ZAGÓRSKI, Karol, KOZIK, Mateusz, SKALSKA-DZIOBEK, Nina, MAŁAGOCKA, Weronika, CHYBOWSKA, Karolina, NARUSZEWICZ, Maria and CETNAROWSKI, Przemysław. The Impact of Antibiotics on the Development of Colorectal Cancer – A Review of Current Insights and Directions for Future Research. Quality in Sport. 2025;38:57935. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.38.57935
https://apcz.umk.pl/QS/article/view/57935

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 18.01.2025. Revised: 10.02.2025. Accepted: 11.02.2025 Published: 11.02.2025.

The Impact of Antibiotics on the Development of Colorectal Cancer – A Review of Current Insights and Directions for Future Research

Karol Zagórski, Mateusz Kozik, Nina Skalska-Dziobek, Weronika Małagocka, Karolina Chybowska, Maria Naruszewicz, Przemysław Cetnarowski

Karol Zagórski
Edward Szczeklik Specialist Hospital in Tarnów, Poland
https://orcid.org/0009-0000-6407-8075
Mateusz Kozik
Stefan Żeromski Specialist Hospital in Cracow, Poland
https://orcid.org/0009-0002-6078-2836
Nina Skalska-Dziobek
Edward Szczeklik Specialist Hospital in Tarnów, Poland
https://orcid.org/0009-0005-3755-0350
Weronika Małagocka
Stefan Żeromski Specialist Hospital in Cracow, Poland
https://orcid.org/0009-0008-3714-9278

Karolina Chybowska
University Clinical Hospital in Bialystok, Poland
https://orcid.org/0009-0006-0660-2645
Maria Naruszewicz
University Hospital in Cracow, Poland
https://orcid.org/0009-0005-2417-6937
Przemysław Cetnarowski
Gabriel Narutowicz Specialist Municipal Hospital in Cracow, Poland
https://orcid.org/0009-0007-1940-0003

Abstract

Introduction and purpose: Colorectal cancer (CRC) is one of the most common neoplasms in the world. In Poland, CRC has a third place in incidence. There are numerous well-established risk factors for CRC, such as a western diet, low physical activity, alcohol consumption, and cigarettes smoking. Currently, the role of the colonic microbiome and the overuse of antibiotics is also highlighted in the pathogenesis of CRC. This review aims to assess the impact of antibiotic use on CRC risk, clinical characteristics, and pathological features.

Material and methods: A comprehensive literature search was conducted through the following databases: PubMed, Cochrane Library, Embase, and Google Scholar. Systematic reviews, meta-analyses, clinical trials and observational studies were included if they were relevant and provided data on the influence of antibiotics on CRC.

State of knowledge: This review identified several key systematic reviews with meta-analyses of observational studies indicating that antibiotics have an impact on the onset, time of development, and localisation of CRC. The classes and spectrum of antibiotics were found to differ in the risk of occurrence of CRC.

Summary: Recently, great progress has been made in understanding a variety of antibiotics-microbiota-cancer interactions. However, further research is needed to deepen our knowledge about the contribution of antibiotic use to CRC. Clinicians should carefully consider the benefits

and risks of prescribing antibiotics, including possible long-term adverse events such as cancer onset.

Key words: Colorectal cancer, Antibiotics, Gut microbiota, Dysbiosis

Introduction

Colorectal cancer (CRC) is one of the most common neoplasms in the world. In 2022, 1 142 233 new cases of colon cancer and 729 707 new cases of rectal cancer were reported. 538 136 and 343 757 people died from colon and rectal cancer, respectively. Globally, CRC has a third place in incidence and a second place in mortality (1). In Poland, CRC is the third most common cancer in incidence, accounting for 12.4% of new cancer cases per year. CRC is the second leading cause of cancer-related deaths in Polish men and the third in women (2). Despite the fact that CRC incidence rates have been reduced in high-income countries, in Poland they are increasing, including in young patients (3).

