

# ADVANCES IN ENDOSCOPY

Current Developments in Diagnostic and Therapeutic Endoscopy

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## Colorectal Cancer Prevention With Colonoscopy: Recent Research and Debate

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**G&H** Several recent studies have suggested that colonoscopy reduces distal colorectal cancers, but not proximal lesions. Could you discuss these surprising findings?

**DR** First of all, it is important to emphasize that these findings do not apply to screening colonoscopy. The patient populations in these studies were not well characterized in regard to their indication for colonoscopy; however, based upon where the studies were performed (primarily Canada, which does not frequently use colonoscopy as a screening tool) and the time periods in which they were performed, it is likely that most of the patients had symptoms, positive fecal occult blood tests, or a combination of these indications.

These case-control Canadian studies showed that, compared to the general population, people who have undergone a colonoscopy appear to have a substantially reduced risk of left-sided cancer, but not right-sided cancer. The clearest conclusion from these studies was that colonoscopy is not as effective in the left colon as it is in the right colon.

The only US study on this issue was presented as an abstract at the 2007 Digestive Disease Week and was conducted in the California Medicaid population. (The study has never been fully published, though it has been submitted for publication.) This study showed a similar trend, though it also differed slightly due to the protective effect shown in the proximal colon compared to the inci-

dence of cancer in the general population. (This contrasts with the lack of protection shown in the right colon in the Canadian studies.) However, the effect shown in the right colon in the US study was not as great as the protective effect found in the left colon.

These data raise an important question: Is there truly no protection in the right colon? The answer depends upon whether the expected incidence of cancer in this population is known. To determine this, it is necessary to know how many cancers were detected at the baseline colonoscopy; however, this information is not evident in these studies. In other words, because these patients are not from screening populations, if they had symptoms or positive fecal occult blood tests, for example, it would be expected for them to be enriched in cancers compared to the general population. Thus, if colonoscopy brought the incidence of cancer down to the level of the general population, that would indicate some degree of protective effect. The trouble in this scenario is that the actual rate of prevalent cancers at the index colonoscopy is unknown, making it difficult to determine whether any protective effect occurred.

Another study, this one published in the *Journal of the National Cancer Institute* earlier this year from a German group, was also concerning. This study examined a different endpoint in the German nationalized screening colonoscopy program. The researchers evaluated the rate of advanced neoplasms in patients who were undergoing their first screening colonoscopy compared to patients who were undergoing a screening colonoscopy but had undergone a prior colonoscopy 1–10 years earlier. For those in the second group, it was expected that if the prior colonoscopy had identified and removed large polyps, then these people should have a low rate of advanced neoplasms. What was actually observed was that people who had undergone a prior colonoscopy experienced a dramatically reduced risk of having an advanced neoplasm in the rectum and a reduced risk in the sigmoid and distending colon, but in the colon proximal to the splenic flexure there was no reduction in the rate of detecting advanced neoplasms by having a prior colonoscopy.

Taken together, these data suggest that endoscopists are not as effective in the right colon as they are in the left colon; in fact, it is not possible to even conclude whether there is much of an impact at all in the right colon. Additional studies and data are clearly needed.

### G&H What are serrated colon polyps, and should endoscopists be concerned about them?

**DR** Endoscopists should certainly be concerned about serrated polyps and maintain a high level of vigilance in regard to them. Serrated polyps, in general, comprise a group of polyps that have been variously classified, but in their simplest classification, there are 3 subgroups. The least dangerous histology is the hyperplastic polyps. In the middle ground, there is a group of polyps usually referred to as sessile serrated adenomas or sessile serrated polyps. These polyps can have cytologic dysplasia and may be quite subtle endoscopically. They are usually located in the proximal colon and are often quite flat. Clues to their endoscopic appearance can include a mucus cap, which is a coating of mucus over the surface. The color of these lesions is typically very similar to that of the surrounding normal mucosa.

It is commonly thought that serrated polyps are potentially a contributor to the ineffectiveness of colonoscopy in the right colon because of uncertain data involving their miss rate. Emerging data, some of which were presented at Digestive Disease Week, show that the level of detection of these lesions varies quite dramatically among different endoscopists. In fact, the level of variation is at least as great as it is for adenomas and likely greater. This means that a fair number of endoscopists are missing a very large percentage of serrated lesions, which are not uncommon by any means.

Traditional serrated adenomas, in contrast, are the smallest portion of the 3 categories of serrated polyps and are relatively uncommon. Endoscopically, they tend to be more polypoid and therefore more easily recognized. Thus, merely based upon their shape and morphology, there is a fair chance that these lesions are less likely to be missed.

Endoscopists should be concerned about sessile serrated adenomas, as they have some molecular features that are very similar to a group of cancers that are relatively common in the proximal colon. For example, they commonly have *BRAF* mutations and appear to be precursors of a group of tumors that have relatively high rates of microsatellite instability as well as CpG island methylator phenotype (CIMP). Presently, with serrated polyps, colonoscopy is where it was perhaps 10–15 years ago with adenomas—we are realizing that they are important and that detection rates are quite variable, and now education

of endoscopists is under way to aid in detection. Ultimately, detection targets may be set for serrated lesions the same way that adenoma detection targets were set. It appears that there is a correlation between adenoma detection and serrated lesion detection; in other words, endoscopists who are very good adenoma detectors are also very good at detecting serrated lesions.

