Colonoscopy: the current king of the hill in the United States

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Abstract

Colonoscopy is the dominant colorectal cancer screening strategy in the United States. There are no randomized controlled trials completed of screening colonoscopy, but multiple lines of evidence establish that colonoscopy reduces colorectal cancer incidence in both the proximal and distal colon. Colonoscopy is highly operator dependent, but systematic efforts to measure and improve quality are impacting performance. Colonoscopy holds a substantial advantage over other strategies for detection of serrated lesions, and a recent case-control study suggests that once-only colonoscopy or colonoscopy at 20 year intervals, by a high level detector, could ensure lifetime protection from colorectal cancer for many patients.

Introduction and historical perspective on screening colonoscopy

The first printed suggestion of which I am aware that colonoscopy might be an appropriate screening test for colorectal cancer was in 1988 by Al Neugut and Ken Forde [1]. Any sense of rashness associated with such an idea was based on factors such as the need for sedation for colonoscopy compared to sigmoidoscopy, the considerably higher complication rate of colonoscopy, the greater technical expertise needed for performance of colonoscopy, and the knowledge that colorectal cancer is more common in the left colon. However, in 1988 there were already several cross sectional studies of colonoscopy in asymptomatic volunteers underway [2-5], and the results were published in 1990 and 1991 [2-5]. These 4 studies eventually totaled just over 1000 patients [2-6], and demonstrated that the prevalence of adenomas in asymptomatic persons is substantial, age-related, and higher in males [2-6]. During the 1990s it was common for the relative merits of colonoscopy and sigmoidoscopy to be debated by experts at national meetings, and clinicians in practice began to commonly perform what was in reality screening colonoscopy but which was labeled as diagnostic colonoscopy for trivial symptoms of bleeding and change in bowel habits. This approach secured reimbursement, which was not then available for screening colonoscopy.

In the year 2000, two pivotal multicenter trials confirmed the prevalence of adenomas and cancer in asymptomatic average risk persons [7, 8], and established that screening colonoscopy could be safely performed. These trials were VA Cooperative Study 380 [7] and the results of screening colonoscopy performed on Eli Lilly employees, retirees, and their spouses in several Indianapolis hospitals [8]. These studies confirmed that many

patients with advanced proximal colonic neoplasia detected at screening colonoscopy had no polyps or neoplasia of any type in their distal colon [7, 8].

The studies were followed by intense lobbying of Congress by gastrointestinal professional societies for approval of screening colonoscopy. It was common to draw the analogy of "why would a woman choose to have only one breast examined by mammography?" when both breasts are at risk for cancer. Why then would a patient choose to have the left colon examined, and leave the right colon unexamined examined? The logic of such arguments, combined with the observational evidence that advanced right colon neoplasia was frequently unaccompanied by left colon neoplasia, resulted in the United States Congress passing legislation directing The Center for Medicaid and Medicare Services to cover screening colonoscopy for all beneficiaries age 50 and older every 10 years. This law became active on July 1, 2001, and initiated not only rapid growth in screening colonoscopy, but transformation of gastrointestinal medicine in the United States. Gastroenterologists actively sought out new partners to meet the demand for screening colonoscopy, hired physician extenders to attend clinics, and sometimes gave up more complex, time consuming and risky procedures such as endoscopic retrograde cholangiopancreatography.

The wave of enthusiasm for screening colonoscopy was irresistible, aligning with the interests of American patients who generally seek out the most effective and comfortable procedure available for screening, and the financial incentives of endoscopists and ultimately anesthesia providers.

Yet since its inception nearly 3 decades ago, the use of colonoscopy screening for average risk persons has had detractors both within and outside the United States. While colonoscopy has come to dominate colorectal cancer screening in the United States, and has spread to Germany, Poland, Italy, and to some extent is used in many advanced countries. Cost and lack of endoscopic resources are major barriers to increasing use of colonoscopic screening in other nations and many prefer screening with fecal occult blood testing, particularly fecal immunochemical testing. Detractors have argued that no randomized controlled trial of screening colonoscopy is available, and in 2001 there were no results published of randomized trials of flexible sigmoidoscopy. Reasoning that high level evidence for screening colonoscopy in average risk persons is still lacking, 4 randomized controlled trials comparing colonoscopy to fecal immunochemical testing have been organized, including one in the U.S. Veterans Administration system. The results of all these trials are pending, and only the results of the first round of screening from one of the studies are published [9].

