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REVIEW

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Effects of antibiotic exposure on risks of colorectal tumors: a systematic review and meta-analysis

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Abstract

Background Increasing evidence suggests that the gut microbiome may play an important role in the development of colorectal tumors. Antibiotic use can affect the gut microbiome and may increase the risks of benign and malignant colorectal tumors.

Methods Eligible studies assessing the relationship between antibiotic exposure and the risk of developing benign or malignant colorectal tumors were identified. Odds ratios (ORs) were pooled for antibiotic use versus no use using a random-effects model. Further subgroup and sensitivity analyses were conducted to confirm the consistence and robustness of the main findings. The study protocol was registered with PROSPERO.

Results Twenty-three studies including 1,145,853 participants were finally included in the analysis. People who had used antibiotics had a 13% increased risk of colorectal tumors compared with those who had never used antibiotics [OR: 1.13; 95% confidence interval (CI) 1.04–1.22; P < 0.01]. Subgroup analysis showed that antibiotic exposure was associated with increased risks of both benign (OR: 1.13; 95% CI 1.00–1.27; P < 0.01) and malignant colorectal tumors (OR: 1.13; 95% CI 1.03–1.23; P < 0.01). In addition, colorectal tumor risk was significantly increased by antibiotic exposure, especially the use of combined antibiotics and a longer period after antibiotic exposure. The main findings were consistent and robust across most subgroups and sensitivity analyses.

Conclusions The current findings suggested that antibiotic use increased the risk of developing benign or malignant colorectal tumors. These results highlighted the need for clinicians to prescribe antibiotics cautiously, to reduce colorectal cancer risk.

Keywords Antibiotic exposure, Colorectal tumor, Benign and malignant tumor, Cancer risk

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Background

Colorectal cancer is the third most prevalent and second most lethal malignancy globally, affecting approximately two million individuals [1, 2]. Emerging evidence implicates the gut microbiota as a crucial factor in colorectal tumorigenesis [3]. Antibiotics are known to alter the composition of the gut microbiota. They can reduce bacterial diversity and disrupt the microbial balance, thereby impairing essential physiological functions, such as energy metabolism and immune regulation, which can in turn contribute to tumorigenesis [4, 5]. Conversely however, infections also constitute a notable risk factor for cancer development [6], suggesting that antibiotics might mitigate tumor risk by combating infections.

Previous studies have explored the association between antibiotic exposure and the risk of colorectal tumors [7–10]; however, these meta-analyses only reported on malignant tumors in a limited number of studies, and the association between antibiotic exposure and the risk of benign colorectal tumors thus remains unclear. In addition, although recent studies have reported on the associations between antibiotic exposure and the risk of colorectal tumors, the results have been controversial [11–18], and the precise relationship between past antibiotic exposure and future colorectal tumor risk remains unclear. Here, we performed a comprehensive meta-analysis to examine the associations between antibiotic exposure and benign and malignant colorectal tumors.

Methods

We assessed the association between antibiotic exposure and the risk of developing colorectal tumors. Odds ratios (ORs) were summarized for antibiotic use compared with no antibiotic use using a random-effects model. The protocol was registered with the Prospective Register of Systematic Reviews (PROSPERO, CRD42024596495). This meta-analysis was reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Assessing the Methodological Quality of Systematic Reviews (AMSTAR-2) guidelines [19, 20] (Supplementary Materials 1–2).

Eligibility criteria

All articles reporting the association between antibiotic exposure and the risk of colorectal tumors were considered relevant. Studies were considered to be eligible if they met the following criteria: (1) population: all types of populations, with no restrictions on age, country, and sex; (2) exposure: any past or present antibiotic exposure; (3) comparison: healthy participants with no past or present antibiotic exposure; (4) outcomes: colorectal tumors (benign or malignant), expressed in terms of number of events or an estimate (hazard ratio [HR], risk ratio [RR], or OR); and (5) type of study: cohort or case–control study. Studies were excluded if they fulfilled the inclusion criteria but did not report the number of events or an estimate (HR, RR, or OR), or if they had insufficient data, use of antibiotics to prevent postoperative infection, if they reported animal experiments, other tumors, or other diseases, or if they were comments or reviews. In this study, colorectal malignant tumors were specifically defined as colorectal cancers, whereas colorectal adenomas and polyps, comprising both conventional adenomas and serrated polyps, were defined as benign tumors (Supplemental Table 2).

