Psychosocial factors associated with withdrawal from the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) following one episode of repeat screening

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Objective: The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) aims to establish the efficacy of two different ovarian cancer screening schedules. The psychosocial sub study examines the psychological factors associated with the screening programme.
Methods: Women aged 50 to 75 years from 16 UK gynaecological centres randomised to annual multimodal screening (MM), or ultrasound screening (US) groups were followed for seven years. Psychosocial data from women who withdrew from the study following a repeat screen were examined.
Results: 16% (3499/21733) of women requiring a repeat screening test in addition to annual screen withdrew from the study; 12.9% (1560/12073) from the MM group, and 20.1% (1939/9660) from the US group; an estimated relative risk of withdrawal of 1.46 (95%CI: [1.36, 1.56]; p=<0.001) for the US arm. High anxiety trait and increased psychological morbidity significantly influenced withdrawal even when age, screening centre, and group were taken into account (p<0.001). The risk of withdrawal decreased significantly the longer a woman stayed in UKCTOCS, irrespective of the number of screens and intensity in the preceding year.
Conclusions: Withdrawal rate was greater in women undergoing US screening and in those who had repeats earlier in UKCTOCS. Having a high predisposition to anxiety, high current state anxiety and above threshold general psychological morbidity all increased the withdrawal rate.

Trial Registration: This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN22488978

Keywords: Ovarian cancer; population screening programme, withdrawal, anxiety, psychological morbidity, UKCTOCS

Introduction

Ovarian cancer is the fourth highest common cause of cancer death in UK women.[1] The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) aims to establish the efficacy of two different screening schedules. If screening has a positive effect on mortality then issues such as the acceptability of screening methods and identification of factors that might influence adherence to annual screening will be important factors in effective implementation.

Screening of healthy populations may have harms as well as benefits. Establishing the myriad of factors that might contribute to the acceptability of ovarian cancer screening and maintain regular attendance is therefore important. In UKCTOCS, women who experienced pain during a trans vaginal ultrasound scan (TVS) were less likely to attend the following year's scan compared with those not reporting pain.[2] We have also shown that anxiety is not unduly raised in general in UKCTOCS especially when compared with the variation in anxiety levels that occur over time within individuals. Anxiety decreased significantly with every year spent in the study and was lower in older women.[3] The number of people diagnosed with cancer at screening is relatively low, but a substantial proportion will experience false positive results, which may increase anxiety and lead to withdrawal.[4-6] One concern is that people who withdraw from screening programmes or are lost to follow up may experience higher levels of distress than those who remain in studies. There is some evidence of this in the National Cancer Institute's Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial in which trial adherence was significantly better among participants who had received all normal results in the previous year's screening tests than in those who received at least one abnormal result. [7].

In this paper we examine the association of anxiety, general psychological morbidity and randomisation group on withdrawal from UKCTOCS, following test results requiring a repeat screen. Knowledge that a screening test is abnormal in any way might reasonably be expected to cause concern. If following further testing the abnormality was shown to have been a false positive result, this might produce relief, a loss of confidence in screening or make individuals more anxious especially in those with a predisposition towards anxiety. Non-attendance or withdrawal from further screening could be the consequence.

A meta-analysis of breast cancer screening indicated that false positives had variable impacts upon subsequent attendance for screening, with no significant relationship between false positives and re-attendance in European women, decreased re-attendance in Canadian women and increased attendance in the US.[8] Furthermore the type of screening and false positives might have a measurable effect; TVS is a more invasive procedure than a blood test, so one could hypothesise that false positives following additional scans might be more likely to foster withdrawal from further screening.

Methods

The design of the multicentre screening trial UKCTOCS and the psychosocial sub-study has been described in detail elsewhere.[3,9,10,11] The programme involved 202,638 postmenopausal women from 13 UK screening centres randomised to a control group or annual screening in either 1) a multimodal (MM) group who had serum CA125 interpreted via a Risk of Ovarian Cancer algorithm, followed if necessary by transvaginal ultrasound scan (TVS) as a second-line test, or 2) a TVS ultrasound screening (US) group. In addition to these tests, acceptability of screening, and physical and psychological morbidity was measured following an abnormal screen and at annual screen, for 7 years post randomisation.

