Editorial Commentary

Population effects associated with colorectal cancer screening in Europe

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Comment on: Cardoso R, Guo F, Heisser T, *et al.* Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study. Lancet Oncol 2021;22:1002-13.

Received: 24 September 2021; Accepted: 10 October 2021; Published: 30 December 2021.
doi: 10.21037/dmr-2021-12
View this article at: https://dx.doi.org/10.21037/dmr-2021-12

In most European countries, colorectal cancer (CRC) is the second most common cause of cancer death, and the 5-year survival rate is in the region of 50%. It is well established that length of survival is dependent on stage at diagnosis, and randomized, population-based trials have clearly demonstrated that screening for CRC reduces disease-specific mortality in those who are invited.

For this reason, screening for CRC is now widespread world-wide. However, while the public health aim of screening for CRC is to reduce disease specific mortality in the population, there is a paucity of population-level data in the literature. In addition, the effect of CRC screening programmes on disease incidence has been little studied. In the paper by Cardoso *et al.*, the Heidelberg Group has collaborated with cancer and death registries across Europe to address these gaps and have produced an impressive account of changes in CRC incidence and mortality since 2000 in the context of a variable level of screening activity (1).

The main messages to take from this work are that: (I) countries with long standing screening programmes were those most likely to have seen reductions in CRC mortality; (II) these mortality reductions were greatest in the countries with the earliest implementation of screening; (III) CRC incidence has also fallen in countries with established screening programmes, although this observation is more evident where the programmes have an endoscopic screening modality component. It is also worthy of note that these patterns are essentially restricted to the distal colon and rectum and the screening participant age groups.

The obvious inference from these data is that screening has been responsible for both incidence and mortality reductions, although, as with all purely observational studies, there may be confounding factors and alternative explanations. In particular, it may be possible that countries with established CRC screening also have better CRC diagnosis in patients presenting with lower abdominal symptoms and overall superior cancer care, as well as healthier lifestyle behaviours than those with no screening programmes, although the observation that incidence reductions are confined to the age ranges invited would make this explanation less likely.

Another approach would have been to correct for screening participation as we have done in our study of changing incidence of CRC in the Scottish population in which we observed that incidence only fell in the population accepting the screening invitation (2). However even this approach is subject to the possibility of bias, since it is well-known that those who accept screening invitations are more likely to have healthier lifestyles than those who do not (3). Because CRC is associated with excess body weight, low levels of physical activity, smoking and high alcohol intake (4), participating in screening may be a marker of behaviour that makes a diagnosis of CRC less likely.

Nevertheless, population-level data are very important, and it would be worrying if screening programmes were not associated with disease-specific mortality reductions in the population offered screening. The observations related to CRC incidence are particularly interesting in the study reported. The only feasible explanation for

screening having a direct effect on incidence is that the process identifies substantial numbers of participants with colorectal adenomas which are subsequently removed. The adenoma-carcinoma sequence has been understood for a number of years (5), and the randomised studies of flexible sigmoidoscopy screening provided incontrovertible evidence that endoscopic screening reduces the incidence of CRC, at least in the distal colon (6).

In keeping with this evidence, the European countries in which endoscopy played a major role as a primary screening test have seen the largest reductions in CRC incidence, which is hardly surprising since adenoma detection rates are much higher with endoscopy than with either guaiac faecal occult blood tests (gFOBT) or faecal immunochemical tests (FIT) in CRC screening (7). However, the problem with first-line endoscopic screening is poor uptake when compared with faecal testing (8) and the consequent exaggeration of the inequalities that inevitably result from the well-described deprivation gradient in screening participation (9). On the other hand, tests for faecal haemoglobin do detect adenomas, particularly advanced and distal adenomas, and are associated with population reductions in CRC incidence (2). The quantitative nature of most FIT that are now used in screening programmes facilitates faecal haemoglobin concentration (f-Hb) thresholds to be set to optimise detection of adenomas, since it is known that this increases with a reduction in the threshold that is used to trigger an invitation for colonoscopy (10). It is also very interesting that, although the positive predictive value (PPV) for CRC declines with a decreasing f-Hb threshold, the same does not happen to the same extent with adenomas (10). Thus, a low f-Hb threshold FIT-based programme combines a high participation rate with a high PPV for adenoma and a consequently high adenoma detection rate and can therefore be expected to result in more substantial reductions in CRC incidence than have been seen with the traditional gFOBT approach.

One important aspect of the data presented in the Heidelberg paper that seems to have been passed over is the differential effect of screening in men and women. Inspection of Figure 1 of this paper clarifies that both incidence and mortality fall in both men and women where endoscopic screening is prominent. However, in countries that have engaged in gFOBT and FIT screening, the effect on women has been negligible. We now know that women have substantially lower f-Hb concentrations than men (11) with this difference varyings between and even within countries (12,13). For a given f-Hb threshold both CRC and adenoma detection rates are lower in women (14). This is likely to translate into lower incidence and mortality reductions in women, and indeed, prolonged follow-up of the Minnesota trial of gFOBT screening has demonstrated this quite clearly (15).

So, what does this tell us about fruitful future directions for CRC screening? As with previous evidence, an increase in CRC incidence in individuals younger than 50 years was seen in many countries. Although evolution of screening guidelines may be considered advisable, it should be realised that the numbers of individuals aged less than 50 years with CRC are small and efforts to reduce the age that screening commences to 50 years might be a priority for those countries with invitations beginning at older ages. More importantly and while innovations such as faecal DNA analysis (16) and genomic profiling (17) have attracted considerable attention in recent years, more intelligent use of the information currently available from existing CRC screening programmes is far more likely to pay dividends. In particular, driving down the f-Hb threshold employed in FIT-based programmes, while at the same time investing in colonoscopy services to cope with the increased demand that this would incur, seems to be an obvious direction of travel. In addition, exploring differential f-Hb thresholds for men and women, as has been done in Sweden (18) and Finland (19) with success, should be an urgent priority in all countries using FIT, since this is a simple way to correct the gender inequality that is now coming to light.

Finally, one issue that should not be forgotten is that of direct invitation to screening. It is known that this is one of the most important strategies for optimising uptake and, while the data from Germany and Austria indicate that an opportunistic approach to colonoscopy screening has been associated with marked reductions in both incidence and mortality, population uptake rates are not reported, and there is little doubt that an organised, proactive invitation strategy would have a greater effect.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Digestive Medicine Research*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/dmr-2021-12). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/dmr-2021-12
Cite this article as: Steele RJC, Clark G, Fraser CG. Population effects associated with colorectal cancer screening in Europe. Dig Med Res 2021;4:79.