Are We Getting Closer to Molecular Population Screening for Colorectal Cancer?

Gad Rennert

The best methods to bring about a reduction in the incidence and mortality of colorectal cancer in the world have been the subject of much debate in recent years. Colorectal cancer is highly preventable through behavioral changes in diet and physical activity; still, much effort has been invested in developing efficient screening technologies for secondary prevention.

Public health theory stresses a number of requirements that must be met before screening for a disease can be initiated (1). This line of thought differs from the usual clinical situation in which symptomatic patients present themselves to the health system in search of medical help. The screening setting refers to very large populations that are usually symptom free and at a very low probability of having the disease of interest at any given round of screening. The disease of concern needs to be clinically significant in terms of incidence, prevalence, mortality, or suffering and have a natural history that can be influenced by a timely intervention. Screening technologies need to have proven and substantial efficacy. Specificity takes priority over sensitivity, contrary to the case when diagnosing symptomatic patients. Efficacy is best proven through randomized controlled trials that show disease-specific mortality reduction. Studies that are designed in a nonrandomized manner are prone to major biases, such as length bias, lead-time bias, and selection bias (1), all of which can seriously diminish the validity of the results in terms of the direction and the magnitude of the effect. The screening technology needs to be as simple as possible, easy to perform, cheap, and, most importantly, acceptable to the population, that is, noninvasive and with an overall balance of more benefit than harm.

Clinical practice, however, often strays from these rules, which leads to unjustified, unnecessary, and sometimes risky screening recommendations and behavior.

Colorectal cancer fulfills a number of the basic requirements for suitability for screening. It is common, with a lifetime probability of approximately 6% in Western countries, and is responsible for substantial mortality (it is the second leading cause of cancer death in the United States) with a relative 5-year survival rate of only 67% (2,3). Its clinical natural history is suitable for screening because there is a long precancerous phase that is identifiable in the form of polyps or adenomas (4). This cancer precursor enables the screening efforts to be directed not only toward early detection but also toward primary prevention.

A plethora of technologies is currently suggested as possible tools for screening for colorectal cancer. Several policy statements appeared last year on the role of various screening tools for colorectal cancer (5,6), statements that unfortunately only partially adhered to the classical and important rules of screening decision making outlined above.

Tests that detect occult blood in the stool have repeatedly been shown to lead to a statistically significant reduction in mortality from colorectal cancer in randomized controlled trials (7–10). Despite these findings, the low sensitivity of the first generation of these tests made them distasteful to clinicians, mainly those in the United States. However, their simplicity, low cost, noninvasiveness, and efficacy led to their incorporation as the tests of choice in the vast majority of Western countries that have a public policy of organized population screening (11,12). Newer generations of these fecal occult blood tests, such as Hemoccult SENSA (Beckman Coulter, Inc, Fullerton, CA) or immunological tests, have demonstrated vast improvements in test sensitivity, thus leading to very high detection rates with acceptable rates of false-positive results (13–15).

Endoscopic techniques are considered by some as state of the art for colorectal cancer detection, although no well-designed randomized controlled trial has ever shown the true magnitude of their efficacy. Several publications have shown that the sensitivity of endoscopic techniques is less than perfect when compared with findings in radiology-based colonography (16) and that the true mortality reduction potential is far from clear (17,18). In addition, these techniques are invasive, costly, and frequently involve the removal of an extremely large number of benign tumors that probably would never have become malignant. A lower-than-expected mortality reduction coupled with a relatively high rate of complications (18) when performed outside of a study setting precludes the use of these techniques as suitable screening tools for most of the world’s population. Colonography is a relatively recent addition to the arsenal of screening technologies that has the advantage of being practically noninvasive and has similar detection qualities to optic colonoscopy and minor rates of complications in expert hands (16,19). Nevertheless, this technology is also still awaiting demonstration of its overall level of efficacy and involves exposure to radiation, as well as requiring the distasteful bowel preparation disliked by so many.

With the evolving field of molecular medicine, interest in testing for genetic fingerprints of shed tumor cells in the stool as a means to detect tumors was inevitable. Such efforts have been in
practice for more than a decade. Although the original studies, which relied on known genetic markers in the Wnt pathway and in the microsatellite instability pathway, were less successful than anticipated (20,21), a new generation of tests incorporating detection of methylated markers is more promising (22), with clinical evaluations of vimentin gene methylation and methylation of other genes currently underway (23–25).

In this issue of the Journal, Melotte et al. (26) report on a promising biomarker of colorectal cancer, N-Myc downstream-regulated gene 4 (NDRG4). Methylation of the promoter of this tumor suppressor gene, which leads to inactivation of gene expression, was shown to be highly prevalent in colorectal cancers and very uncommon in noncancerous colon mucosa. When NDRG4 promoter methylation was tested in small groups of colorectal cancer patients and healthy control subjects, it was found to have a sensitivity rate, although not yet optimal, that was higher than that previously reported for genetic stool tests. This sensitivity was achieved with very high specificity in both training and validation sets. Adding this marker to a panel with other promising markers previously shown to be of relevance may further improve the precision of this type of technology for colorectal cancer screening.

As the practice of medicine at large is moving away from invasive diagnostic technologies to sophisticated and advanced non-invasive technologies, so is the forefront of cancer screening. Genetic diagnosis of colorectal cancers and meaningful adenomas has now reached a new phase that, when further fine-tuned, may carry the promise of becoming a suitable and affordable means of prevention and early detection of colorectal cancer in the general population.

References