Antibiotic use and colorectal cancer: a causal association?

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Antibiotics have revolutionised our ability to fight infectious diseases that are major causes of morbidity and mortality. However, the widespread use of these powerful agents has led to unintended consequences that reflect their broad effects on microbial community structure. Even short-term antibiotic treatment causes shifts in gut microbiota including, but not limited to, alterations in the abundance of specific taxa and a decrease in overall diversity. *Clostridium difficile* colitis and vaginal candidiasis are established examples of conditions that originate from gut dysbiosis and opportunistic pathogen colonisation induced by short-term antibiotics. Emerging data also suggest that antibiotic-induced perturbations can persist for years after treatment and contribute to long-term dysregulation of host immune homeostasis.[1] In turn, this can potentially increase susceptibility to chronic disorders with an immune basis, including asthma, inflammatory bowel disease and obesity.

Recent epidemiological studies have extended the association between antibiotic exposure and chronic disease to risk of colorectal adenoma and colorectal cancer (CRC).[2] In parallel, increasing evidence has demonstrated a pivotal role for the interplay between the gut microbiome and lifestyle factors in initiating and promoting CRC.[3] Several species of bacteria have been shown to be potential drivers of carcinogenesis through specific biological mechanisms. For example, *Fusobacterium nucleatum* expresses adhesins, including FadA and Fap2, which bind to tumour cells and directly promote carcinogenesis by activating oncogenic Wnt/β-catenin signalling and dysregulating immune cell infiltration and antitumour immunity. Enterotoxigenic *Bacteroides fragilis* forms biofilms in the colonic mucosal membrane, promoting inflammation and tumour development. Similarly, polyketide synthase-expressing *Escherichia coli* may influence carcinogenesis through generation of the genotoxin colibactin and subsequent DNA damage.[4 5] In addition to these specific microbes, altered abundance of other microbial members and shifts in metabolic potential, including enriched amino acid and choline metabolism and depleted carbohydrate degradation, have been shown to differ in CRC cases compared with controls.[6]

Thus, the association between the gut microbiome and colorectal carcinogenesis lends critical biological plausibility to the potential link between antibiotic exposure and development of CRC. The disruption in gut microbiota induced by antibiotics may promote acquisition or colonisation of proneoplastic microbiota that influence CRC pathogenesis. Evidence from animal studies also suggests that antibiotic treatment may impact microbiome-related pathways of CRC. In mouse models, antibiotics have been shown to decrease levels of short-chain fatty acids derived from microbial fermentation.[7] These fatty acids are critical mediators in colorectal carcinogenesis by virtue of their role in regulating inflammation, immune response, cell proliferation, differentiation and apoptosis. Moreover, antibiotics can increase intestinal permeability, which contributes to bacteria translocation and activation of components of the innate and adaptive immune system, thereby promoting chronic inflammation.[8] Taken together, this evidence supports a potential detrimental role for antibiotics on colorectal carcinogenesis. However, data also exist suggesting a potential beneficial effect of antibiotics. A recent study reported that the antibiotic metronidazole could slow the growth of *Fusobacterium nucleate*-positive tumour samples in patient-derived mouse xenograft models.[9] Therefore, the association between antibiotics and CRC is likely complex, reflecting multiple potential mechanisms of action of these drugs and the biological heterogeneity of the human host.

In *Gut*,[10] Zhang *et al* used the Clinical Practice Research Datalink (CPRD), a large electronic medical record database of general practices in the UK, to examine the association between oral antibiotic use and risk of CRC in a matched case–control study of 28 980 CRC cases and 137 077 controls. They report an association between use of antibiotics, primarily with antianaerobic activity, and increased risk of colon cancer, which was limited to the proximal colon. Risk was increased after even minimal antibiotic use. In contrast, antibiotic use was associated with a reduced risk of rectal cancer. In analyses according to antibiotic class, use of penicillins was associated with an increased risk of colon cancer (especially of the proximal colon), whereas use of tetracyclines was associated with a reduced risk of rectal cancer. This striking difference in the association with cancers of the proximal colon compared with rectum has not been previously reported. This result is consistent with our growing appreciation of the biogeographical heterogeneity in gut microbial abundance and function as well as the distinct molecular pathways underlying tumourigenesis in different regions of the intestine.

The investigators should be applauded for leveraging a large dataset with prospectively collected, detailed information about classes of antibiotics, duration of exposure and diagnoses of CRC according to anatomic subsite to enable a more comprehensive analysis of the antibiotic–CRC association than has been previously reported. However, the study has several limitations. First, although studies have validated the quality of CPRD data, antibiotic exposure is derived from prescription records that may not reflect actual use. Furthermore, the results on subsite-specific CRC are largely dependent on the accuracy of the coding of the tumour locations which, to the best of our knowledge, has not been validated. In the UK, the majority of diagnoses of CRC are made in the course of secondary/specialist or hospital-based care rather than in the primary care setting, with the diagnosis subsequently communicated to general practitioners (GPs). These GPs then record and select the appropriate READ codes. Thus, this process may be susceptible to miscommunication or miscoding, which will lead to measurement error. Second, there is potential for reverse causation since these drugs are commonly prescribed for treatment of conditions that either predispose to cancer or symptoms associated with CRC prior to formal diagnosis. Although the authors

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tried to mitigate this possibility through sensitivity analyses limited to antibiotic use more than 10 years before CRC diagnosis, this remains a key concern for any pharmacoepidemiological studies. Finally, the relatively modest effect estimates leave open the possibility of confounding by key risk factors for CRC, including diet, physical activity and family history of CRC, for which data were not available. Thus, causal interpretation of the antibiotic–CRC association still requires caution.

Further studies are warranted to better understand the impact of antibiotic exposure on gut microbial composition and function, particularly as related to mechanisms that underlie colorectal carcinogenesis. Prospective, longitudinal cohort studies, ideally with collection of data on antibiotic exposure and concurrent sampling of the gut microbiota prior to development of colorectal adenomas and CRC, would provide critically important data to additionally validate these results and better infer causality.

The observations that even short-term or low-dose antibiotic treatment may perturb the gut microbiome and lead to long-term detrimental effects on CRC offer yet another rationale for minimising inappropriate use of broad-spectrum antibiotics.[11] Moreover, these results lend support for the critical role of the gut microbiome in colorectal carcinogenesis, validating the human relevance of the exciting data emerging from experimental model systems. This sets the stage for another revolution associated with manipulating gut bacteria that can address new challenges beyond the treatment of infections. Perhaps in the not too distant future, microbiome-based interventions may soon be available to prevent or treat chronic diseases such as CRC.

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