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ORIGINAL REPORT

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

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ABSTRACT

Purpose
To establish the performance characteristics of annual transvaginal ultrasound and serum CA125 screening for women at high risk of ovarian/fallopian tube cancer (OC/FTC) and to investigate the impact of delayed screening interval and surgical intervention.

Patients and Methods
Between May 6, 2002, and January 5, 2008, 3,563 women at an estimated ≥ 10% lifetime risk of OC/FTC were recruited and screened by 37 centers in the United Kingdom. Participants were observed prospectively by centers, questionnaire, and national cancer registries.

Results
Sensitivity for detection of incident OC/FTC at 1 year after last annual screen was 81.3% (95% CI, 54.3% to 96.0%) if occult cancers were classified as false negatives and 87.5% (95% CI, 61.7% to 98.5%) if they were classified as true positives. Positive and negative predictive values of incident screening were 25.5% (95% CI, 14.3 to 40.0) and 99.9% (95% CI, 99.8 to 100) respectively. Four (30.8%) of 13 incident screen-detected OC/FTCs were stage I or II. Compared with women screened in the year before diagnosis, those not screened in the year before diagnosis were more likely to have ≥ stage IIIc disease (85.7% *v* 26.1%; $P = .009$). Screening interval was delayed by a median of 88 days before detection of incident OC/FTC. Median interval from detection screen to surgical intervention was 79 days in prevalent and incident OC/FTC.

Conclusion
These results in the high-risk population highlight the need for strict adherence to screening schedule. Screening more frequently than annually with prompt surgical intervention seems to offer a better chance of early-stage detection.

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INTRODUCTION

Approximately 10%[1-3] of ovarian cancers (OCs) are a result of familial/genetic predisposition, predominantly germline mutations in *BRCA1* and *BRCA2* and mismatch repair genes in Lynch syndrome (LS). The risk of OC (until age 70 years) varies between 3.4% to 33% in LS,[4-6] 11% to 37% in *BRCA2* carriers, and 39% to 65% in *BRCA1* carriers.[7-10]

Given the poor survival associated with OC,[11] women with a known predisposing mutation or strong family history are offered risk-reducing bilateral salpingo-oophorectomy (RRSO) to prevent OC/fallopian tube cancers (FTCs).[12] In premenopausal women, RRSO halves the risk of expected breast cancers[13] but results in infertility and premature menopause, with associated increased cardiovascular[14] and osteoporosis[15] risks. Delaying surgery until age 50 years carries OC/FTC risks of 15% to 27% in *BRCA1* and 0.4% to 4% in *BRCA2* carriers.[7-9,16] Screening might enable women to delay RRSO until menopause.

OC/FTC survival inversely correlates with stage.[17] Although improved medium-term survival has been shown with general population screening,[18] with a high proportion of early-stage cancers detected in the prevalence screen of an ongoing trial,[19] recently another trial found no mortality benefit.[20]

Random assignment to a nonscreening arm is unacceptable to high-risk women and clinicians (United Kingdom Familial Ovarian Cancer

Screening Study [UK FOCSS] consensus meeting, London, United Kingdom, 2004). Best evidence in this population will probably come from prospective cohort studies. Here we present the largest such study to date, to our knowledge, to define screening performance characteristics and investigate the impact of delayed screening interval and surgical intervention.

PATIENTS AND METHODS

Between May 6, 2002, and January 5, 2008, 3,563 women at an estimated minimum 10% lifetime OC risk were recruited, and data on screening and outcomes were collected prospectively. The study was designed to estimate sensitivity within ± 10% (expected 95% CI), assuming 0.5% annual OC incidence.

Entry Criteria

The inclusion criteria originally defined a minimum 10% lifetime OC risk (Appendix, online only) on the basis of family history or predisposing mutations, including LS-associated mutations. OC in the family was defined as epithelial OC, FTC, or primary peritoneal cancer (PPC). Borderline and nonepithelial OC were excluded. Women were excluded if they had undergone bilateral salpingo-oophorectomy, were age < 35 years, or were participating in other OC screening trials.

Recruitment

After ethical approval (Eastern Multicentre Research Ethics Committee 97/5/007), women were recruited by specialist nurses, clinical geneticists, or gynecologists at 37 regional centers in the United Kingdom. Before consenting, women were counseled that RRSO was recommended management, being the only method of preventing OC/FTC. The limitations of screening were highlighted. Documentation (death certificates, histopathology reports) of relevant familial cancers was required, and eligibility was confirmed by the coordinating center (CC). Recruiting centers forwarded screening results to the CC for database entry (UK FOCSS Trial Management System, developed in MS Visual Basic 6 and Classic ASP 3, Microsoft SQL Server 2000).

