Briefing Paper
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Does annual ovarian cancer screening reduce deaths among women in the general population?

Ovarian cancer in the UK

More than 7,000 women are diagnosed with ovarian cancer and 4,000 women die from ovarian cancer in the UK each year. Ovarian cancer can be difficult to diagnose. Symptoms are often slow to appear, and can be mistaken for other, less serious, conditions. More than half of cases are diagnosed at a late stage (Stage III or IV), when it has already spread beyond the pelvis. This makes the disease harder to treat.

Finding a reliable screening method that picks up ovarian cancer earlier, when treatments are more likely to be effective, could help reduce deaths from the disease. However, in order for a screening programme to be considered by Public Health England, "There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity."[1]

This briefing paper draws on evidence from the UKCTOCS trial, which tested two screening approaches to assess if they were able to identify ovarian cancer at an earlier stage, and if this led to improvements in survival.

Did multimodal screening help diagnose ovarian cancer earlier?

Nine and half years after end of screening, there was a 47% increase in the incidence of stage I and 24·5% decrease in stage IV in women diagnosed with ovarian cancer in the multimodal group compared to no screening. Overall, the incidence of Stage I/II was 39% higher and Stage III/IV 10% lower in the multimodal group lower compared to the no screening group. This demonstrates that the multimodal screening approach diagnosed women with ovarian cancer earlier. No other randomised trial has reported evidence of earlier diagnosis.

Key messages

- Ovarian cancer is often diagnosed when it is at an advanced stage and harder to treat
- Finding a reliable screening method that picks up ovarian cancer earlier, when treatments are more likely to be effective, could help reduce deaths from the disease
- UKCTOCS is the largest ever ovarian cancer screening trial, with more than 200,000 participants followed up for more than 16 years on average
- UKCTOCS tested two different ovarian cancer screening methods, comparing these to no screening:
  - » multimodal screening (annual blood tests with transvaginal ultrasound as a second line test in case of abnormality)
  - » ultrasound screening (annual and second line tests were transvaginal scans)
- The incidence of Stage I/II ovarian cancer was 39% higher and Stage III/IV cancer was 10% lower in the multimodal screening group compared to the no screening group
- UKCTOCS found no evidence that either screening approach reduced deaths from ovarian cancer, compared to no screening

[1] https://www.gov.uk/government/publications/evidence-review-criteria-national-screening-programmes/criteria-for-appraising-the-viability-effectiveness-and-appropriateness-of-a-screening-programme

Did ultrasound screening help diagnose ovarian cancer earlier?

UKCTOCS found no difference in stage between women diagnosed with ovarian cancer in our ultrasound group compared to no screening group. Ultrasound screening did not help diagnose women at an earlier stage.

Did either screening approach reduce ovarian cancer deaths?

UKCTOCS found no evidence that either screening approach reduced deaths from ovarian cancer, compared to no screening. Even though multimodal screening identified some women at an earlier stage, this did not lead to improvements in survival for these women.

This shows that in ovarian cancer, approval of a screening test must be based upon evidence that it reduces deaths and not just evidence that it finds more individuals with early disease. Population screening for ovarian cancer can only be supported if a new test is shown to reduce deaths in a future randomised controlled trial.

The UKCTOCS trial

UKCTOCS was a large randomised controlled trial testing two screening approaches versus no screening, among women aged 50-74 from the general population in the UK. Women at increased risk of familial ovarian cancer were excluded.

» 50,640 women were in the multimodal group and had a yearly blood test. We looked for changes in a woman's levels of a protein called CA125 until 2011.

» 50,639 women were in the ultrasound group and had a yearly vaginal ultrasound scan to check their ovaries) till 2011

» 101,359 women were in the no screening group

Women joined the trial between 2001-2005, and had yearly screening (if they were in one of the screening groups) until the end of 2011. The results of screening were published in 2015 and details can be found in the appendix. Women were followed up until mid-2020, to allow the researchers to find out if either of the screening approaches reduced ovarian cancer deaths compared to no screening.

Why did screening not reduce ovarian cancer deaths?

In UKCTOCS, screening did not detect:

- ovarian cancer in women early enough in the course of the disease to allow available treatments to be successful and
- early stage disease in a large enough proportion of women, nor sufficiently reduce the number of women with late stage disease

In UKCTOCS, screening took place between 2005-2011, so patients received the treatment approaches used at the time. It may be that more benefit would be seen from earlier diagnosis with the treatment options now available to patients, such as ultraradical surgery, earlier treatment modulation, or targeted therapies directed to tumour genomics or the immune response.

How do these results compare to those from previous trials of ovarian cancer screening?

The only other large randomised controlled trial to explore whether screening reduces ovarian cancer deaths was the ovarian cancer screening arm of the PLCO trial in the US. The PLCO trial had 78,216 participants, who were followed up for an average of 14.7 years. The PLCO trial found no evidence that the screening strategy they used detected ovarian cancer at an earlier stage. The screening in the PLCO trial also did not reduce ovarian cancer deaths compared to control. The PLCO results were similar to the results of the ultrasound arm of UKCTOCS. The results in the multimodal arm of UKCTOCS were different as there was evidence of more women detected with earlier stage disease, and fewer with late stage disease compared to the no screening group, although this did not translate into lives saved.