In essence, the United States undertook an enormous, expensive, non-nationalized (except for reimbursement), non-quality controlled effort to apply screening colonoscopy to colorectal cancer prevention. This effort was founded on low level evidence consisting of observational cross-sectional studies, combined with faith and passion.

Now 13 years into the American experiment in screening colonoscopy, it is fair to ask whether the experiment has been successful. Has screening colonoscopy lowered the

incidence and mortality of colorectal cancer, and particularly right-sided colorectal cancer? Have other less invasive and less expensive forms of screening progressed to the point they should supplant screening colonoscopy? Are there aspects of American screening colonoscopy, and colonoscopy in general, that can be improved? Has screening colonoscopy saved more people than it harmed? Was average-risk screening colonoscopy a success or a mistake?

What is the best question to ask about efficacy of screening colonoscopy?

Limited understanding of the biology of colorectal cancer lead to the logical, but incorrect assumption that preventing left-sided and right-sided colorectal cancer would be equally easy. The basic principles of inspection, detection, and endoscopic resection seemed similar for both sides of the colon. However, in the past 2 decades it has become clear that the molecular basis of colorectal cancer is complex, and that the precursor lesions of cancer vary by histology and morphology in the right versus left colon. For example, for Paris classification type II lesions (flat and depressed lesions), the distribution of these lesions is shifted toward the right colon [10]. In addition, a hypermethylation or serrated pathway occurs primarily in the right colon [11], and the precursor lesion (the sessile serrated polyp or sessile serrated adenoma) is universally flat or sessile, consistently similar in color to the surrounding normal mucosa [12, 13], and more subject to failed detection and incomplete resection compared to conventional adenomas [14, 15]. These factors, if appreciated in 2000,

might have raised alarms that perhaps the benefits of flexible sigmoidoscopy cannot be easily extrapolated to the proximal colon.

Further, we now have 2 completed randomized control trials showing that sigmoidoscopy does reduce distal colon cancer incidence and mortality [14, 15]. Since sigmoidoscopy is considerably less expensive than colonoscopy, does not require sedation, and has a lower complication rate, the key question is not whether colonoscopy prevents colorectal cancer, but whether it prevents right-sided colorectal cancer. The following section reviews available evidence regarding the effect of colonoscopy on overall colorectal cancer incidence and mortality, as well the more relevant issue of the effect of colonoscopy on proximal colorectal cancer incidence and mortality.

Evidence that colonoscopy prevents overall incident colorectal cancer and cancer mortality.

Evidence from randomized controlled trials of fecal occult blood testing

The first randomized controlled trial to establish that colorectal cancer screening works was conducted by the University of Minnesota and published in 1993 [16]. As with all FOBT trials, patients with positive tests underwent colonoscopy. While colorectal cancer mortality reductions can be attributed to detection of early stage cancers followed by

endoscopic or surgical treatment, incidence reductions in colorectal cancer are attributable only to polyp or large polyp detection followed by colonoscopic polypectomy.

In 2000, Mandel et al reported that the 2 screened arms of the trial (which had been randomized to annual vs biennial rehydrated guaiac based FOBT with a 3rd arm assigned to no screening), had statistically significant 20% and 17% reductions, respectively, in incident colorectal cancer compared to the non-screened group [17].

Evidence from the randomized controlled trials of sigmoidoscopy

In 2010, Atkin et al reported a randomized controlled trial of once only flexible sigmoidoscopy screening compared to no screening in the UK [18]. The risk of proximal colorectal cancer in the screened group was 0.97 (95% CI 0.80-1.17) compared to the non-screened group. However, only 5% of attendees were referred for colonoscopy, because of relatively strict criteria for patient selection for colonoscopy. In this context, flexible sigmoidoscopy screening did not impact the identification of patients with proximal colon cancer.