All women completed baseline questionnaires; thereafter any women in the MM and US groups receiving abnormal results after annual screening were sent further psychosocial questionnaires following each abnormal screen requiring extra testing. If no abnormality was detected, women returned to annual screening (for a maximum of 7 years) whilst on study. If surgery for ovarian cancer (OC) was needed women had no further screening but for non-ovarian cancer or if ovaries were not removed at surgery, then women could continue in the study. Over 23,000 women from the MM and US groups in UKCTOCS had abnormal events at screening in the 7 years post randomisation.

Repeat screens were categorised as Level 1 or 2. The level of the test following results of an abnormal annual screen depended on a) the group (MM or US) and b) the degree of invasiveness of the test. For example, a Level 1 screen in the MM group was merely a repeat blood test in three months, while a Level

2 screen was a repeat blood test and a transvaginal ultra sound scan (TVS) in six weeks. A Level 1 screen for women in the US group was a repeat TVS by an experienced ultra-sonographer in three months and a Level 2 screen was a repeat TVS by a senior ultra-sonographer or consultant in six weeks.

Study measures

Participants provided socio-demographic details and highest education level, personal and family history of breast & OC and use of oral contraception; these were obtained from the main UKCTOCS dataset. Women also completed several questionnaires including the Spielberger State/Trait Anxiety Inventory (STAI)[12] and the General Health Questionnaire 12 (GHQ-12).[13] .

Trait anxiety was measured at baseline only and reflects an individual's underlying predisposition towards anxiety. State anxiety measures how a person feels right now, and was assessed at all other times together with the GHQ, which is a general psychological morbidity assessment.

Statistical Methods

The psychosocial and basic demographic data of women who withdrew from the study at some point after their first repeat screen were compared to women having one or more repeat screens but not withdrawing subsequently. Women with no randomisation date and those without baseline questionnaires (n=410) were not included in the dataset as were two women without withdrawal dates. Withdrawals due to death (n=364), any cancer diagnosis (n=370), and removal of ovaries (n=199) were censored, Also censored at withdrawal time as were women who had surgery following an abnormal screen result (n=1291), the majority of whom never returned to the screening programme thereafter. Missing values for any variable led to the exclusion of that year's information for the relevant women in analyses requiring that variable. Scores from the 20 item STAI State questionnaire range from 20 to 80, and were treated as a continuous variable. The 12 item GHQ-12 scores range from 1 to 12 and were dichotomised, with $\geq$4 signifying probable psychological morbidity.

Withdrawal rates were examined through use of time-to-event analyses based on Cox's relative risk regression model.[14] Analysis results are presented as relative risk estimates with 95% confidence intervals and significance levels (p-values) for tests of relative risks being unity which corresponds to no effect. The planned duration of screening was 6 years. Because dates of screening during a year are

irregular or fluctuate, a cut off duration of 7 years was used in the analysis to avoid losing any 6th year screens. Women were thus censored at the time of their last annual screen if this occurred before 7 years and at 7 years otherwise. Counts of withdrawals are given for illustrative purposes.

STAI and GHQ12 scores were updated at each annual screen if possible. Imputation using last value carried forward was applied for two years if necessary but thereafter treated as missing. Age and STAI scores were centred at their respective means, 35.9 and 61 years. STAI trait baseline scores were used to create a three level factored variable, low, medium and high. Low and high anxiety were respectively defined as a STAI trait score lower or higher than one standard deviation (10.1) from the sample mean (36.5), both calculated previously.[11]

Results

For the events sample of 21,733 women, 5723 withdrawals took place during the first 7 years of screening and after exclusions, 3,499 were available for analysis. Table 1 shows the participants' characteristics at time of first screening event. Table 2 shows the withdrawal rates per centre.