### G&H Could you discuss interval cancers and how they might relate to polypectomy technique?

**DR** Interval cancers are cancers that occur in a given time period (typically 3 or 5 years) after a colonoscopy is performed but before the next colonoscopy is scheduled. These cancers are more likely to occur on the right side than the left side of the colon, and they express an increase in certain molecular features, including microsatellite instability and CIMP. On average, interval cancers are biologically different from cancers that are detected during an initial colonoscopy.

Some studies have concluded that the most common reason for interval cancers is missed lesions. This does not mean that the initial colonoscopy was performed in a negligent fashion. Even in experienced hands, colonoscopy is not perfect. It does mean that endoscopists should try to miss as few lesions as possible. Biology could be a factor that contributes to the missing of lesions, but it is also true that these biological differences could potentially be overcome if the relatively subtle precursors (serrated lesions and, perhaps, flat lesions) were detected. Bowel preparation also plays a role here, as it tends to be worse on the right side than the left side of the colon.

Another potential contributor to interval cancers is failed polypectomy, in which a polyp is detected but not successfully removed. It is unknown whether polypectomy technique contributes to more interval cancers on one side of the colon than on the other side. It has been estimated that polypectomy techniques may contribute to approximately one quarter of all interval cancers, but this argument may be a ceiling on the rate at which polypectomy techniques contribute to these cancers. The calculations are usually performed by looking back at the previous colonoscopy that failed to prevent the cancer and assuming a polyp seen in the same segment where the cancer developed was not completely removed and thus led to the cancer. However, in many of these cases, it is quite possible that the polyp that was seen was completely removed and that another polyp happened to be in the same section of the colon but was missed. Ineffective polypectomy techniques likely do contribute to interval cancers, but the extent to which this occurs is unknown; the best guess is that a substantial minority of interval cancers are caused by ineffective polypectomy techniques.

**G&H** Flat lesions in the colon are often missed on a regular basis, particularly by average-skilled endoscopists. How can endoscopists detect and treat more of them?

**DR** There are numerous ways of classifying flat lesions. I use the Paris classification system, in which type 2 lesions constitute both flat and depressed lesions. Flat lesions are very common and tend to have a histology that is not any worse or better than that of polypoid lesions (Paris classification type 1 lesions). Unquestionably, any given colonoscopic technique is more likely to miss flat lesions because they are more subtle than polypoid lesions. Some endoscopists likely miss a substantial number, if not the majority, of flat lesions.

The most concerning lesions are depressed lesions. These are quite uncommon, but, unlike flat lesions, they have very bad histology (ie, very high rates of high-grade dysplasia and invasive cancer). Because these lesions are quite uncommon, endoscopists should exercise a substantial degree of vigilance and educate themselves, particularly by studying journal articles and images, to aid in detection. These lesions appear to be, at least in some studies, more prevalent on the right side of the colon than the left side. This could help explain why protection on the right side of the colon is not as effective, particularly if an ineffective bowel preparation is used. Evening-before dosing (not split dosing) tends to produce a preparation in the right colon that can easily obscure flat and depressed lesions.

Among the different types of lesions, serrated lesions are clearly important, flat lesions have some degree of importance, and depressed lesions are clearly very important. Of the three different types, both serrated and flat lesions are quite common, and depressed lesions are uncommon. However, all of them occur more commonly in the right colon than the left colon. Each type of lesion likely contributes to the observation that endoscopists are not as effective in the right colon as they are in the left colon.

**G&H** You stated in a recent editorial that “colonoscopy is at a pivotal turning point as a screening test.” Could you explain this statement?

**DR** In the United States, Germany, and Poland, endoscopists have moved toward using colonoscopy as a screening tool. In fact, in the United States, colonoscopy has

become the primary form of cancer screening. There are many reasons to think that colonoscopy is producing many benefits. Nevertheless, there have been no randomized controlled trials comparing colonoscopy to no screening or to any other form of screening. Thus, much of the movement toward colonoscopy has been based upon the faith that endoscopists could extrapolate the benefits of sigmoidoscopy, which are very apparent in case-control studies, and, more recently, in a randomized controlled trial from the United Kingdom, and, to a certain extent, a randomized controlled trial from Norway. These studies have offered a very strong evidence base that sigmoidoscopy is effective at preventing left-sided colorectal cancer. Endoscopists have made the assumption that we could extrapolate those benefits to the right colon by performing colonoscopy rather than sigmoidoscopy. However, it appears that, to some extent, we were wrong. We are currently at a pivotal turning point because we need to prove that this decision to move from sigmoidoscopy to colonoscopy was a good one and provides real benefit for patients in terms of protection from right-sided colorectal cancer. Additional studies are needed to further evaluate this issue and answer questions such as: Can this problem be fixed by factors such as improved bowel preparation; better training for weaker endoscopists so they can recognize accurately when the cecum has been reached; better techniques for the examination of the proximal colon; or better training and recognition of serrated, flat, and depressed lesions? If there is an effect of colonoscopy in the right colon, it is necessary to determine how great the effect is. Can good technique and good colonoscopic performance create a very substantial protective effect, or will biologic factors in the right colon prevent colonoscopy from being an effective screening test for the right colon? We are at a turning point from the perspective that doubt has been cast, and now it is essential to answer these questions about colonoscopy.

### Suggested Reading

Rex DK. Preventing colorectal cancer and cancer mortality with colonoscopy: what we know and what we don't know. *Endoscopy*. 2010;42:320-322.

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