Numerous risk factors for CRC are known. Inappropriate diet, lack of physical activity, obesity, inflammatory bowel diseases, alcohol consumption, and cigarette smoking play a role in the pathogenesis of CRC (4). Although these risk factors are well established in the literature, there is emerging new evidence for the development of CRC. One of the interesting areas that requires further investigation is the influence of the gut microbiota on the incidence and development of CRC (5). Scientists also emphasise the role of antibiotic overuse as a risk factor for carcinogenesis in the large intestine (6).

Today, the excessive use of antibiotics has become a major concern for public health worldwide (7). The growing resistance to antibiotics leads to a vicious circle of even greater antibiotic consumption (8). In developed nations, antibiotics are used more frequently than in developing countries, which is in line with the higher incidence of CRC in these first countries (3,9).

Antibiotics have a negative impact on the normal colonic microbiome, resulting in destruction of protection against colonisation by pathogenic bacteria. Antibiotics also affect the secretion of bacteriocins, which naturally acts against infection-induced inflammation (10). Chronic inflammation is one of the hallmarks of cancer (11). Antibiotics kill the beneficial human gastrointestinal microflora and promote the growth of pro-inflammatory pathogens. This reshuffle in the composition of microorganisms results in an increase in the production of reactive oxygen species, creating a favourable environment for tumour formation (12).

Fusobacterium nucleatum is one of the most common pathogenic bacteria found in cancer samples, also identified in distant metastatic cancer cells (13). The contribution of this bacterium increases in dysbiosis which may be the result of antibiotic therapy (14). Other pro-inflammatory and carcinogenic bacteria settle in a niche after a healthy microbiota, as well. Dysbiosis is an important trigger for the development of CRC. The gut microbiota is one of the components of the human immune system that provides surveillance over the appearance of unknown cells for the immune system, including cancer cells (11). It was proven that there is a faecal bacterial distinction between CRC patients and healthy individuals (15).

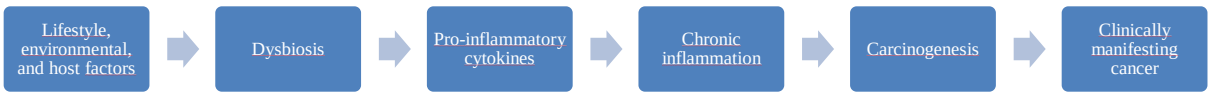

Figure 1. Process of development of colorectal cancer.

Materials and Methods:

A comprehensive literature search was conducted through the following databases: PubMed, Cochrane Library, Embase, and Google Scholar databases from database construction to August 1, 2024. The search terms involved the following keywords: 'antibiotics', 'antimicrobial drugs', 'antibacterial agents', 'colorectal', 'colon', 'rectal', 'cancer', 'malignancy', 'neoplasm', and 'neoplasia'. The search was not limited by language or region. Systematic reviews, meta-

analyses, clinical trials and observational studies were evaluated for eligibility. Studies were excluded if they were not human studies or did not assess antibiotic exposure or the development of colorectal neoplasia.

State of knowledge:

Use of antibiotics and risk of CRC

Most of the studies included in this review show that antibiotics increase the risk of CRC by approximately 10% (6,16–18). However, the relationship between antibiotic exposure and the appearance of CRC is not simple because it is influenced by the class of antibiotics, the location of the tumour, the time period between antibiotic exposure and diagnosis, the duration and intensity of antibiotic therapy.