In 2012, Schoen et al reported the results of a randomized controlled trial of flexible sigmoidoscopy versus no screening in the PLCO (prostate, lung, colon, ovarian) study in the United States [19]. Using more liberal criteria for referral of sigmoidoscopy patients for colonoscopy, 21.9% of attendees were referred for colonoscopy. The proximal colon

cancer incidence was 0.86 (95% CI 0.76, 0.97) compared to the non-screened group. This result supports a benefit for colonoscopy in reducing proximal colon cancer incidence, since colonoscopy is the only apparent mechanism for the reduction.

Evidence from adenoma cohorts

When the U.S. Congress voted to cover screening colonoscopy for Medicare beneficiaries, the most heavily utilized studies in lobbying efforts were not the 2000 screening colonoscopy studies, but the National Polyp Study [20]. The National Polyp Study was a randomized controlled trial testing whether patients with adenomas could undergo their first followup surveillance at 3 years rather than 1 year [21]. In 1993 Winawer et al reported that the observed incidence of colorectal cancer in the overall cohort was reduced by 76 to 90% relative to the expected risk in 3 reference populations [20]. These data suggested that colonoscopy was almost universally effective in preventing colon cancer, and while these results [20] from an adenoma cohort represent a low level of evidence, they were widely quoted to support the rationale for screening colonoscopy. In 2012, Zauber et al reported that at a mean of 15.8 years of follow-up, there was a 53% reduction in death from colorectal cancer in the cohort compared to reference populations (12 deaths in the study versus 25.4 expected deaths) [22]. What is perhaps most impressive about these data is that 57.3% of the cohort had advanced adenomas at their baseline colonoscopy, a rate about 10 times higher than the rate of advanced adenomas typically seen in average risk cohorts. These risk reductions were achieved despite the very high risk of the cohort.

Cohort studies on overall incidence and mortality of colorectal cancer

In 2010 Singh et al from Manitoba, Canada reported a significant 29% reduction in overall colorectal cancer mortality associated with a colonoscopy in a non-screening population [23]. Data from Canada has been criticized because most colonoscopy there is performed by general surgeons [24], and virtually every study that has examined the issue has found that gastroenterologists on average are more effective than general surgeons in preventing incident colorectal cancer [24-27].

In 2009 Kahi et al evaluated the long-term follow-up of volunteers in the original Indiana screening colonoscopy study [28]. Prior to the year 2000, this was the largest average risk screening colonoscopy trial available for evaluation. There was a 67% reduction in the overall incidence of colorectal cancer in a screening cohort compared to the Surveillance End Epidemiology Results (SEER) cohorts, though 6 of 7 observed cancers occurred in the proximal colon.

Case-control studies on overall incidence of colorectal cancer

Case-control design is generally considered a more powerful form of evidence than cohort studies. Three recent case-control studies [29-31], including 2 performed in screening trials

[30, 31], have shown very substantial reductions in risk after colonoscopy, ranging from 77% to 91%. These trials were performed in the U.S. and Germany, where colonoscopy is performed largely by gastroenterologists.

Case-control studies on overall mortality from colorectal cancer

Case-control studies in non-screening populations have shown overall reductions in mortality from colorectal cancer of 37% in Canada [32], 44% in the Netherlands [33], and 60% in the United States [26].

Case-control studies of colonoscopy on right-sided incidence and mortality

Initial trials from Canada failed to demonstrate a reduction in right-sided cancer incidence or mortality associated with colonoscopy in non-screening populations [23, 32]. However, in the U.S. and Germany, where colonoscopy is performed largely by gastroenterologists, colonoscopy has produced consistent reductions in incidence (27 to 42%) [29, 34] and mortality (53-56%) [26, 34], and a right-sided incidence reduction associated with screening colonoscopy was observed in a German case-control study of 78% [31].

