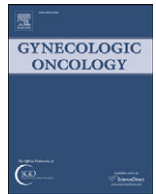




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## Psychological outcomes of familial ovarian cancer screening: No evidence of long-term harm<sup>☆</sup>

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### HIGHLIGHTS

- Abnormal results of familial ovarian cancer screening may raise women's concerns in the short-term but not in the longer-term.
- Women receiving abnormal test results are more likely to withdraw from screening, primarily for salpingo-oophorectomy.
- Decision support is needed for women who are considering options for managing their risk of familial ovarian cancer.

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### ABSTRACT

**Objectives.** Ovarian cancer screening for women at increased genetic risk in the UK involves 4-monthly CA125 tests and annual ultrasound, with further tests prompted by an abnormal result. The study evaluated the longer-term psychological and behavioural effects of frequent ovarian screening.

**Methods.** Women completed T1 questionnaires before their first routine 4-monthly CA125 test, and T2 follow-up questionnaires one week after their result. Women with abnormal results completed a further questionnaire one week after return to routine screening (T3 primary end-point). T4 questionnaires were sent at nine months. Measures included cancer distress, general anxiety/depression, reassurance, and withdrawal from screening.

**Results.** A total 1999 (62%) of 3224 women completed T1 questionnaires. T2 questionnaires were completed by 1384/1609 participants (86%): 1217 (89%) with normal results and 167/242 (69%) with abnormal results. T3 questionnaires were completed by 141/163 (87%) women, with 912/1173 (78%) completing T4 questionnaires. Analysis of covariance indicated that, compared to women with normal results, women with abnormal results reported moderate cancer distress ( $F=27.47$ ,  $p\leq.001$ ,  $\eta^2=0.02$ ) one week after their abnormal result and were significantly more likely to withdraw from screening ( $OR=4.38$ ,  $p\leq.001$ ). These effects were not apparent at T3 or T4. The effect of screening result on general anxiety/depression or overall reassurance was not significant.

**Conclusions.** Women participating in frequent ovarian screening who are recalled for an abnormal result may experience transient cancer-specific distress, which may prompt reconsideration of risk management options. Health professionals and policy makers may be reassured that frequent familial ovarian screening does not cause sustained psychological harm.

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### Introduction

Ovarian cancer is one of the leading causes of cancer death in women in the UK and US [1,2]. Diagnosis of early stage ovarian cancer is associated with improved survival rates compared with late stage disease, hence the expectation that screening for early disease may reduce mortality. Approximately 10% of women who develop ovarian

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cancer have a strong family history of breast and/or ovarian cancer. In some of these families a BRCA1 or BRCA2 gene mutation can be identified, which is associated with a 25–45% lifetime risk of developing ovarian cancer [3]. Despite clear evidence that risk-reducing salpingo-oophorectomy (RRSO) substantially reduces the risk of ovarian, fallopian tube and breast cancer [4–6], it is not the choice of all women mainly due to loss of fertility and quality of life issues associated with the onset of early menopause [7]. Early detection or prevention strategies such as ovarian cancer screening (OCS) are still being investigated and are not recommended outside clinical trials. In response to the growing literature of lack of efficacy of annual OCS in these high-risk women, the UK Familial Ovarian Cancer Screening Study was established to determine the effectiveness of an annual serum CA125 test and transvaginal ultrasound scan (UKFOCSS Phase 1) [8] and more recently, 4-monthly CA125 tests combined with annual transvaginal ultrasound scans (UKFOCSS Phase 2, 2007–2011).

Evidence regarding the psychological as well as clinical outcomes of frequent familial OCS is essential. The combination of transvaginal ultrasound (TVS) and CA125 yields a significant rate of false positive abnormalities, particularly in pre-menopausal women [9]. This is magnified by use of the Risk of Ovarian Cancer (ROC) algorithm [10] that recalls 15% of women with the highest risk based on change in CA125 levels from individual baseline. Population breast screening studies suggest that women who have to undergo further tests following an abnormal result may experience adverse psychological consequences, even if further tests are normal [11], and may be discouraged from attending subsequent screening [12]. In familial OCS, false positive results of ovarian scans have been associated with transient increases in anxiety compared to normal results [13]. A US study of women at increased familial risk found reduced quality of life six months after receiving an abnormal (yet benign) result of combined CA125 and TVS screening [14]. Population-based studies of the impact of abnormal OCS results show mixed findings [15–17].

The longer-term psychological and behavioural consequences of increasing the frequency of OCS tests have not previously been evaluated. Cross-sectional data from the study suggested that withdrawal from screening in favour of surgery was influenced by prior experience of screening, past recall due to an abnormal result, and higher levels of cancer distress [18]. The present study reports prospective longitudinal data regarding the short- and longer-term impact of UKFOCSS Phase 2 screening on ovarian cancer-specific distress, anxiety and depression, overall reassurance, and rate of withdrawal from screening in a large sample of women at increased risk. The primary hypothesis was that women recalled for further tests due to an initial abnormal result would report higher cancer-specific distress shortly after being returned to routine screening compared with women who received a normal result. Secondary hypotheses were that initial recall would be associated with distress and a lack of reassurance in the longer-term, and would prompt withdrawal from familial OCS.

