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Reviewing the Evidence That Polypectomy Prevents Cancer

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INTRODUCTION

The concept of CRC screening has transformed over the past few decades, with the realization that the benefit is less from the detection of early curable-stage cancer, than it is from prevention of cancer via detection and elimination of premalignant lesions. The amenability to primary prevention is a fundamental characteristic of CRC which distinguishes it from other "screenable" cancers, where the focus is generally on secondary prevention via detection of early stage malignancy[1]. This paradigm originated in 1965 with Gilbertsen[2], who postulated that CRC could be prevented by polypectomy, and was later supported by the biologic framework of the Fearon-Vogelstein adenoma-carcinoma sequence[3]. It is now accepted that most CRCs develop within precursor adenomatous or serrated polyps, and that interruption of the polyp-to-cancer sequence prevents the development of CRC. The effect of this interruption on patient outcomes has been the subject of multiple investigations. Several observational studies have reported reduced CRC incidence and mortality after colonoscopy [4-14]. However, patients in

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these studies were heterogeneous, including those with no findings and those with various precursor polyp types and numbers. This affects the interpretability of the findings, because it is known from several "negative colonoscopy" studies[15-19] that patients without polyps are a lower-risk group among the larger average-risk population. It is important to make a distinction between these groups, because prevention of CRC by endoscopic procedures is not due to the identification of persons without polyps, but rather to the detection and complete resection of polyps in patients with colorectal neoplasia. In other words, the main effector of CRC prevention is polypectomy.

There are presently no data from randomized controlled trials (RCT) to determine the effect of polypectomy on CRC incidence and mortality. Isolating the effect of polypectomy would require a randomized design with a control group where polyps are left *in situ* without resection, which is not a reasonable nor ethical consideration. There are 4 large ongoing RCTs[20-23] in Europe and the U.S. comparing colonoscopy to fecal immunochemical testing for CRC screening that could clarify the impact of polypectomy, but their results will not be available for years. Despite the lack of RCT-level data, the effectiveness of polypectomy to prevent CRC is indisputable. Proof of this assertion is derived from several lines of evidence, including epidemiologic data, RCTs of fecal occult blood tests (FOBT) and flexible sigmoidoscopy, and from observational colonoscopy studies.

Epidemiologic observations

Colorectal Cancer (CRC) is a worldwide scourge with globally increasing burden. However, from the epidemiologic standpoint, the United States has been an exception, with steadily decreasing incidence rates since the 1980s[24], and long-term projections predicting declines through 2030[25]. There has been debate regarding the relative contribution of risk factor modification to the US CRC epidemiological trends, because the declines began prior to the mass screening era[26]. However, it is impossible not to attribute a majority of the benefit to

widespread awareness and compliance with screening, and resultant removal of precancerous polyps: In the US, CRC declines have been most noticeable in those 65 years and older, and have accelerated for proximal colon cancer in the past decade[24], an observation likely driven by increased use of colonoscopy and polypectomy. The more recently noted increases in CRC incidence in persons < 50 years old[27], who are not routinely screened for CRC, provides an indirect argument that polypectomy is largely responsible for CRC decreases in screening-eligible age groups. That more colonoscopy and polypectomy could alter CRC epidemiology at the population level is supported by recent evidence from Germany, where CRC incidence and mortality have begun to decrease 10 years after colonoscopy was added to the German national cancer screening program[28].

