

Title: Cancer after colonoscopy: Are we sowing bad seeds?

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Abbreviations: Percutaneous endoscopic gastrostomy, PEG; FIT, Fecal Immunochemical testing

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Main Manuscript

Colorectal cancer is a preventable disease¹. Bowel cancer screening whether via Fecal Immunochemical Testing (FIT), flexible sigmoidoscopy or primary colonoscopy, reduces risk of future colorectal cancer significantly, and colonoscopy is the final common pathway in screening to remove polyps and prevent cancer^{1,2}; however despite this effectiveness it has also become evident that colonoscopy is not perfect and cancers occur after a “clear” colonoscopy at a rate of between 2.5% and 8.7% of the total cancers diagnosed, depending on the method used to calculate and the population^{3,4}. The suggested mechanisms for post-colonoscopy colorectal cancer include incomplete colonoscopy, missed lesions, incomplete polypectomy and rapidly growing lesions⁵. These mechanisms apply both to cancers occurring after a “clear” colonoscopy, and to metachronous cancers occurring after a colorectal cancer is resected, which occurs after up to 3% of surgical resections^{6,7}. In this issue of *Gastroenterology* Backes et al. in a proof-of-principle study suggest a fifth mechanism for development of colorectal cancer after colonoscopy: iatrogenic mechanical tumor seeding via the biopsy channel of the colonoscope (Figure 1)⁸.

Causality of seeding post-biopsy is difficult to prove. Koch’s postulates have been adapted as a framework to consider causality outside microbiology, including for cancer stem cells⁹. By replacing the term “microorganisms” with “cancer cells” we might require the following to be demonstrated for causality:

1. Cancer cells must be isolated from a diseased organism and grown in pure culture
2. Cultured cancers cells should cause disease when introduced into a healthy organism
3. Cancer cells must be reisolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent

The authors are able to demonstrate cancer cells can be isolated from the biopsy channel of a colonoscope that has been used to biopsy a cancer, and that at least in one of five attempts, they grew organoids which had the same genetic mutation profile “fingerprint” as the original tumor,

meeting the first criteria. The authors may also meet the third criteria, by showing that in three tumors suspected of being due to mechanical seeding, the genetic profile is identical to that of the original tumor, and different to that of polyp from the polypectomy site, excluding incomplete resection as cause for a metachronous tumor. In five metachronous tumors which were suspected to occur by other mechanisms e.g. missed lesions, analysis showed different mutation profiles to the original tumors. Meeting the second criteria is challenging, because deliberate inoculation of human would be unethical. Inoculation of immunodeficient mice would be a possibility, but the tumor microenvironment here would differ from inoculation into an immunocompetent human colon wall. The occurrence of tumors with an identical genetic profile after tumor biopsy following subsequent endoscopic intervention elsewhere in the colon essentially represents a form of “natural experiment” to test this; however it is difficult to be sure that transfer did not occur via passive spread of exfoliated tumor cells or is related to field cancerization.

Mechanical seeding of tumor cells is considered to occur after other gastrointestinal cancer manipulations. Port site metastases after laparoscopic gallbladder cancer surgery were initially estimated to occur in 19% of cases before the year 2000 but have dropped to 10% since 2000¹⁰. Similarly, high rates of port site metastases were initially reported after laparoscopic colorectal cancer surgery, as high as 21%, but more recent estimates now suggest this has fallen to approximately 1%¹¹. This is likely to be a result of modification in operative techniques to minimize tumor cell seeding such as use of extraction bags, deflating the abdomen with trocars in place, and avoiding fluid spillage. Similarly PEG site metastases have been reported after pull-through PEG placement passing oropharyngeal or esophageal tumors, with tumor cells able to be recovered from the PEG tube in 23% of cases¹². PEG site metastases were estimated to occur in 0.6% of large series of 777 PEG placements in such cases¹³. Consideration of direct gastric puncture methods are advised to reduce this risk^{14,15}.

The authors estimated risk of mechanical seeding after biopsy is low in absolute terms 0.3-0.6% of cancers biopsied with subsequent polypectomy or biopsy, but these make up a significant

proportion of the metachronous cancers overall between the two pathological and clinical cohorts reported 5/31 (16%, 95% confidence interval 6-34%; *my calculation*). This is broadly equivalent to the author's risk estimate attributed to incomplete colonoscopy and exceeds their risk of incomplete polypectomy or unknown causes, though numbers are small. Half the risk for metachronous cancers was attributed to missed lesions.

While not definite, the most plausible explanation for the data, when viewed with experience at other sites in the gastrointestinal tract, the contamination of the channel with viable tumor cells, and the identical molecular profiles of tumors suspected of occurring from mechanical seeding, is that direct tumor seeding may occur at colonoscopy. Given clinicians take precautions to avoid seeding at port sites and PEG sites on perhaps less compelling evidence, modification of colonoscopy practice may also be appropriate until more definitive evidence on mechanism and risk is gathered. The risk of seeding is modifiable, or perhaps completely avoidable, either by performing all necessary polypectomy and other actions e.g. tattooing, prior to biopsying the cancer as the last action, or after cancer biopsy changing for a fresh colonoscope that has not been contaminated with cancer cells. How often might this be necessary? In the authors series only 23% of cancer cases (443/1903) required further endoscopic intervention after biopsy of the primary tumor which might lead to seeding, which could be easily accommodated in most practices.

Although rates of cancer after colonoscopy are falling, we should view this as a wider opportunity to bear down on all five causes of cancer after colonoscopy (Figure 1)^{4,5}. Four of the five causes can be minimized through improved technique¹⁶, and the fifth, rapidly progressive lesions, may become less frequent as Lynch syndrome is more comprehensively detected through universal tumor testing¹⁷. Ultralow levels of cancer after colonoscopy should be the new norm after high-quality modern colonoscopic screening and surveillance.

Figure legends

Figure 1. Proposed mechanisms leading colorectal cancer after colonoscopy

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