Comparison of withdrawal rates in the screening groups

12.9% (1560/12073) of women with repeat testing in the MM arm withdrew and 20.1% (1939/9660) withdrew in the US arm. This led to an estimated relative risk of withdrawal of 1.44 (95%CI: [1.34, 1.54]; p=<0.001) for the US arm versus the MM arm. Adjustment for centre, through stratification, and age, through the inclusion of a continuous age variable, standardised at age 61, in the model, led to a relative risk estimate of 1.46 (95%CI: [1.36, 1.56]; p<0.001) for the comparison of US and MM arms in this sample.

Effects of other factors

Tables 3a and 3b show the times to withdrawal of participants and withdrawal rates by year of entry into the events sample. Table 4 presents the results of the analyses. In single factor analyses after adjustment for centre, age and randomisation group, GHQ≥4, current STAI state score (standardised at mean 35.9), a high STAI trait value, the level of the women's last screen and the maximum screening level experienced, along with randomisation to the US arm, demonstrate very significant (p<0.001)

relationships with withdrawal rate. Other weaker but significant relationships were observed including having a perceived chance of OC of 1 in 10 (p=0.01), having used hormone replacement therapy (HRT) (p=0.03) and with the year of the women's first screening event (p=0.01). There was no evidence of an ethnicity (White v non-White) effect.

Multivariate analyses demonstrate that GHQ≥4 and current STAI score retain their relationship when STAI trait is included in the model. High STAI trait retains a significant but less strong relationship with withdrawal when GHQ≥4 is in the model but low STAI trait does not. However low STAI trait is significant and high STAI trait is not significant if STAI state is in the model and not GHQ≥4. When both GHQ≥4 and STAI state are in the model, then the significance of STAI trait dominates that of GHQ≥4. There is also a suggestion that some increase in withdrawal rate may be associated with a low STAI trait (p=0.10).

Also maintained in the multivariate analysis is the finding that an increased risk of withdrawal is associated with a woman last having Level 1 or Level 2 screens. However, if a woman has previously had a Level 2 screen it brings a reduced risk of withdrawal. It appears therefore that a recent event does increase the chance of withdrawal but if a woman had a Level 2 screen previously and stayed in the programme then subsequently the risk of withdrawal is reduced. There is no evidence for an interaction between past screening level and current level. Thus relative to a woman whose last screen was an annual screen and who only ever had a Level 1 screen previously, the risk of withdrawal is estimated to be increased by a factor of 1.32. For women who last had a Level 1 and Level 2 screen respectively it increased by a factor of 1.49. However, if a the previous screen was at Level 2, the rate of withdrawal is estimated to be decreased by factors of 0.56, 0.74 and 0.83 if the woman last had an annual, a Level 1 and a Level 2 screen respectively. Also maintained in the multivariate analysis is an increased risk of withdrawal for women who took HRT and a decreased risk the longer the woman has been in the screening programme prior to their first screening event.

If interactions between randomisation group and past screening level and between randomisation group and current screening level are added to the multivariate model then the former is highly significant (p<0.001) and the latter has a suggestive significance level of p=0.055. The estimated relative risk associated with level 1 and level 2 screen are 1.15 (CI: 0.94, 1.40) and 1.35 (CI: 1.05, 1.73) respectively

for the MM group but have the higher values of 1.54 (CI: 1.29, 1.84) and 1.54 (CI: 1.31, 1.80) for the US group. The estimated relative risk for a previous level 2 screen is 0.82 (CI: 0.67, 1.00) and 0.46 (CI: 0.40, 0.55) in the MM and US groups respectively. There was no evidence of an interaction between randomisation group and ethnicity (p=0.37)

If the interaction between STAI state and last screen level is introduced into the multivariate model (c), then there is marginal evidence for an interaction (p=0.07 on 2df test). If a model is fit to the groups' last Level 1 and last Level 2 classes together then the interaction between this variable and STAI state is more significant (p=0.026 on 1 df test). The magnitude of the interaction effect is relatively small with the estimated effect of a Level 1 or Level 2 screen corresponding to a relative risk of withdrawal of 1.38 for a STAI state score at its mean of 35.9 but of 1.51 if the STAI state score is 10 units higher.