Evidence from FOBT studies

Randomized controlled trials have consistently shown that screening with FOBT is associated with reductions in CRC mortality ranging from 15% to 33%[29-33]. The FOBT is primarily a test for the detection of CRC, and it can be argued that the beneficial effect of FOBT-based screening strategies is derived from detection of early-stage cancers. However, studies reporting the long-term outcomes of patients after FOBT screening suggest that colonoscopy with polypectomy is in fact a major contributor to the observed reductions in CRC mortality. The Minnesota Colon Cancer Control Study[34] randomized 46,551 participants to annual or biennial FOBT screening or usual care. Through 30 years of follow-up, screening was associated with lower CRC mortality with annual (RR 0.68; 0.56-0.82) and biennial screening (RR 0.78, 0.65-0.93) compared to usual care, while all-cause mortality was not significantly different. Importantly, the CRC mortality reduction of 32% at 30 years was sustained throughout the observation period, and similar to estimates at earlier time points. If early detection of CRC was the primary mechanism by which FOBT screening leads to decreased CRC mortality, the

benefit would be most apparent during the first few years of follow-up after removal of CRC cases from the cohort, then deteriorate over time. The lack of such an observation strongly suggests that in patients with positive FOBT, colonoscopy with polypectomy and subsequent colonoscopic surveillance are responsible for the sustained long-term reduction in CRC mortality. An earlier analysis of the Minnesota FOBT cohort attributed a 20% reduction in CRC incidence after 18 years to colonoscopy with resection of polyps[35].

A more modest reduction in CRC mortality of 13% was reported after 20 years of follow-up of patients in the Nottingham FOBT RCT, and no reduction in CRC incidence despite the removal of over 600 large adenomas in the intervention arm[36]. It is important to note, though, that the Nottingham and Minnesota trials differed in key aspects, notably the use of non-rehydrated FOBT leading to lower positivity and subsequent colonoscopy rates, and lower participant compliance rates in the Nottingham RCT.

Evidence from sigmoidoscopy studies

The results of sigmoidoscopy-based screening have been extrapolated to colonoscopy because they are both structural examinations of the colon and utilize the same endoscopic technology. Four large sigmoidoscopy RCTs have reported significant reductions in CRC incidence and mortality (Table 1) and meta-analyses have reported overall CRC mortality reductions of about 28%[37, 38].

The UK RCT[39] assessed over 170,000 participants who were assigned to sigmoidoscopy or control groups, and of which about 5% were referred to colonoscopy for large, histologically advanced, or multiple adenomas. In intention-to-treat analyses, after 11 years of follow-up, CRC incidence was reduced by 23% (hazard ratio 0.77, 95% CI 0.70-0.84) and mortality by 31% (0.69, 0.59-0.82) in the sigmoidoscopy group. After median follow-up of 17 years, CRC incidence and mortality reductions were 26% and 30%, respectively[40]. The

Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer RCT[41] randomized 154,900 participants to screening sigmoidoscopy (repeated at 3 or 5 years) or to usual care. After a median of 12 years, CRC incidence was reduced by 21%, and CRC mortality by 26%. It is, however, difficult to isolate the effect of polypectomy performed in the sigmoidoscopy RCTs and separate it from that of subsequent colonoscopies, because these employed different polyp resection policies at the time of sigmoidoscopy, different colonoscopy referral strategies, and colonoscopy utilization and contamination varied between studies. For example, in the PLCO trial, patients with polyps at sigmoidoscopy were advised to undergo colonoscopy with about 80% compliance rate; conversely, the contamination rates in the usual care arm were 26% for flexible sigmoidoscopy and 34% for colonoscopy[41]. A meta-analysis showed that colonoscopy was associated with a 40% to 60% lower risk of incident CRC and death from CRC than sigmoidoscopy, which was statistically significant only for deaths due to proximal cancer[42].

Evidence from colonoscopy studies

The first colonoscopy study to demonstrate unequivocally that polypectomy prevents CRC was the National Polyp Study (NPS)[43]. The NPS cohort included 1418 patients who underwent colonoscopy with resection of at least one adenoma, and followed for a mean of 6 years. Five asymptomatic CRCs were detected during surveillance, corresponding to a 76% reduction in CRC compared with a Surveillance, Epidemiology, and End Results (SEER) reference group, and no CRC deaths occurred. The long-term NPS follow up study[44] provides compelling proof of the effectiveness of polypectomy to prevent CRC: The cohort included 2602 patients with adenomas (including the 1418 who were randomized in the original NPS assessing surveillance intervals after colonoscopy) followed for up to 23 years after polypectomy. Compared to a SEER control population, CRC mortality was reduced by 53% (95% CI 20%-74%), and the reduction for the first 10 years was similar to after 10 years of

follow-up**.** In addition, CRC mortality was similar among for adenoma patients compared to an internal control group with nonadenomatous polyps for the first 10 years after polypectomy (relative risk, 1.2; 95% CI, 0.1 to 10.6).