Screening

Phase I of UK FOCSS comprised annual transvaginal ultrasound scans (TVSs) and serum CA125 measurements, arranged and performed locally. Annual scans were performed by experienced National Health Service ultrasonographers, and follow-up scans for abnormalities were performed by expert gynecologists or radiologists. Where practical, scans were scheduled for menstrual cycle days 3 to 6. Collaborating centers were asked to complete datasheets describing ovarian volume and morphology, which were classified according to predetermined criteria (Appendix, online only). Guidelines for management of results were provided (Appendix Fig A1, online only), but management remained at the discretion of collaborating gynecologists. Serum CA125 was measured using preferred assays at collaborating clinical laboratories. We recommended cutoffs of 35 and 30 IU/mL in premenopausal and postmenopausal women, respectively.[21] Between 2007 and 2009, phase II screening (once every 4 months) was introduced in response to concerns[22] about the ability of annual screening to detect early-stage disease. Phase II is currently in follow-up and will be reported separately.

Documentation of Surgical Procedures and Diagnoses

Whenever women underwent salpingo-oophorectomy, the CC obtained documentation explaining surgical indication, whether CA125 and/or scan results had prompted surgery, the operation note, and histopathology and cytopathology reports. These were reviewed by a gynecologic oncologist (A.N.R.) and pathologist (E.B., N.S.). Serial sectioning of tubes/ovaries was not mandatory for RRSO specimens.

Criteria for Screening Performance Characteristics

Women undergoing salpingo-oophorectomy were only classified as having had RRSO if they were asymptomatic and had normal screening tests in the year before surgery and if the recruiting center indicated RRSO as the reason for withdrawal from the study. Cases in which abnormal screening results prompted surgery were true positive if invasive epithelial OC/FTC was diagnosed. All other diagnoses (including borderline/benign ovarian tumors) resulting from surgery prompted by abnormal test results were false positive. Cases in which a nonconcerning test result (eg, simple ovarian cysts, transiently raised CA125) had contributed to the decision to undergo surgery were classified as screening-related surgery to provide estimates of likely additional surgeries in any future screening program. True-negative patients were those in whom the last screen was normal, and no diagnosis of OC/FTC was made in the subsequent 365 days. Prevalent cases were those in which patients were diagnosed at first screen. Incident cases were those in which patients were diagnosed after subsequent screens.

Cancers diagnosed > 365 days after a woman's last screen are reported but not included in the analyses of annual screening performance. PPC (defined according to recognized pathologic criteria[23]) is unlikely to be amenable to early-stage detection using current techniques; however, data are presented both including and excluding PPC from the screening performance analysis.

Interval cancers (false negatives) were those presenting clinically < 365 days after the last screen. Occult cancers found in RRSO specimens < 365 days after the last annual screen can be classified as either false negative or true positive, because they might have been missed or detected at the next annual screen had RRSO not been performed. We therefore report screening performance using both these scenarios, on the assumption that the true sensitivity of screening in a population not undergoing RRSO falls between these two estimates.

Follow-Up

Collaborators notified the CC when women withdrew from the study. In December 2006, all women were invited to join phase II of the study and to confirm they still had one or more ovaries/fallopian tubes. All women were flagged with the relevant national cancer registry (National Health Service Information Centre for Health and Social Care, General Registrar Office for Scotland, and Northern Ireland Cancer Registry).

For women who withdrew, data was censored 365 days after withdrawal date. Details of OC/FTCs occurring after censoring are reported but not

Table 1. Indication for Inclusion and Mutation Status of Study Participants

Indication for Inclusion or Mutation Status	No.	%
Indication for Inclusion		
Known mutation in family and/or proband	867	24.4
Breast/ovarian family history; no known mutation	1,499	42.1
Ovarian only family history; no known mutation	889	25.0
Lynch syndrome family history; no known mutation	25	0.7
Not fitting standard inclusion criteria but deemed high risk by recruiting center and study clinical geneticist (J.M.)	283*	7.9
Total	3,563	100
Mutation status of proband at censor date		
BRCA1	282	7.9
BRCA2	250	7.0
BRCA1 and *BRCA2*	6	0.2
MLH1	28	0.8
MSH2	33	0.9
MSH6	4	0.1
PMS1	0	0.0
PMS2	0	0.0
Tested negative	322	9.0
Tested but result pending	109	3.1
Untested	2,529	71.0
Total	3,563	100

NOTE. Documentation (death certificates or histopathology reports) of relevant cancers in the family was required. This was available for 63.9% of women included for reasons other than a predisposing mutation in themselves or first-degree relative.