## Materials and methods

### Participants

Women aged over 35 years and identified as at increased genetic risk (estimated lifetime risk > 10%) were recruited from those consenting to UKFOCSS Phase 2. UK FOCSS participants were recruited from women registered with the UK Familial Ovarian Cancer Registry, attending clinical genetic centres participating in UK FOCSS, or were identified in other clinics (e.g., gynaecology clinics, medical oncology clinics) as being at high risk of ovarian cancer due to their family histories. All women recruited to UK FOCSS Phase 2 received an assessment and explanation of their ovarian cancer risk and advice about prevention and screening. Women were excluded if they had a past history of bilateral oophorectomy or were participating in other OCS trials. Eligibility criteria are described in detail elsewhere [18,19]. The study received ethics approval (ref: 97/5/007).

### Screening protocol

UKFOCSS Phase 2 routine screening involved 4-monthly CA125 blood tests combined with annual TVS. ROC results were classified as normal, intermediate (requiring a repeat CA125 test with/without TVS), or elevated (requiring immediate referral to a gynaecologist). ROC cut-offs were designed to recall 15% of the population with the highest ROC levels for repeat testing. Abnormal TVS was defined as any with a simple cyst  $\geq 5$  cm in diameter or 60 cm<sup>3</sup> in volume, multiple simple cysts, or any complex morphology. If an abnormality was identified on either of these screening tests, the CA125 and/or TVS was repeated within two months to determine whether the participant needed to be referred to a specialist gynaecologist for further investigation, or returned to the routine screening protocol.<sup>1</sup> Women with a normal result remained on routine screening, i.e. they continued to receive routine 4-monthly CA125 blood tests and annual TVS. Women were informed of their result by letter within two weeks.

### Procedures

Thirty seven of 43 UKFOCSS centres took part. All eligible women consenting to UKFOCSS Phase 2 (N = 3224) were invited to participate. Invitation packs including a study information sheet, consent form and baseline (T1) questionnaire were mailed by the UKFOCSS research team one month before the first routine Phase 2 blood test. Data were not available for women who did not consent to the psychological study. Follow-up questionnaires were sent by the psychological study team one week after women received their initial screening result (T2), with women in the recall group receiving a further T3 questionnaire one week after being returned to routine screening (primary end-point). A T4 questionnaire was sent to all eligible women nine months after the primary study end-point of receiving a normal result or after return to routine screening following recall for further tests due to an abnormal result. In order to avoid questionnaire burden, reminders were sent to those who did not respond within two weeks, with the exception of T2 reminders which were not sent to women in the recall group and T4 reminders which were not sent to any participants. Data exclusions are shown in Fig. 1.