Data sources and literature search

We conducted a comprehensive search of the PubMed and Embase databases from their inception up to August 31, 2024. The search strategy was divided into three main components: (1) antibiotic use, (2) colorectal tumors, and (3) tumor risk, followed by combinations of synonym substitutions. The comprehensive search strategies are delineated in Supplemental Table 1. To enhance the search scope, reference materials were also systematically reviewed. Retrieved articles underwent rigorous screening to assess their eligibility for inclusion. Conference abstracts were also scrutinized to identify and consider potential unpublished studies.

Study selection

Two authors independently selected original literature using relevant search terms, and carefully read the full text to assess the relevance of each study.

Data extraction

Two authors independently extracted the following data from all the included studies, according to a standardized procedure: first author, year of publication, country, database, study period, number of participants, antibiotic types, number of events in each group, follow-up years, adjusted covariates, and study design. A third author reviewed the data and any discrepancies were resolved through discussion and consensus.

Quality assessment

Two authors independently assessed the quality of the included studies using the Newcastle–Ottawa Scale (NOS) for cohort design. All studies were systematically evaluated for participant selection, measurement of exposure, comparability, assessment of outcomes, and adequacy of follow-up. The studies were then classified

into three quality categories: high (7–9), moderate (4–6), or low (0–3).

Statistical analysis

The ORs and their corresponding 95% confidence intervals (CIs) were pooled to compare the association between antibiotic exposure (use versus no use, with no use as the reference group) and the risk of developing colorectal tumors. In this study, we extracted all reported OR values (adjusted and unadjusted) from the original studies. We preferentially used adjusted ORs for the primary analysis, but if these were not provided, then unadjusted ORs were used instead. Random-effect models were applied to account for potential clinical heterogeneity across all the included studies. Heterogeneity across studies was evaluated using the Q statistic (I^2 and P value), with I^2 values < 25%, 25%–50%, and > 50% categorized as low, moderate, and high, respectively. A P value < 0.05 was considered statistically significant. All statistical analyses were conducted using RStudio software, version 4.4.1 (available at: https://www.rstudio.com/products/rstudio/download/).

Subgroup analyses

We further confirmed the robustness of the findings by conducting subgroup analyses according to patient type (malignant and benign), tumor location (colon, rectum, and mixed), sample size (> 5,000 and < 5,000), country (Western and Eastern), antibiotic type (combined and single antibiotics), study design (case–control and cohort study), adjusted estimates (yes and no), study period (after 2020 and before 2020), NOS comparability (= 2 and < 2), and follow-up (≥ 5 years, < 5 years, and not reported).

Sensitivity analyses

We conducted sensitivity analyses focusing on studies with large sample sizes (> 1000), studies in Western countries, studies of early-onset tumors, antibiotic combinations, adjusted ORs, cohort studies, study periods during 2014–2024, nationwide database, NOS scores ≥ 7, NOS comparability = 2, and follow-up > 3 years. We also performed sensitivity analyses for all the subgroup analyses by including only high-quality studies (NOS score ≥ 7) and using the leave-one-out method.

Publication bias

We assessed potential publication bias by mapping funnel plots using Begg's and Egger's tests. The trim and fill method was further applied to estimate the potential missing studies, and the pooled OR was re-calculated after adding the potential missing studies [21].

Results

After removing 138 duplicates, 5118 studies remained. Among these, 5070 were discarded after reviewing the titles and abstracts and 48 studies were assessed for eligibility. Twenty-five of these were excluded because of insufficient data, use of antibiotics to prevent postoperative infection, or because they involved animal experiments, other tumors or other diseases, or were comments. Finally, 23 studies were included in this study [11–18, 22–36]. Details of the literature search and study selection are shown in Fig. 1.

Study characteristics

The characteristics of the 23 included studies are shown in Supplemental Table 2. The number of participants ranged from 139–243,265, with a total of 1,145,853 participants. Six studies were retrospective cohort studies and 17 were case–control studies. The adjusted factors incorporated in the studies included age, sex, smoking status, alcohol consumption, physical activity, body mass index, family history, and dietary habits. The specific adjusted factors varied among studies. Detailed information on the adjusted factors for OR are shown in Supplemental Table 3. Study quality assessed using the NOS is shown in Supplemental Table 4. The average NOS score was 7.5, indicating a high quality of the included studies.