Evidence from variable detection.

The adenoma detection rates of endoscopists, including those within groups of gastroenterologists, vary widely [35-38]. No substantial study examining adenoma detection rates has ever shown a less than 2.5 fold difference between the highest and lowest detectors in the same group, and this variation has ranged to up to 8 fold [35-38]. If colonoscopy has no impact on colorectal cancer incidence, then the risk of post colonoscopy cancer should not vary between endoscopists with different detection rates. However, in the screening colonoscopy study from Poland, the hazard ratio for development of cancer after colonoscopy performed by gastroenterologists with adenoma detection rates below the recommended threshold of 20% was consistently much higher than the risk of colorectal cancer in patients colonoscoped by doctors with adequate adenoma detection rates [39]. In a recent study from Northern California Kaiser Permanente, the risk of cancers after colonoscopy was examined for 136 gastroenterologists whose patients suffered 714 interval cancers [40]. The patients of doctors in the highest adenoma detection rate quintile had a 0.52 risk of interval cancer compared to patients of doctors in the lowest ADR quintile. There was a 3% reduction in incidence and a 5% reduction of mortality for each 1% increase in the adenoma detection rates of the doctors. These effects were present for proximal and distal colon cancers, men and women, early and late stage cancers, and regardless of screening, surveillance or diagnostic indications for colonoscopy. These data also indicate that screening colonoscopy prevents both distal and proximal colorectal cancer.

Evidence from population trends on incidence and mortality

Declines in colorectal cancer mortality began in the United States in 1975. In 2010, Edwards et al examined these trends and attributed 12% to improved treatment, 32% to changing patterns in risk factors, and 53% to increases in screening [41]. In 2014, the US Centers for Disease Control described accelerations in the decline of colorectal cancer incidence beginning in 2001 and corresponding to the availability of screening colonoscopy in the United States [42]. There was a 3.4% annual decline in incidence during the interval 2001-2010, including a 3.9% incidence decline in the screening eligible age group of 50 to 75 years and a 1.1% per year incidence increase in age less than 50. The overall decline in colorectal cancer incidence during that interval was 30%, and corresponded to an increase in screening rates from 19% in 2000 to 55% in 2010. Screening rates were 55% in the 50 to 64-year age group and 64% in the age eligible Medicare population of $\geq$ 65 years [42].

Taken together, these lines of evidence provide near certainty that colonoscopy prevents both overall and right sided colorectal cancer and mortality.

Advantages of screening with colonoscopy relative to other strategies

Colonoscopy is widely viewed in the U.S. as a comfortable procedure, which in addition to its capacity to examine the entire colon, has contributed to the progressive decline in flexible sigmoidoscopy screening. Patients within the same practice who were screened

with unsedated flexible sigmoidoscopy were more than twice as likely to say they would not be screened again compared to patients screened with sedated colonoscopy [43]. The use of propofol for sedation in combination with carbon dioxide insufflation has allowed many patients to have a painless procedure and post-procedure experience and function normally (except driving is usually not allowed) on the same day as the procedure.

The major advantage of colonoscopy remains its unmatched potential for detection of precancerous lesions, and its ability to detect cancer is matched only by CT colonography. CT colonography has not been well received because it still requires bowel preparation to approach colonoscopy for polyp detection, its high cost as a strategy, and the risks associated or believed to be associated with radiation.

Colonoscopy appears to hold a substantial advantage for detection of serrated lesions. These lesions are not well seen at CT colonography [44, 45], and CT colonography trials never report serrated lesions as a separate outcome. Absence of blood vessels on the surface of serrated lesions has long led to suspicion that guaiac based FOBT and FIT could not detect them, which proved completely true when finally tested [46]. Only fecal DNA has shown some sensitivity for serrated lesions among non-invasive tests [46].