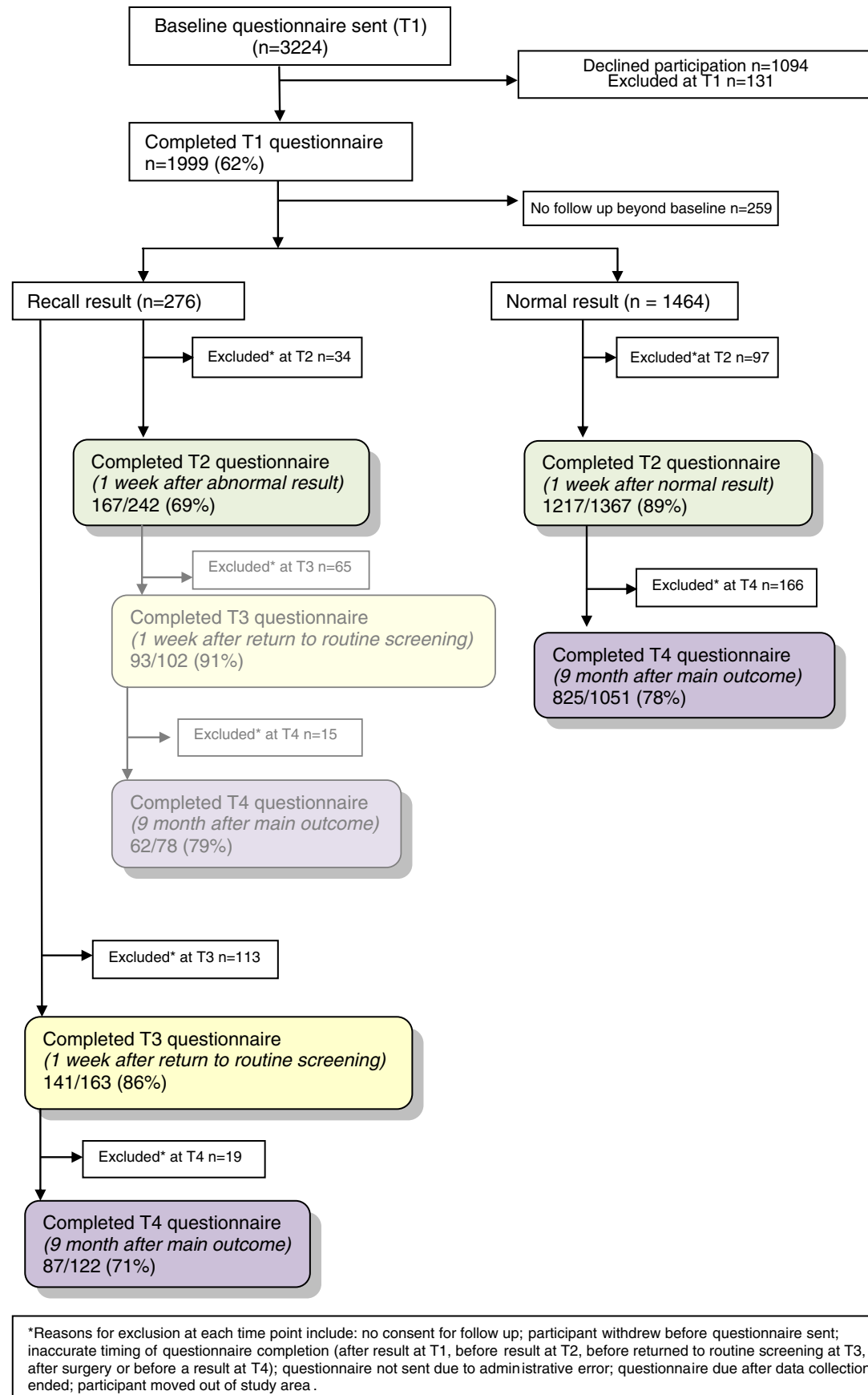
At T1, 1999 (62%) women consented to take part and completed a baseline questionnaire. T2 questionnaires were completed by 1384 (86%) of 1609 women who remained eligible, i.e. 1217 (89%) participants with a normal result and 167 (69%) participants with a recall result. Within the recall group, 141 (87%) participants completed further T3 questionnaires and of these 93 (66%) completed both T2 and T3 questionnaires. T4 questionnaires were completed by 912 (78%) of 1173 eligible women (825, 78% with a normal result and 87, 71% with a recall result). The study was powered to detect a difference of 5 points on the Impact of Event Scale with 85% power at a significance level of 5% for the primary comparison between women receiving a normal result (T2) and those who were returned to routine screening following recall for further tests due to an abnormal result (T3). This required 150 T3 follow-up questionnaires from women in the recall group. Primary analyses were conducted on 1358 participants (1217 normal vs. 141 recall result).

### Measures

#### Ovarian cancer-specific distress

Ovarian cancer-specific distress was measured using the Impact of Event Scale (IES) [20]. The IES includes 15 items assessing intrusive thoughts (7 items e.g. "I thought about it when I didn't mean to")

<sup>1</sup> Women who required further tests due to an abnormal (i.e. intermediate/elevated) ROC and/or abnormal transvaginal ultrasound scan are hereafter referred to as the recall group.



\*Reasons for exclusion at each time point include: no consent for follow up; participant withdrew before questionnaire sent; inaccurate timing of questionnaire completion (after result at T1, before result at T2, before returned to routine screening at T3, after surgery or before a result at T4); questionnaire not sent due to administrative error; questionnaire due after data collection ended; participant moved out of study area.

Fig. 1. Study flow diagram.

and avoidance of such thoughts (8 items e.g. “I stayed away from reminders of it”). Items were anchored to thoughts about ovarian cancer risk during the previous week. The IES allows the calculation of a total score (0–75), with thresholds for low (<8.5), moderate (8.6–19), and high (>19) levels of global distress corresponding to clinical levels of concern [21]. The IES has been widely used [22–24]. Internal reliability in the present study was high (T1  $\alpha = 0.93$ , T2  $\alpha = 0.93$ , T3  $\alpha = 0.95$ , T4  $\alpha = 0.94$ ).

#### General anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) [25] assesses the presence and severity of general anxiety (7 items) and depression (7 items). Total subscale scores yield cut-off values for mild (scores from 8 to 10), moderate (11–15) or severe (>16) depression or anxiety. The HADS showed strong reliability and validity in women at increased risk of breast cancer [26]. The study data indicated good internal reliability of the anxiety (T1  $\alpha = 0.86$ , T2  $\alpha = 0.87$ , T3  $\alpha = 0.90$ , T4  $\alpha = 0.87$ ) and depression (T1  $\alpha = 0.82$ , T2  $\alpha = 0.84$ , T3  $\alpha = 0.81$ , T4  $\alpha = 0.85$ ) subscales.