Type of antibiotics and risk of CRC

Particular antibiotic classes are associated with different potential risks of CRC. The systematic review and meta-analysis conducted by Simin J. et al. provided evidence that cephalosporins (ES = 1.33, 95% CI: 1.15–1.52), nitroimidazoles (ES = 1.28, 95% CI: 1.10–1.49), quinolones (ES = 1.23, 95% CI: 1.17–1.29), sulfonamides (ES = 1.17, 95% CI: 1.14–1.20), penicillins (ES = 1.16, 95% CI: 1.07–1.25), and modestly macrolides and lincosamides (ES = 1.04, 95% CI: 1.00–1.08) increase the incidence of CRC. There was no clear connotation for other antibiotic classes studied. Broad-spectrum antibiotics, in contrast to narrow-spectrum ones, were risk factors for CRC (ES = 1.70, 95% CI: 1.26–2.30 and ES = 1.11, 95% CI: 0.93–1.32, respectively) (19). However, the results of other meta-analyses are not completely consistent with the results of the aforementioned paper. Weng L. et al. did not demonstrate an increased risk of CRC for quinolones (OR = 1.15, 95% CI: 0.95–1.39) and sulfonamides (OR = 1.06, 95% CI: 0.99–1.13) (20), while Qu G. et al. did not show a higher probability of CRC for cephalosporins (OR = 1.07, 95% CI: 0.99–1.16) and sulfonamides (OR = 1.07, 95% CI: 0.98–

1.16) (6). The differences between antibiotic classes in the risk of CRC are partially explicable. For example, quinolones are known to cause DNA damage (21) which is also an important mechanism of carcinogenesis (11). On the other hand, quinolones are type II topoisomerase inhibitors and microtubule inhibitors. Thus, this class of antibiotics presents cytotoxic activity against cancer cells (22). Regarding broad-spectrum antibiotics, they facilitate colonisation with pathogenic bacteria to a greater extent than narrow-spectrum antibiotics (23). Metronidazole in one meta-analysis was found to decrease the risk of CRC (OR = 0.82, 95% CI: 0.68–0.98) (20). Some preliminary studies suggest that metronidazole has anticancer properties. It represses tumour growth to some extent, supresses liver metastasis, and regulates the structure of intestinal flora (24).

Aneke-Nash C. et al. showed that the risk of CRC appears to be higher for anti-anaerobic agents compared to anti-aerobic agents. The risk of colon cancer in those who have ever used anti-anaerobic antibiotics is even twice as high as in never-users (ES = 2.31, 95% CI: 2.12–2.52) (16). This observation is biologically plausible because the human gastrointestinal tract is mostly colonised by anaerobic microbial flora. The most predominant are members of the genus *Bacteroides* and anaerobic gram-positive cocci, such as *Peptostreptococcus* sp., *Eubacterium* sp., *Lactobacillus* sp., and *Clostridium* sp. (25). Anti-anaerobic antibiotics exert a stronger effect on bacterial composition in the intestine, leading to dysregulation of the mucosal immune system (26). Surprisingly, one meta-analysis showed that the use of anti-aerobic antibiotics was associated with a lower risk of rectal cancer (OR = 0.93, 95% CI: 0.88–0.98) (6). However, this finding requires cautious interpretation due to the limited number of high-quality studies focused on the association between aerobic/anti-anaerobic antibiotics and colon and rectal cancer.

Sidedness of CRC

The current largest systematic review and meta-analysis by Weng L. et al., which consists of 5 164 138 patients, revealed that antibiotic use is associated with the risk of left colon cancer, but not with right colon cancer and rectal cancer (20). The reason for this difference could be a high degree of microbial activity, e.g. biofilm formation and fermentation in the distal colon (27). Another meta-analysis did not show an increased risk of colon or rectal cancer apart, only for CRC collectively (6). Other scientific reports show that there is a spatial differentiation of

the impact of the antibiotic class. For example, penicillins have been shown to increase the risk of developing cancer only in the proximal colon and not in more distal parts of the large intestine (28). A possible explanation for this observation is that the right colon is the site of the first exposure to penicillins. Subsequently, these drugs can undergo modification or degradation in the distal colon and rectum, diminishing their anti-anaerobic effects (29).