*Nine were possible Lynch syndrome families, and 271 were breast/ovarian cancer families.

included in the analyses of annual incidence or screening performance. OC/FTCs diagnosed within 365 days of a woman's last screen were included in the analyses. Of women in phase I of UK FOCSS, 66.2% transferred to phase II of the study and subsequently underwent CA125 testing once every 4 months and annual TVS. For these women, withdrawal date from phase I was the date of their first screen on phase II (ie, > 4 months after their last annual phase I screen), and data were censored 365 days after withdrawal date. Because no cancers occurred within 1 year of a woman transferring to phase II, sensitivity was not artificially increased by the introduction of screening once every 4 months.

To investigate potentially avoidable delays (which could influence stage at detection), we analyzed screening delays in women diagnosed with OC/FTC and the interval between abnormal test results and surgical investigation. Detection screens were defined as an abnormal TVS and/or elevated CA125 result found at an annual screen leading to surgery/diagnostic biopsy resulting in diagnosis of OC/FTC. Delays in annual screens were defined as any detection screen (CA125 or TVS) performed > 365 days after previous normal annual screen. Delay was calculated as days between detection screen and prior normal annual screen minus 365. Interval from screen to diagnosis was calculated to the date of surgery/diagnostic biopsy. Composite delay was calculated as the sum of screening delay and screen to diagnosis interval. To investigate any effect of delayed screening, we analyzed International Federation of Gynecology and Obstetrics stage, optimal debulking (< 1 cm residual disease), and overall and disease-specific survival from diagnosis (irrespective of whether cancers were screen detected), comparing women screened in the year before diagnosis with those not screened in the year before diagnosis. We excluded LS-associated cases from these analyses to avoid contaminating the predominant *BRCA*-associated cases.

RESULTS

The median age of participants at recruitment was 44.6 years (range, 35 to 81 years). Table 1 lists indications for inclusion. One thousand thirty-four women (29.0% of the cohort) had undergone mutation testing before censoring. Six hundred three women (65.2% of those in whom test results were known; 16.9% of the cohort) were known mutation carriers.

The study accumulated 11,366 women-years of screening (mean, 3.2 years per woman). Figure 1 shows the flow of participants. Although 182 women (5.1%) were lost to direct follow-up by the CC, they remained flagged by the cancer registries. The commonest reason for withdrawal was RRSO (14.3% of the study population), but an additional 4.2% withdrew because they were subsequently found not to carry their family's predisposing mutation.

Index Cancers

Table 2 shows cancers occurring during screening and follow-up according to whether cancers were detected at prevalence or incidence

