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The Impact of Colonoscopy on Colorectal Cancer Incidence and Mortality

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1. Introduction

In the United States, periodic colorectal cancer (CRC) screening rates increased from 45% of the eligible population in 2002 to 63% in 2008 (Richardson et al., 2010). Over a similar time period, colonoscopy has become the most widely utilized colorectal cancer screening tool in the United States. In other countries, colonoscopy is the most commonly recommended screening test, particularly in Europe. However, in many locales in which other screening tests such as fecal occult blood tests (FOBT) are preferred due to cost or availability, colonoscopy is used to follow up on patients screening positive (Brenner et al., 2001; Hoff & Dominitz, 2010; Classen & Lambert, 2008).

The ascendance of colonoscopy in the US corresponds with a significant reduction in colorectal cancer incidence and mortality. In the Annual Report to the Nation on the Status of Cancer from 1975-2006, microsimulation modeling demonstrated the relatively large contributions of screening, along with risk factor modifications and improved cancer treatments, to this decline (Edwards et al., 2010).

The focus of this chapter is the effectiveness of colonoscopy, as a means to decrease CRC incidence and mortality. In addition, we identify factors including tumor biology, instrumental, patient-related issues and endoscopist characteristics that may influence the impact of colonoscopy on these rates.

2. Randomized controlled trials in CRC screening using endoscopy

Currently, there are no published randomized controlled trials examining the impact of colonoscopy on CRC incidence and mortality. Before we review the published studies involving the colonoscopy, we will first examine two randomized, controlled trials of sufficient size and duration using screening flexible sigmoidoscopy to address the same questions. The results of these studies are often extrapolated to support the efficacy of colonoscopy, which is often thought to be an extended sigmoidoscopy. In the first study, Atkin and colleagues randomized more than 170,000 people in 14 United Kingdom medical centers to either once-only flexible sigmoidoscopy or no screening, with 71% included in the exam arm. The median follow-up was 11.2 years. The incidence and mortality of colorectal cancer were measured in both intention-to-treat and per-protocol analyses. Overall CRC incidence reduction was 23%-33%. Overall CRC mortality reduction was 31%-43% and distal CRC mortality reduction was 50% (Atkin et al., 2010). The protective effect appears

persistent, with reduction of left-sided CRC incidence continuing at the rate of 0.02% to 0.04% per year after year 5.

In the second study with similar design, Hoff and colleagues in the NORCAP trial randomized more than 55,000 men and women between 55 to 64 years of age in Norway to once-only screening flexible sigmoidoscopy or no screening. The planned duration of follow-up was 15 years. The published study reported cumulative incidence after 7 years of follow-up. Interestingly, by intention-to-treat analysis, there was an insignificant (P= 0.16) reduction in overall CRC mortality by 27% and in rectosigmoid cancer mortality by 37%. Per-protocol analysis with its inherent risk of selection bias yielded a significant 59% reduction in overall CRC incidence and a significant 76% reduction in distal CRC incidence. The authors suggested that these findings might be the results of a short timeframe for the follow-up period (Hoff et al., 2009).

Two other randomized controlled trials using screening flexible sigmoidoscopy, namely, the SCORE trial in Italy and the PLCO trial (US National Cancer Institute-led Prostate, Lung, Colorectal and Ovarian cancer screening trial) are expected to report on their results within the next few years (Segnan et al., 2002; PLCO NCI web page).

In addition, researchers in Europe and the US are currently conducting a randomized controlled trial examining the efficacy of screening colonoscopy on CRC incidence and mortality. The Northern-European Initiative on Colorectal Cancer (NordICC) trial will randomly draw 66,000 individuals from population registries to compare screening colonoscopy with a control group of unscreened individuals for a planned follow-up period of 15 years. Final data collections and analyses are not expected until 2026 (Baxter & Rabeneck, 2010).

3. CRC incidence and mortality after colonoscopy with adenomatous polypectomy

Muto et al first proposed the adenoma-carcinoma sequence of colorectal cancer in 1975 (Muto et al., 1975). Endoscopic polypectomy interrupts the carcinogenic sequence by preventing the transformation of adenomas, thereby inhibiting cancer development. The seminal National Polyp Study (NPS) in 1993 provided primary evidence in support of this theory as well as the rationale for colonoscopy with polypectomy as the major method to prevent colorectal cancer (Winawer et al., 1993). In this study, 1418 patients were randomized post-adenoma removal to frequent (follow-up exams in years 1 and 3) and less frequent (exams in year 3) colonoscopies. Outcomes in each group were compared with three historical reference groups, two where polyps were simply observed and one general-population cohort (the Surveillance, Epidemiology, and End Results or SEER). After an average follow-up of 5.9 years, the interventional groups showed a 76% to 90% reduction in CRC incidence compared with the observed incidence in the reference groups (standardized incidence ratios (SIRs), 0.10, 0.12 and 0.24, respectively). The cancer incidence rate was 0.6 cancers per 1000 person-years.