Time between antibiotic exposure and CRC diagnosis

The time it takes antibiotics to increase the risk of cancer is controversial. The study by Zhang J. et al. found that antibiotic use increases the risk of CRC only after 10 years (28). Another study showed that the risk of CRC was increased in individuals who used antibiotics between 3 and 8 years (ES = 1.37, 95% CI: 1.10 to 1.70) versus between 2 and 7 years prior to diagnosis (ES = 1.33, 95% CI: 1.08 to 1.64) (30). As is generally known, colorectal adenomas are precursor lesions to CRC. It takes about a decade for adenomas to develop in a malignant tumour (31). Cao Y. et al. showed that long-term use of antibiotics increases the risk of colorectal adenoma. The association is marginally stronger for left-sided adenomas than for distal adenomas, but similar for low-risk and high-risk ones (32). The most harmful seems to be the use of antibiotics in newborns and infants. This early exposure probably predisposes to many chronic diseases, including cancer (33). Preclinical experiments showed that antibiotic administration, especially in the first years of life, leads to loss of biological diversity in the gut microbiota and sustained metabolic derangements (34).

Duration of antibiotic exposure and CRC risk

The prolonged use of antibiotics seems to be more harmful than the short course of antibiotic therapy. Qu G. et al. proved that antibiotic use that exceeds 60 days increased the risk of CRC (OR = 1.22, 95% CI: 1.07–1.40). Similarly, prescribing more than five prescriptions for antibiotics compared to none was significantly associated with the incidence of CRC (OR = 1.39, 95% CI: 1.06–1.83) (6). Sanyaolu L. et al. showed that a higher exposure defined as more than six courses during the study period is associated with an increased risk of CRC (OR = 1.20, 95% CI: 1.10–1.32). (18)

Early-onset CRC

Early-onset CRC is defined primarily as the diagnosis in patients younger than 50 years of age. It accounts for approximately 10% of CRC cases and its prevalence is increasing, especially in wealthy countries (35). It should be noted that most risk factors for CRC exert their effect later in life. On the contrary, the association between antibiotic use and the incidence of CRC is expressed more strongly in younger people than in older people. Antibiotics are estimated to increase the risk of CRC by approximately 50% in people under 50 years of age. The results of a British case-control study based on a national clinical database showed that antibiotic consumption was associated with colon cancer, particularly in patients under 50 years of age (adjusted OR = 1.49, 95% CI: 1.07–2.07). No association was found with rectal cancer (36). The systematic review and meta-analysis by Weng L. et al. found that antibiotic use increases the risk of early-onset CRC (OR = 1.19, 95% CI: 1.07-1.30) (20). On the contrary, Nguyen et al. demonstrated that antibiotic exposure is not associated with the risk of early-onset CRC (37). From a health policy point of view, the implementation of earlier colonoscopy screening should be considered in high-risk patients with prior excessive antibiotic use.

Other cancers

The role of antibiotics in the morbidity of other cancers was also investigated. The results remain inconsistent. Petrelli F. et al. demonstrated that antibiotics increased the risk of breast, gastric, lung, pancreatic, bladder, renal, prostate, liver, and biliary tract cancers, but not oesophagus, uterine, ovarian, and cervix cancers. Antibiotics have even been shown to have a protective effect on ovarian and cervical cancers. In this latter even by 25% (17).

Basic data				
Author	Guangbo Qu et al.	Johanna Simin et al.	Chino Aneke-Nash et al.	Lifang Weng et al.
Year of publication	2020	2020	2021	2022
Databases searched	3	3	3	4

