Antibiotic use and risk of colorectal cancer: a meta-analysis of 412 450 participants

We read with interest the study by Zhang *et al*[1] which investigated the associations between oral antibiotic use and risk of colorectal cancer (CRC). The study included 166 057 participants and found that antibiotic use was associated with an increased risk of colon cancer but a reduced risk of rectal cancer. We also noticed another study by Armstrong *et al*[2] reporting that patients prescribed antibiotics in up to 15 years preceding diagnosis were associated with a higher risk of CRC. However, the study by Armstrong *et al* did not analyse the risk of colon cancer and rectal cancer, respectively. Considering current studies about antibiotic use and risk of CRC were inconsistent, we conducted this meta-analysis.

The PubMed and Web of Science were searched for relevant studies published before 20 January 2020. The inclusion criteria were studies investigating the impact of antibiotic use on the risk of CRC and reporting the relative risk, OR or other measures of association. The pooled OR and 95% CIs were estimated to investigate the associations between antibiotic use and risk of CRC. If the significant heterogeneity existed (I^2 >50%), we would report the results with random-effects model. All studies included in this meta-analysis were evaluated according to the Newcastle–Ottawa Scale.

Finally, five case–control studies[1–5] with a total of 412 450 participants were included (table 1). The total antibiotics use was not associated with risk of CRC (OR 1.18; 95% CI 0.97 to 1.39). After stratified by type of antibiotics, we found that participants with penicillin and anti-anaerobic antibiotics use had 18% and 49% increased risk of CRC, respectively. However, no significant associations were showed in quinolone, tetracycline, macrolide and antiaerobic antibiotics use. Interestingly, subgroup analysis showed that antibiotics use increased the risk of colon cancer (OR 1.16; 95% CI 1.10 to 1.22) but decreased the risk of rectal cancer (OR 0.86; 95% CI 0.80 to 0.93), which was similar to the results reported by Zhang *et al*.[1] Additionally, we found that high number of antibiotic prescriptions (≥5) was associated with higher risk of CRC compared with low number of antibiotic prescriptions (<5) (table 2).

This meta-analysis demonstrated that not all antibiotics but penicillin and anti-anaerobic antibiotics use could be related to an increased risk of CRC, and the impacts of antibiotics use on the risks of colon cancer and rectal cancer were different. Although the mechanisms of how antibiotics use influencing the risk of CRC was not completely clear, Ma and Chan[6] thought that the alterations of gut microbiota after antibiotic use could contribute to long-term dysregulation of host immune homeostasis and influence CRC pathogenesis. Moreover, the composition of gut microbiota between colon and rectum was highly different,[7] which may explain why the risks of colon cancer and rectal cancer were opposite after antibiotic use. This meta-analysis also suggested that higher number of antibiotic prescriptions was associated with higher risk of CRC. Therefore, it should be taken into consideration when balancing the risks

Table 1 Characteristics of studies investigating antibiotic use and risk of colorectal cancer

Author, year	Country	Study design	Antibiotic	Participants (n)	Follow-up	Quality assessment*	Adjustments (n)
Armstrong *et al*, 2020	UK	Case–control study	Quinolones, penicillins	95 562	Median 6 years (3–9)	7	11
Zhang *et al*, 2019	UK	Case–control study	Penicillins, tetracyclines, cephalosporins, macrolides, sulpha and trimethoprim	166 057	Median 8.1 (4.9–12.3)	8	6
Dik *et al*, 2016	The Netherlands	Case–control study	Penicillins, quinolones, tetracyclines, amphenicols, cephalosporins, sulfonamides and trimethoprim, macrolides, aminoglycosides, imidazoles, nitrofuran derivates,	20 017	5 years	8	8
Boursi *et al*, 2015	UK	Case–control study	Penicillins, quinolones, cephalosporins, macrolides, tetracyclines, sulphonamides, nitroimidazoles	103 044	Median 6.5 years (2.5–10.5)	8	6
Wang *et al*, 2014	China	Case–control study	B-Lactam/b-lactamase inhibitor combinations, cephamycin cephalosporin, carbapenems, lincosamides, imidazoles, moxifloxacin	27 860	Colon cancer: 1424±645 days; rectal cancer: 1397±641 days	7	12

*According to the Newcastle–Ottawa Scale.

and benefits of using antibiotics. Because studies included in this meta-analysis were case–control studies, the evidences might be limited. Prospective studies about this issue are required in the future.

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Table 2 Analysis of antibiotic use and risk of colorectal cancer*

Subgroup	Number of studies	OR	95% CI	I^2%
Type of antibiotic				
Total antibiotics	4	1.18	0.97 to 1.39	94.0
Penicillin	4	1.18	1.08 to 1.29	89.1
Quinolone	4	1.29	0.92 to 1.66	95.4
Tetracycline	2	0.97	0.92 to 1.01	0
Macrolide	2	1.09	0.93 to 1.24	81.6
Antiaerobic antibiotics	3	0.98	0.86 to 1.11	64.2
Antianaerobic antibiotics	3	1.49	1.07 to 1.90	98
Site of cancer				
Colon cancer	2	1.16	1.10 to 1.22	17.3
Rectal cancer	2	0.86	0.80 to 0.93	30.8
Number of antibiotic prescriptions				
<5	2	1.47	1.12 to 1.82	98.7
≥5	2	1.64	1.09 to 2.19	98.8

*OR, odds ratios; 95% CI, 95% confidence intervals.

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