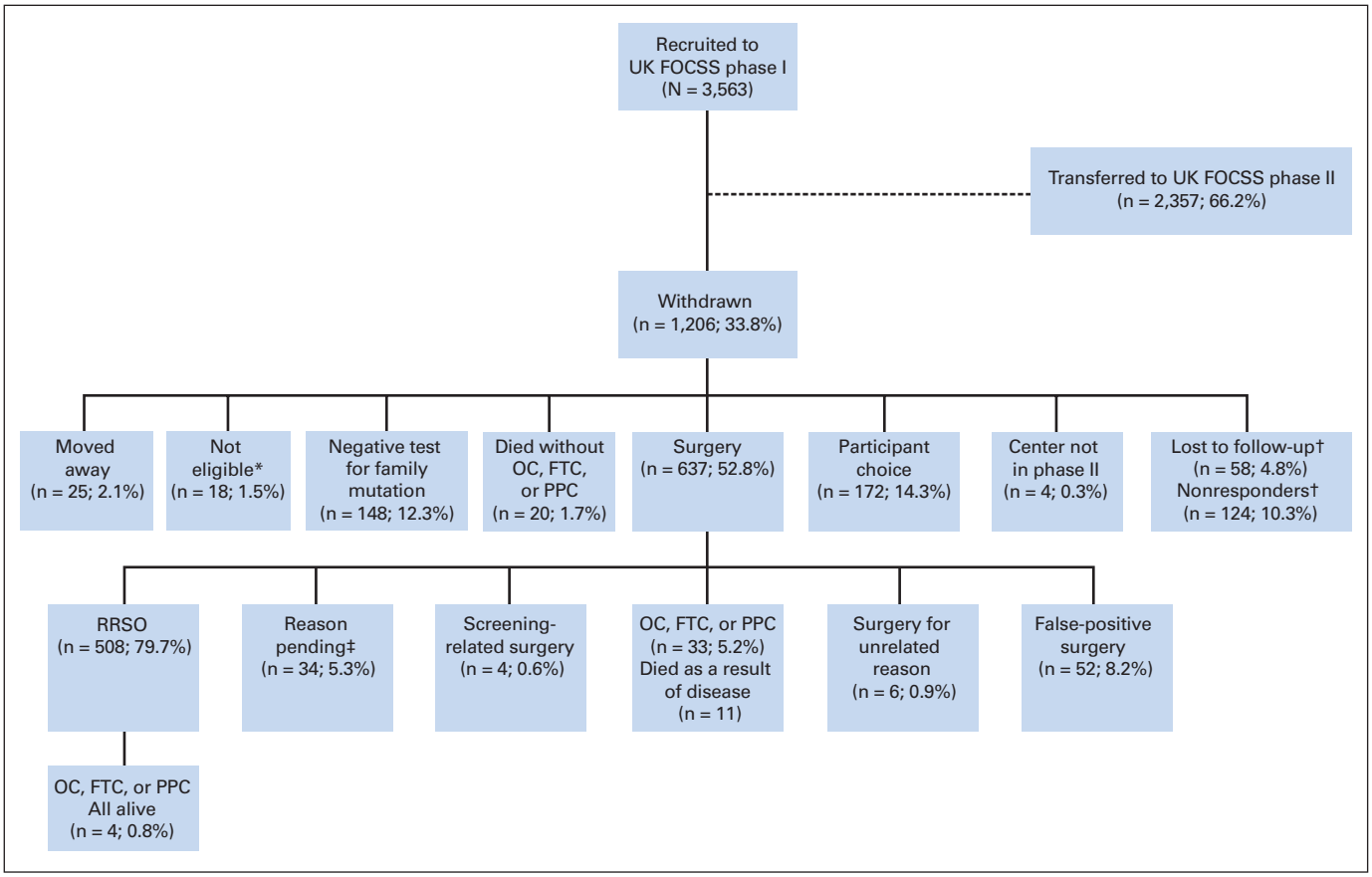

Fig 1. Flow of participants through study. All percentages refer to proportion of population defined in preceding row. UK FOCSS, United Kingdom Familial Ovarian Cancer Screening Study; FTC, fallopian tube cancer; OC, ovarian cancer; PPC, primary peritoneal cancer; RRSO, risk-reducing salpingo-oophorectomy. (*) Ineligible on basis of new information regarding diagnoses in family history becoming available subsequent to recruitment. (†)Lost to follow-up: unable to establish current whereabouts; nonresponders: failed to respond despite confirmation of correct contact details. (‡) Reason for surgery pending, but known not to have had OC, FTC, or PPC.

Table 2. Ovarian, Tubal, and Peritoneal Cancers Occurring During Screening and Follow-Up

FIGO Stage	No. of Patients	Tumor				Gene Mutation	Age (years)	CA125 at Diagnosis (u/mL)	Imaging Modality[a]	Delay in Annual Screen at Detection (days)[b]	Interval Between Abnormal Test and Surgery (days)	Composite Interval (days)[c]
		Substage	Grade	Histotype	Site							
Prevalent cancers	9											
I	5	Ia	G3	Clear cell	OC	*MSH2*	35	24	TVS	NA	141	NA
		Ic	G3	Serous	OC	*MLH1*	60	128	TVS	NA	36	NA
		Ic	G3	Serous	OC	*BRCA2*	51	22	TVS	NA	126	NA
		Ic	G2	Serous	FTC	*BRCA1*	55	21	TVS	NA	20	NA
		Ic	G3	Clear cell[d]	OC	*MSH2*	49	94	TVS	NA	36	NA
II	1	IIb	G3	Serous	FTC	*BRCA1*	47	103	TVS	NA	79	NA
III	3	IIIa	G3	Serous	OC	*BRCA2*	53	48	TVS	NA	96	NA
		IIIb	G3	Serous	OC	*BRCA1*	48	88	TVS	NA	92	NA
		IIIc	G3	Serous	OC	*BRCA1*	57	223	TVS	NA	74	NA
Incident screen-detected cancers	13											
I	2	Ia	G1	Endometrioid	OC	Untested[e]	45	21	TVS	49	19	68
		Ia	G2	Serous	FTC	*BRCA1*	43	11	TVS	−52	79	27
II	2	IIc	G3	Adenocarcinoma/ endometrioid	OC	*BRCA1*	55	39	TVS	737	138	875
		IIc	G3	Serous	OC	*BRCA1*	52	192	TVS	231	21	252
III	9	IIIa	G3	Endometrioid	OC	*BRCA1*	45	124	TVS	27	184	211
		IIIb	G2	Serous	OC	*BRCA1*	46	73	TVS	−1	69	68
		IIIb	G2	Serous	OC	Untested[f]	42	45	TVS	102	107	209
		IIIb	G3	Serous	OC	*BRCA1*	48	3,874	TVS	−50	15	−35
		IIIb	G3	Adenocarcinoma/ mucinous	OC/FTC	*BRCA1*	57	4	TVS	30	147	177
		IIIc	G2	Endometrioid	OC	*BRCA1*	52	246	TVS	78	20	98
		IIIc	G3	Serous/ endometrioid	OC/FTC	*BRCA1*	49	323	TVS	98	32	130
		IIIc	G3	Serous	FTC	*BRCA2*	60	17	TVS	236	177	413
		IIIc	G3	Serous	FTC	VUS[g]	58	166	TVS	6	96	102

