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Ovarian Cancer Screening: There may be light at the end of the tunnel?

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Prof Uziel Beller

Editor in Chief

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Dear Sir,

Jacobs, Menon et al[1, 2] recently reported results of the United Kingdom Collaborative trial of Ovarian Cancer Screening (UKCTOCS). The investigators are to be congratulated on successfully undertaking and completing such a large complex population-based randomised trial. The only other screening trial to report on mortality was the PLCO study,[3] which found no mortality benefit and a significantly high 15% complication rate from surgical diagnostic evaluation. Several things stand out which differentiate UKCTOCS from previous PLCO and Japanese Shizuoka randomised studies.[3, 4] These include the concept of a longitudinal biomarker algorithm analysis for screening using the Risk of Ovarian Cancer algorithm (ROCA), a web-based trial management and call recall system as well as tight protocol-driven centralised co-ordination and management. It is the results of the ROCA driven multimodal screening arm which appear particularly encouraging. The authors report a high sensitivity of 84%-85.9%, specificity of 99.8%, and an extremely acceptable 2.7 operations per case of cancer detected, with a 3% complication rate.[1, 2] Although, the Cox model showed a 15% non-significant mortality benefit, on post-hoc analysis the authors found a potential statistically significant delayed effect on mortality >7 years post-randomisation. Their finding of a statistically significant stage shift of 14% (40% vs 26%) ≤Stage-3a disease is noteworthy and adds biological plausibility to this. This would have resulted in a higher R'0' resection rate (nil-residual disease) in the screened group. R'0' resection is well documented as the critically important factor associated with higher survival rates following debulking surgery for advanced ovarian cancer.[5, 6] The philosophy of ovarian cancer debulking surgery has changed over the last few years with far more complex ultra-radical surgeries being undertaken in most major cancer centres, to achieve 'nil-residual' disease or R'0' resection. If screening is associated with an increase in lower volume disease

this may well lead to the need for proportionally fewer ultra-radical surgical procedures with lower morbidity and potentially beneficial cost implications. At the same time, it remains unknown if screening also resulted in less bulky or lower volume stage 3b/3c disease which may be more amenable to achieving R'0' resection and better outcomes. This is an important issue and it would be helpful if this were further evaluated and reported by the research team. Maximising translation of a screening strategy into patient benefit also requires increasing awareness and changing the mind set of gynaecological oncologists and multidisciplinary teams to act/operate on a rising biomarker without any radiological confirmation of disease.

This report also highlights for all investigators and trialists the importance of the critical issue of 'pre-specified' analysis and choice of statistical plan. Unlike some other large population based screening trials (PLCO[3] and National Lung Cancer[7] trials), the UKCTOCS pre-specified analysis plan does not appear to have taken into account any statistical adjustment for a potential delayed effect on mortality. The time needed for the process of diagnosis, treatment, recurrence and occurrence of death, can result in a lag/delay between initiation of screening and observation of a mortality impact. This has been reported in other screening trials. In such situation mortality rates for the screened group relative to those of the control group are not likely to be constant as a function of years from randomisation and thus the log-rank test for differences in mortality between the two randomised groups is not optimal.[8, 9] This leads to a loss in power which may be recovered or adjusted for by using other tests that are more sensitive to non-proportional odds alternatives like an adaptive weighted log rank test[8] or likelihood ratio test[9]. The trial was underpowered to detect a <30% difference that may exist between the arms. The observed stage shift of 14% may well be associated with a lower than 30% mortality impact. However, even a lower level of mortality benefit could have significant impact on this poor prognostic disease at a population level. This possibility of lower volume disease and higher complete cyto-reduction rates translating into a <30% mortality benefit may be corroborated by the statistically significant results of the weighted log-rank and Royston Palmer tests, which helps boost power of the study to enable identification of a smaller

difference between screening and control arms which may exist. The authors have suggested further follow-up of the cohort to establish this.

While many of us hope this will be positive, the possibility that the mortality impact will remain non-significant despite additional follow-up cannot be discounted. It is critically important for these results to be published and benefits of OC screening well-established to enable appropriate inferences before considering introduction into practice/ a national programme. The harms of false positive surgery and complications from screening are not insignificant. A negative outcome would once again highlight the current limitations of early detection technologies and difficulties linked to disease biology. A successful strategy may need to detect tumours 0.4-1.3cm in size and surmount the signal-to-noise conundrum associated with this.[10] Circulating DNA and multimarker algorithms used in a longitudinal analysis may hold promise, but new biomarkers which add significantly to Ca125 in the screening context remain to be validated. Novel/innovative functional imaging modalities also need to be developed and evaluated.

We await with interest and hope the results from further follow-up and additional analysis of surgical outcomes.

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