Time frame	inception - Nov 2019	inception - Feb 2020	inception - Dec 2019	inception - Jun 2020
Number of studies included	10		6	15
Types of studies included	2 cohort, 8 case-control	2 cohort, 8 case-control	2 cohort, 4 case control	2 cohort, 13 case-control
Number of patients	4 853 289	4 147 560	4 058 557	5 164 138
Risk of CRC – OR*/ES (95% CI)**				
All antibiotics	**1.09* (1.02-1.17)**	**1.17** (1.05–1.30)**	**1.10** (1.01-1.18)**	**1.11* (1.05–1.18)**
Anti-anaerobic antibiotics	**1.22* (1.04–1.44)**	N/A	N/A	**1.24* (1.02–1.52)**
Anti-aerobic antibiotics	1.03* (0.98–1.08)	N/A	N/A	1.07* (1.00–1.15)
Penicillins	**1.09* (1.04–1.13)**	**1.16** (1.07–1.25)**	N/A	**1.09* (1.02–1.16)**
Quinolones	**1.15* (1.03–1.35)**	**1.23** (1.17–1.29)**	N/A	1.15* (0.95–1.39)
Cephalosporins	1.07* (0.99–1.16)	**1.33** (1.15–1.52)**	N/A	**1.36* (1.02–1.82)**
Macrolides and lincosamides	1.02* (1.00–1.04)	1.04 (1.00–1.08)	N/A	1.03* (0.97–1.08)
Sulfonamides	1.07* (0.98–1.16)	**1.17** (1.14–1.20)**	N/A	1.06* (0.99–1.13)
Tetracyclines	0.99* (0.94–1.03)	0.97 (0.94, 1.00)	N/A	0.99* (0.92–1.07)
Nitroimidazoles and nitrofurans	1.06* (0.83–1.36)	**1.28** (1.10–1.49)**	N/A	1.08* (0.84–1.40)
Broad-spectrum antibiotics	N/A	**1.70** (1.26–2.30)**	N/A	N/A

Narrow-spectrum antibiotics	N/A	1.11 (0.93–1.32)	N/A	N/A
More than 60 days of antibiotic therapy	**1.22* (1.07–1.40)**	N/A	N/A	N/A
More than 5 prescriptions for antibiotics	**1.39* (1.06–1.83)**	N/A	N/A	N/A
Risk of colon cancer – OR*/ES (95% CI)**				
All antibiotics	1.07* (0.99–1.16)	1.06** (0.89–1.26)	1.06** (0.89 to 1.26)	**1.12* (1.03–1.21)**
Anti-anaerobic antibiotics	**1.28* (1.04–1.58)**	N/A	**2.31** (2.12 to 2.52)**	N/A
Anti-aerobic antibiotics	1.02* (0.98–1.05)	N/A	0.94** (0.79 to 1.12)	N/A
Penicillins	**1.09* (1.05–1.12)**	N/A	N/A	N/A
Quinolones	**1.09* (1.04–1.15)**	N/A	N/A	N/A
Cephalosporins	1.71* (0.69–4.23)	N/A	N/A	N/A
Macrolides and lincosamides	N/A	N/A	N/A	N/A
Sulfonamides	N/A	N/A	N/A	N/A
Tetracyclines	N/A	N/A	N/A	N/A
Nitroimidazoles and nitrofurans	N/A	N/A	N/A	N/A
Exposure to antibiotics more than 10 years before diagnosis	N/A	N/A	**1.17** (1.06 to 1.31)**	N/A
Exposure to antibiotics less than 10 years before diagnosis	N/A	N/A	1.00** (0.89-1.10)	N/A
Risk of rectal cancer – OR*/ES (95% CI)**				

All antibiotics	1.03* (0.92–1.16)	1.01** (0.96–1.06)	0.98** (0.80 to 1.20)	0.98* (0.89–1.08)
Anti-anaerobic antibiotics	1.07* (0.90–1.26)	N/A	N/A	N/A
Anti-aerobic antibiotics	**0.93* (0.88–0.98)**	N/A	N/A	N/A
Penicillins	1.17* (0.81–1.70)	N/A	N/A	N/A
Quinolones	0.92* (0.86–1.00)	N/A	N/A	N/A
Cephalosporins	1.40* (0.67–2.95)	N/A	N/A	N/A
Macrolides and lincosamides	N/A	N/A	N/A	N/A
Sulfonamides	N/A	N/A	N/A	N/A
Tetracyclines	N/A	N/A	N/A	N/A
Nitroimidazoles and nitrofurans	N/A	N/A	N/A	N/A

Table 1. Results of the most important systematic reviews with meta-analyses on the topic of antibiotic influence on CRC. Abbreviations: CRC – colorectal cancer, OR – odds ratio, ES – effect size, CI – confidence interval, N/A – not applicable. Bold font indicates statistical significance. Red font indicates an increased risk of cancer. Green font indicates a decreased risk of cancer.