What next for improving outcomes from ovarian cancer?

We need to persist in our efforts to diagnose the disease earlier. Funding agencies have renewed focus on early detection of cancer. Alongside, there have been significant advances in the biomarker field. This is likely to result in a test that can detect more women with early stage disease and fewer with late stage disease than was possible with multimodal screening. Many such biomarkers are being tested using the large bioresource created during the course of UKCTOCS, called the UKCTOCS Longitudinal Women's Cohort. It includes a unique sample set of up to 11 annual blood samples predating cancer diagnosis from 12,082 women in the multimodal group.

In addition, worldwide campaigns to increase symptom awareness are likely to decrease intervals to diagnosis, while significant improvements in treatment of advanced disease is slowly and surely increasing survival rates in women diagnosed with ovarian cancer.

Meanwhile the UKCTOCS team will work on further analyses of the data to better understand the natural history of ovarian cancer and why earlier diagnosis did not save lives. This would be critical to developing new screening strategies.

Conclusion

UKCTOCS has clearly shown that, for women in the general population, annual multimodal screening was able to detect disease earlier compared to no screening, but that this earlier detection did not translate into a survival benefit.

The UKCTOCS team are disappointed about this outcome given our quest over 30 years to save lives of women who develop ovarian cancer. However, we are proud of the way this large, complex study was conducted. The trial has provided a clear answer on whether current screening strategies can save lives, and will continue to contribute to our understanding of the natural history of ovarian cancer and more broadly to the design and conduct of major population based trials.

Recommendations

- Based on the results of this very large, well-conducted trial, we cannot recommend population screening for ovarian cancer using either the multimodal or ultrasound approach
- Future decisions about screening tests for ovarian cancer in the general population should be based on evidence that it reduces deaths and not just evidence that it finds more individuals with early disease

Further information

Menon, U, Gentry-Maharaj, A, Burnell, M, et al. **General population screening and ovarian cancer mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial.** *The Lancet*, 2021.

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. *The Lancet,* 2016; 387(10022): 945-56

UKCTOCS Longitudinal Women's Cohort **http://uklwc.mrcctu.ucl.ac.uk**

Pinsky PF, Yu K, Kramer BS, et al. Extended mortality results for ovarian cancer screening in the PLCO trial with median 15years follow-up. *Gynecol Oncol,* 2016; 143(2): 270-5.

Acknowledgements

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Appendix - details about UKCTOCS

UKCTOCS tested two different ovarian cancer screening methods, versus no screening: these were multimodal screening (annual blood tests with transvaginal ultrasound as a second line test in case of abnormality) and ultrasound screening (annual and second line tests were transvaginal scans).

Between April 2001-Sept 2005 a total of 202,638 postmenopausal women, aged 50-74 years from the general population joined the trial. Women who were at high-risk of familial ovarian cancer were excluded.

- 50,640 women were in the multimodal group and had a yearly blood test. We looked for changes in a woman's levels of a protein called CA125 until 2011.
- 50,639 women were in the ultrasound group and had a yearly vaginal ultrasound scan to check their ovaries) till 2011
- 101,359 women were in the no screening group

Women in the screened groups underwent an average of 8 annual screens till 31 Dec 2011. Overall, there were 345,570 screens in the multimodal group and 327,775 in the ultrasound group.

Women were then followed up for 3 further years until 31 Dec 2014.

In 2015 we released the results of the trial which showed that screening picked up 84% of all ovarian cancers diagnosed in the multimodal group and 73% of all ovarian cancers in the ultrasound group.

Only one in four women shown to have invasive ovarian cancer, had reported symptoms commonly associated with ovarian cancer (pelvic or abdominal pain, increase in abdominal size, loss of appetite/feeling full).

Compared to women who had no screening, more of those in the multimodal screening group were diagnosed with ovarian cancer at an earlier stage (stage I and II). There was no evidence of earlier diagnosis of ovarian cancer in the ultrasound group compared to the no screening group.

Both screening methods picked up changes that were not in fact ovarian cancer. This meant that some women had unnecessary surgery together with the worry and risk of complications that goes with it:

- In the multimodal group 14 woman had unnecessary surgery for every 10,000 women screened. This means that for each woman detected by multimodal screening to have ovarian cancer, an additional 2 women had unnecessary surgery
- In the ultrasound group 50 woman had unnecessary surgery for every 10,000 women screened. This means that for each woman detected by ultrasound screening to have ovarian cancer, an additional 10 women had unnecessary surgery

There was not enough data in 2015 to be sure whether screening helped reduce deaths from ovarian cancer.

However, the results suggested that following up the women for a few more years would allow us to definitely decide whether screening did or did not reduce deaths from ovarian cancer.