While not included in the multivariate model because it is potentially on the causal pathway to withdrawal, women also answered a question about the likelihood of returning for the following year's screen. Available responses were "yes", "unsure" and "no". As expected the withdrawal rates in the next year varied greatly with the response to this question, with rates of 3% (2600/83508), 23% (332/1447) and 41% (186/453) observed over all patient-year observations. A formal analysis of time to withdrawal, adjusting for group, age and centre leads to a relative risk of 5.4 (CI: 4.8, 6.1) and 4.9 (CI: 4.1, 5.7) for the "unsure" and "no" groups relative to the "yes" group. The unadjusted relative risk estimates were 6.1 (CI: 5.5, 6.9) and 5.2 (CI: 4.5, 6.1).

Discussion

Establishing the sensitivity and specificity of different types of screening is vital prior to initiating a population screening programme, but it is also crucial to ascertain all potential factors that might influence participation and regular attendance. For example, a survey examining the acceptability of trans-vaginal ultrasound scan (TVS) within UKCTOCS showed that the majority of women (72%) did not rate the procedure painful and only a small proportion (4%) felt embarrassed during the scan, but most shared apprehensions about the intrusive nature of the test. However, those who did rate TVS as uncomfortable and painful were less compliant with attendance at the following year's scan compared with those who did not experience pain.[2]

The findings from this UKCTOCS analysis suggest that postmenopausal women who have experienced a screening event are more likely to withdraw from ovarian cancer screening programmes utilising more invasive screening procedures such as TVS. High trait anxiety and increased psychological morbidity significantly influenced the rate of withdrawal even when age, screening centre, and screening group were taken into account. It is recognised that people who are anxious about their health are more likely to misinterpret health information; the likelihood of withdrawal from UKCTOCS increased in women with the incorrect perception that their chance of developing ovarian cancer was as high as 1 in10. The cognitive-behavioral theory of health anxiety predicts atypical responses in health anxious individuals when exposed to health related information.[15] Information is more likely to be viewed as personally threatening and they are less likely to be reassured by medical investigations. This has been shown in a study of colorectal cancer screening. Health anxious people reported lower levels of reassurance after a clear test result than non-anxious participants, although the size of the effect was small.[4]

In the context of UKCTOCS, there was some evidence that a volunteer who was more anxious before annual screening, and who then required additional screening because of a false positive result, was also more likely to withdraw from the programme than someone less anxious having a false positive result. As the experience of a “near miss” might heighten awareness of cancer and illness, and increase anxiety, one might predict that an already anxious woman experiencing a number of false positive results would be more likely to withdraw from screening. This supposition was not upheld by our results.

In an earlier paper that examined the psychological sequelae associated with abnormal screen results for women in UKCTOCS, screening did not appear to raise anxiety but psychological morbidity was slightly elevated by more invasive testing following annual screens. Anxiety in fact decreased with every year a volunteer stayed in the study.[3] Likewise, in this withdrawal analysis, women were less likely to leave the study the later they experienced a repeat screening event during the 7 years of screening.

In the Psychological aspects of Familial Ovarian Cancer Screening Study (PsyFOCS), the main reasons for withdrawal from ovarian cancer screening (OCS) prior to surgery were:- previous experience of UK

FOCCSS Phase 1 screening, repeat tests during previous screens, higher cancer-specific distress and a belief that ageing caused OC.[16] In this situation, where there is a familial risk of developing ovarian cancer, it could be that having repeat tests heightened anxiety to such an extent that women decided to undergo risk-reducing surgery.