Subsequent studies based on NPS demonstrated the persistent reduction in CRC mortality associated with the initial polypectomy. Zauber and colleagues used mathematical modeling to show that at 20 years, the cumulative mortality rate was 2.5% for patients who had an initial polypectomy, compared to 5.5% for patients who did not (Zauber et al., 2007). Colonoscopic polypectomy could reduce CRC deaths by about 90% among patients with adenomas and by about 50% in the general population. Furthermore, these significant reductions in CRC mortality were mainly associated with the index clearing colonoscopy, not with the subsequent surveillance examinations.

Similar strong reduction in CRC incidence was also reported in two other studies involving patients with adenoma removal. The Italian Multicentre Study Group, a retrospective, observational study of 1693 men and women who had polypectomy with a mean follow-up of 10.5 years, reported SIR of 0.34 and cancer incidence rate of 0.4 cancers per 1000 person-years (Citarda et al., 2001). The Telemark Polyp Study, a prospective cohort study of 799 men and women with a mean follow-up of 10 years, showed SIR of 0.2, and cancer incidence rate of 0.5 cancers per 1000 person-years, although the trend toward CRC mortality reduction was not significant (Thiis-Evensen et al., 1999).

However, other studies examining the adenoma cohorts have demonstrated much less dramatic impact of colonoscopy with polypectomy. The Polyp Prevention Trial, the Wheat Bran Fiber Trial, the Funen Adenoma Follow-Up Trial, the Australian Polyp Study and the Combined Chemoprevention Trial have all shown cancer incidence rates 2 to 4 times higher than that of the NPS, actually approaching or exceeding the expected rate in the SEER data (1.7 cancers per 1000 person-years).

The Polyp Prevention Trial was a randomized, double blind study of 2079 men and women with history of adenoma removal examining the effects of a low-fat, high-fiber diet on the adenoma incidence. Patients had surveillance colonoscopy at years 1 and 4 post-randomization. The study found no benefits of nutritional intervention on incident adenomas. In addition, the cancer incidence rate was 2.2 cancers per 1000 person-years and more than 50% of prevalent cancers could be prevented or detected earlier if the quality of colonoscopy had been improved (Schatzkin et al., 2000; Pabby et al., 2005).

The Wheat Bran Fiber Trial using a similar design studied the effects of high fiber on adenoma recurrence in 1429 men and women with adenomas. It found 41-48% recurrent adenomas located in the proximal colon and cancer incidence rate of 2.4 cancers per 1000 person-years (Alberts et al., 2000).

The Funen Adenoma Follow-Up Trial by Jorgensen et al randomized 1056 men and women with adenomas to surveillance colonoscopy at varying intervals between 6 and 48 months after the index colonoscopy with polypectomy. Its cancer incidence rate was 2.2 cancers per 1000 person-years. It found a significant six-fold reduction in CRC incidence in the post-polypectomy group if all carcinomas were assumed to develop from large (> or = 10 mm) adenomas or adenomas with severe dysplasia according to the adenoma-carcinoma sequence (Jorgensen et al., 1993). It also found a significant reduction in CRC mortality when compared with the normal population.

The Australian Polyp Study by a single surgeon studied 645 patients with adenoma removal for a mean follow-up period of 4.4 years. The cancer incidence rate was 1.05 cancers per 1000 person-years, which was at first glance indistinguishable from that of the general population. However, based on analysis of previously published data, the authors found that the risk of developing colorectal cancer in patients with adenomas was approximately 2.5 times higher than that of the general population (3.3 cancers per 1000 person-years). Therefore, the authors concluded that colonoscopy did reduce CRC incidence (Meagher & Stuart, 1994).

The Combined Chemoprevention Trial consisted of 2915 patients drawn from three previous chemoprevention trials using calcium, aspirin and antioxidant vitamins in an effort to reduce polyp recurrence. It involved a large number of endoscopists from across North America, in both university and private practices. Its cancer incidence rate was 1.74 cancers per 1000 person-years, with 84% in the early stage and approximately half found in the proximal colon (Robertson et al., 2005). The lowered cancer incidence rate, compared with the other studies, was partially attributed to the chemopreventive properties of aspirin and calcium.

