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Editorial

EDITORIAL

Antibiotic Use Impacts Colorectal Cancer: A Double-Edged Sword by Tumor Location?

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Antibiotic overprescribing and misuse remain prominent clinical practice issues worldwide, particularly in the outpatient setting. In Europe and the United States, approximately 90% of antibiotic prescriptions are issued in the outpatient setting with approximately 30% deemed unnecessary or inappropriate (1,2). Antibiotic overuse promotes antimicrobial resistance and *Clostridioides difficile* infection. Further, even narrow spectrum or short-course antibiotic use exerts strong, long-lasting effects on the composition, structure, and function of the gut microbiota (3,4). This may increase susceptibility, possibly through initiation of local and systemic inflammation, to chronic diseases including asthma, inflammatory bowel disease, obesity, and cancer (5). Thus, understanding if and how antibiotics impact disease expression is of high interest and public health impact.

In this issue of the Journal, Lu et al. (6) conducted a matched case-control study of 40 545 colorectal cancer (CRC) cases and 202 720 controls using data from the Swedish population registers from 2005 to 2016 to investigate the association between antibiotic use and CRC risk. Approximately 80% of participants received at least 1 dose of antibiotics with about 20% having more than 2 months exposure. The authors identified a positive dose-response antibiotic–cancer association primarily confined to the proximal colon with an inverse association between antibiotic exposure and rectal cancer. The striking divergence of regional risk patterns in the colon provides independent validation of previous studies that examined antibiotic CRC risk in the Clinical Practice Research Datalink in the United Kingdom (7) and antibiotic colon polyp risk in the Harvard Nurses' Health Study (8). Regional differences in antibiotic colon tumor risk likely reflect the biogeographic heterogeneity in gut physiology, microbiota, and carcinogenic mechanisms along the lower intestinal tract. For example, the proximal colon, the site of first exposure to spillover antibiotics not absorbed in the small intestine, may experience the greatest microbiota disruption. Putative tumorigenic, sometimes toxin-producing bacteria, such as Fusobacteria (9), *Porphyromonas*, Enterobacteriaceae, and *Bacteroides-Prevotella*, may differentially colonize or impact epithelial cells along the colorectal axis. Murine models and human studies suggest that colon biofilms, an assemblage of mucus-invasive bacteria associated with nearly 90% of right-sided CRCs, contribute to the initiation of colon cancer (10-13). Importantly, biofilms on histologically normal colon induce changes in epithelial biology suggestive of early, procarcinogenic mechanisms (12). Thus, even short-term antibiotic-induced dysbiosis may enable overgrowth and invasion of tumorigenic bacteria (14). The results of Lu et al. (6) add to the plausible biological linkage between antibiotic-induced dysbiosis and colon carcinogenesis.

The authors are to be commended for providing the largest epidemiological study to date on antibiotic–CRC association. Study strengths include leveraging the large, well-established and well-linked Swedish national population-based registries; an incidence density–based, matched case-control design; well-annotated data on antibiotic exposure; and CRC diagnosis (including anatomic tumor site and stages) as well as the use of methenamine hippurate, a clever negative control, showing the specificity of gut microbiota dysbiosis as a risk factor for CRC (6). Further, the authors are the first to report a statistically significant interaction between antibiotic use and sex on rectal cancer risk, where antibiotic exposure was protective only among women. This antibiotic protective effect may relate to eliminating pathogenic bacteria of sexually transmitted infections (15), sex-specific differences in their immune system, and/or gut microbiota composition (16). Though intriguing, this sex-specific, antibiotic–rectal cancer association requires validation. By leveraging available cancer staging data, the authors found antibiotic use associated with increased risk for early stage proximal colon cancer but decreased risk for late stage rectal cancer. The authors suggest that, in the colon, antibiotic use may alter colon tumor initiation but, in the rectum, mitigate tumor pro-

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gression. The authors report that antibiotics with anti-aerobic activity (eg, quinolones, trimethoprim-sulfonamide) seemed to drive the increased proximal colon risk, whereas multiple antibiotic classes associated with diminished rectal cancer risk. These results differ with most previous studies where penicillin and antibiotics with anti-anaerobic activity had the greatest detrimental effects (5,7,17,18). Given that most people are exposed to more than 1 antibiotic class over time (7), the independent effect of antibiotic class might be best revealed by studying prescriptions of single antibiotic classes.

However, as acknowledged by the authors, there are several limitations. First, information bias exists that may distort or underestimate the association. The validity of CRC data in the Swedish Colorectal Cancer Registry is approximately 90% when compared with re-abstracted data from hospital records (19), whereas the coding accuracy for the tumor sublocations has not yet been validated yielding possible misclassification error. Similarly, exposure measured from prescriptions may not reflect actual use. Second, there is the potential for confounding by indication, due to antibiotics prescribed to patients having, a priori, a higher susceptibility for CRC (eg, inflammatory bowel disease, hereditary CRCs that were not excluded conditions) (20). Third, reverse causation, a common problem with pharmaco-epidemiological studies, is another concern. Patients with CRC prior to confirmed diagnosis may present with symptoms requiring antibiotic treatment. Although the authors tried to address this concern by excluding antibiotic exposure 2 years before diagnosis, this enhanced the study's short timeline of only 9 years with 6 years median follow-up. This is potentially important given the estimated 10 years for polyp development with further time expected for progression to CRC. Thus, much of the antibiotic exposure putatively contributing to CRC development may not have been captured, limiting the authors' ability to establish temporality. Finally, residual confounding is possible as data on variables associated with CRC susceptibility and with gut microbiota changes were not available (eg, body mass index, diet, and lifestyle factors such as smoking and alcohol use).

The study by Lu et al. (6) adds to a growing body of evidence that the detrimental effect of antibiotic use on colon cancer risk primarily involves the proximal colon with potential inverse actions in the rectum. This work, along with other studies, supports, but does not prove, a causal link between disrupted microbiota and CRC development. Further study, including attention to consistent variable classifications (eg, colon risk site, antibiotic class, and time of exposure), is warranted to confirm the specific antibiotic class(es), pathogenic microbes, and mechanisms of pro- or anti-carcinogenesis involved in the antibiotic–cancer association. Moving from correlations to causation of the microbiota for CRC will require a better understanding of interactions within microbial communities and with the host and account for unique subsites within the colorectal tract. Judicious use of antibiotics and the development of microbiota modulation strategies for therapeutic purposes and chronic disease prevention remain paramount goals.

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