Fecal Immunochemical Screening for Advanced Colorectal Neoplasia in Patients with CKD: Accurate or Not?

We read with interest the report by Wong *et al.*[1] of the Detecting Bowel Cancer in CKD (DETECT) study of colorectal cancer screening in 1706 patients with CKD. DETECT investigated the test performance characteristics of fecal immunochemical testing (FIT) to detect advanced colorectal neoplasia. The authors reported a high sensitivity (90%) and negative predictive value (99%), with a positivity rate of 22%.

Unfortunately, the estimates of sensitivity, specificity, and negative predictive values are unreliable because not all participants had the reference standard (colonoscopy) performed. In DETECT, only participants with a positive FIT were invited for colonoscopy (323 of 1706; 19%). The authors attempted to mitigate verification bias by using clinical follow-up at 2 years as an alternative reference standard. Although this provided colonoscopy outcomes for 98 of 1337 (7%) patients who were FIT negative at baseline, absence of neoplasia was presumed for the other 1239 patients if there were no symptoms or a subsequent positive FIT result. However, advanced neoplasia is usually asymptomatic, and the opportunity to identify it with colonoscopy was limited to a subgroup of patients, most of whom were FIT positive. This results in differential verification bias and inaccurate estimates of neoplasia prevalence, sensitivity, and specificity.[2]

The high FIT-positive rate (22%) is also notable. DETECT used a relatively low fecal hemoglobin threshold of 10 μg/g (many screening programs use >20 μg/g) in a population where aspirin and anticoagulant use were common. Unsurprisingly, specificity was relatively low (83%). Given the high rate of serious colonoscopy complications observed (1.5%), this gives cause for concern.

Further, the data from DETECT give an estimate of sensitivity for advanced adenoma (*i.e.*, excluding the seven cases of cancer) of 89%. This is much higher than published general population studies with low risk of verification bias that used a 10 μg/g threshold (pooled sensitivity, 40%; specificity, 90%),[3] and our previous study in patients with CKD (transplant) where all participants had colonoscopy (FIT positivity, 12%; sensitivity, 25%; specificity, 91%; negative predictive

value, 90%).[4] Such comparisons highlight the likely biased nature of the DETECT estimates.

We therefore believe that the reported diagnostic accuracy results from DETECT are misleading. Both sensitivity and negative predictive value are likely overestimated and, unfortunately, the data are insufficient to determine the accuracy of FIT. Without an unbiased estimation of sensitivity, and with the reported high false positivity rate and high colonoscopy complication rate, it remains unclear whether screening with FIT to detect premalignant advanced neoplasia in patients with CKD is appropriate.

DISCLOSURES

None.

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Authors' Reply

We appreciate the interest shown by Collins *et al.*[1] in our study of screening advanced colorectal neoplasia in people with CKD (DETECT). They assert that the performance characteristics of fecal immunochemical testing (FIT) arising from our study are unreliable because of verification bias and that high false positive rates were found due to low test thresholds.[1]

We note that the authors have conducted a similar study but found lower test-positive and sensitivity values.[2] The observed differences in the test estimates are not unexpected. Their study was conducted in a single center, restricted only to transplant recipients, and of smaller sample size. A quantitative FIT (Eiken OC-Sensor) was the chosen screening tool for DETECT, because it is the screening test of choice by the National Bowel Cancer Screening program in Australia and Spain, rather than the InSure FIT (brush techniques) used by Collins *et al.*[1] Prior studies have also indicated lower positivity rates and sensitivity estimates for advanced colorectal neoplasia with the InSure FIT compared with the Eiken OC-Sensor FIT in the general population.[3,4]

We suggest that the two-step reference standard (colonoscopy for FIT-positive patients and clinical follow-up for both FIT-positive and FIT-negative patients) is in fact the correct one and not colonoscopy for all for three reasons. First, given the appreciable risk of colonoscopy in potentially high-risk patients, we could not ethically justify subjecting FIT-negative patients to an unnecessary procedure. Second, what Collins *et al.*[1] have not considered is the potential for overdiagnosis. We acknowledge that this has only been recognized as a major issue recently, postdating their publication in 2012. Overdiagnosis occurs when the disease detected through screening does not cause morbidity and/or death.[5] This is an important concept to consider, particularly in patients with limited life expectancy, such as those with CKD, and when competing events, such as cardiovascular diseases, predominate as the major cause of death. Overdiagnosis, the downside of cancer screening, will trigger a sequence of overtreatment, with the attendant adverse events and without benefit, because the screened individual will never experience the health consequences of the target condition. We anticipated that the harms associated with diagnostic colonoscopies are likely to be higher among those with CKD and thus, limit the benefits of routine screening. Our findings confirmed that colonoscopies and subsequent treatments, including polypectomy, incurred at least a 10-fold increased risk of major complications, including perforations and infections, in patients with CKD compared with those reported in the general population. Third, our two-step process is clinically feasible and allows for external generalizability.

In our study, a follow-up of 2 years was chosen to ensure that all clinically relevant colorectal cancers had enough time to progress to a detectable stage and that new (interval) cancers that develop after the index test (FIT) were also being detected. Importantly, only 14 additional patients (0.9%) were diagnosed with advanced colorectal neoplasia at the end of the 2-year follow-up, indicating that, even if differential verification bias may exist in theory, it is unlikely to be clinically relevant.

DISCLOSURES

None.

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