FIGO Stage	No. of Patients	Tumor				Gene Mutation	Age (years)	CA125 at Diagnosis (u/mL)	Imaging Modality[a]	Last Screen to Diagnosis Interval (days)	Presentation
		Substage	Grade	Histotype	Site						
Screen-negative cancers	8										
I	1	Ic[h]	G3	Serous/ endometrioid	OC	*BRCA1*	67	Not done[i]	Not done[i]	221	Ovarian cyst torsion
III	5	IIIc	G3	Serous	OC	*BRCA1*	65	582	CT	382	GI symptoms
		IIIc	G3	Serous	OC	*BRCA1*	67	527	TVS	421	GI symptoms
		IIIc	G3	Serous	FTC/OC	*BRCA1*	74	278	TVS	1,369	Abdominopelvic pain
		IIIc	G3	Serous	OC[j]	*BRCA1*	60	724	TVS	593	Postmenopausal bleeding
		IIIc	G3	Serous	OC	*BRCA2*	62	550	CT	1,073	Breast cancer restaging
IV	2	IV	G2	Serous	OC	*BRCA1*	62	1,513	TVS	327	Postmenopausal bleeding
		IV	G3	Small cell	OC	*BRCA2*	58	560	CT	982	GI symptoms
Occult and primary peritoneal cancers	7										
I	2	Ia	G2	Serous	FTC	*BRCA1*	53	Not done[k]	Not done[k]	76	Occult found at RRSO
		Ic	G3	Serous/mucinous	OC	*BRCA1*	38	Not done	Not done	539	Occult found at RRSO
II	1	IIc	G2	Serous	OC/FTC	*BRCA1*	60	Not done[l]	Not done[l]	106	Occult found at RRSO
III	4	IIIb	G3	Serous	Peritoneal	*BRCA1*	61	404	CT	497	Screen detected
		IIIc	G2	Serous	Peritoneal	Untested[m]	60	1173	CT	255	GI symptoms

(continued on following page)

Table 2. Ovarian, Tubal, and Peritoneal Cancers Occurring During Screening and Follow-Up (continued)

FIGO Stage	No. of Patients	Tumor				Gene Mutation	Age (years)	CA125 at Diagnosis (u/mL)	Imaging Modality[a]	Last Screen to Diagnosis Interval (days)	Presentation
		Substage	Grade	Histotype	Site						
		IIIc	G2	Serous	Peritoneal	*BRCA1*	40	Not done	Not done	411	Occult found at RRSO
		IIIc	G3	Serous	Peritoneal	*BRCA2*	57	613	CT	678	CA125 taken approximately 1 year after RRSO

Abbreviations: CT, computed tomography (instead of ultrasound); FTC, fallopian tube cancer; NA, not applicable; OC, ovarian cancer; RRSO, risk-reducing salpingo-oophorectomy; TVS, transvaginal ultrasound; VUS, variant of unknown significance.

[a]Imaging was abnormal in all patients for whom it was performed.

[b]Negative number denotes annual screen scheduled early.

[c]Sum of delay in annual screening and interval from abnormal test to surgery (negative number results from annual screen scheduled early).

[d]Occurring against a background of endometriosis.

[e]Confirmed diagnoses of bowel cancer in paternal cousin (at age 61 years), paternal grandmother (at age 50 years), and sister (at age 51 years, with synchronous OC) and possibly breast cancer in maternal cousin (at age 35 years). Family has tested negative for *BRCA1*, *BRCA2*, and immunohistochemical Lynch syndrome markers. Patient herself had previous unilateral oophorectomy for endometriosis.

[f]Confirmed OC diagnoses in mother at age 52 years and maternal grandmother at age 73 years.

[g]VUS in *BRCA1* (5313-12 G>A).

[h]Incompletely staged.

[i]Last screen 221 days before emergency surgery; ovaries not seen on scan because of bowel gas; no CA125 taken; prior screen (scan and CA125) normal 574 days before presentation.

[j]This patient had a synchronous stage II grade 2 endometrioid endometrial cancer.

[k]Last screen 76 days before RRSO; CA125, 18 u/mL; normal scan.

[l]Last screen 106 days before RRSO; CA125, 21 u/mL; one normal ovary seen on scan (other obscured by bowel gas).

[m]Personal history of bilateral breast cancer at ages 49 and 52 years; one sister had breast cancer at age 47 years; another sister had OC at age 71 years and breast cancer at age 63 years; another sister had OC at age 53 years.

screens, screen negative, occult, or PPC. Twenty-six primary invasive epithelial OC/FTC and one PPC were observed during 11,366 women screen–years before censoring (annual OC/FTC/PPC incidence, 0.24%). An additional 10 cancers occurred beyond censoring 365 days after a last screen (median, 539 days; range, 382 to 1369).