Similarly in the case of breast cancer screening programmes, a false positive result brings with it several disadvantages to the participant and provider. There is the cost related to the provision of further tests, biopsies in order to deliver a diagnosis, and the anxiety experienced by the participant that would never have happened in the absence of screening.[4] An earlier study reported that despite having received a final clear result during routine breast screening, women who had undergone further investigations, for example, fine needle aspiration, surgical biopsy or been placed on early recall, suffered significantly greater adverse consequences at 1 month before their next routine breast screening appointment than women who had received a clear result after their initial mammogram at their last routine breast screening.[6] The authors concluded that undergoing further investigations did not necessarily motivate women to attend for their next routine appointment. Whether these women had a high anxiety trait characteristic is unknown.

Strengths and limitations

The primary strengths of the UKCTOCS psychosocial study are its size and unlike much previous research in this area, its longitudinal design. Cross-sectional work does not permit the prospective detailed examination over-time of putative psychosocial factors that might influence withdrawal from a screening programme following at least one repeat screen. A limitation of the study is that those women who consent to participate in a trial of different screening modalities, which also included a control group, might be a self-selected population; however the socio-demographic characteristics of the 202,638 volunteers in UKCTOCS appear to be wide-ranging.

Interpretation

There are no other ovarian cancer screening studies of comparable design and size with which to compare these UKCTOCS withdrawal results. What we have shown is that women with a high pre-

disposition towards anxiety are more likely to drop out of screening as do those who experience high anxiety following their most recent scan. Furthermore, the more invasive the initial screening procedure is, that is (TVS) rather than a multi-modal approach the more likely withdrawal will be following a repeat scan or false positive result.

Conclusion

UKCTOCS included a comprehensive psychosocial arm that has permitted an in depth appraisal of not only the psychosocial harms and benefits of OC screening but also some of the factors that might enhance or inhibit attendance and re attendance. Next year the National Screening Committee is scheduled to review its policy on ovarian cancer screening in women following the UKCTOCS study against criteria that include psychosocial factors. These results should assist policy makers when considering the optimal screening methods and any accompanying educational resources, especially aimed at ameliorating anxiety.

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Authors' contributions: LF, IJ, UM & VF devised the psychosocial study. CL, AR, JK organised the data for analysis, VF& JB analysed the data, VJ, LJF, VF wrote the manuscript. IJ & UM contributed to the manuscript. All authors read and commented on the final version. LJF is the guarantor for the psychosocial data.

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Table 1: Characteristics of participants at baseline

Characteristic	MM Group n = 12073	USS Group n = 9660	Overall n = 21733
Age in years, (n = 21698)			
Median (Mean)	61.2 (61.0)	60.7 (60.0)	61 (61.0)
Range (Standard deviation)	49-74 (6.3)	50-74 (6.4)	49-74 (6.3)
Ethnicity, % (n = 17828)			
White	97.7	97.9	97.8
STAI trait anxiety (minimum = 20, maximum = 80), % (n = 21232)			
Low score (20-26)	16.8	16.8	16.8
Average score (27-46)	66.5	66.0	66.2
High score (47-80)	16.7	17.2	16.9
GHQ 12 (minimum = 0, maximum=12),% (n = 16224)			
'Case' (score = 4 or more)	17.7	17.7	17.7
Highest educational qualification, % (n = 18333)			
O-level or equivalent	8.3	8.4	8.3
A-level or equivalent	2.4	2.5	2.4
Clerical or commercial qualification	19.6	18.7	19.2
Nursing or teaching	7.4	7.3	7.3
College/university degree	15.5	15.2	15.4
None specified/or stated none of the above	46.8	47.9	47.3
HRT, % (n = 18333)			
Used HRT	19.9	20.2	20.0
Contraceptive pill, % (n = 18333)			
Used pill	58.9	58.2	58.6
Cancer history, % (n = 18333)			
Had cancer	6.5	6.6	6.5
Family cancer history, % (n = 18333)			
At least 1 relative with OC	4.6	4.7	4.6
At least 1 relative with BC	21.7	22.3	22.0

