-125 continued to increase.

^cReluctant to have surgery. TVS repeated and showed complex adnexal mass.

^dReluctant to have surgery. Magnetic resonance imaging scan done and reported as nonmalignant. Underwent surgery when CA-125 continued to increase.

^eReluctant to have surgery. TVS repeated but still normal. Eventually, computed tomography showed complex adnexal and omental masses.

^fFor these cases, ultrasound scan result pre-RRSO is by definition normal.

^gIntermediate result classified as an incomplete screen, because ROC value prior to RRSO was abnormal and would have triggered a repeat test had participant not undergone RRSO. The case was classified as occult for screening performance analysis.

^hIncompletely staged.

ⁱFor these cases, ultrasound scan result is that at time of last UK FOCSS screen.

^jNormal TVS 74 days before diagnosis; CA-125 level of 522 IU/ml 69 days before diagnosis; widespread disease on computed tomography scan 41 days before diagnosis.

^kCA-125 level of 25 IU/ml 336 days before diagnosis, then a level of 506 IU/ml 14 days before diagnosis. Normal TVS 10 days before diagnosis. Underwent diagnostic laparoscopic bilateral salpingo-oophorectomy, then debulking.

^lIntermediate result classified as an incomplete screen, because patient was noncompliant with request for repeat test.

^mFound to have CA-125 level of 258 IU/ml and adnexal mass on TVS.

ⁿFound to have CA-125 level of 581 IU/ml and widespread disease on computed tomography.

^oIntermediate result classified as an incomplete screen, because test was not repeated as patient was withdrawn by center for RRSO.

^pFound to have CA-125 level of 1,094 IU/ml and widespread disease on computed tomography.

^qUnderwent laparotomy and was found to have nonresectable disease. Subsequently deemed unfit to receive chemotherapy.

^rCA-125 level of 12 IU/ml 522 days before diagnosis, then 339 IU/ml 55 days before diagnosis.

^sUnderwent laparoscopy for consideration of IDS but had excellent response to chemotherapy, and multidisciplinary team decided not to perform IDS.

(eight [44.4%] of 18 women; CI, 21.5% to 69.2%; $P = .008$). The mean surgical complexity score²⁸ in women diagnosed during screening or less than 365 days after the final screen was 2.7 compared with 4.3 in those diagnosed subsequently (Mann-Whitney U test, $P = .16$).

Screening/Surgical Intervals

The median delay in incident detection screens in this Phase II study was 6 days (range, 0 to 87 days) compared with 88 days (range, 6 to 737 days) in Phase I (gamma generalized linear model, $P = .004$). The median interval between detection screen and diagnosis in this Phase II study was 82 days (range, 9 to 209 days) compared with 79 days (range, 15 to 184 days) in Phase I ($P =$ not significant). Reasons for the delay included falsely reassuring scans and reluctance to undergo surgery (Table 3).

Screening Performance

All 13 cancers (100%) in women who did not undergo RRSO were screen detected (CI, 75.3% to 100%). Hence, for modeled sensitivity, the lower confidence limit of 75.3% was used to conservatively estimate the proportion of occult cancers which would have been screen detected had women not undergone RRSO.

Modeled sensitivity, PPV, and negative predictive value (NPV) for the detection of OC/FTC at 1 year for the whole population were 94.7% (CI, 74.0% to 99.9%), 10.8% (CI, 6.5% to 16.5%), and 100% (CI, 100% to 100%), respectively. PPV was significantly better in *BRCA1/2* carriers than in women who had an unknown mutation status (Table 4).

Comparison of Phase I With Phase II

Key comparisons of UK FOCSS Phase I and Phase II are listed in Table 5. Rates of clinically presenting interval cancers, zero

residual disease after surgery, modeled sensitivity, proportions of women diagnosed with cancer stage less than IIIB, screening delays, and proportions with normal scans at referral were all better in Phase II, but only the comparisons of screening delays and proportions with normal scans at referral were significant.