#### Reassurance

Two items created for the purposes of the present study were included at T4 to gauge the degree of overall reassurance gained from CA125 tests and TVS during the preceding year. Each item was rated on a 7 point scale (1 = not at all reassured, 7 = extremely reassured, total score range 2–14). Items were significantly inter-correlated ( $r = 0.66$ ,  $p \leq .01$ ) and were combined to create a composite reassurance measure ( $\alpha = 0.79$ ).

#### Withdrawal from screening

A participant was considered to have discontinued UKFOCSS Phase 2 screening if she withdrew for a variety of reasons (see Table 4 for classification and timing of withdrawal from screening).

#### Background information

Demographic information and past OCS history were included in the T1 questionnaire. Clinical information (e.g. gene mutation status, participation in UKFOCSS Phase 1 screening, menopausal status at first Phase 2 CA125, first Phase 2 screening result, repeat Phase 2 tests due to an abnormal result, and screening withdrawal) was extracted from the UKFOCSS database.

#### Statistical analysis

Descriptive analyses were conducted on all variables using SPSS v.18. Multivariate assumptions of linearity and homogeneity of regression slopes were checked, and IES and HADS-Depression scores were log transformed due to non-normal distribution. Participation bias and sample characteristics were examined using t-tests and chi-square tests of independence. Psychological effects of screening result at T2, T3 and T4 were examined using separate Analysis of Covariance (ANCOVA), adjusted for T1 scores and other potentially important variables.<sup>2</sup> Effect size was calculated using the  $\eta^2$  statistic. Sensitivity analyses were undertaken to examine the potential effects of participation bias and protocol deviations relating to the timing of questionnaire completion at each assessment point. A conservative p value ( $\leq .01$ ) was used to denote significance in the context of multiple testing. The impact of initial screening result on withdrawal from screening was examined using chi-square tests, with logistic regression to examine the relative contributions of screening result and distress outcome.

<sup>2</sup> T1 variables were identified as covariates if they 1) differed significantly between screening result groups and 2) were significantly related to T1 scores (both at  $p \leq .01$ ).

## Results

### Participation bias

Table 1 displays T1 scores for questionnaire completers and non-completers at each subsequent stage. Women who were sent but did not complete T2 questionnaires reported significantly higher T1 HADS-Anxiety ( $p \leq .01$ ) and T1 HADS-Depression ( $p \leq .01$ ), and were significantly more likely to have had an abnormal result ( $p \leq .001$ ), than T2 completers. Within the recall group, there were no significant T1 differences between women who were sent but did/did not complete the T3 questionnaire. T4 non-completers were significantly younger ( $p \leq .001$ ) and reported higher T1 IES ( $p \leq .001$ ), HADS-Anxiety ( $p \leq .01$ ) and HADS-Depression ( $p \leq .01$ ) scores compared to T4 completers.

### Sample characteristics

Table 2 displays T1 participant characteristics separately for the primary comparison between women with a normal result versus those recalled for further tests. Women in the recall group were significantly older ( $p \leq .001$ ) but other group differences were not significant. Higher T1 IES scores were significantly related to younger age ( $p \leq .01$ ), newly participating in Phase 2 screening ( $p \leq .001$ ), previous recall ( $p \leq .01$ ), and being a gene mutation carrier ( $p \leq .001$ ). Younger age ( $p \leq .01$ ) and previous recall ( $p \leq .01$ ) were significantly associated with higher T1 HADS-Anxiety, while older age ( $p \leq .01$ ) and being post-menopausal ( $p \leq .01$ ) were associated with higher T1 HADS-Depression.<sup>2</sup>

Overall, most women were married or cohabiting (79%,  $n = 1060$ ), educated beyond 16 years (65%,  $n = 875$ ), and of white ethnic origin (99%,  $n = 1315$ ). The average age was 47 years ( $SD = 9.25$ ). Overall 57% ( $n = 773$ ) had participated in UKFOCSS Phase 1 screening, 24% ( $n = 312$ ) had undergone further tests after OCS in the past, 63% ( $n = 855$ ) were pre-menopausal, and 13% ( $n = 158$ ) were gene mutation carriers.

### Initial psychological outcomes (T2)

Table 3 indicates significantly higher IES scores in women who received an initial abnormal result compared to women who received a normal result ( $p \leq .001$ ). The potential effect of higher T2 non-completion in women with an abnormal result was considered by examining outcomes at T2 separately for 93 women with an abnormal result who completed all three questionnaires (T1, T2, T3). After controlling for baseline scores, their T2 IES scores ( $M = 2.22$ ,  $SE = 0.12$ ,  $CI\ 1.99\text{--}2.45$ ) were significantly higher than those of women who received a normal result ( $F(1, 1306) = 12.18$ ,  $p \leq .001$ ,  $\eta^2 = .009$ ). Further sensitivity analyses showed small changes in F values, but the effect of screening result on IES scores at T2 remained significant.

The effect of screening result at T2 was non-significant for general anxiety ( $p = 0.22$ ) and depression ( $p = 0.38$ ), after adjusting for baseline scores and following sensitivity analyses.