4. Why these differences?

Although all of these studies include participants who had an adenoma removed, methodological differences make comparisons of results difficult. First, criteria for patient enrollment differed in these studies. For instance, the NPS patients underwent rigorous baseline colonoscopic clearance of adenomas, with some (13%) receiving at least 2 examinations, before randomization. The NPS also excluded patients with polyps larger than 3 cm in size, or with prior history of adenomas, while other trials included patients with history of adenomas and any-sized polyps (Rex & Eid, 2008). Second, colonoscopic follow-up periods varied among the studies (Table 1). The NPS, Italian Multicentre Study and the Telemark Polyp Study had a mean follow-up of 6 to 13 years, whereas the others had much shorter follow-up periods, 3-4 years at most. As discussed below, cancers detected during the shorter follow-up periods were possibly due to lesions missed initially, not true incident cancers seen in longer follow-up (Robertson et al., 2007). Third, the expected cancer incidence rates in the various cohorts are difficult to measure due to differences in the type and size of adenomas removed at study entry (Kahi et al., 2009). Fourth, differences in the rate and the timing of the follow-up colonoscopy might also lead to variable outcomes. For example, one-fifth of the NPS and one-fourth of the Italian Trial subjects did not have follow-up colonoscopic surveillance, while most of the subjects in the chemoprevention trials did. Fifth, other confounding factors such as the use of chemopreventive agents such as aspirin, family history of CRC, cigarette smoking history were not fully accounted for and might not be comparable in these studies.

Study	Number of patients	Cancer incidence rate (per 1000 pr-yrs)	Number of cancer in follow-up	Mean follow-up (years)	SIR
SEER		1.7			
NPS--Winawer 1993	1481	0.6	5	5.9	0.1-0.24
Italian Polyp Study--Citarda 2001	1693	0.4	6	10.5	0.34
Telemark Polyp Study--Thiis-Evensen 1999	799	0.5	1	10	0.2
Polyp Prevention Study--Schatzkin 2000	2079	2.2	13	3.1	
Wheat Bran Trial Alberts 2000	1429	2.4	9	3.0	
Funen Adenoma Trial--Jorgensen 1993	1056	2.2	10	4.3	
Combined Chemoprevention Trial--Robertson 2005	2915	1.74	19	3.7	
Australian Polyp Study—Meagher 1994	645	1.05	3	4.4	

Table 1. Adenoma Cohorts and Interval Cancers

5. CRC incidence in screening cohorts

Despite the significant, although variable, reduction in CRC incidence risk for patients with prior adenoma removal, these higher risk populations may not have direct applicability to screening settings where only a proportion of participants have adenomas.

The incidence of CRC has been examined in a number of screening cohorts. Lieberman et al in 2000 studied 3121 individuals, 97% of who were men, for the Veterans Affairs Cooperative Study 380. They found that 37.5% of patients had neoplastic lesions. The presence of distal lesions increased the risk of proximal lesions (OR 3.4). However, 52% of proximal advanced neoplasms had no distal lesions (Lieberman et al., 2000). When 1193 previously screened patients had a follow-up colonoscopy within 5.5 years, 22 cancers and high-grade dysplastic lesions (1.8%) were identified. Most of these lesions (15/22) were found within 36 months of the initial colonoscopy and 6 out of 9 cancers were located in the proximal colon (Lieberman et al., 2007).

In 2005, Schoenfeld et al investigated the prevalence and location of advanced colonic neoplasia in women of average and high risk (15.7% had a family history of colon cancer). Among 1463 asymptomatic women who underwent screening colonoscopy, 72 had advanced neoplasia (4.9%). Had flexible sigmoidoscopy, which visualizes only the distal colon, been the screening tool, only 35.2% of women with advanced neoplasia would have been identified, compared to 66.3% of men from the VA Cooperative Study 380 ($P<0.001$) (Schoenfeld et al., 2005). The Schoenfeld study provided support for the concept that screening needs of women may differ from those of men.

In a similar vein, the use of the screening colonoscopy in high-risk families was further advocated by the prospective, observational study with a long follow-up period of 16 years by Dove-Edwin et al. In this study, 1678 individuals from high-risk families with hereditary non-polyposis colorectal cancer (HNPCC) and moderate-risk families with up to 3 affected first-degree relatives had screening colonoscopy. Significant reduction of CRC incidence in these screening cohorts were 80% and 43% in the moderate-risk and high-risk groups, respectively, when compared to the expected incidence in similar families lacking surveillance (Dove-Edwin et al., 2005).

Brenner and colleagues studied two different patient populations in Germany, one in the state of Saarland and the other in the Rhine-Neckar region, by two different methods to assess the question of CRC protection from previous screening colonoscopy. In the study from Saarland, the prevalence of advanced neoplasms including CRC in 586 participants following colonoscopy within the previous 10 years was compared to that in 2701 participants with no previous colonoscopy. Adjusted prevalence ratios were 0.52 for overall CRC, 0.33 for combined left colon and rectum, and 1.05 for right-sided colon (cecum to transverse colon) (Brenner et al., 2010a). Thus, this study showed that in the community setting with experienced endoscopists (completing at least 200 colonoscopies and 50 polypectomies), screening colonoscopy reduced the CRC incidence strongly in the distal, but not in the proximal, colon.