Conclusions

In the literature, there are many studies on the relationship between antibiotic consumption and CRC development. The association between antibiotic use and CRC remains a topic of discussion. Recently, great progress has been made in understanding a variety of antibiotics-microbiota-cancer interactions. The systematic reviews and meta-analyses included in this article clarify current knowledge. Nevertheless, there are still unexplored issues, such as the comparison of the oral and parenteral antibiotics route of administration. The effect of antibiotics on malignant neoplasms in other sites also appears to be an interesting research direction. More research is needed to deepen our understanding of the contribution of antibiotic use to CRC. Actually, there are mainly observational studies that are not able to depict a causal

relationship. On the other hand, conducting randomised controlled trials in this research area seems to be a challenge. The large number of participants that should be followed for a long period limits the feasibility of clinical trials in this scientific field. Antibiotic stewardship should be of crucial importance and a priority in health policy. Clinicians should carefully consider the benefits and risks of prescribing antibiotics, including possible long-term adverse events such as cancer onset.

Disclosures

Author contribution: Conceptulization: Karol Zagórski and Mateusz Kozik; ***methodology:*** Nina Skalska-Dziobek; ***software:*** Weronika Małagocka; ***check:*** Karolina Chybowska; ***formal analysis:*** Maria Naruszewicz; ***investigation:*** Weronika Małagocka; ***resources:*** Przemysław Cetnarowski; ***data curation:*** Nina Skalska-Dziobek; ***writing – rough preparation:*** Karol Zagórski; ***writing – review and editing:*** Mateusz Kozik, Weronika Małagocka, Karolina Chybowska; ***visualization:*** Przemysław Cetrnarowski; ***supervision:*** Maria Naruszewicz; ***project administration:*** Weronika Małagocka.

All authors have read and agreed with the final, published version of the manuscript.

Funding statement: No external funding was received to perform this review.

Institutional Review Board Statement: Not applicable – this review included analysis of the available literature.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflict of interest: The authors declare no conflict of interest.

References:

1. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023 Jan;73(1):17–48. https://doi.org/10.3322/caac.21763
2. Didkowska J, Wojciechowska U, Barańska K, Miklewska M, Irmina Michałek, Olasek

P. Nowotwory złośliwe w Polsce w 2021 roku (Cancer in Poland in 2021). Warszawa; 2023. Report No.: ISSN 0867-8251.

3. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017 Apr;66(4):683–91. https://doi.org/10.1136/gutjnl-2015-310912

4. Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. Nat Rev Gastroenterol Hepatol. 2019 Dec;16(12):713–32. https://doi.org/10.1038/s41575-019-0189-8

5. Wong CC, Yu J. Gut microbiota in colorectal cancer development and therapy. Nat Rev Clin Oncol. 2023 Jul;20(7):429–52. https://doi.org/10.1038/s41575-019-0189-8

6. Qu G, Sun C, Sharma M, Uy JP, Song EJ, Bhan C, et al. Is antibiotics use really associated with increased risk of colorectal cancer? An updated systematic review and meta-analysis of observational studies. Int J Colorectal Dis. 2020 Aug;35(8):1397–412. https://doi.org/10.1007/s00384-020-03658-z

7. Browne AJ, Chipeta MG, Haines-Woodhouse G, Kumaran EPA, Hamadani BHK, Zaraa S, et al. Global antibiotic consumption and usage in humans, 2000–18: a spatial modelling study. Lancet Planet Health. 2021 Dec;5(12):e893–904. https://doi.org/10.1016/S2542-5196(21)00280-1

8. Pulingam T, Parumasivam T, Gazzali AM, Sulaiman AM, Chee JY, Lakshmanan M, et al. Antimicrobial resistance: Prevalence, economic burden, mechanisms of resistance and strategies to overcome. Eur J Pharm Sci. 2022 Mar;170:106103. https://doi.org/10.1016/j.ejps.2021.106103

9. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci. 2018 Apr 10 ;115(15). https://doi.org/10.1073/pnas.1717295115