### Primary psychological outcomes (T3)

In 141 women with an abnormal result who completed T1 and T3 questionnaires, T3 IES scores were not significantly different from the T2 scores of women who received a normal result ( $p = 0.50$ ). Sensitivity analysis involving 93 women with an abnormal result who completed all three questionnaires confirmed that their T3 IES scores ( $M = 1.90$ ,  $SE = 0.12$ ,  $CI\ 1.67\text{--}2.13$ ) were not significantly different from those of women with normal results ( $F(1, 1306) = 0.72$ ,  $p = 0.40$ ,  $\eta^2 = .001$ ) after adjustment for baseline covariates. Further sensitivity analyses showed small changes in F values, but the effect of screening result on cancer-specific distress at T3 remained non-significant.

**Table 1**  
Comparison of questionnaire completers and non-completers.

|                              | T2 (one week after result) |                          |                      | T3 (one week after return to routine screening) |                         |                    | T4 (nine months)     |                          |                      |
|------------------------------|----------------------------|--------------------------|----------------------|-------------------------------------------------|-------------------------|--------------------|----------------------|--------------------------|----------------------|
|                              | Completer<br>n = 1384      | Non-completer<br>n = 225 | Test statistic       | Completer<br>n = 141                            | Non-completer<br>n = 22 | Test statistic     | Completer<br>n = 912 | Non-completer<br>n = 261 | Test statistic       |
| T1 variables                 |                            |                          |                      |                                                 |                         |                    |                      |                          |                      |
| Age in years mean (SD)       | 47.23 (9.38)               | 46.79 (9.14)             | −0.66 <sup>a</sup>   | 51.56 (9.71)                                    | 48.73 (9.96)            | −1.27 <sup>a</sup> | 47.52 (9.49)         | 45.52 (8.34)             | −3.30 <sup>***</sup> |
| Married/cohabiting % (n)     | 78 (1072)                  | 74 (165)                 | 1.91 <sup>b</sup>    | 82 (115)                                        | 68 (15)                 | 1.36 <sup>b</sup>  | 78 (705)             | 78 (202)                 | 0.00 <sup>b</sup>    |
| Educated > age 16% (n)       | 66 (894)                   | 59 (130)                 | 3.57 <sup>b</sup>    | 56 (79)                                         | 62 (13)                 | 0.07 <sup>b</sup>  | 66 (594)             | 63 (163)                 | 0.63 <sup>b</sup>    |
| White ethnic origin % (n)    | 99 (1340)                  | 98 (215)                 | ^                    | 99 (138)                                        | 95 (20)                 | ^                  | 98 (880)             | 98 (253)                 | ^                    |
| UKFOCSS P1 screening % (n)   | 58 (807)                   | 59 (133)                 | 0.02 <sup>b</sup>    | 53 (75)                                         | 55 (12)                 | 0.00 <sup>b</sup>  | 60 (546)             | 54 (140)                 | 2.99 <sup>b</sup>    |
| Previous recall % (n)        | 24 (318)                   | 23 (48)                  | 0.19 <sup>b</sup>    | 29 (38)                                         | 18 (4)                  | ^                  | 24 (206)             | 25 (61)                  | 0.05 <sup>b</sup>    |
| Pre-menopausal % (n)         | 63 (867)                   | 66 (148)                 | 0.69 <sup>b</sup>    | 60 (84)                                         | 73 (16)                 | 0.89 <sup>b</sup>  | 62 (566)             | 70 (183)                 | 5.36 <sup>b*</sup>   |
| Positive gene mutation % (n) | 13 (165)                   | 11 (22)                  | 0.56 <sup>b</sup>    | 7 (9)                                           | 10 (2)                  | ^                  | 12 (99)              | 13 (30)                  | 0.07 <sup>b</sup>    |
| IES log mean (SD)            | 1.64 (1.45)                | 1.82 (1.52)              | 1.73 <sup>a</sup>    | 1.64 (1.46)                                     | 1.71 (1.47)             | 0.22 <sup>a</sup>  | 1.53 (1.44)          | 1.93 (1.42)              | 4.00 <sup>a***</sup> |
| HADS-A mean (SD)             | 6.51 (4.01)                | 7.32 (4.11)              | 2.78 <sup>a**</sup>  | 6.81 (4.09)                                     | 6.97 (3.81)             | 0.17 <sup>a</sup>  | 6.34 (3.98)          | 7.13 (3.96)              | 2.82 <sup>a**</sup>  |
| HADS-D log mean (SD)         | 1.10 (0.76)                | 1.26 (0.73)              | 2.95 <sup>a**</sup>  | 1.20 (0.68)                                     | 1.26 (0.58)             | 0.39 <sup>a</sup>  | 1.05 (0.76)          | 1.19 (0.72)              | 2.76 <sup>a**</sup>  |
| Abnormal result % (n)        | 12 (167)                   | 33 (75)                  | 66.85 <sup>***</sup> | –                                               | –                       | –                  | 10 (87)              | 13 (35)                  | 2.86 <sup>b</sup>    |

<sup>a</sup>Sample size not large enough in some cells to conduct statistical tests.