Table 2: Withdrawal rate per centre

Centre	All events sample withdrawal rate %
10	18.1 (259/1432
11	18.8 (312/1664)
12	16.9 (217/1284)
13	17.4 (272/1566)
14	15.4 (265/1721)
15	11.3 (172/1524)
16	18.5 (394/2124)
18	21.4 (489/2283)
20	11.6 (214/1844)
22	14.0 (273/1955)
23	12.5 (191/1522)
25	15.5 (236/1527)
26	15.9 (205/1287)

Table 3a: Times of the withdrawals (rounded to nearest year)

Year	0	1	2	3	4	5	6	7
Number withdrawn	115	404	448	491	496	538	721	286

Table 3b: Withdrawals by time of first screening event (rounded to nearest year)

Year	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Number not withdrawing	4941	4658	3151	2896	2107	434	47	0
Number withdrawn	1365	1061	487	320	178	81	7	0
% withdrawn	21.7	18.6	13.4	10.0	7.8	15.7	13.0	

Table 4: Table of analyses presenting estimated relative risks, significance levels and 95% confidence intervals

	Single Factor Analyses*	Multivariate Analysis (a)	Multivariate Analysis (b)	Multivariate Analysis (c)
US	1.46 (p<0.001) [1.36, 1.56]	1.44 (p<0.001) [1.33, 1.56]	1.44 (p<0.001) [1.33, 1.56]	1.55 (p<0.001) [1.41, 1.69]
GHQ≥4	1.33 (p<0.001) [1.21, 1.46]	1.28 (p<0.001) [1.16, 1.42]		1.08 (p=0.22) [0.95, 1.23]
STAI	1.012(p<0.001) [1.009,1.015]		1.013 (p<0.001) [1.009.1.017]	1.01 (p<0.001) [1.005,1.015]
STAI TRAIT				
Low	1.01 (p=0.74) [0.92,1.11]	1.03 (p=0.627) [0.92, 1.14]	1.14 (p=0.022) [1.02, 1.27]	1.11 (p=0.10) [0.98, 1.25]
Medium	1	1	1	1
High	1.16 (p<0.001) [1.07, 1.27]	1.12 (p=0.035) [1.01,1.25]	1.02 (p=0.677) [0.91,1.15]	1.02 (p=0.794) [0.90, 1.15]
Cumulative Events > 2	0.92 (p=0.36) [0.77, 1.10]			
Withdraw psychosocial study	1.15 (p=0.17) [0.94, 1.39]			
Worried about screening	1.05 (p=0.28) [0.96, 1.15]			
Education				
College or equivalent	1.04 (p=0.40) [0.95,1.14]			
No formal qualification	0.99 (p=0.81) [0.91, 1.08]			
Ethnicity				
White vs non-White	1.10 (p=0.46) [0.84, 1.45]			
Perceived chance				
1 in 500	0.95 (p=0.19) [0.89, 1.02]			
1 in 10	1.19 (p=0.01) [1.04, 1.35]			
HRT	1.10 (p=0.03) [1.01, 1.20]			1.13 (p=0.02) [1.02, 1.25]
Cancer history	0.92 (p=0.27) [0.79, 1.07]			
Contraceptive pill (used)	1.07 (p=0.08) [0.99,1.15]			
Family cancer history				
1+ relative OC	1.13 (p=0.13) [0.96,1.33]			
1+ relative Breast C	0.92 (p=0.39) [0.76, 1.11]			
Screening year of 1st event	0.96 (p=0.01) [0.93,0.99]			0.96 (p=0.05) [0.92,1.00]
Last screen level				
Annual	1.00 [reference]			1.0 [reference]
Level 1	1.36 (p,0.001) [1.25, 1.49]			1.32 (p<0.001) [1.15, 1.53]
Level 2	1.34 (p<0.001)			1.49 (p<0.001)

	[1.22, 1.48]			[1.30, 1.70]
Max previous screen level	0.63 (p<0.001) [0.57, 0.69]			0.56 (p<0.001) [0.50, 0.64]

* Adjusted for centre, age and randomisation group