10. Huang F, Teng K, Liu Y, Cao Y, Wang T, Ma C, et al. Bacteriocins: Potential for Human Health. Qin S, editor. Oxid Med Cell Longev. 2021 Jan;2021(1):5518825. https://doi.org/10.1155/2021/5518825

11. Hanahan D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022 Jan 1;12(1):31–46. https://doi.org/10.1158/2159-8290.CD-21-1059

12. Liou GY, Storz P. Reactive oxygen species in cancer. Free Radic Res. 2010 Jan;44(5):479–96. https://doi.org/10.3109/10715761003667554

13. Bullman S, Pedamallu CS, Sicinska E, Clancy TE, Zhang X, Cai D, et al. Analysis of *Fusobacterium* persistence and antibiotic response in colorectal cancer. Science. 2017 Dec 15;358(6369):1443–8. https://doi.org/10.1126/science.aal5240

14. Wang N, Fang JY. Fusobacterium nucleatum, a key pathogenic factor and microbial biomarker for colorectal cancer. Trends Microbiol. 2023 Feb;31(2):159–72. https://doi.org/10.1016/j.tim.2022.08.010

15. Wang T, Cai G, Qiu Y, Fei N, Zhang M, Pang X, et al. Structural segregation of gut microbiota between colorectal cancer patients and healthy volunteers. ISME J. 2012 Feb 1;6(2):320–9. https://doi.org/10.1038/ismej.2011.109

16. Aneke-Nash C, Yoon G, Du M, Liang P. Antibiotic use and colorectal neoplasia: a systematic review and meta-analysis. BMJ Open Gastroenterol. 2021 Jun;8(1):e000601. https://doi.org/10.1136/bmjgast-2021-000601

17. Petrelli F, Ghidini M, Ghidini A, Perego G, Cabiddu M, Khakoo S, et al. Use of Antibiotics and Risk of Cancer: A Systematic Review and Meta-Analysis of Observational Studies. Cancers. 2019 Aug 14;11(8):1174. https://doi.org/10.3390/cancers11081174

18. Sanyaolu LN, Oakley NJ, Nurmatov U, Dolwani S, Ahmed H. Antibiotic exposure and the risk of colorectal adenoma and carcinoma: a systematic review and meta-analysis of observational studies. Colorectal Dis. 2020 Aug;22(8):858–70. https://doi.org/10.1111/codi.14921

19. Simin J, Fornes R, Liu Q, Olsen RS, Callens S, Engstrand L, et al. Antibiotic use and risk of colorectal cancer: a systematic review and dose–response meta-analysis. Br J Cancer. 2020 Dec 8;123(12):1825–32. https://doi.org/10.1038/s41416-020-01082-2

20. Weng L, Jin F, Shi J, Qiu Z, Chen L, Li Q, et al. Antibiotics use and risk of colorectal neoplasia: An updated meta-analysis. Int J Colorectal Dis. 2022 Nov 3;37(11):2291–301. https://doi.org/10.1007/s00384-022-04276-7

21. Bush NG, Diez-Santos I, Abbott LR, Maxwell A. Quinolones: Mechanism, Lethality and Their Contributions to Antibiotic Resistance. Molecules. 2020 Dec 1;25(23):5662. https://doi.org/10.3390/molecules25235662

22. Gao F, Zhang X, Wang T, Xiao J. Quinolone hybrids and their anti-cancer activities: An overview. Eur J Med Chem. 2019 Mar;165:59–79. https://doi.org/10.1016/j.ejmech.2019.01.017

23. Hibberd AA, Lyra A, Ouwehand AC, Rolny P, Lindegren H, Cedgård L, et al. Intestinal

microbiota is altered in patients with colon cancer and modified by probiotic intervention. BMJ Open Gastroenterol. 2017 Jul;4(1):e000145. https://doi.org/10.1136/bmjgast-2017-000145

24. Wang M, Li Y, Yang X, Liu Z, Wang K, Gong D, et al. Effects of metronidazole on colorectal cancer occurrence and colorectal cancer liver metastases by regulating *Fusobacterium nucleatum* in mice. Immun Inflamm Dis. 2023 Nov;11(11):e1067. https://doi.org/10.1002/iid3.1067

25. Gorbach S. Microbiology of the Gastrointestinal Tract. In: Medical Microbiology 4th edition. University of Texas Medical Branch at Galveston: Galveston (TX); 1996.