In contrast, a second study by Brenner and colleagues suggested that colonoscopy protected against proximal CRC in average risk populations. This population-based, case-control study based in the Rhine-Neckar region of Germany, examined 1688 CRC cases and 1932 controls and their history of previous colonoscopy within 1 to 10 years. The adjusted odds ratios were 0.23 for overall CRC, 0.16 for left-sided CRC and 0.44 for right-sided CRC. Significant risk reduction increased over the years in both right and left colon, in both sexes,

and among those with and without family history of CRC, with the exception of moderate, non-significant risk reduction for right-sided CRC in persons aged 50-59 years (Brenner et al., 2011).

Two main factors are likely explanations for the different results in these two studies. The first report included participants with advanced adenomas and CRC, while the second included only CRC patients. The development of advanced adenomas may take less time that that of CRC. In addition, the 10-year cumulative risk of progressing from advanced adenoma to CRC is estimated to be less than 50% in individuals 55 years or older (Brenner et al., 2007). Second, the frequency of patients with right-sided CRC in the second study was much higher compared to the number of patients with right-sided advanced neoplasms in the first study, resulting in better statistics.

6. CRC mortality associated with colonoscopy

Prospectively demonstrating the beneficial effect of any intervention on CRC mortality is difficult given the disease's relatively long latency, and methodological needs for many participants with long follow-up. Disease latency also contributes to a possible underestimate of CRC prevalence. In addition, prevalent and incident cancer rates are often indistinguishable in the reference groups such as SEER data. If colonoscopy reduces the incidence of CRC in different screening populations, then could we logically deduct that it has to reduce CRC mortality as well?

In a population-based, observational cohort study, Kahi et al reported on 10,492 asymptomatic average-risk patients with screening colonoscopy in a university hospital setting. Median post-colonoscopy follow-up was 8 years (range 3-16 years). Compared to expected rates from the SEER data, the SIR was 0.33 (a relative risk reduction of 67%). Likewise, the standardized mortality rate was 0.35 (a relative risk reduction of 65%) (Kahi et al, 2009).

Another study by Singh et al used Manitoba's billing claims database to follow, until 2008, a large cohort of 24,342 men and 30,461 women, who had their first colonoscopy between 1987 and 2007. CRC mortality after the index colonoscopy was compared with that of the general population. Standardized mortality ratios (SMRs) were 0.71 (29% reduction) in overall mortality, 0.53 (47% reduction) in distal CRC mortality and 0.94 (no reduction) in proximal CRC mortality (Singh et al., 2010a).

Baxter et al using a different administrative claims database from Ontario selected 719 case patients with a CRC diagnosis between 1996 and 2001, all of whom died of CRC by 2003. They were matched against 5031 controls. Colonoscopy was strongly associated with fewer deaths from left-sided CRC (adjusted OR 0.33 [95% CI, 0.28-0.39]), but not from right-sided CRC (adjusted OR 0.99 [95% CI, 0.86-1.14]) (Baxter et al., 2009). In this study, screening colonoscopy could not be differentiated from diagnostic procedures and completeness of exams could not be verified.

Because of the methodological challenges associated with the studies of CRC mortality, other investigators have turned to mathematical models in an attempt to answer the same questions. As mentioned above, Edwards and colleagues have shown by micro-simulation modeling that declines in CRC mortality rates are consistent with a relatively large contribution from screening. These declines could be accelerated further with favorable trends in higher utilization of screening (Edwards et al., 2010). Similar findings were also found by other studies (Zauber et al., 2007; Vogelaar et al., 2006). Vogelaar et al also applied

a microsimulation model to the 2000 US population to study CRC risk factor prevalence, screening use and treatment use. They concluded that without many changes to the current trends (e.g., CRC screening in the eligible population rates are 43% and 47% in women and men, respectively), CRC mortality would be reduced by 17% by 2020. However, if screening use were increased to 70% of the target population, in tandem with improvement of CRC risk factors and chemotherapy effectiveness, then the reduction in CRC mortality could reach almost 50% by 2020. Screening and surveillance methods in this study included both sigmoidoscopy and colonoscopy with FOBT.