UKFOCSS P1 = Phase 1.

IES = Impact of Event Scale, HADS-A = HADS-Anxiety, HADS-D = HADS-Depression.

<sup>a</sup> Independent *t*-test.

<sup>b</sup> Chi-square test.

\* *p* < .01.

\*\* *p* < .001.

\*\*\* *p* < .05 marginal.

Differences in T3 general anxiety (*p* = 0.13) and depression (*p* = 0.12) were not significant, after controlling for baseline covariates and following sensitivity analyses.

#### Longer-term psychological outcomes (T4)

After adjusting for baseline and T4 covariates, there were no significant differences in cancer distress (*p* = 0.13) or depression (*p* = 0.16) nine months after receiving a normal result vs. nine months after being returned to routine screening following initial recall for further tests due to an abnormal result. T4 anxiety scores were marginally lower in the recall group (*p* = 0.02). There was no significant difference in distress (*p* = 0.05) for those receiving a normal (*M* = 1.60, *SD* = 0.05) vs. an abnormal (*M* = 1.96, *SD* = 0.18) T4 blood result.

**Table 2**  
Primary sample characteristics.

| T1 variables                       | Normal<br>result<br>n = 1217 | Recall result<br>n = 141 | Test statistic        | p Value             |
|------------------------------------|------------------------------|--------------------------|-----------------------|---------------------|
| Age in years mean (SD)             | 46.62 (9.06)                 | 51.56 (9.71)             | $t_{(1356)} = -6.08$  | 0.00 <sup>***</sup> |
| Married/cohabiting % (n)           | 78 (945)                     | 82 (115)                 | $\chi^2_{(1)} = 0.65$ | 0.42                |
| Educated beyond age 16 years % (n) | 66 (796)                     | 56 (79)                  | $\chi^2_{(1)} = 5.53$ | 0.02 <sup>*</sup>   |
| White ethnic origin % (n)          | 99 (1177)                    | 99 (138) <sup>^</sup>    | –                     | –                   |
| UKFOCSS Phase 1 screening % (n)    | 57 (698)                     | 53 (75)                  | $\chi^2_{(1)} = 0.73$ | 0.39                |
| Previous recall % (n)              | 24 (274)                     | 29 (38)                  | $\chi^2_{(1)} = 1.51$ | 0.22                |
| Pre-menopausal % (n)               | 63 (771)                     | 60 (84)                  | $\chi^2_{(1)} = 0.62$ | 0.43                |
| Positive gene mutation % (n)       | 14 (149)                     | 7 (9)                    | $\chi^2_{(1)} = 3.91$ | 0.05 <sup>*</sup>   |
| IES log mean (SD)                  | 1.66 (1.45)                  | 1.64 (1.46)              | $t_{(1356)} = 0.16$   | 0.88                |
| HADS-A mean (SD)                   | 6.53 (3.98)                  | 6.81 (4.09)              | $t_{(1356)} = -0.79$  | 0.43                |
| HADS-D log mean (SD)               | 1.08 (0.76)                  | 1.20 (0.68)              | $t_{(183.5)} = -1.95$ | 0.05 <sup>*</sup>   |

<sup>a</sup>Sample size not large enough in some cells to conduct statistical tests.

IES = Impact of Event Scale, HADS-A = HADS-Anxiety, HADS-D = HADS-Depression.

\* *p* < .05 marginal.

\*\*\* *p* < .001.

Sensitivity analyses involving 62 women who had had an abnormal result and completed all four questionnaires confirmed no difference between groups on distress (*p* = 0.30), anxiety (*p* = 0.04), or depression (*p* = 0.27).

As shown in Fig. 2, raw IES scores in women who received an initial abnormal result (i.e. before they received additional testing) were moderate at T2 compared to low levels in women with normal results. At T3 (one week after women received additional testing which indicated that their results had normalised), raw IES scores were equivalent to the low levels seen in women with normal results and they remained low at T4. Anxiety and depression scores were low at all time points.

T4 adjusted reassurance scores of women who had received an initial normal result (*M* = 11.80, *SE* = 0.08, *CI* 11.64–11.95) were not significantly different ( $F(1, 880) = 2.06$ , *p* = 0.15,  $\eta^2 = 0.002$ ) to those of women in the recall group (*M* = 12.17, *SE* = 0.25, *CI* 11.69–12.67). These results were unchanged following sensitivity analysis. Overall, scores indicated high reassurance gained from screening in the preceding year.

#### Withdrawal from screening

As shown in Table 4, withdrawal from screening (primarily for salpingo-oophorectomy) was significantly higher in the short-term in women who received an abnormal result (*p* ≤ .001). Logistic regression indicated that T2 withdrawal was significantly associated with receiving an abnormal result (*OR* = 4.38, *p* ≤ .001), marginally associated with T2 distress (*OR* = 1.39, *p* = .05), but not associated with T1 distress (*OR* = .94, *p* = .68). There was no difference in longer-term withdrawal (*p* = .21).