DISCUSSION

These UK FOCSS Phase II results suggest that in a high-risk population, ROCA-based multimodal screening every 4 months, alongside reminders of the effectiveness of RRSO, is associated with high sensitivity, significantly lower high-volume disease, and a high zero residual disease rate after surgery compared with women from the same cohort in whom cancer was diagnosed > 1 year after screening ended. Two similar US studies were published while this paper was in press as a combined analysis, with three of six incident cancers found at stage I/II.²⁹

The strengths of this study are its size, multicenter setting, centralized screening with a validated algorithm, and reliable multiple-source follow-up. A limitation is the nonrandomized design. However, data about OC diagnosed after screening ended allowed comparisons in the absence of a nonscreening arm. Other limitations include the unknown mutation status of many participants and the small number of incident cancers, which limited power. Although screening delays were effectively eliminated (median, 6 days), the median interval between abnormal results and surgery continued to be > 2 months (82 days in this Phase II study v 79 days in Phase I). There were still some long intervals as a result of patient reluctance to undergo surgery and falsely reassuring imaging associated with an abnormal ROC at referral, as seen in UKCTOCS.²³

During and within 1 year of UK FOCSS screening, no patients with interval cancers presented with symptoms, sensitivity was

Table 4. Overall Prevalence and Incidence Screening Performance Characteristics According To Population Screened

Characteristic	Screened Population (N = 4,348)	<i>BRCA1/2</i> Mutation Carriers Only* (n = 804)	Unknown Mutation Status at Recruitment (n = 3,580)	<i>P</i> (<i>BRCA</i> carriers to unknown mutation status)
No. (%) of women who underwent screen-positive surgery	162 (3.7)	25 (3.1)	141 (3.9)	.307
No. (%) of those undergoing surgery of screen-detected OC/FTC	13 (8.0)	9 (36.0)	9 (6.4)	$< .001$
No. (%) RRSO occult cancers diagnosed < 1 year of screen	6 (0.1)	5 (0.6)	3 (0.1)	.007
No. of interval cancers diagnosed < 1 year of screen	0	0	0	—
Sensitivity, % (95% CI)				
Occults as true positive	100 (82.4 to 100)	100 (76.8 to 100)	100 (73.5 to 100)	1.0
Occults as false negative	68.4 (43.5 to 87.4)	64.3 (35.1 to 87.2)	75.0 (42.8 to 94.5)	.683
Modeled sensitivity, % (95% CI)	94.7 (74.0 to 99.9)	85.7 (57.2 to 98.2)	91.7 (61.5 to 99.8)	1.0
Specificity (occults NA), % (95% CI)†	98.9 (98.7 to 99.1)	99.3 (98.9 to 99.6)	98.9 (98.7 to 99.1)	.059
PPV, % (95% CI)				
Occults as true positive	11.3 (7.0 to 17.1)	46.7 (28.3 to 65.7)	8.3 (4.4 to 14.1)	$< .001$
Occults as false negative	8.0 (4.3 to 13.3)	36.0 (18.0 to 57.5)	6.4 (3.0 to 11.8)	$< .001$
Modeled PPV, % (95% CI)	10.8 (6.5 to 16.5)	42.9 (24.5 to 62.8)	7.7 (3.9 to 13.4)	$< .001$
NPV, % (95% CI)				
Occults as true positive	100 (100 to 100)	100 (99.8 to 100)	100 (100 to 100)	1.0
Occults as false negative	100 (99.9 to 100)	99.8 (99.5 to 99.9)	100 (99.9 to 100)	.005
Modeled NPV, % (95% CI)	100 (100 to 100)	99.9 (99.7 to 100)	100 (100 to 100)	.074

Abbreviations: FTC, fallopian tube cancer; NA, not applicable; NPV, negative predictive value; OC, ovarian cancer; PPV, positive predictive value; RRSO, risk-reducing salpingo-oophorectomy.

*BRCA status was determined via National Health Service clinical genetic testing or research testing using next-generation sequencing. Gene test result may be subsequent to recruitment, so total includes some in the group of unknown mutation status at recruitment.