7. CRC protection in patients after a negative colonoscopy

A number of studies have demonstrated that CRC protection after a negative colonoscopy is durable, perhaps as long as 10-15 years. In two prospective cohort studies of average-risk subjects, Rex and Imperiale showed that no CRC was detected at re-screening 5 years after the negative baseline colonoscopy. In the first, the investigators re-screened 154 persons with initial negative colonoscopy at a mean of 66 months. None had cancer while 27% had at least one adenoma, only one of which was advanced. The presence of hyperplastic polyps in the baseline colonoscopy did not predict incident adenomas at re-screening. However, confounding factors including the use of non-steroidal anti-inflammatory agents might have reduced the rate of incident adenomas (Rex et al., 1996). The second study had a larger number of participants with negative initial colonoscopy (1256 persons, 56.7% of who were men). Again, baseline hyperplastic polyps did not predict incident advanced adenomas. At repeat colonoscopy, no participants had cancer and 16% had at least one adenoma. Only 1.3% of participants had advanced adenomas, more than 50% of which were located in the distal colon. Men were more likely than women to have any adenoma, especially advanced adenoma (RR 1.88 and 3.31, respectively) (Imperiale et al., 2008).

In 2006, two population-based studies confirmed that CRC risk following a negative colonoscopy remained low, for as long as 10-20 years. In a case-control study in the Rhine-Neckar region of Germany, Brenner et al analyzed the records of 380 colonoscopy cases and 485 controls without previous colonoscopy. They found a 74% risk reduction (OR 0.26 [95% CI, 0.16-0.40]) in subjects with negative colonoscopy compared to those without previous colonoscopy. This lower risk persisted even when the colonoscopy had been done up to 20 years previously. Interestingly, risk was lower among subjects with multiple colonoscopies, who more often had a family history of CRC. On the other hand, with less than 20% of multiple-colonoscopy persons reporting previous polypectomy, the possibility of missed polyps on repeat colonoscopy would be very low indeed, thus contributing partly to this particular finding (Brenner et al., 2006). In addition, this study still demonstrated less CRC protection for the right colon compared to the left (OR 0.39 vs. 0.17, respectively), even when colonoscopies without documented completeness were excluded from analysis.

Using Manitoba Health's physician claims database, Singh et al retrospectively analyzed 32,203 individuals with negative colonoscopy. They found that a negative colonoscopy was associated with 31% reduction in the CRC incidence up to 10 years (SIR of 0.66 at 1 year, 0.55 at 5 years, and 0.28 at 10 years). The proportion of right-sided CRC (defined as cecum to hepatic flexure in this study) was significantly higher in the colonoscopy cohort compared to that in the provincial population (47% vs. 28%; $P<0.001$). Colorectal cancer cases were more likely to be right-sided if diagnosed within the initial 2 years, compared to those diagnosed more than 5 years, following the index colonoscopy. There was a non-significant

trend toward general practitioners performing the index colonoscopy cases with subsequent CRC detection (Singh et al., 2006).

In yet another population-based retrospective analysis in Saarland, Germany, which examined a larger number of participants (533 with negative colonoscopy and 2701 without previous colonoscopy), Brenner et al arrived at similar conclusions. No cancer was detected in participants within an average of 11.9 years from negative baseline colonoscopy. The prevalence of advanced neoplasms was more than 60% reduced at 15 years, and approximately 50% reduced beyond 16 years, compared to those without colonoscopy (Brenner et al., 2010b).

Certainly, a negative colonoscopy in and of itself is not a tool that can reduce CRC incidence as a colonoscopy with polypectomy can. Its inherent value exists in its ability to reliably predict the sustained low risk of CRC in the near and distant future. Consequently, a negative colonoscopy supports the lengthening of colonoscopic screening intervals up to 10 years or longer, which in turn increases the cost-effectiveness of the CRC screening process in clinical practice.

8. Gender and location in CRC protection by colonoscopy

The weight of evidence suggests that overall, colonoscopy protects against the development of CRC. However, the degree of benefit apparently varies by colonic location and by gender. Studies by Brenner (Brenner et al., 2010a) and Singh (Singh et al., 2010a) demonstrated reduced incidence and mortality of distal, but not proximal CRC. Even in studies, which suggest protection against proximal CRC, that effect appears muted (Brenner et al., 2011).

In addition, there are differences in the CRC incidence and protection by colonoscopy in men and women. In a large meta-analysis consisting of 17 studies involving 924,932 men and women, Nguyen et al provided strong evidence that men are at greater risk for advanced colorectal neoplasia across all age groups. The pooled relative risk for advanced neoplasia for men compared with women was 1.83 (95% CI, 1.69 -1.97) (Nguyen et al., 2009). Although men in general appear to be more likely to develop incident adenomas of all types (Imperiale et al., 2008), Schoenfeld and colleagues urged the use of the full colonoscopy in women for CRC screening in particular due to the increased prevalence of proximal advanced lesions in women (Schoenfeld et al., 2005).