Twenty-nine (78.4%) of 37 cancers contained serous carcinoma; the remainder were predominantly endometrioid. Two clear-cell carcinomas occurred in LS mutation carriers. The median age of diagnosis was 53 years (range, 35 to 74 years), and 15 (40.5%) of 37 were premenopausal. Thirty-three (89.2%) of 37 cancers occurred in pathogenic mutation carriers. Of these, 24 (72.7%) were *BRCA1* mutation carriers, six (18.2%) were *BRCA2* mutation carriers, and three (9.1%) were carriers of LS mutations *MLH1* (one patient) and *MSH2* (two patients). An additional woman had a *BRCA1* variant of unknown significance. Three women (8.1% of all OC/FTC/PPC) had not undergone mutation testing (Table 2). Twenty-two (66.7%) of 33 women with a pathogenic mutation knew their mutation status before diagnosis of OC/FTC/PPC, and 13 women (35.1%) with OC/FTC/PPC had a prior diagnosis of breast cancer (11 women) or ductal carcinoma in situ (two women).

Of prevalent OC/FTCs, six (66.7%; 95% CI, 35.1% to 88.2%) of nine were International Federation of Gynecology and Obstetrics stage I or II. Four (30.8%; 95% CI, 12.4% to 58.0%) of 13 incident screen-detected OC/FTCs were stage I or II. When LS cases were excluded, six (85.7%; 95% CI, 42.1% to 99.6%) of seven OC/FTCs in women not screened in the year before diagnosis were stage IIIc or higher, compared with six (26.1%; 95% CI, 10.2% to 48.4%) of 23 women who were screened in the year before diagnosis (Fisher's test $P = .009$). Four (57.1%; 95% CI, 18.4% to 90.1%) of seven women not screened in the year before diagnosis underwent optimal debulking surgery (residual < 1 cm), compared with 21 (91.3%; 95% CI, 72.0% to 98.9%) of 23 women who were screened in the year before diagnosis (Fisher's test $P = .068$). Both mean overall and disease-specific survival (to March 31, 2011) were 48.4 months (95% CI, 39.4 to 57.4) in women not screened in the year before diagnosis, compared with 71.9 months (95% CI, 60.7 to 83.2) in those who were screened in the year before diagnosis (log-rank [Mantel-Cox] $P = .233$); all deaths resulted from OC/FTC.

Screening Performance

Annual screening performance characteristics are listed in Table 3. Two women were diagnosed with interval OCs within 365 days of normal screens. Four women had occult OC/FTC/PPC found at RRSO (prevalence, 0.8%; 95% CI, 0.2% to 2.0%). Two of these were within 365 days of normal screens and were includable as false negatives or true-positives in the sensitivity analysis. Two of the eight screen-negative OC/FTCs were diagnosed < 365 days of an annual screen and so were included as false negatives. Fifteen (68.2%) of 22 of all screen-detected cancers had a raised CA125 at detection (median, 80.5 IU/mL; range, 4 to 3,874) according to the predetermined cutoffs. All screen-detected cancers had abnormal TVS at detection.

Fifty-two women (1.5%) underwent false-positive surgery prompted at least in part by abnormal screening test results. Five of these women (9.6%) had raised CA125 alone, 43 (82.7%) had a suspicious scan alone, and four (7.7%) had abnormal results in both tests. Four (7.7%) of these 52 women had gynecologic pathology (one benign teratoma, one mucinous borderline tumor, one serous borderline tumor, one fibroid). All these lesions were detected on TVS, and only the fibroid had raised CA125. An additional four women (0.1%) underwent surgery after equivocal ultrasound results or transient nonconcerning small rises in CA125. Because documentation from the collaborating center indicated that test results had contributed to the woman's decision to undergo RRSO, these cases were classified as screening-related surgery.

