Occult blood in faeces: a window into health beyond the colorectum?

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After decades of research, testing for occult blood in faeces is firmly established as a method to screen for colorectal cancer (CRC). Such testing is based on the relatively simple premise that asymptomatic CRCs, and some CRC precursors, may lose small amounts of blood into faeces. The provocative study by Libby *et al* in *Gut*,[1] which reports the associations between a positive guaiac faecal occult blood test (gFOBT) result and all-cause as well as non-CRC mortality in the National Health Service Tayside Board area of Scotland, suggests that occult blood in faeces may be telling us more than we might have thought. If the eye is the window to the soul, is a faecal test the window to general health?

The current study confirms and expands on the observations of Chen *et al*, who reported a gradient relationship between all-cause mortality and faecal haemoglobin (f-Hb) concentration in population-based screening programmes in Keelung and Tainan, Taiwan.[2] Chen *et al* and Libby *et al* found associations between occult blood in faeces and CRC mortality, which is not surprising. However, in the study by Chen *et al*, with median follow-up of 3.5 years and longest follow-up of 8 years, the adjusted HRs for all-cause mortality ranged from 1.15 (95% CI 1.07 to 1.24) to 1.67 (95% CI 1.54 to 2.07) for persons with f-Hb concentrations of 20–49 and ≥450 ng Hb/mL, respectively (trend test $p<0.0001$), compared with the reference group of 1–19 ng Hb/mL (whose risk did not differ from that of persons with undetectable f-Hb).[2] The current study by Libby *et al*, with longest follow-up of 16 years, reports an adjusted HR for all-cause non-CRC mortality of 1.58 (95% CI 1.45 to 1.73) for persons with a positive versus a negative gFOBT, as well as increased risk for multiple categories of non-CRC death.[1]

The results of these studies raise important epidemiological and mechanistic questions. Perhaps more importantly, if occult blood in faeces is a predictor of life expectancy and multiple non-CRC causes of death, the inevitable next questions concern the implications for organised CRC screening programmes or opportunistic CRC screening.

Although the current indication for faecal occult blood testing is screening the colorectum, the possible initial surprise that it may be telling us more than anticipated might be attenuated when we consider that multiple disease risk factors and diseases are interrelated. Libby *et al* and Chen *et al* do not explicitly report results for those found to have colorectal neoplasia, but those with an abnormal faecal test are a population enriched for CRC and CRC precursors.[3] Given that the recognised risk factors for CRC include overweight and obesity, diabetes, tobacco, alcohol, lack of regular physical activity, and diets low in fruits and vegetables and fibre and high in fat, one might hypothesise that the effects reported by Libby *et al* and Chen *et al* may be due at least in part to the associations between these risk factors and non-CRC death, including the specific disease categories explored by Libby *et al*. The authors of these studies tried to account for some of these factors in their multivariable models.

For those with faecal occult blood who truly do not harbour any colorectal neoplasia, alternative explanations are needed. One must at least consider that the downstream consequences of finding faecal occult blood might lead to harm, such as during colonoscopy. However, colonoscopy complication rates are much too low[4] to contribute to the observed effects on mortality, and it is difficult to account for the time course of deaths, even if one speculates about use of surveillance colonoscopy over the years.

Chen *et al* first proposed that the impact of f-Hb on all-cause mortality may be mediated through systemic inflammation, acknowledging that the exact mechanisms require further investigation,[2] and Libby *et al* expand on this concept in their discussion.[1] It is possible that a single unifying explanation does not exist, and it seems likely that elucidating all relevant mechanisms will not be a quick and simple endeavour.

Focusing on CRC screening, it would be troublesome if, on average, persons in whom death from CRC is averted instead go on to experience non-CRC death without any gain in life expectancy. Screening decreases CRC incidence and mortality,[5 6] which are important outcomes on their own. Beyond this, a pooled analysis suggests that it may also decrease all-cause mortality,[7] an effect that is very difficult to demonstrate in single trials, which are not powered for this outcome, but that nonetheless reached borderline statistical significance in the UK flexible sigmoidoscopy screening trial, which reported an HR for all-cause mortality of 0.97 (95% CI 0.94 to 1.00) for the intervention versus the control arm.[8] Multiple decision analyses have quantified the clinical benefits of screening in terms of life-years gained, with these results depending directly on the models' assumptions that those who are spared CRC death instead experience the general population's average age-specific other-cause mortality rates. We have estimated the average population-wide benefits of CRC screening as 37–51 undiscounted life-days gained per person screened, depending on the strategy, but estimated life expectancy gains actually apply to only the small percentage of the screened population who benefit by avoiding CRC death, with average gains for these persons of 3.5–4.6 undiscounted life-years.[9] Libby *et al* report median (IQR) ages at death of 71 (65–76) years for the gFOBT-negative group versus 70 (64–75) years for the gFOBT-positive group.[1] It is not known if this approximate 1 year difference applies specifically to those who might have had CRC death prevented, but it is reassuring that a difference of this magnitude is unlikely to eliminate the potential benefits of CRC screening on life expectancy that are estimated by multiple decision analyses.

The most challenging question is whether the findings of Libby *et al* and Chen *et al* should lead to anything other than recommending a prompt colonoscopy for those with abnormal faecal occult blood test results.[10] Libby *et al* suggest that such results might be used to alert invitees to the risk of other disease, possibly leading to interventions based on diet, weight management, exercise or medications.[1] I suspect that an abnormal faecal occult blood test is rarely the exclusive piece of information that would trigger such recommendations for a given patient.

Establishing a CRC screening programme that minimises failures along all the steps in the continuum of

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interventions, including ensuring appropriate follow-up of abnormal faecal tests,[10] is challenging enough. I fear that tasking such programmes, let alone screening in opportunistic settings, with also addressing risk mitigation in multiple disease areas beyond CRC would be too demanding. Possibly a general alert to the patient and her or his primary care physician might be reasonable, but my hope is that primary care physicians would be addressing risk factors for these other diseases already.

Occult blood in faeces may be telling us about health beyond the colorectum. However, it seems likely that what it tells us about non-CRC risk might be gleaned also from other pieces of information about a patient. Future research avenues, including those proposed by Libby *et al*,[1] will help clarify the implications of the current study. For now, I believe that our enthusiasm for the established CRC screening methods should not be affected, and that the focus after an abnormal faecal occult blood test should be to ensure prompt delivery of a follow-up colonoscopy.

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