Why colonoscopy might not protect as well against proximal CRC is not well understood. The questions are: (1) Are more missed or early cancers located in the proximal colon? (2) Do cancers arise de novo or from missed or incompletely resected lesions following colonoscopy? (3) What patient or provider factors might contribute to this clinical observation?

Pohl and Robertson found that a significant number of interval cancers came from missed lesions, which could be either cancer or adenomas. They estimated the adenoma prevalence in the screening cohort, adenoma miss rates, cancer prevalence among patients with adenomas based on size, and rates of adenoma-to-cancer transitions from the literature. They then used a model to apply these risk estimates to a hypothetical average-risk population that received screening colonoscopies. They found that the expected rate of persons with CRC from missed cancer and adenomas was 1.8 per 1000 persons within 5 years (range: 0.5-3.5 per 1000 screened persons) (Pohl & Robertson, 2010). This rate would more than double (5.1 per 1000 screened persons) if colonoscopy is applied to an entirely adenoma-bearing population. When this model was extrapolated to average-risk patient populations (Kahi et al., 2009; Lieberman et al., 2007), they found that approximately 65% of the interval cancers might have been related to

missed adenomas. When compared against the observed risks in the adenoma-bearing populations (Alberts et al., 2000; Winawer et al., 1993, Pabby et al. 2005), between 70% and 80% of interval cancers might be attributed to a missed lesion.

Bressler et al determined that the rates of missed cancer in the proximal colon were more than twice as high as those in the distal colon. Using the data from Ontario registries, they calculated the rates of interval colorectal cancers in different locations. The interval cancers were defined as cancers found within 6 and 36 months following a colonoscopy. The rates of the right-sided and transverse colon cancers were 5.9% and 5.5%, respectively, while those of the left-sided colon (distal to the splenic flexure) were halved (2.1%-2.3%) (Bressler et al., 2007). The independent risk factors for these interval cancers were older age, diverticular disease, proximal CRC, colonoscopy in an office setting, and colonoscopy by an internist or family physician.

Although women tend to have fewer adenomas than men, their adenomas tend to occur in the proximal colon. Therefore, it is not surprising to find that proximal CRC protection is lower in women than in men.

Additional studies confirm that the issues of gender and CRC location are intertwined. Singh et al in a population-based study using the Manitoba Cancer Registry examined a cohort of 4883 patients with CRC. They classified 388 (7.9%) of these as early or missed cancers, i.e. those that were detected in the time frame of 6-36 months after a colonoscopy, with a range of 4.5% of distal cancers in men to 14.4% of proximal cancers (cecum to splenic flexure) in women (Singh et al., 2010b). In another case-control study in the California Medicaid population with 4458 CRC cases and 43,815 controls, Singh et al again found that despite the overall CRC risk reduction of 45% (RR 0.55 [95% CI, 0.46-0.65]), CRC protection for the left colon after negative colonoscopy (0.16) was disproportionately higher than that for the right side (0.67). The CRC risk reduction for both sexes was equivalent in the left colon (84%), but that for women in the right colon was only 18%, compared to 62% for men (Singh et al., 2007).

Even in patients with negative colonoscopy, differential CRC protection by colonic location was also observed. In a large population-based retrospective analysis, Lakoff et al studied 111,401 patients with negative previous colonoscopy. As in other studies on negative colonoscopy, they found a significant CRC risk reduction up to 14 years of follow-up, compared to the Ontario population (RR 0.21 [95%CI, 0.05-0.36]). However, the sustained reduction in incidence of proximal CRC only started in year 8 (Lakoff et al., 2008).

9. Factors that influence the impact of video colonoscopy

There are several possible explanations for missed or early CRC, particularly in the proximal colon. We can divide these into two categories, operator-independent and operator-dependent. The operator-independent category includes tumor biology, patient-related factors and endoscopic technology. The operator-dependent category includes a set of key skills required for a successful colonoscopy performance, i.e., high adenoma detection rate and cecal intubation rate, adequate instrument withdrawal time and adequate training in both endoscopic techniques and conceptual knowledge of colon cancer.

9.1 Operator-independent factors

The traditional adenoma-to-carcinoma sequence characterized by chromosomal instability or mismatch repair defects explains most, but apparently not all, CRC. Recently, there is a