†Specificity does not depend on false-negative or true-positive rate.

Table 5. Key Comparisons Between UK FOCSS Phase I and Phase II

Screening Strategy	Phase I	Phase II	<i>P</i>
	Annual CA-125 (with cutoff) Plus TVS, Arranged Locally	ROCA Every 4 Months Plus Annual TVS, Arranged Centrally	
Time period	May 6, 2002 to January 1, 2008	June 14, 2007 to May 15, 2012	NA
No. of participants	3,563	4,348	NA
Women-screen years	11,366	13,728	NA
Median age (range), years	44.6 (35-81)	45.5 (34-84)	NA
No. (%) of known <i>BRCA1/2</i> mutation carriers* as a proportion of population	607 (17.0)	804 (18.5)	NA
No. (%) of occult cancers in known <i>BRCA</i> carriers* who underwent RRSO	3 (1.8) in 169	9 (4.0) in 227	.249
No. (%) of incident screen-detected cancers diagnosed at stage IIIa or earlier	5 (38.5) in 13	6 (50.0) in 12	.695
Modelled incident sensitivity, (%)	82.4	88.9	.658
No. (%) of incident screen-detected cancers that had zero residual disease	8 (61.5) in 13	11 (91.7) in 12	.160
No. (%) of cancers that had zero residual disease < 365 days after last screen	19 (70.4) in 27	18/19 (94.7%)	.061
Proportion of incident cancers presenting clinically	2 of 18 (n = 1, stage I; n = 1, stage IV)	0 of 18	.486
Proportion (%) of incident screen-detected cancers with a normal scan at referral	0 of 13 (0)	5 of 12 (41.7)	.015
Median incident screen delay prior to detection (range), days	88 (6-737)	6 (0-87)	.004†
Median interval between detection screen and surgery (range), days	77 (15-184)	80 (9-209)	.460†

Abbreviations: NA, not applicable, because statistical comparison was not appropriate (eg, because the Phase II denominator included proportion of those in Phase I denominator); RRSO, risk-reducing salpingo-oophorectomy; TVS, transvaginal scan.

*Identified by a combination of National Health Service clinical genetics testing and next-generation sequencing.

†By using a generalized linear model with a gamma distribution and log link.

high, and there was a significant stage shift compared with patients who had cancers diagnosed more than 1 year after screening ended. The significantly higher proportion of cancers diagnosed at stage IIIa or lower (ie, microscopic abdominal disease at worst) during the study was associated with more primary surgery and with higher zero residual disease achieved with less complex surgery. Published complete cytoreduction rates in clinically presenting *BRCA1/2* carriers ranged from 28% to 30%.^{2,30} The overall findings suggest a screening-mediated reduction in disease volume. It is likely this would translate into reduced surgical morbidity and fewer incomplete resections. It remains unknown whether this would improve survival in screened high-risk women. We were unable to analyze survival, because there were only three deaths in the 37 women with invasive OC/FTC/PPCs at censorship on March 14, 2016. Although this is encouraging, medium-term survival of OC in *BRCA1/2* carriers is better than that of *BRCA1/2*-negative patients.^{7,8}

The performance characteristics of screening every 4 months were encouraging; overall incident sensitivity was 94.7%, with occult cancer detection modeled, and PPV was 10.8% (ie, greater than the suggested 10% level for general-population screening).¹⁶ However, PPV is less relevant in high-risk populations for whom RRSO is already recommended as optimal management. As expected, PPV was better in *BRCA1/2* carriers (42.9%) than in women who had an unknown mutation status (7.7%) because of the lower cancer incidence in women with an unknown status.

The high compliance with blood tests and TVS suggests that the protocol is feasible and acceptable. However, compliance might not be maintained outside a trial. A parallel psychological study found moderate cancer distress at 1 week in women with abnormal ROCA and/or scan results, which led to higher withdrawal from screening.³¹ However, there was no significant effect on general anxiety and/or depression on return to routine screening or at 9 months.

