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Guaiac fecal occult blood tests for colorectal cancer screening: A 30-year follow-up of two pooled trials

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Aug 4th 2020

Dear Professor Kahi,

Thank you for inviting me to write an Editorial for CGH-D-20-00812R1 "Effects of Screening Compliance on Long-term Reductions in All-cause and Colorectal Cancer Mortality".

I have coauthored this Editorial with Emma Robbins from my research group. We have provided two suggested titles and you should find that the Editorial is the desired length (excluding the title page).

Please do let us know if we can provide anything else.

Yours sincerely,

Amanda J Cross

Title option 1: Guaiac fecal occult blood tests for colorectal cancer screening: A 30-year follow-up of two pooled trials

Title option 2: Guaiac fecal occult blood tests and mortality: A 30-year follow-up of two pooled trial

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Colorectal cancer (CRC) is a leading cause of morbidity and mortality globally.¹ Survival of the disease is strongly associated with stage at diagnosis, with five-year survival rates reaching over 90% when diagnosed at stage I, compared to just 10% when diagnosed at stage IV.² This underscores the need for early detection of CRC, in addition to preventative measures that can stop CRC developing in the first place. Fortunately, CRC is amenable to screening which enables detection of CRCs at early, treatable stages, as well as prevention via the detection of premalignant polyps.³ Several screening modalities exist. Structural examinations such as colonoscopy and flexible sigmoidoscopy allow direct visualisation and detection of abnormalities on the inner lining of the colorectum. In comparison, stool-based tests aim to detect aberrations in stool indicative of colorectal neoplasia, such as the presence of occult (hidden) blood in the case of fecal occult blood tests (FOBTs).³

Results from a national survey in the US suggest that the vast majority (~80%) of individuals undergoing CRC screening participate in a regime of colonoscopy every 10 years, while <10% undergo annual FOBT screening and only ~1% undergo flexible sigmoidoscopy every 5 years with FOBT every 1–3 years.⁴ A different pattern is observed elsewhere around the world, with little use of colonoscopy and a much greater reliance on FOBTs in screening programmes in the UK and across Europe and Australasia.⁵

Colonoscopy and flexible sigmoidoscopy are highly sensitive for the detection of premalignant polyps and CRCs located within the reach of the scope.⁶ However, these endoscopic examinations are time-consuming and resource-intensive; require specially trained healthcare professionals; need bowel preparation; and carry a small risk of serious complications (such as bowel perforation) due to their invasive nature. In comparison, FOBTs are less sensitive, particularly for premalignant polyps and early CRCs which tend not to bleed, but are non-invasive, less resource-intensive, and can be performed by patients at home.⁷

The guaiac FOBT (gFOBT), developed in the 1950s, was the first widely used test for CRC screening. It detects hemoglobin by use of guaiac-impregnated test cards which turn blue in the presence of heme (with the addition of hydroperoxidase). Typically, gFOBTs comprise three cards each with two windows, requiring six samples from three separate stools, and dietary restrictions are advised because the test is

not specific for human hemoglobin.⁸ Several large randomized trials with long-term follow-up have examined the effects of gFOBT screening on CRC outcomes.⁹⁻¹⁴ The study by Shaukat et al. in *Clinical and Gastroenterological Hepatology* pooled data from two of these trials, the Minnesota (US) and Funen (Denmark) trials, providing some novel insights not reported previously.^{10, 11} Three other trials were not included due to methodological reasons,^{13, 14} or because they declined the invitation to participate.¹²

In the Minnesota trial, approximately 50,000 individuals aged 50–80 years were randomized between 1975 and 1977 to either usual care (control) or to annual or biennial screening with gFOBT (Hemoccult II).¹⁰ All individuals in the annual and biennial arms were offered 11 and six screening rounds, respectively, regardless of whether they had complied with a previous round. Overall, 90% of individuals complied with at least one screening round. Participants with a positive gFOBT were invited for diagnostic follow-up, mainly by colonoscopy, during which any detected polyps were removed. Compliance with diagnostic follow-up was 83%. After a median follow-up of 30 years, CRC mortality was reduced by 32% and 22% among those invited to annual and biennial screening, respectively, compared with controls. There was no observable reduction in all-cause mortality.¹⁰

In the Funen trial, approximately 60,000 individuals aged 45–75 years were randomized in 1985 to either usual care (control) or biennial screening with gFOBT (Hemoccult II).¹¹ Among those invited to the first round of screening, 67% complied. Only those compliant with screening were invited to the next screening round, for up to a total of nine rounds. Participants with a positive gFOBT were invited for colonoscopy, during which any detected polyps were removed. Compliance with follow-up colonoscopy was also 83% in this trial. After a median follow-up of 17 years, the investigators reported no significant reduction in CRC-related or all-cause mortality in the invited to screening arm, compared with controls.¹¹

In light of these findings, Shaukat et al. noted a few areas of uncertainty: Does gFOBT screening have any impact on all-cause mortality? How does the benefit of gFOBT screening vary by age and sex? What is the effect of gFOBT screening when non-compliance with screening is accounted for? This provided the impetus to pool data from these two trials, creating a large dataset with a high number of events, to

examine the combined 30-year effects of multiple rounds of biennial gFOBT screening on CRC-related and all-cause mortality. Compliance was defined as participation in at least one screening round.

