Evidence-Based Medicine Online First, published on June 14, 2016 as 10.1136/ebmed-2016-110385

Ovarian cancer screening: could you recommend it? No

Juan Gérvas

10.1136/ebmed-2016-110385

Avda Alfonso XIII, Madrid, Spain

Correspondence to:
Dr Juan Gérvas,
Avda Alfonso XIII,
19, Madrid 28002, Spain;
jjgervas@gmail.com

Abstract

Last December, *The Lancet* published the final results of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). The summary of the study, distributed in advance, was misleading and the exaggeration was translated in news all over the world. This author reviewed the results and highlights that the UKCTOCS is just one more randomised controlled trial demonstrating that screening reduces neither ovarian cancer-specific mortality nor all-cause mortality.

Strictly speaking, cancer screening never 'saves lives'. Cancer screening can only change the cause of death and/or prolong life in the short term (the timing of this end point of interest can be up to 30 years after diagnosis for some cancers). To evaluate a cancer screening programme, one must consider the following basic information: (1) cancer-specific mortality (a fall in cancer-specific mortality is expected), (2) total cancer mortality (a fall in total cancer mortality is expected, if the screening test/treatment of the screened-for cancer do not themselves increase mortality or the cause of death is not systematically misclassified) and (3) all-cause mortality (in the short term, a fall is expected, if the screening text/treatment of the screened-for cancer do not themselves increase mortality).[1]

Sadly, no single cancer screening has ever demonstrated a decrease in all-cause mortality.[2] This is generally a problem for screening tests as reductions in disease-specific mortality are uncommon and reductions in all-cause mortality are very rare or non-existent.[3] For example, a systematic review and meta-analysis of ovarian cancer screening, published in 2013, found 10 randomised clinical trials demonstrating that screening reduced neither ovarian cancer-specific mortality nor all-cause mortality.[4]

In December 2015, *The Lancet* published the final results of the UKCollaborative Trial of Ovarian Cancer Screening (UKCTOCS),[5] which was 'designed to determine how many lives could be saved by screening for ovarian cancer'.[6] The trial cost £15,223,455.00.[7]

In 2001, the UKCTOCS team set out to compare two different methods of screening to see whether either of them could detect ovarian cancer early, and whether this early detection could decrease ovarian cancer-specific mortality. From 2001 to 2005, across the UK, they recruited more than 200 000 women, aged 50–74 years, and randomly assigned them to one of three groups. The control group of about 100 000 women was not screened. A second group, about 50 000 women, had an annual blood test to measure their levels of cancer antigen (CA) 125, interpreted using a Risk of Ovarian Cancer Algorithm (ROCA). A third group was made up of about 50 000 women who were screened every year with a vaginal ultrasound scan, to look for ovarian abnormalities. If this showed something unusual, the woman had further investigations.

All the women provided a blood sample at recruitment. According to the screening and diagnostic strategy, there were three levels: screening tests, clinical evaluation and surgery. Women randomised to the CA125 group had their blood tested for CA125 and those randomised to the ultrasound group were given an appointment for the scan. Women with abnormal screens had repeat tests. Women with a persistent abnormality on repeat tests underwent clinical evaluation and, where appropriate, surgery. For the screening test, clinical evaluation and surgery, respectively, the positive predictive values for all primary ovarian and tubal cancers were 1%, 25.1% and 43.3% in the CA125 group, and 0.8%, 2.4% and 5.3% in the ultrasound scan group.[8]

The original protocol specified six annual screens and follow-up for 7 years from randomisation. In 2008, an analysis of overall and cause-specific standardised mortality in the no screening group showed a lower than expected mortality rate. Screening was extended to 31 December 2011, resulting in women being offered 7–11 screens, depending on the year of randomisation.[5]

The primary analysis initially consisted of comparison of the combined CA125 and ultrasound scan groups with the no screening group, and individual comparisons of both experimental groups with the no screening group. The assumption was that the sensitivity of the two screening strategies would be similar. During the trial, the data monitoring and ethics committee concluded that this assumption was not true. On the basis of differences in performance characteristics of the two strategies at the initial screen, the committee updated the primary statistical analysis to separate comparisons of CA125 versus no screening and ultrasound scan versus no screening.

The primary outcome was death due to ovarian cancer by 31 December 2014. All analyses were by modified intention to screen. They analysed all randomly allocated women except for those who later came to be known as having a bilateral oophorectomy or ovarian cancer, or those exiting the registry before recruitment.

At a median follow-up of 11.1 years, ovarian cancer was diagnosed in 1282 (0·6%) women: 338 (0·7%) in the CA125 group, 314 (0·6%) in the ultrasound scan group and 630 (0·6%) women in the no screening group. Of these women, 148 (0·29%) in the CA125 group, 154 (0·30%) in the ultrasound scan group and 347 (0·34%) women in the no screening group had died of ovarian cancer. The ovarian cancer mortality reduction was not significant in the primary analysis, but a significant mortality reduction in the CA125 group was noted in a subgroup analysis after prevalent cases were excluded. There were no differences in deaths from other causes between the CA125, ultrasound and no screening groups.

True positives were 199 (59%) women in the CA125 group and 161 (51%) in the ultrasound scan group.

False negatives were 79 (23%) women in the CA125 group and 106 (34%) in the ultrasound scan group. Complication rates of the screening process were 8.6 per 100 000 in the CA125 group and 18.6 per 100 000 in the ultrasound scan group. For each ovarian and peritoneal cancer detected by screening, an additional two women in the CA125 group and 10 women in the ultrasound scan group had unnecessary surgery. About 3% of women who had surgery had major complications, including infections or damage to other organs.

