Editorial

Quantitation of Hemoglobin Makes Fecal Immunochemical Tests a Better FIT for Non-Invasive Screening

There are many tests options available for screening for colorectal cancer (CRC). These include endoscopy, imaging techniques, fecal tests, and emerging blood tests. Screening guidelines differ markedly between and even within countries but, recently, studies have shown that participant preferences should be considered when making CRC screening recommendations.¹ Greater emphasis is now being directed to ensuring that offering a choice of test takes account of the preferences of the individual or the groups making the decisions.² This has led to a growing realization that non-invasive tests have considerable advantages.³ Of these, fecal immunochemical tests (FIT) for hemoglobin (Hb) have so many advantages over traditional guaiac-based fecal occult blood tests (gFOBT) and other published to date fecal biomarkers such as DNA, RNA, and proteins, that they are generally recognised to be the best currently available.⁴ FIT fulfil the criteria suggested as desirable because they can detect both advanced adenomas and early cancers, have high specificity to keep the costs of screening low and minimize risks to the healthy, and are user-friendly, affordable, and widely available.⁴

FIT are available in two formats, qualitative tests that simply give a dichotomous positive or negative result and quantitative tests that provide high quality measurement of the fecal Hb concentration. In this issue of the journal, Chiu et al⁵ report on the association between early-stage neoplasia and false-negative FIT results. Using a qualitative FIT, those with non-advanced adenoma, advanced adenoma, and cancer were identified with sensitivities of 10.6, 28.0, and 78.6% respectively, with proximal advanced adenomas (AA) and non-polypoid lesions being detected with lower sensitivities than distal AA. The FIT used gave a high false-negative rate in the detection of adenomas <15 mm and non-polypoid adenomas, and also detection of what were described as “carcinoma in situ” and T1 cancer as compared to T2–T4 cancers. These data could impact on the design of FIT-based screening programs, but a number of pertinent questions arise.

Firstly, are these results applicable to other qualitative FIT? It is vital for users to recognize that all FIT are not the same and that, using the same specimens, different FIT yield markedly different positivity rates, sensitivities, and specificities.⁶ Thus, the exact results obtained by Chiu et al⁵ may not be applicable directly to other FIT. Moreover, we have shown that these clinical characteristics are not directly related to the stated cut-off Hb concentrations when these are expressed in units of ng Hb/mL buffer.⁷ The FIT used had a cut-off Hb concentration of 50 ng Hb/mL buffer. Our guideline urges all involved with FIT to report cut-off concentrations in μg Hb/g feces (here: 10 μg Hb/g feces), because this will facilitate more objective comparison of clinical outcome data across different FIT.⁷

Secondly, is it surprising that the FIT gave a high rate of false-negative results for small or non-polypoid adenomas? We think that the reported results for early stage cancers should not include neoplasms labelled “carcinoma in situ”, a term no longer used in clinical pathology. They should be labelled stage 1(T1) cancers provided that they show signs of invasion: if not, then they represent high grade dysplasia. However, irrespective of terminology, it was shown that these had more false-negative FIT results compared to more
advanced cancers. Even with the now near-obsolete gFOBT, significant evidence was gathered over many years that positivity was greater the more advanced the colorectal neoplasia. Quantitative FIT have allowed this to be explored in more detail, including by Levi et al, who demonstrated that adenoma size was related to mean fecal Hb concentration, and Ciato et al, who showed that 191 colorectal cancers and 890 adenomas were detected at colonoscopy in 2597 FIT positive individuals, and, among adenomas, higher faecal Hb concentration was significantly associated with size, presence of severe dysplasia, and presence of villous component. Further studies have shown that fecal Hb concentration increases in individuals with no colonic neoplasia through clinically less important lesions through non-advanced and small adenomas through larger and more advanced adenomas to cancer, although there is considerable overlap between these groups. Indeed, screening using FIT would only be successful if a relationship did exist between fecal Hb concentration and disease.

The work of Chiu et al provides additional supports for this relationship by showing that small and early lesions have negative FIT results, equivalent to low fecal Hb concentrations. A number of studies have investigated the effect of fecal Hb cut-off concentration on the performance characteristics of FIT; these have used quantitative FIT, which usually involve automated immunoturbidimetry. As cut-off Hb concentration is lowered, positivity rate and sensitivity for neoplasia increase, but at the expense of specificity and positive predictive value. Thus, as pointed out by Chiu et al, their documented sensitivity and specificity for adenomas and cancer could be modified by changing the cut-off fecal Hb concentration. Qualitative FIT do not allow this desirable opportunity. In contrast, quantitative FIT have the major advantage, particularly for countries with national programmatic screening approaches, that the organizers of screening programs can select the cut-off Hb concentration that fulfils their pre-set objectives. Moreover, instead of taking more than one sample or decreasing inter-screening interval as mentioned, the cut-off Hb concentration could simply be made lower to achieve the stated desirable outcome of increased sensitivity. Quantitative FIT have so many advantages over qualitative FIT that they ought to be available everywhere, particularly recommended in screening guidelines, and approved for use by all relevant regulatory bodies.

Thirdly, what would be gained by using different cut-off fecal Hb concentrations for different groups? It has become very well recognized that fecal Hb concentration is affected by age, older people having higher concentrations than younger, and by sex, men having higher concentrations than women. Indeed, many have commented that these relationships should affect the design of FIT-based screening programs. Although undoubtedly difficult to institute in practice, it is likely that programs would benefit considerably if different cut-off fecal Hb concentrations were used as criteria for the initiation of further investigation, usually colonoscopy, for different groups. Selecting the appropriate cut-off Hb concentrations for different groups would be based on the FIT performance characteristic that was decided to be the most important by the individual program organizers, such as positivity rate, sensitivity, specificity, or positive predictive value. Using a qualitative FIT, Chiu et al treated their large study population as a single entity. It would be of much interest to examine the influence of age and sex on false-negative FIT results with quantitative FIT using different cut-off fecal Hb concentrations.
Finally, how correct is the often quoted take-away message that FIT are not good screening tests because they have “high” false-negative rates for small and non-polypoid adenoma and early cancers? This conclusion does not take into consideration that the reported sensitivities\(^5\) are examples of test application sensitivity (test once only) and not test programmatic sensitivity (test repeatedly done in a program of repeated screening episodes over time) as per recommendations for population screening with FIT. As pointed out by Chiu et al,\(^5\) good programmatic sensitivity allows for missed advanced adenomas and early cancers to be detected in subsequent screens before they become fatal cancers. It also important to explain that the term “advanced neoplasms”, as used in the gastroenterology literature, actually refers most commonly to advanced adenomas and not cancers. Advanced adenomas are benign lesions of a certain size and histology and their natural history is unknown. Only a very few actually become fatal cancers. Labelling these neoplasms “advanced” is a form of over-diagnosis for most of them. Over-diagnosis is the detection of lesions that require treatment where the treatment will confer no benefit to survival in the course of the patient’s lifetime.

This study\(^5\) is a valuable addition to the literature on FIT for screening. It adds some information on sensitivity of the FIT used for proximal and distal advanced neoplasms as well as for polypoid versus flat neoplasms. It raises important questions that will hopefully be answered by investigators using quantitative FIT and standardized reporting of FIT results. We will then come closer to the day when guidelines can make evidence-based recommendations on which FIT are best for any given screening strategy.

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References


Conflicts of interest

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