In conclusion, our protocol achieves encouraging performance characteristics, is associated with a low rate of high-volume

disease at primary surgery, and had a high zero residual disease rate at low levels of surgical complexity. RRSO remains the treatment of choice for women at high-risk of OC/FTC. In those not ready or willing to undergo surgery, multimodal screening using ROCA every 4 months and TVS (at an interval determined by the ROCA), with regular discussions about the effectiveness of RRSO, appears to be a better option than symptom awareness alone. Such screening should not be viewed as an alternative to surgery, but it does seem to offer a better chance of avoiding a diagnosis of advanced incompletely resectable OC/FTC in the interim.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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REFERENCES

1. Rubin SC, Blackwood MA, Bandera C, et al: *BRCA1*, *BRCA2*, and hereditary nonpolyposis colorectal cancer gene mutations in an unselected ovarian cancer population: Relationship to family history and implications for genetic testing. *Am J Obstet Gynecol* 178:670-677, 1998
2. Alsop K, Fereday S, Meldrum C, et al: *BRCA* mutation frequency and patterns of treatment response in *BRCA* mutation-positive women with ovarian cancer: A report from the Australian Ovarian Cancer Study Group. *J Clin Oncol* 30:2654-2663, 2012
3. Antoniou A, Pharoah PD, Narod S, et al: Average risks of breast and ovarian cancer associated with *BRCA1* or *BRCA2* mutations detected in case series unselected for family history: A combined analysis of 22 studies. *Am J Hum Genet* 72:1117-1130, 2003
4. Evans DG, Shenton A, Woodward E, et al: Penetrance estimates for *BRCA1* and *BRCA2* based on genetic testing in a clinical cancer genetics service setting: Risks of breast/ovarian cancer quoted should reflect the cancer burden in the family. *BMC Cancer* 8:155, 2008
5. Ramus SJ, Song H, Dicks E, et al: Germline mutations in the *BRIP1*, *BARD1*, *PALB2*, and *NBN* genes in women with ovarian cancer. *J Natl Cancer Inst* 107:djv214, 2015
6. Song H, Dicks E, Ramus SJ, et al: Contribution of germline mutations in the *RAD51B*, *RAD51C*, and *RAD51D* genes to ovarian cancer in the population. *J Clin Oncol* 33:2901-2907, 2015
7. Chetrit A, Hirsh-Yechezkel G, Ben-David Y, et al: Effect of *BRCA1/2* mutations on long-term survival of patients with invasive ovarian cancer: The national Israeli study of ovarian cancer. *J Clin Oncol* 26:20-25, 2008
8. Candido-dos-Reis FJ, Song H, Goode EL, et al: Germline mutation in *BRCA1* or *BRCA2* and ten-year survival for women diagnosed with epithelial ovarian cancer. *Clin Cancer Res* 21:652-657, 2015
9. Marchetti C, De Felice F, Palaia I, et al: Risk-reducing salpingo-oophorectomy: A meta-analysis on impact on ovarian cancer risk and all cause mortality in *BRCA 1* and *BRCA 2* mutation carriers. *BMC Womens Health* 14:150, 2014
10. Finch AP, Lubinski J, Møller P, et al: Impact of oophorectomy on cancer incidence and mortality in women with a *BRCA1* or *BRCA2* mutation. *J Clin Oncol* 32:1547-1553, 2014
11. Domchek SM, Friebel TM, Singer CF, et al: Association of risk-reducing surgery in *BRCA1* or *BRCA2* mutation carriers with cancer risk and mortality. *JAMA* 304:967-975, 2010
12. Michelsen TM, Pripp AH, Tonstad S, et al: Metabolic syndrome after risk-reducing salpingo-oophorectomy in women at high risk for hereditary breast ovarian cancer: A controlled observational study. *Eur J Cancer* 45:82-89, 2009
13. Tuppurainen M, Kröger H, Honkanen R, et al: Risks of perimenopausal fractures: A prospective population-based study. *Acta Obstet Gynecol Scand* 74:624-628, 1995