Table 3. Screening Performance Characteristics

Screen Type	Total Screened Population (N = 3,563)						*BRCA1* and *BRCA2* Mutation Carriers (n = 538)				Unknown Mutation Status at Enrollment (n = 3,065)						LS Mutation or Family History (n = 99)			
	Prevalent		Incident*		Incident†		Prevalent		Incident‡		Prevalent		Incident*		Incident†		Prevalent		Incident	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Sensitivity																				
Occult FN	90.0	55.5 to 99.8	81.3	54.3 to 96.0	76.5	50.1 to 93.2	85.7	42.1 to 99.6	76.9	46.2 to 95.0	NA§		91.7	61.5 to 99.8	75.0	19.4 to 99.4	100	29.2 to 100	100	2.5 to 100
Occult TP	100	69.2 to 100	87.5	61.7 to 98.5	82.4	56.6 to 96.2	100	59.0 to 100	91.7	61.5 to 99.8	NA§		100	73.5 to 100	75.0	19.4 to 99.4	100	29.2 to 100	100	2.5 to 100
Specificity‖	99.7	99.5 to 99.9	98.9	98.5 to 99.2	98.9	98.5 to 99.2	99.2	98.0 to 99.8	99.2	97.9 to 99.8	99.7	99.4 to 99.8	99.8	98.3 to 99.2	99.8	98.3 to 99.2	100	96.1 to 100	100	96.1 to 100
PPV																				
Occult FN	42.9	21.8 to 66.0	25.5	14.3 to 40.0	25.5	14.3 to 40.0	60.0	26.2 to 87.8	71.4	41.9 to 91.6	NA§		23.9	12.6 to 38.8	23.9	12.6 to 38.8	100	29.2 to 100	100	2.5 to 100
Occult TP	45.4	24.4 to 67.8	27.0	15.6 to 41.0	27.0	15.6 to 41.0	63.6	30.1 to 89.1	73.3	44.9 to 92.2	NA§		25.5	14.0 to 40.3	25.5	14.0 to 40.3	100	29.2 to 100	100	2.5 to 100
NPV																				
Occult FN	100	99.8 to 100	99.9	99.8 to 100	99.9	99.7 to 100	99.8	98.9 to 100	99.4	98.2 to 99.9	99.9	99.8 to 100	99.9	99.7 to 100	100	99.8 to 100	100	96.1 to 100	100	96.1 to 100
Occult TP	100	99.9 to 100	99.9	99.8 to 100	99.9	99.8 to 100	100	99.3 to 100	99.6	98.5 to 100	99.9	99.8 to 100	100.00	99.9 to 100	100	99.8 to 100	100	96.1 to 100	100	96.1 to 100

		Prior Study for Comparison[24]¶							
		No. of Cancers		Sensitivity		Specificity		PPV		NPV	
Screen Type	Occult Status	Total	Prevalent	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Incident plus prevalent	Occult excluded	7	2	42	14 to 70	99	98 to 99	23	5 to 40	99	99 to 100
Incident plus prevalent	Occult FN	12	2	71	38 to 11	99	98 to 99	23	5 to 40	100	100 to 100

Abbreviations: FN, false negative; LS, Lynch syndrome; NA, not applicable; NPV, negative predictive value; PPC, primary peritoneal cancer; PPV, positive predictive value; TP, true positive.
*Excluding PPC.
†Including PPC.
‡No PPCs in *BRCA* carriers occurred within 1 year of prior screen.
§Not applicable because no prevalent cancers occurred in unknown mutation status group.
‖Occult cancers not applicable (specificity does not depend on false-negative or true-positive rate).
¶Only large prior study to our knowledge with data reported in a fashion that allows some comparison of performance characteristics with our study.

Table 4. Screening and Surgery Intervals in Screen-Detected Cancers

Screen Type	No. of Cancers	Screen Delay (days)		Surgery Interval (days)		Composite Interval (days)	
		Median	Range	Median	Range	Median	Range
Prevalent	9	NA*		79	20-141	NA*	
Incident screen detected	13	88	6-737	79	15-184	154	27-875
Stage I/II	4	231	49-737	50	19-138	160	27-875
Stage III	9	78	6-236	96	15-184	154	68-413

Abbreviation: NA, not applicable.
*Prevalent screen is the first screen and cannot be delayed. Calculation of composite delay for prevalent cases is not appropriate.

Intervals in Screening and Surgical Investigation

Table 4 shows delays in annual screens detecting incident OC/FTCs and intervals between abnormal results and diagnosis in prevalent and incident cases. Reasons for delays included: temporarily leaving the United Kingdom, assuming abnormal results were the result of endometriosis, and women's reluctance to undergo surgery.

DISCUSSION

The present study is the first large prospective high-risk population screening study reported to our knowledge. The other large ongoing studies are the US Cancer Genetics Network and Gynaecologic Oncology Group 199[25] studies. The strengths of our study are its size, reliable follow-up via multiple routes, and analysis of intervals in screening and surgical investigation not previously studied in this context. Its limitations are the lack of an enforced screening/management protocol, incomplete documentation confirming relatives' cancers, and incomplete screening results for those not undergoing surgery. This prevents reliable estimates of repeat testing rates. Finally, there was no mandatory pathology protocol for RRSO specimens, possibly explaining the low occult cancer prevalence (0.8%).