A major advantage of colonoscopy is the potential for long lasting protection from cancer. Of available tests, only colonoscopy is recommended at 10 year intervals [47]. Case-control studies of screening sigmoidoscopy identified protection against left-sided cancer following sigmoidoscopy of 10 and 16 years, which were the longest periods for which

protection was assessed [48, 49]. A recent case control study of colonoscopy in Germany found that protection against colorectal cancer remained substantial for more than 20 years [50]. If intervals between screening can be linked to the adenoma detection rates of examiners, this evidence suggests the possibility that patients could have life-long protection from a single negative colonoscopy by a high detecting colonoscopist at about age 60, or perhaps two examinations at ages 50 and 70 years.

Disadvantages of colonoscopy as a screening strategy

In the past patients who had never undergone colonoscopy listed fear of the procedure as the major deterrent, but today both those who have and have not undergone colonoscopy consider the need for bowel preparation the major problem with the procedure [51]. The advent of split-dosing and low volume preparations has improved tolerability, but low volume preparations may not adequately prepare all patients and a stratified approach to assigning preparations (based on known predictors of inadequate preparation) is the best way to optimize rates of adequate preparation. Much more work is needed to find preparations that optimize efficacy, tolerability and safety.

Colonoscopy has high complication rates for a screening test. Although the efficacy of colonoscopy outweighs its harms on a population basis, the occurrence of non-polypectomy induced perforation, aspiration, or splenic injury in asymptomatic patients is costly when viewed from an individual patient perspective and occasionally tragic.

Colonoscopists should be well trained in avoidance of complications and fully capable and prepared to manage complications.

There is increasing awareness in the U.S. that colonoscopy charges are often too high. High charges and in some regions limited capacity are major challenges to the dominance of screening colonoscopy. A principle culprit in the cost trend is hospitals, which charge high fees that have little or no transparency or association with actual costs. The rising use of anesthesia specialists for sedation contributes to the trend. Experience in California with reference payment has demonstrated that many centers can perform colonoscopy profitably for charges considerably lower those to which they are accustomed. Bundled payment in which colonoscopists share the risk of factors such as anesthesia charges, pathology charges, repeat procedures for poor preparation, etc. has been effectively implemented by a single large practice in Minnesota [52], and is under evaluation by the Centers for Medicare and Medicaid services. Even at high charges, colonoscopy remains a cost effective colorectal cancer screening strategy, as do all of the available tests [53]. This high level of cost-effectiveness has been created in part by the enormous costs of cancer care in the United States which are substantially greater in absolute terms that the cost of colorectal cancer screening [54]. While efforts to improve the cost-effectiveness of colonoscopy and colorectal cancer screening are appropriate, it seems also important to limit the high pharmaceutical and care costs associated with end of life colorectal cancer care.

A major disadvantage of colonoscopy as a screening strategy is operator dependence [35-40]. While the adenoma detection rate has been demonstrated to predict protection from post

colonoscopy cancer [39, 40], it has also been shown to be remarkably variable within groups of gastroenterologists [35-38]. Correcting low-level performers has been challenging [38], though recent evidence suggests that training targeted to lesion recognition skills and colonoscopy withdrawal skills will consistently improve performance [55, 56]. The advent of high definition colonoscopy [57] and split dosing of bowel preps [58] produces detection gains, and tools such as chromoendoscopy [59] and electronic chromoendoscopy [60] could be mandated by groups for their low-level detectors in an effort to improve performance. The recognition of variable performance has fostered a major movement in the gastroenterology community to measure and improve colonoscopy quality [61, 62], but there is currently no means of mandating quality measurements in American colonoscopy practice. There is little evidence of movement toward quality measurement within the non-GI community performing colonoscopy, and this group has lower performance on average for detection of adenomas [63] and prevention of colorectal cancer [24-27] compared to gastroenterologists. Awareness of post colonoscopy cancer and the general phenomenon of missing lesions during colonoscopy have also been used as an excuse for shortening surveillance intervals and systematic performance of screening colonoscopy at 5-year intervals [64]. Overuse of colonoscopy of course substantially reduces cost-effectiveness.