The ratio of women who had surgery finding normal ovaries or benign pathology to those diagnosed with ovarian and peritoneal cancer was 2.3 times higher in the CA125 group and 5.3 times higher in the ultrasound group than in the no screening group. It is not necessary to remember that women without ovaries have no ovarian cancer in any case. Previous findings from the UKCTOCS group show that, following unnecessary surgery for a false alarm, women were more likely to be worried and distressed, as were women who had more repeat blood tests as part of screening.[9]

In the study, adherence to annual screening decreased over time, from 98.4% (CA125 group) and 94.9% (ultrasound group) to 47.2% and 35.9%, respectively, in the last (11th) year.

In summary, the UKCTOCS trial found significant impact on neither ovarian cancer mortality nor all-cause mortality, but did find a significant ovarian cancer mortality benefit in a subgroup analysis with most of the benefit, unexpectedly, in the later years of follow-up (8% during years 0–7 and 23% during years 7–14 in the CA125 group and 2% and 21%, respectively, in the ultrasound group). One of my main concerns with this finding is that the benefit was pyrrhic and unexpected as the original protocol specified six annual screens and follow-up for 7 years, but was extended (see above). My other concern is that the only significant benefit was in a subgroup analysis and, as such, this result should be treated with scepticism. Finally, for repeat screening, a fair comparison should address ovariectomy. Clearly, the outcome of ovarian cancer can happen only to women who have ovaries. However with screening, one outcome can be ovariectomy. Repeat screening cannot benefit these women. The comparison group is less likely to have an ovariectomy. As a result, any comparison of women—either screened or not screened-assessing benefit, should be among women with ovaries.

Commenting on the results, Fiona Osgun, from Cancer Research UK (who provided co-funding for the study), wrote: 'We don't think there's enough evidence for the NHS to introduce a national screening programme at this stage, neither to recommend women use a privately available ovarian cancer blood test'.[10]

In *The Lancet* press release, the chief investigator (IJJ) said: 'These results from UKCTOCS provide estimates of the mortality reduction attributable to ovarian cancer screening which range from 15% to 28%. Further follow-up in UKCTOCS will provide greater confidence about the precise reduction in mortality which is achievable. It is possible that the mortality reduction after follow-up for an additional 2–3 years will be greater or less than these initial estimates'.[11] This summary of the study that was distributed in advance of the study publication was misleading and the exaggeration was translated in news all over the world.[12]

IJJ and UM are the chief and the principal investigator, and both have relationships and stock ownership of Abcodia, a specialist company that focuses on biomarkers for cancer screening. IJJ and SJS (another author) have a patent for the ROCA. Some other authors report personal fees or research grants from Abcodia and have other conflicts of interest such as having a patent for the ultrasound simulation training system, MedaPhor. These conflicts of interest should be considered when assessing the possible influence on interpretation of study findings, particularly that of the subgroup analysis highlighting the benefits of biomarkers, the presentation of the final results and the press release. Conclusions and recommendations should be interpreted in light of these conflicts.

In summary, the UKCTOCS is another ovarian cancer screening trial demonstrating that screening reduces neither ovarian cancer-specific nor all-cause mortality. Ovarian cancer screening should not be recommended.

Twitter Follow Juan Gérvas at @JuanGrvas

Competing interests None declared.

Provenance and peer review Commissioned; internally peer reviewed.

References

1. **Gigerenzer G**. Full disclosure about cancer screening. *BMJ* 2016;**352**:h6967.
2. **Prasad V**, Jeanne Lenzer J, Newman DH. Why cancer screening has never been shown to "save lives"—and what we can do about it. *BMJ* 2016;**352**:h6080.
3. **Saquib N**, Saquib J, Ioannidis JP. Does screening for disease save lives in asymptomatic adults?. Systematic review of meta-analyses and randomized trials. *Int J Epidemiol* 2015;**44**:1–14.
4. **Reade CJ**, Riva JJ, Busse JW, *et al*. Risks and benefits of screening asymptomatic women for ovarian cancer: a systematic review and meta-analysis. *Gynecol Oncol* 2013;**130**:674–81.
5. **Jacobs IJ**, Menon U, Ryan A, *et al*. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. *Lancet* 2016;**387**:945–56.
6. The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). http://www.instituteforwomenshealth.ucl.ac.uk/womens-cancer/gcrc/ukctocs (accessed 10 Jan 2016).
7. MRC Transferred Portfolio—09/800/32: United Kingdom Collaborative Trial of Ovarian Cancer (UKCTOCS) G9901012. http://www.nets.nihr.ac.uk/projects/ememrc/0980032 (accessed 10 Jan 2016).
8. **Menon U**, Gentry-Maharaj A, Hallett R, *et al*. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Lancet Oncol* 2009;**10**:327–40.
9. **Barrett J**, Jenkins V, Farewell V, *et al*. UKCTOCS trialists. Psychological morbidity associated with ovarian cancer screening: results from more than 23,000 women in the randomised trial of ovarian cancer screening (UKCTOCS). *BJOG* 2014;**121**:1071–9.

10. **Osgun F.** Ovarian cancer screening trial: a tantalising result? http://scienceblog.cancerresearchuk.org/2015/12/17/ovarian-cancer-screening-trial-a-tantalising-result/ (accessed 10 Jan 2016).
11. **Public Release: 17-Dec-2015.** The Lancet: largest ever ovarian cancer trial suggests that screening reduces mortality, but longer follow-up is needed. http://www.eurekalert.org/pub_releases/2015-12/tl-tll121515.php (accessed 10 Jan 2016).
12. **Sumner PS**, Vivian-Griffiths S, Boivin J, *et al*. The association between exaggeration in health related science news and academic press releases: retrospective observational study. *BMJ* 2014;**349**:g7015.