An Italian observational prospective cohort study[45] of 1693 patients who underwent colonoscopic polypectomy of adenomas ≥ 5 mm reported a 66% (95% CI 37%-77%) CRC incidence reduction, compared to the general Italian population. Adenoma cohort studies published after the NPS and Italian study showed far less impressive reductions in CRC incidence after polypectomy. The Funen Adenoma Follow-up Study[46], which assessed surveillance intervals in patients with adenomas, reported significant reductions in CRC incidence and mortality for up to 24 years after adenoma resection: Compared to the Danish population, CRC incidence RR was 0.65 (95% CI 0.43–0.95) and CRC death RR was 0.12 (95% CI 0.03–0.36). The Wheat Bran Fiber Trial[47] and Polyp Prevention Trial[48] assessed the effect of fiber to prevent adenoma recurrence after polypectomy, and both reported much higher CRC incidence rates compared to the NPS (2.2 versus 0.6 per 1000 patient-years). Another study[49] combined data from 3 adenoma chemoprevention RCTs which assessed the effect of calcium, folic acid, antioxidants, and aspirin on recurrence rates of colorectal adenomas after colonoscopy and polypectomy. The overall incidence of CRC was 1.74 (95% CI, 1.05–2.72) per 1000 person-years of follow-up, compared to 0.6 and 0.4 in the NPS and Italian studies, respectively, and was not significantly different from expected incidence based on SEER data (standardized incidence ratio for CRC, 0.98; 95% CI, 0.63–1.54).

The potential reasons for these discrepant findings are many[50]. First, the NPS included a small number of experienced endoscopists, and there was significant focus on ensuring complete adenoma clearance prior to enrollment: patients with adenomas larger than 3 cm were excluded, and about 13% of the cohort underwent more than one baseline colonoscopy. Second, there were important methodological differences, including duration of follow up,

distinction between prevalent and incident CRC cases, the characteristics and CRC risk of the groups chosen for comparison, and frequency of surveillance colonoscopies after the index procedure. Finally, the quality of colonoscopy, notably neoplasia detection and completeness of polypectomy, were likely a contributing factor. These studies were conducted in an era which preceded the recognition of the importance of colonoscopy quality and its impact on the risk of post-colonoscopy CRC[51, 52]. While information about endoscopists' adenoma detection rates and completeness of polypectomy is not available, the characteristics of the incident cancers reported in these studies strongly suggest that colonoscopy quality is a major factor, as most would qualify as interval or post-colonoscopy CRC based on current definitions. For example, in the NPS, 3 of 5 incident cancers were detected 3 years after the index procedure, all 9 cancers in the Wheat Bran Fiber Trial were found within 3 years, whereas 10 of 13 CRC in the Polyp Prevention trial were judged to be due to missed cancer, incomplete polypectomy, or inadequate biopsy. In the combined chemoprevention trial, 17 of 19 CRC were detected within 4 years of the baseline colonoscopy and most were in the proximal colon.

The central importance of polypectomy quality is not a theoretical one. In the landmark Complete Adenoma Resection (CARE) study[53], investigators biopsied the margins of 346 polypectomy sites, and found an incomplete resection rate (IRR) of 10.1% (95% CI 6.9%-13.3%), and ranged from 6.5% to 22.7% among endoscopists. Larger polyps were more likely to be incompletely resected than smaller polyps (17.3% vs. 6.8%). The IRR of 10%, alarming enough by itself, is likely an underestimate of the true prevalence of this problem in clinical practice, because study endoscopists were aware that they participating in research and that their performance was being scrutinized. It is currently estimated that between 10% and 25% of PCCRC are due to incomplete polypectomy.