Previously, a meta-analysis[22] suggested that annual screening might not provide adequate sensitivity for early-stage disease. However, when duplicate cases were excluded, 14 (45.2%) of 31 detected cases were stage I or II.[26] Subsequently, additional cohort studies were reported separately[24,27-31] and as a pooled analysis.[32] We reanalyzed these data[33] and found a borderline significant ($P = .046$) improvement in the stage distribution of screen-detected *BRCA1/2*-associated cancers (52.6% of incident *v* 19.0% of prevalent cancers were stage I or II). Our study suggests that screening in the year before diagnosis reduces the proportion of patients diagnosed at stage $\geq$ IIIc but does not increase the proportion diagnosed at stage I. This is consistent with the hypothesis that high-grade serous OC undergoes early transcoelomic spread.[34] The nonsignificantly higher optimal debulking rate and nonsignificant trend to increased survival in those screened in the year before diagnosis suggest that screening might have an effect on survival, but they do not prove screening will reduce mortality. In particular, there could be a lead-time effect, with longer survival resulting solely from earlier diagnoses rather than screening efficacy. In addition, this analysis compares small nonrandomized groups determined by screening interval, so there could be other important differences between them.

We found 66.7% of the prevalent cases were early stage. This could be chance, or it could reflect the fact that three of five stage I cancers occurred in LS mutation carriers. The prognosis of LS OC is better than that associated with *BRCA1/2* mutations,[35] possibly because presentation occurs earlier.[36] We therefore speculate that LS-associated tumors have a longer sojourn time, explaining the high proportion of early-stage disease in the prevalence screen. Given that 33 of 37 OC/FTC/PPCs occurred in women with a predisposing mutation, clearly mutation carriers are at highest cancer risk. However, first-degree relatives of cancer-affected individuals from untested high-risk families should also be considered high risk and counseled accordingly.[37] Where an unaffected relative is the only family member tested, and she is mutation negative, then her risk would be considerably lower than that of a mutation carrier, but not as low as that of a woman testing negative for a relative's known pathogenic mutation. We are not aware of any data on OC incidence in mutation-negative women from otherwise untested high-risk families. However, given our findings, we speculate that they may not be at sufficiently high risk to justify familial OC screening.

The performance characteristics of annual screening were encouraging. The incident sensitivity ($>$ 80%) was higher than that previously reported[24] (Table 3). However, the proportion of early-stage disease was disappointing (two of 13 incident screen-detected cases were stage I), supporting the current assertion in the National Comprehensive Cancer Network guideline[38] that annual screening is ineffective in high-risk women. The high incident PPV (similar to that previously reported[24]) means that only four women underwent surgery for each case of cancer detected. As expected, the PPV was greater in mutation carriers than in those of unknown mutation status. Only 0.6% underwent screening-related surgery prompted by nonnormal but clinically nonsuspicious screening results.

The high negative predictive value is relevant to this population of women, who may undergo screening to delay RRSO to complete childbearing or delay surgically induced menopause. Although much of the high negative predictive value derives from the low annual incidence of OC/FTC even in *BRCA1*/*BRCA2* mutation carriers, the knowledge that normal test results provide 99.9% (99.4% in known mutation carriers) probability a woman will not be diagnosed with OC in the next year should help decision making regarding timing of RRSO.

Many cancers had long intervals between annual screens and/or between abnormal results and diagnosis. The United Kingdom mandates a 62-day maximum acceptable interval from suspected cancer referral to treatment.[39] However, this limit was not consistently delivered nationally until 2006,[40] when UK FOCSS had been running for 4 years. In this high-risk population, it is essential that screening is not delayed, that abnormal results are assumed to represent possible cancer, and that the threshold for rapid follow-up tests or surgery is set much lower than in the general population. Stricter protocols may increase the false-positive rate, but the PPV achieved was sufficiently high to remain acceptable even if some increase in false positives occurs.

Given the delays we observed, we speculate that rigorous adherence to screening schedules and swifter action on abnormal results might result in earlier stage at diagnosis. Phase II of UK FOCSS has implemented the following modifications: one, the screening frequency has been increased to once every 4 months; two, the threshold for and timing of repeat tests is protocol driven; three, CA125 is

assayed in a single laboratory to reduce interassay variability; four, serial CA125 values are analyzed by a risk of OC algorithm,[41] which has demonstrated superior performance to CA125 when used as a cutoff[42]; and five, collaborators are prompted to organize scans and referrals via an Internet-based database, modeled on the successful UKCTOCS (United Kingdom Collaborative Trial of Ovarian Cancer Screening) database.[43] It is hoped that these changes will optimize early-stage OC detection in the high-risk population. If this is achieved, and if UKCTOCS demonstrates reduced general population OC mortality, then high-risk women wishing to delay RRSO can be offered a risk-minimizing screening strategy before surgery. Until then, RRSO remains the only proven method of preventing mortality from OC/FTC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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