Headline findings included a significant reduction in CRC mortality (relative risk [RR]: 0.84, 95%CI 0.74–0.96) and all-cause mortality (RR: 0.98, 95%CI 0.97–0.99) among compliers, after 30 years of follow-up.

Subgroup analyses found that the effect on CRC mortality was greater among compliant men (RR: 0.75, 95%CI 0.62–0.90) than women (RR: 0.91, 95%CI 0.75–1.09), with the largest effects seen among men aged 60–69 years (RR: 0.59, 95%CI, 0.42–0.81) and women aged ≥ 70 years (RR: 0.53, 95%CI 0.30–0.94).

Based on these results, the authors concluded that biennial gFOBT screening provides sustained protection against long-term CRC mortality among those compliant with screening. This is perhaps not surprising given that previous analyses of the Minnesota trial reported reductions in CRC mortality, even when all individuals invited for screening were included in analysis (not just those complying).^{9, 10} While any reduction in CRC mortality is a laudatory achievement, the 16% reduction observed among compliers is lower in magnitude than reductions reported for other screening modalities. In the UK Flexible Sigmoidoscopy Screening Trial, a single flexible sigmoidoscopy screen performed between ages 55 and 64 years reduced CRC mortality by 41% among compliers after 17 years of follow-up.¹⁵

The authors drew particular attention to the finding that gFOBT screening was associated with a reduction in all-cause mortality. The reduction was only observed among compliers and so the authors suggested that the effect might have been due to the screening itself, as well as healthy lifestyle behaviors or indirect effects of accessing health services as a result of screening. We do wonder why such importance was placed on the effect on all-cause mortality. Firstly, as CRC only accounts for a small proportion of all deaths (~2% globally),¹⁶ it is not expected that a reduction in CRC mortality would necessarily translate into a reduction in all-cause mortality. Moreover, as the aim of CRC screening is to minimise the devastation this specific disease causes, we do not think that the evidence for gFOBT screening would have been any less compelling even if no reduction in all-cause mortality was observed.

Another conclusion was that the benefit of gFOBT screening was less pronounced in women than men, although it is important to note that the interaction between screening and sex was not statistically

significant. Similarly, no reduction in CRC mortality was seen among women in a pooled analysis of flexible sigmoidoscopy screening trials,¹⁷ although the largest of these trials did demonstrate a significant effect in women.¹⁸ The explanation for this remains uncertain, although Shaukat et al. suggested it could be due to the female preponderance of proximal adenomas and CRC, which are unlikely to be detected by flexible sigmoidoscopy and possibly less sensitive to detection by gFOBT than lesions in the distal colon.

The authors also noted that the benefit of gFOBT screening appeared to be delayed in women compared to men, with a time lag of approximately 10 years. This led them to suggest that greater screening efficiency could be achieved by starting and stopping screening at later ages in women than men. This comes with the caveat, however, that the number of individuals aged ≥ 70 years in the study was low, preventing clear conclusions from being drawn about screening at older ages.

Limitations of the study were well described. The authors were not able to pool data from the Nottingham gFOBT screening trial (UK), the largest such trial including approximately 150,000 individuals.¹² Information was not available on screening procedures performed in trial participants during follow-up. As CRC screening started to be widely implemented in the US and Denmark at the turn of the century, it is possible that there was contamination in the control arms due to screening; this would have likely diluted the observed benefit of screening in the screening arm.

On a final note, Shaukat et al. pointed to fecal immunochemical tests (FITs) as the newer generation of FOBTs which, compared with gFOBTs, are more user friendly (requiring only one stool sample and no dietary restrictions); are associated with improved compliance; can provide quantitative readouts of fecal haemoglobin concentration (f-Hb), enabling adjustment of the f-Hb threshold for test positivity; and can achieve higher sensitivities for CRC.⁸ In light of these advantages, many CRC screening programmes around the world have replaced the gFOBT with FIT.⁵ It is expected that FIT will have a greater impact on CRC mortality than the gFOBT via the improved detection of early CRCs. There is even hope that FIT will reduce CRC incidence by enabling the detection and removal of premalignant polyps, which has never been demonstrated for gFOBT.¹⁹

The findings presented by Shaukat et al. highlight the benefit that can be achieved by complying with gFOBT screening. Sustained reductions in CRC mortality due to biennial gFOBT screening were observed through 30 years of follow-up. Further research is needed to understand why gFOBT and other screening modalities may be less effective in women than in men, and how the benefit of screening varies by age.

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