growing body of evidence pointing to other lesions as the precursors in CRC carcinogenesis (Jass, 2001). In 1990, Longacre and Fenoglio-Preiser first coined the term "serrated adenoma" as a distinct form of colonic neoplasia, 11% of which contained foci of intramucosal carcinoma (Longacre & Fenoglio-Preiser, 1990). Mäkinen et al showed that 5.8% of all CRC in their study developed through the sessile serrated adenoma (SSA) pathway. These lesions have a predilection for the proximal colon (51% in the cecum) and excessive mucus production (Mäkinen et al., 2001). Sessile serrated adenomas in the proximal colon tend to be slightly larger, mucus-covered, flatter, and harder to detect than distal lesions (Spring et al., 2006; Torlakovic et al., 2003). Instead of the progressive accumulation of APC, K-ras, DCC and p53 gene mutations in the traditional adenoma-to-cancer sequence (Vogelstein et al., 1988), sessile serrated adenomas are characterized by the CpG island methylator phenotype (CIMP) and three-fold increase in DNA microsatellite instability (MSI) as a result of hypermethylation-related gene silencing and BRAF oncogene mutations (Mäkinen et al., 2001). This carcinogenic pathway may also be associated with more rapid transformation to cancer (Sawhney et al., 2006; Arain et al., 2008). Other studies also showed significantly higher MLH1 and MGMT promoter methylation in the normal proximal colon in older women (Worthley et al., 2010; Menigatti et al., 2009) and K-ras mutations in 80% of hyperplastic polyps in women, compared to 36% in men (Otori et al., 1997), suggesting the intriguing possibility that the epigenetic signatures of cancers may have sex- and segment-specific, early-stage and normal-tissue counterparts.

The failure to detect proximal lesions may also be caused by incomplete colonoscopy, which in turn is associated with patient-related factors such as prior history of pelvic or abdominal surgery (i.e., hysterectomy, gastrectomy), old age and inadequate bowel prep (Lee et al., 2006). For the first two factors, adequate conscious sedation or water immersion technique has been used to improve the colonoscopy performance (Leung et al., 2010). For the third factor, poor colon preparation reduces polyp detection, both large and small, especially in the right colon (Froelich et al., 2005; Harewood et al., 2003). Split-prep protocol has been used to address this problem (Marmo et al., 2010).

Another way of rendering the colonoscopy safe and painless is the use of computer-assisted self-propelled colonoscopes and swallowed video capsules for atraumatic locomotion through the colon. Several different systems have been tested for their feasibility. The Invendoscope™ (Invendo Medical, Kissing, Germany) is a single-use colonoscope based on motor driven inverted sleeve technology with a working channel (Rösch et al., 2008). This system has been shown to nearly painlessly achieve high cecal intubation rate comparable to that of the video colonoscope (Groth et al., 2011). However, no data are currently available on its diagnostic accuracy. The Endotics System (ES) is another robotic device composed of a workstation and a disposable probe, the advancing of which through the colon follows a cyclic sequence of steps (Cosentino et al., 2009). Although taking longer time to complete and having lower cecal intubation rate, the ES has been shown to have comparable sensitivity and specificity for the detection of lesions and require no sedation (Tumino et al., 2010). The Aeroscope (GI View Ltd, Ramat Gan, Israel), a self-propelled, disposable endoscope using low-pressure carbon dioxide to propel a balloon device through the colon, on the other hand, did not reduce abdominal discomfort in healthy volunteers although it did achieve cecal intubation (Vucelic et al., 2006). The Video Capsule Endoscopy (Given Imaging Ltd., Yoqneam, Israel), a pill-size capsule activated upon swallowing, demonstrated lower sensitivity compared to that of standard colonoscopy (Van Gossum et al., 2009).

Regular white light technology may contribute to the under-recognition of the neoplastic lesions in the proximal colon. For paler, smaller, flatter adenomas, the use of high-definition white light and chromoendoscopy with methylene blue or indigo carmine has been shown to improve adenoma detection rate (Rex, 2010). Electronic highlighting such as narrow band imaging (NBI), Fuji Intelligent Chromo Endoscopy (FICE), autofluorescence and I-scan have not consistently proved effective to augment adenoma detection rate.

Another method of increasing the rate of polyp detection is to improve the view through the colonoscopic lens. Wide-angle-view (> 170 degrees) colonoscopy, hooded colonoscopy and the Third-Eye Retroscope are several new technologies being developed to expose hidden mucosa during colonoscopy. They have shown some initial promise in improving adenoma detection and are under active investigation (Rex, 2010).

9.2 Operator-dependent factors

Colonoscopy performance is clearly operator-dependent requiring quality training and experience. Tandem endoscopic studies showed miss rates of 0-6% for adenomas 1 cm or larger, and 12-13% for adenomas 6-9 mm in size, and 15-27% for adenomas 5 mm or smaller (Rex et al., 1997; Hixson et al., 1990). When computed tomography colonography (CTC) was used in segmental unblinding to assess polyp detection during colonoscopy, the miss rates increased to 12% for adenomas 1 cm or larger (Pickhardt et al., 2004).