#### Discussion

The present study evaluated the short- and longer-term psychological consequences of frequent OCS in a large sample of women at increased risk. It revealed a small, significant short-term adverse effect, with higher cancer-specific distress in women who received an abnormal result. The effect of screening result on general anxiety and depression was not significant, suggesting that measures of cancer-specific distress such as the IES are more sensitive to subtle

**Table 3**

Psychological outcomes of screening at T2 (top line of each comparison), T3 primary outcome (middle line), and T4 (bottom line).

| Outcome variable                      | Normal result<br>T2 n = 1217<br>T2 n = 1217<br>T4 n = 825 | Recall result<br>T2 n = 167<br>T3 n = 141<br>T4 n = 87 | Test statistic          | p              | $\eta^2$     |
|---------------------------------------|-----------------------------------------------------------|--------------------------------------------------------|-------------------------|----------------|--------------|
| IES log adjusted mean (SE, 95% CI)    | <b>1.79 (0.03, 1.72 – 1.85)</b>                           | 2.28 (0.09, 2.11 – 2.46)                               | $F_{(1, 1380)} = 27.47$ | <b>0.00***</b> | 0.020        |
|                                       | -                                                         | <b>1.87 (0.10, 1.68 – 2.06)</b>                        | $F_{(1, 1354)} = 0.47$  | <b>0.50</b>    | <b>0.000</b> |
|                                       | 1.65 (0.04, 1.57 – 1.73)                                  | 1.44 (0.13, 1.19 – 1.69)                               | $F_{(1, 906)} = 2.27$   | 0.13           | 0.002        |
| HADS-A adjusted mean (SE, 95% CI)     | <b>6.48 (0.08, 6.33 – 6.64)</b>                           | 6.77 (0.21, 6.36 – 7.18)                               | $F_{(1, 1380)} = 1.52$  | 0.22           | 0.001        |
|                                       | -                                                         | <b>6.90 (0.23, 6.44 – 7.36)</b>                        | $F_{(1, 1354)} = 2.33$  | <b>0.13</b>    | <b>0.002</b> |
|                                       | 6.60 (0.11, 6.39 – 6.80)                                  | 5.79 (0.33, 5.14 – 6.43)                               | $F_{(1, 906)} = 5.46$   | 0.02*          | 0.006        |
| HADS-D log adjusted mean (SE, 95% CI) | <b>1.14 (0.02, 1.11 – 1.17)</b>                           | 1.10 (0.04, 1.01 – 1.19)                               | $F_{(1, 1380)} = 0.78$  | 0.38           | 0.001        |
|                                       | -                                                         | <b>1.22 (0.05, 1.12 – 1.31)</b>                        | $F_{(1, 1354)} = 2.47$  | <b>0.12</b>    | <b>0.002</b> |
|                                       | 1.13 (0.02, 1.09 – 1.17)                                  | 1.04 (0.06, 0.91 – 1.16)                               | $F_{(1, 906)} = 1.94$   | 0.16           | 0.002        |

Primary comparisons are in bold type.

IES = Impact of Event Scale, HADS-A = HADS-Anxiety, HADS-D = HADS-Depression.

 $\eta^2 = .01$  represents a small effect, .06 a moderate effect, .14 a large effect.

Note: ANCOVAs at T2 and T3 were adjusted for corresponding baseline score and age. ANCOVAs at T4 were adjusted for baseline score, age, most recent ROC blood result, and being sent information about end of UKFOCSS.

\*  $p < .05$  marginal.\*\*\*  $p < .001$ .

psychological consequences of familial OCS. The IES asks women to report the presence of intrusive/avoidant thoughts about their ovarian cancer risk. Although receiving an abnormal result of OCS does not generate clinically significant levels of concern or anxiety, it may cause women to think more about their risk in the short-term. In the current study, mean IES scores were in the moderate range after receiving an abnormal test result. However, this effect appeared to resolve upon return to routine screening, with low levels of ovarian cancer-specific distress equivalent to those of women who received an initial normal result. Longitudinal analyses confirmed that the initial distress effect observed in recalled women was not persistent, and indeed, regardless of initial screening result, women reported high overall reassurance gained from participating in familial OCS. This transient effect of an abnormal OCS result mirrors the findings of studies observing the psychological impact of familial breast screening [27,28] and the early studies of familial OCS which found no evidence of prolonged distress [13]. In contrast, Kauff et al. [14] found reduced quality of life six months after receiving an abnormal result, which may reflect the high rate of false positive results and endometrial sampling observed in their study.

