Published in final edited form as:

Gastroenterology. 2014 July ; 147(1): 245–246. doi:10.1053/j.gastro.2014.05.019.

LOWER ENDOSCOPY AND PREVENTION OF COLON CANCER

BRIGID S. BOLAND, JESÚS RIVERA-NIEVES, SAMIR GUPTA

Inflammatory Bowel Disease Center, Division of Gastroenterology, San Diego, California

Colonoscopy is widely recommended for early detection and prevention of colorectal cancer (CRC) based on observational and modeling studies (*Gastroenterology* 2008;149: 627–637). However, the impact of colonoscopy on CRC incidence and mortality (particularly in the right colon), as well as its potential added benefit over other tests, such as sigmoidoscopy, are uncertain (*Ann Intern Med* 2011;154: 22–30).

Nishihara et al used prospectively collected data from 2 large, well-characterized cohorts (the Nurses' Health Study and the Health Professional Follow-up Study), to study outcomes of exposure to lower endoscopy. The primary outcomes were CRC incidence, CRC mortality, and molecular characteristics of post colonoscopy CRCs. The primary exposures were sigmoidoscopy, colonoscopy, and colonoscopy with polypectomy as reported on biennial patient questionnaires.

Lower endoscopy was associated with reduced risk for CRC mortality by 68% for colonoscopy (adjusted hazard ratio [aHR], 0.32; 95% CI, 0.24–0.45) and 41% for sigmoidoscopy (aHR, 0.59; 95% CI, 0.45–0.76) relative to no exposure. Risk reduction relative to no endoscopy differed by colon site; proximal and distal CRC mortality risk reductions were 53% (aHR, 0.47; 95% CI, 0.29–0.76) and 82% (aHR, 0.18; 95% CI, 0.10–0.31) for colonoscopy, and 0% (aHR, 1.04; 95% CI, 0.73–1.48) and 69% (aHR, 0.31; 95% CI, 0.20–0.49) for sigmoidoscopy, respectively. Relative to no exposure, risk for incident CRC was reduced by 66% for exposure to colonoscopy (aHR, 0.44; 95% CI, 0.25–0.68), 40% for exposure to sigmoidoscopy (aHR, 0.60; 95% CI, 0.25–0.68), and 43% for exposure to colonoscopy with polypectomy (aHR, 0.57; 95% CI, 0.45–0.72). Exposure to any form of lower endoscopy reduced incidence of distal CRC; however, only subjects exposed to colonoscopy without polypectomy had reduced proximal CRC risk (aHR, 0.73; 95% CI, 0.57–0.92). Interval CRCs that were diagnosed within 5 years of a colonoscopy were found to have increased frequencies of microsatellite instability, CpG island methylation, and LINE-1 methylation compared with CRC diagnosed >5 years after colonoscopy or without endoscopy exposure (multivariate odds ratios of 2.2, 2.1, and 3.2, respectively). These data support studies showing that cancer after colonoscopy may be biologically different, with a tendency to contain molecular features consistent with the CpG island methylation and microsatellite instability pathways (*Am J Gastroenterol* 2010;105:1189–1195; *Gastroenterology* 2006;131:1700–1705). Results did not differ substantially when restricted to colonoscopies with a screening indication or after propensity score matching CRC risk factors.

Comment. This report confirms and extends our understanding of the impact of sigmoidoscopy, colonoscopy, and polypectomy on CRC incidence and mortality. The

sigmoidoscopy results are consistent with results from 3 randomized trials of sigmoidoscopy screening, which showed consistent reductions in left, but not right-sided CRC incidence and mortality (Lancet 2010;375:1624–1633; BMJ 2009;338:b1846; N Engl J Med 2012;366:2345–2357). The colonoscopy results were similar to some but not all previous observational studies. With respect to mortality, 2 published studies of post colonoscopy mortality showed reduced risk for distal but not proximal CRC (Ann Intern Med 2009;150:1–8; Gastroenterology 2010;139:128–137), whereas results from a third study (done using US Medicare data) showed reduced risk in both segments (J Clin Oncol 2012;30:2664–2669). These 4 mortality studies are difficult to compare directly for several reasons, including use of different study populations, differing specialty mix of endoscopists, and different mechanisms for data collection. The 2 studies reporting no proximal CRC protection were done in Canada, where a substantial proportion of colonoscopies are done by nongastroenterologists, a factor that has been associated with post-colonoscopy CRC (Clin Gastroenterol Hepatol 2010;8:275–279). The 4 study groups were very different; 2 were population-based within regions of Canada and 1 focused only on Medicare individuals (generally age >65), whereas Nishihara sampled health professionals and nurses. Exposures and outcomes were measured via administrative claims data in the Canadian studies, by claims and Surveillance Epidemiology and End Results Cancer registry data in the Medicare study, but through subject survey and medical record review in the Nishihara report, perhaps leading to differences in accuracy of exposure and outcomes measurement. Overall, additional studies, ideally with the ability to take into account colonoscopy quality factors such as adenoma detection rates, are required to understand potential reduced risk for CRC incidence and mortality post colonoscopy, particularly in the right colon.

This study is the largest to date evaluating CRC incidence after polypectomy. The 43% relative post polypectomy reduction in CRC incidence was similar to the 60% reduction reported by Brenner et al within 5 years of polypectomy (J Clin Oncol 2012;30:2664–2669), but markedly lower than the 76%–90% reduction reported by the National Polyp Study that relied on an external control group (N Engl J Med 1993;328:901–906). Importantly, Nishihara et al found no reduction in post polypectomy proximal CRC incidence. The findings that polypectomy reduced cancer incidence by <50% and did not impact proximal cancer risk highlight the potential importance of observations that suggest polyps are often missed and/or incompletely removed (Gastrointest Endosc 2010;72:775–781; Gastroenterology 2013;144:74–80), and that flat and/or small proximal polyps (which are more likely to be missed) are more likely to contain advanced pathology (Gastrointest Endosc 2012;75:1218–1225; Clin Gastroenterol Hepatol 2012;10:1395–1401). It is likely that optimizing post polypectomy outcomes will require novel approaches to management of individuals with polyps, including quality interventions to improve detection and removal, and improved risk stratification strategies.

The strengths of the study include a large sample size, extended follow-up, and careful measurement of CRC risk factors and outcomes. Additionally, benefits of sigmoidoscopy may have been underestimated. If a person had multiple normal sigmoidoscopies, then transitioned to having a colonoscopy that was normal, some of the benefit of having had several normal sigmoidoscopies would be assigned to colonoscopy. This is relevant, because

even a single normal sigmoidoscopy identifies a person at much lower risk for CRC than the general population (Gastroenterology 2004; 127:714–722). Although it would be ideal to have additional studies to compare the incremental benefit of a program of colonoscopy versus sigmoidoscopy on CRC mortality, such a study would likely require tens of thousands of individuals and may not be feasible.

Overall, Nishihara et al provide strong evidence that colonoscopy is associated with a reduced risk of CRC, including proximal cancer. In this report, colonoscopy seemed to be more effective than sigmoidoscopy. Importantly, the study also suggests that the benefits previously ascribed to colonoscopic polypectomy may have been overstated, underscoring the importance of developing novel interventions to optimize colonoscopy outcomes.

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