These miss rates varied among endoscopists, suggesting that skillful colonoscopy performance plays a major role in neoplasia detection and prevention. In a large tandem endoscopic study, Chen et al demonstrated a wide range of adenoma miss rates from 17% to 48% among 26 colonoscopists (Chen et al., 2007). Rex et al in another large study also showed cancer miss rates of 3% for gastroenterologists and 13% for non-gastroenterologists (Rex et al., 1997). Other studies also found that endoscopist quality measures were closely associated with post-colonoscopy or interval colorectal cancer. Colonoscopy by an internist or family physician in the office setting was associated with higher CRC incidence following colonoscopy (Baxter et al., 2011; Bressler et al., 2007). In patients with negative colonoscopy, those who had their procedures performed by a gastroenterologist were less likely to develop CRC (Rabeneck et al., 2010). Interestingly, there was no correlation between high colonoscopy volume and lower CRC incidence, suggesting that ongoing training and tracking of quality indicators for colonoscopy are crucial.

The optimal measures for “high quality” colonoscopy are under debate. Three frequently discussed indicators are adenoma detection rate, cecal intubation rate or endoscopy completion rate, and instrument withdrawal rate. Using the database of the National Colorectal Cancer Screening Program in Poland from 2000 to 2004, Kaminski et al studied a large population of 45,026 subjects who underwent colon cancer screening by 186 endoscopists. They suggested that the higher an adenoma detection rate (ADR) (in this case, 20% or higher), the better CRC protection could be obtained from the screening colonoscopy (Kaminski et al., 2010). The investigators used an ADR of 20% or higher as the gold standard and this ADR is close to those recommended in the US guidelines (15% among women and 25% among men) (Rex et al., 2002). They found that the relative risks of interval cancer following colonoscopy were 10-12 folds higher if the ADR was less than 20%. They also found that the rate of cecal intubation was not significantly associated with the risk of interval cancer.

The need for high cecal intubation or colonoscopy completion rates (95% or higher for screening in healthy adults) is based on repeated observations that CRC protection by

colonoscopy is suboptimal in the proximal colon as discussed above. Documentation of cecal intubation has been encouraged as part of ongoing quality improvement program (Rex et al., 2006). However, evidence for a strong association between cecal intubation and reduction in proximal CRC incidence or mortality has yet to be demonstrated.
Likewise, instrument withdrawal rate emerged as an important quality indicator when withdrawal time quicker than 6 minutes was shown to be associated with a lower rate of adenoma detection (Barclay et al., 2006). However, later, in another study, institution-wide policies to keep the colonoscopic withdrawal time within the recommended limits had no effect on polyp detection rate (Sawhney et al., 2008).

10. Conclusion

In summary, the emergence of colonoscopy as the preferred screening test for colorectal cancer by both the public and the medical profession coincides with the substantial decline in the incidence and mortality related to this disease. The impact of colonoscopy on CRC incidence can be seen in various patient populations, including the adenoma cohorts and average-risk cohorts, and this positive protection effect can be long-lasting in individuals with negative colonoscopy as well. However, colonoscopy is imperfect when it comes to CRC protection in the proximal colon, especially in women, although men are more likely to develop incident adenomas. This gender and location disparity can be caused by multiple factors including tumor biology, technological shortcomings, patient-related issues and endoscopist skill level. When colonoscopy fails, often it is due to inadequate lesion detection by the endoscopist. Therefore, the endoscopist can bring about the most significant positive impact on CRC prevention through continuous quality improvement programs.

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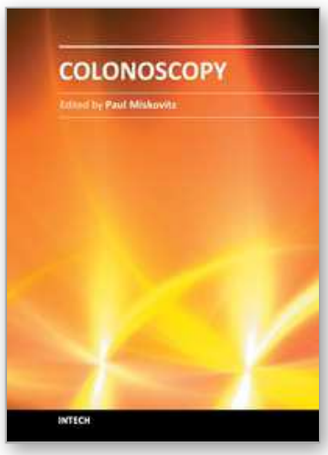

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To publish a book on colonoscopy suitable for an international medical audience, drawing upon the expertise and talents of many outstanding world-wide clinicians, is a daunting task. New developments in videocolonoscope instruments, procedural technique, patient selection and preparation, and moderate sedation and monitoring are being made and reported daily in both the medical and the lay press. Just as over the last several decades colonoscopy has largely supplanted the use of barium enema x-ray study of the colon, new developments in gastrointestinal imaging such as computerized tomographic colonography and video transmitted capsule study of the colonic lumen and new discoveries in cellular and molecular biology that may facilitate the early detection of colon cancer, colon polyps and other gastrointestinal pathology threaten to relegate the role of screening colonoscopy to the side lines of medical practice. This book draws on the talents of renowned physicians who convey a sense of the history, the present state-of-the art and ongoing confronting issues, and the predicted future of this discipline.

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