A final significant disadvantage of colonoscopy is the current dysfunctional post polypectomy surveillance strategy, which results in overuse of surveillance in some of the patients who need it least, and which provides financial incentives for the wrong set of behaviors in colonoscopists. The problems begin with failure to match the quality of the baseline examination sufficiently to the surveillance intervals. Surveillance

recommendations suggest that an examination to the cecum with an adequate preparation can be based solely on the findings of precancerous lesions. However, the findings of precancerous lesions are more dependent on the endoscopist than the preparation or the cecal intubation [35-38]. Since the surveillance intervals are to be applied uniformly without consideration of the adenoma detection rate of the endoscopist, a high performing endoscopist (high ADR) will clear patients' colons better at the baseline examination and bring them back more frequently, providing a sort of double protection against colorectal cancer to their patients [65]. Most of the protection afforded by colonoscopy is certain to be related to the quality of the baseline examination. On the other hand, a low performing endoscopist (low ADR) tells many patients they have a normal colon when they do not, and assigns a long interval for surveillance. This provides a sort of double lack of protection for the patient who is unwittingly pleased to hear that their colonoscopy is normal. It would be very useful to find ways to integrate adenoma detection rates into the post polypectomy surveillance process, and stratify risk and surveillance intervals according to baseline performance. Realizing that economic factors underlie the behavior of most humans, the financial rewards for colonoscopy should be reformed as they currently incentivize "one and done" performance of colonoscopy (removing one polyp during a colonsoscopy and then not searching carefully for other polyps) and overuse of surveillance and screening. A second problem with post polypectomy surveillance intervals is that the risk stratification is likely not optimized. In the current United States guidelines, any individual with 3 or more adenomas is recommended to have repeat colonoscopy in 3 years [66]. However, recent evidence suggests that 3 or more small or diminutive adenomas is a quite different risk predictor compared to when one or more of

those lesions is large [67, 68]. As emphasis on adenoma detection rates and the availability of high definition colonoscopes increases, detection of individuals with multiple or numerous adenomas, all of which are diminutive, is likely to increase. Coupled with awareness of adequate baseline ADR, there is increasing evidence that at least those with 3 or 4 small or diminutive adenomas have risk similar to individuals with 1 or 2 small adenomas [67, 68]. It is quite possible that some risk stratification should be based on diminutive versus small adenomas. Thus, it is possible that in the hands of a high-level detector, the presence of several diminutive adenomas is usually little more than a normal variant.

Summary and new directions for screening colonoscopy

Despite a lack of randomized controlled trials, overwhelming evidence indicates that colonoscopy has had a major and positive impact on colorectal cancer incidence and mortality in the United States, including its application as a screening test. Advances in fecal blood testing (FIT) and tests that combine FIT with fecal DNA assays have become the first serious challenges to colonoscopy as the most effective test from a programmatic perspective. Results on the program sensitivity of these tests (FIT and FIT/fecal DNA) are awaited with great interest. From a single time test perspective, colonoscopy is still the most effective strategy for detection of precancerous lesions, including large conventional adenomas and large serrated lesions. Because colonoscopy is operator dependent, there is little doubt that colonoscopy by a high-level detector is still the most effective colorectal cancer prevention strategy available to patients.

While the effectiveness of other strategies has improved, colonoscopy has also improved. New concepts such as low-volume bowel preparation, split dose preparation, high definition colonoscopy, wide-angle colonoscopy, the adenoma detection rate, and the importance of the serrated pathway have all produced significant advances in colonoscopy. There is considerable room for further improvement to improve patient convenience, reduce operator dependence, improve overall efficacy, improve cost-effectiveness, and reduce complications (Table 1). Colonoscopy's position as a central aspect of gastrointestinal medicine is in question only with regard to its position as a screening test, and as to whether its general application reflects the best data available and the best common sense with regard to financial incentives. If we continue to investigate methods to improve colonoscopy, resist financial pressures, and use common sense and courage, we can refine colonoscopy and define its story as the most effective visceral cancer prevention story ever told. Whether it remains the dominant screening test, or the tool by which the benefits of other screening tests are realized, is a secondary concern.

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