14. Ryan J, Scali J, Carrière I, et al: Impact of a premature menopause on cognitive function in later life. *BJOG* 121:1729-1739, 2014
15. Jacobs IJ, Skates SJ, MacDonald N, et al: Screening for ovarian cancer: A pilot randomised controlled trial. *Lancet* 353:1207-1210, 1999
16. Rosenthal AN, Fraser L, Manchanda R, et al: Results of annual screening in phase I of the United Kingdom familial ovarian cancer screening study highlight the need for strict adherence to screening schedule. *J Clin Oncol* 31:49-57, 2013
17. Hogg R, Friedlander M: Biology of epithelial ovarian cancer: Implications for screening women at high genetic risk. *J Clin Oncol* 22:1315-1327, 2004
18. Stirling D, Evans DG, Pichert G, et al: Screening for familial ovarian cancer: Failure of current protocols to detect ovarian cancer at an early stage according to the International Federation of Gynecology and Obstetrics system. *J Clin Oncol* 23:5588-5596, 2005
19. Vasen HF, Tesfay E, Boonstra H, et al: Early detection of breast and ovarian cancer in families with *BRCA* mutations. *Eur J Cancer* 41:549-554, 2005
20. Hermesen BB, Olivier RI, Verheijen RH, et al: No efficacy of annual gynaecological screening in *BRCA1/2* mutation carriers: An observational follow-up study. *Br J Cancer* 96:1335-1342, 2007
21. Evans DG, Gaarenstroom KN, Stirling D, et al: Screening for familial ovarian cancer: Poor survival of *BRCA1/2* related cancers. *J Med Genet* 46:593-597, 2009
22. Menon U, Gentry-Maharaj A, Hallett R, et al: Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: Results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Lancet Oncol* 10:327-340, 2009
23. Menon U, Ryan A, Kalsi J, et al: Risk algorithm using serial biomarker measurements doubles the number of screen-detected cancers compared with a single-threshold rule in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. *J Clin Oncol* 33:2062-2071, 2015
24. Jacobs IJ, Menon U, Ryan A, et al: Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): A randomised controlled trial. *Lancet* 387:945-956, 2016
25. UK Familial Ovarian Cancer Screening Study: http://www.instituteofwomenhealth.ucl.ac.uk/womens-cancer/gcrc/ukfocss/UKFOCSS_Protocol_P2_v8_Oct_10_Website_20160525.pdf
26. Widschwendter M, Rosenthal AN, Philpott S, et al: The sex hormone system in carriers of *BRCA1/2* mutations: A case-control study. *Lancet Oncol* 14:1226-1232, 2013
27. Skates SJ, Mai P, Horick NK, et al: Large prospective study of ovarian cancer screening in high-risk women: CA125 cut-point defined by menopausal status. *Cancer Prev Res (Phila)* 4:1401-1408, 2011
28. Aletti GD, Dowdy SC, Podratz KC, et al: Relationship among surgical complexity, short-term morbidity, and overall survival in primary surgery for advanced ovarian cancer. *Am J Obstet Gynecol* 197:676.e1-676.e7, 2007
29. Skates SJ, Greene MH, Buys SS, et al: Early detection of ovarian cancer using the risk of ovarian cancer algorithm with frequent CA125 testing in women at increased familial risk: Combined results from two screening trials. *Clin Cancer Res* [Epub ahead of print January 31, 2017]
30. Hyman DM, Long KC, Tanner EJ, et al: Outcomes of primary surgical cytoreduction in patients with *BRCA*-associated high-grade serous ovarian carcinoma. *Gynecol Oncol* 126:224-228, 2012
31. Brain KE, Lifford KJ, Fraser L, et al: Psychological outcomes of familial ovarian cancer screening: No evidence of long-term harm. *Gynecol Oncol* 127:556-563, 2012

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Evidence of Stage Shift in Women Diagnosed With Ovarian Cancer During Phase II of the United Kingdom Familial Ovarian Cancer Screening Study

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Travel, Accommodations, Expenses: Roche

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