26. Langdon A, Crook N, Dantas G. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. Genome Med. 2016 Dec;8(1):39. https://doi.org/10.1186/s13073-016-0294-z

27. Lu SSM, Mohammed Z, Häggström C, Myte R, Lindquist E, Gylfe Å, et al. Antibiotics Use and Subsequent Risk of Colorectal Cancer: A Swedish Nationwide Population-Based Study. JNCI J Natl Cancer Inst. 2022 Jan 11;114(1):38–46. https://doi.org/10.1093/jnci/djab125

28. Zhang J, Haines C, Watson AJM, Hart AR, Platt MJ, Pardoll DM, et al. Oral antibiotic use and risk of colorectal cancer in the United Kingdom, 1989–2012: a matched case–control study. Gut. 2019 Nov;68(11):1971–8. https://doi.org/10.1136/gutjnl-2019-318593

29. Boursi B, Haynes K, Mamtani R, Yang YX. Impact of antibiotic exposure on the risk of colorectal cancer: ANTIBIOTIC EXPOSURE AND CRC RISK. Pharmacoepidemiol Drug Saf. 2015 May;24(5):534–42. https://doi.org/10.1002/pds.3765

30. Dik VK, Van Oijen MGH, Smeets HM, Siersema PD. Frequent Use of Antibiotics Is Associated with Colorectal Cancer Risk: Results of a Nested Case–Control Study. Dig Dis Sci. 2016 Jan;61(1):255–64. https://doi.org/10.1007/s10620-015-3828-0

31. Hossain MdS, Karuniawati H, Jairoun AA, Urbi Z, Ooi DJ, John A, et al. Colorectal Cancer: A Review of Carcinogenesis, Global Epidemiology, Current Challenges, Risk Factors, Preventive and Treatment Strategies. Cancers. 2022 Mar 29;14(7):1732. https://doi.org/10.3390/cancers14071732

32. Cao Y, Wu K, Mehta R, Drew DA, Song M, Lochhead P, et al. Long-term use of antibiotics and risk of colorectal adenoma. Gut. 2017 Apr 4;gutjnl-2016-313413. https://doi.org/10.1136/gutjnl-2016-313413

33. Yallapragada SG, Nash CB, Robinson DT. Early-Life Exposure to Antibiotics,

Alterations in the Intestinal Microbiome, and Risk of Metabolic Disease in Children and Adults. Pediatr Ann. 2015 Nov;44(11). https://doi.org/10.3928/00904481-20151112-09

34. Cho I, Yamanishi S, Cox L, Methé BA, Zavadil J, Li K, et al. Antibiotics in early life alter the murine colonic microbiome and adiposity. Nature. 2012 Aug;488(7413):621–6. https://doi.org/10.1038/nature11400

35. Wu CWK, Lui RN. Early-onset colorectal cancer: Current insights and future directions. World J Gastrointest Oncol. 2022 Jan 15;14(1):230–41. https://doi.org/10.4251/wjgo.v14.i1.230

36. McDowell R, Perrott S, Murchie P, Cardwell C, Hughes C, Samuel L. Oral antibiotic use and early-onset colorectal cancer: findings from a case-control study using a national clinical database. Br J Cancer. 2022 Apr 1;126(6):957–67. https://doi.org/10.1038/s41416-021-01665-7

37. Nguyen LH, Cao Y, Batyrbekova N, Roelstraete B, Ma W, Khalili H, et al. Antibiotic Therapy and Risk of Early-Onset Colorectal Cancer: A National Case-Control Study. Clin Transl Gastroenterol. 2022 Jan;13(1):e00437. https://doi.org/10.14309/ctg.0000000000000437