Despite uncertainty regarding the effectiveness of familial OCS, women who are at increased risk of ovarian cancer view screening as a

“safety net” which supports their efforts to actively cope with their risk [19]. However, a higher rate of withdrawal from screening – primarily for surgery – was observed in the short-term for women who received an abnormal result in the present study. Receiving an abnormal result, and experiencing transient moderate levels of cancer distress, may therefore be the catalyst that prompts some high risk women to re-evaluate the risks and benefits of unproven OCS versus proven RRSO by reminding them of the potential reality of developing ovarian cancer [18,29].

Study limitations relating to sample representativeness are acknowledged, including the absence of comparative data regarding the characteristics of psychological study decliners, such as previous experience of screening and prior receipt of abnormal results. It is possible that these variables influenced study participation, and baseline analyses suggested that they were associated with higher cancer-specific distress and withdrawal before embarking on UKFOCSS Phase 2 screening [18]. The current findings should also be interpreted in light of the potential impact of data loss. Whilst it is possible that women who did not complete follow-up questionnaires were more anxious or distressed, and that the present data may therefore underestimate the negative effects of familial OCS, sensitivity analyses suggested that this was not the case.

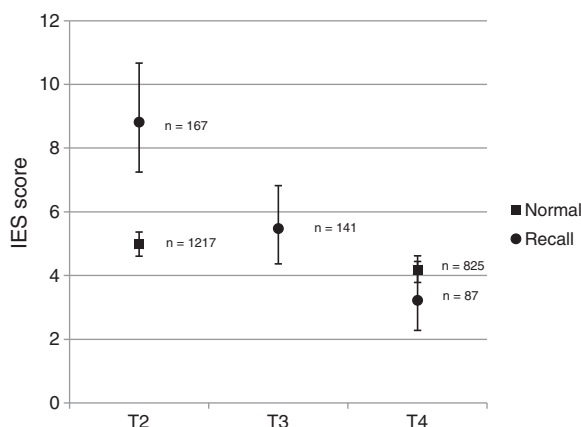
Participating in frequent familial OCS may lead to moderate cancer distress in the short-term in women who are recalled for further tests, but not clinical levels of concern or anxiety. Health professionals and policy makers can be reassured that frequent familial OCS does not cause sustained ill-effects and may be considered an interim risk management option until clinical evidence is available regarding its effectiveness, or the timing is right to consider RRSO as an alternative strategy for coping with genetic risk [18]. Interventions are needed to support women's and health professionals' shared decision making about risk management options [30].

#### Conflict of interest statement

AR: Received honoraria from Fujirebio Diagnostics for lecturing on familial ovarian cancer screening. UM: Financial interest through UCL business and Abcodia Ltd in the third party exploitation of clinical trial biobanks which have been developed through research at UCL. UM also received grant funding from MRC, CRUK, NIHR, Eve Appeal and European Union for research into ovarian cancer screening and biomarkers.

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Note: Means are adjusted for T1 IES score and age. T4 means are also adjusted for most recent blood test result and awareness of UK FOCSS ending.

Fig. 2. Mean cancer-specific distress (IES) scores.

**Table 4**

Withdrawal from screening.

| Withdrawal stage | Withdrawal reason                                                             | Normal result<br>n (% of whole sample) | Recall result<br>n (% of whole sample) | Test statistic               |
|------------------|-------------------------------------------------------------------------------|----------------------------------------|----------------------------------------|------------------------------|
| T2 <sup>a</sup>  | Surgery (risk-reducing or screen prompted surgical oophorectomy)              | 16                                     | 11                                     | $\chi^2_{(1)} = 18.92^{***}$ |
|                  | No longer wanting to take part in UK FOCSS                                    | 3                                      | 1                                      |                              |
|                  | T2 total withdrawal                                                           | 19 (2)                                 | 12 (7)                                 |                              |
| T3 <sup>b</sup>  | Surgery (risk-reducing or screen prompted surgical oophorectomy)              | -                                      | 3                                      | ^                            |
|                  | T3 total withdrawal                                                           | -                                      | 3 (2)                                  |                              |
| T4 <sup>c</sup>  | Surgery (risk-reducing or screen prompted surgical oophorectomy) <sup>d</sup> | 54                                     | 10                                     |                              |
|                  | No longer wanting to take part in UK FOCSS                                    | 5                                      | 1                                      | $\chi^2_{(1)} = 1.56$        |
|                  | Clinical advice                                                               | 1                                      | 0                                      |                              |
|                  | T4 total withdrawal                                                           | 60 (5)                                 | 11 (8)                                 |                              |

<sup>a</sup>Sample size not large enough to conduct statistical tests.<sup>a</sup> Withdrew from UK FOCSS within 4 months of the first routine blood if it was a normal result, or any time within the repeat testing process if the first routine blood was abnormal.<sup>b</sup> Withdrew from UK FOCSS within 4 months of being returned to routine screening following recall for further tests due to an abnormal result.<sup>c</sup> Withdrew from UK FOCSS more than 4 months after the main outcome and before due a T4 questionnaire.<sup>d</sup> Risk reducing or screen prompted surgical oophorectomy.\*\*\*  $p \leq .001$ .

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