More recent studies have further highlighted the effect of polypectomy on CRC prevention, and the importance of continued surveillance in select higher-risk patients. An

administrative claims-based study from Ontario[54] assessed whether characteristics of endoscopists are associated with risk of PCCRC in 14,064 patients. In multivariate analyses, patients with proximal cancers undergoing colonoscopy by endoscopists who performed polypectomies at high rates had a lower risk of PCCRC. Compared to < 10% polypectomy rate reference, the OR was 0.52 if the polypectomy rate was 25% to 29%, and 0.61 for rates > 30%. Conversely, distal CRC was not associated with polypectomy rate. A large prospective study[14] examined the association of colonoscopy and sigmoidoscopy with CRC incidence and mortality among 88,902 participants in the Nurses' Health Study and the Health Professionals Follow-up Study. In follow-up of over 22 years, compared to patients who had not undergone lower endoscopy, the multivariate hazard ratios for CRC among participants were 0.57 (95% CI, 0.45-0.72) after resection of adenomatous polyps, 0.60 (95% CI, 0.53-0.68) after negative sigmoidoscopy, and 0.44 (95% CI, 0.38-0.52) after negative colonoscopy. Polypectomy was associated with reduced distal CRC incidence (HR 0.40; 95% CI, 0.27-0.59), although proximal colon cancer incidence was not significantly different. One possible advantage of this study over the NPS is that the polypectomy and control groups were derived from the same background population, allowing more direct comparison of CRC incidence rates after polypectomy and adjustment for confounding factors.

A French population-based cohort study[55] investigated CRC incidence in 5779 patients with adenomas, followed for a median of 7.7 years. Compared with the general French population, 87 CRC were diagnosed versus 69 expected, for a standardized incidence ratio (SIR) of 1.26 (95% CI 1.01-1.56). CRC risk depended on the features of the index adenoma and whether surveillance colonoscopy occurred: The SIR was 2.23 (95% CI 1.67-2.92) for advanced adenomas compared to 0.68 (95% CI 0.44-0.99) for non-advanced adenomas. For advanced adenomas, the SIR decreased to 1.10 (95% CI 0.62-1.82) for patients who underwent colonoscopic surveillance, but increased to 4.26 (95% CI 2.89-6.04) for those who did not.

A population-based study from Norway[56] followed a cohort of 40,826 patients who underwent resection of colorectal adenomas between 1993 and 2007, and followed for a median of 7.7 years. Compared to the general Norwegian population, 383 CRC deaths were recorded (398 expected) for a standardized mortality ratio of 0.96 (95% CI: 0.87-1.06). CRC mortality was increased in high-risk adenoma patients (SMR, 1.16; 95% CI, 1.02- 1.31), and decreased among those with low-risk adenomas (SMR, 0.75; 95% CI, 0.63-0.88).

A study[57] based on a Northern Ireland polyp registry reported a nearly 3-fold increased CRC risk among 6,972 adenoma patients, and the excess risk was associated with inadequate colon clearance and follow up after polypectomy.

Additional insight can be gained from follow-up of the subgroup of nearly 16,000 participants who underwent colonoscopy following abnormal findings on sigmoidoscopy[58]. When stratified according to adenoma findings at colonoscopy, and after a median of 13 years of follow-up, CRC incidence rates (per 10 000 person-years) were 20.0 (95% CI, 15.3-24.7) for advanced adenoma, 9.1 (95% CI, 6.7-11.5) for nonadvanced adenoma, and 7.5 (95% CI, 5.8-9.7; n = 71) for no adenoma. Participants with advanced adenoma were about 2.5 times more likely to develop or die from CRC compared with participants with no adenoma. There were no significant differences in CRC incidence and mortality between participants with nonadvanced adenoma compared with no adenoma.

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