Antibiotic exposure and risk of colorectal tumors

Twenty-three studies with available data were included in the quantitative analysis. Past or current antibiotic use was significantly associated with an increased risk of developing colorectal tumors (OR: 1.13; 95% CI 1.04–1.22; P < 0.01), suggesting that people who had ever used antibiotics had a 13% increased risk of colorectal tumors compared with those who had never used antibiotics (Fig. 2).

Subgroup analyses

The risks of malignant (OR: 1.13; 95% CI 1.03–1.23) and benign colorectal tumors (OR: 1.13; 95% CI 1.00–1.27) were both significantly increased by 13% after antibiotic use compared with no antibiotic use (Table 1, Supplemental Fig. 1).

Compared with no antibiotic exposure, antibiotic use significantly increased the risk of colon tumors by 13% (OR: 1.13; 95% CI 1.03–1.25) (Table 1, Supplemental Fig. 2). Antibiotic use increased the risk of

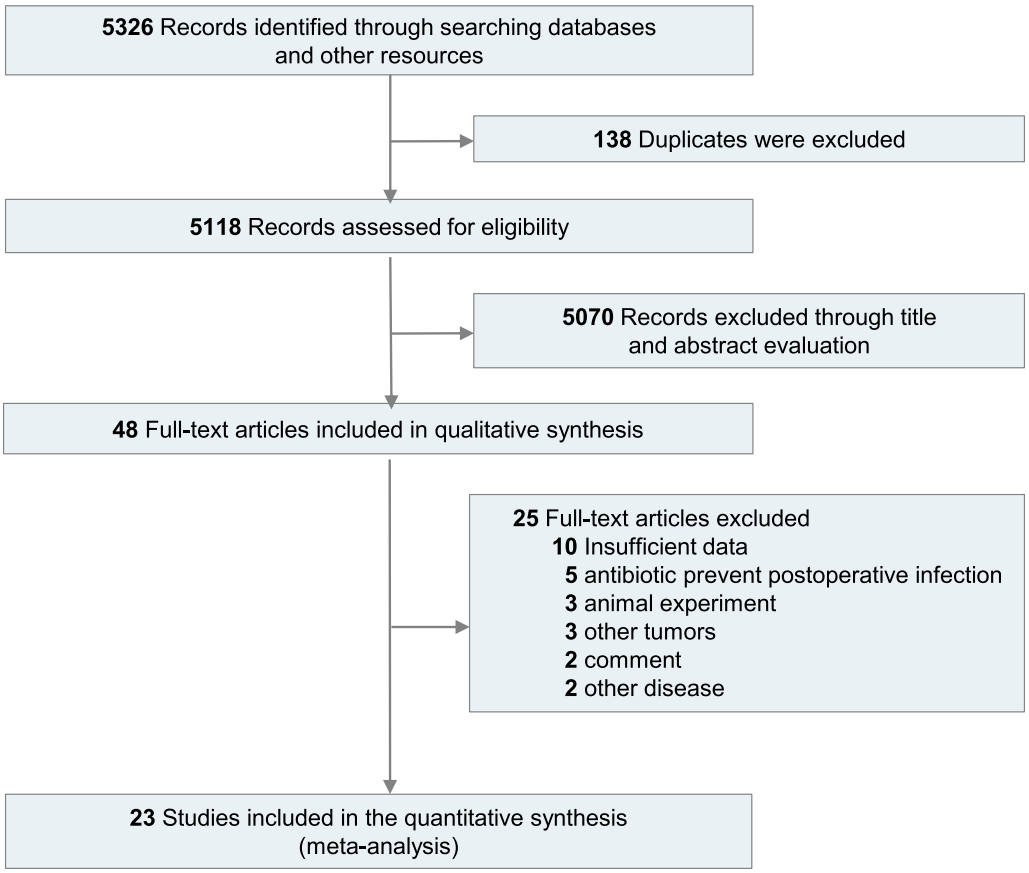

Fig. 1 Flowchart of literature search and study selection

colorectal tumors by 17% in studies with a sample size > 5000 (OR: 1.17; 95% CI 1.07–1.27), by 13% in studies from Western countries (OR: 1.13; 95% CI 1.04–1.23), by 15% in studies with combined antibiotics (OR: 1.15; 95% CI 1.07–1.24), by 11% in case–control studies (OR: 1.11; 95% CI 1.02–1.21), by 23% in cohort studies (OR: 1.23; 95% CI 1.06–1.42), by 15% in studies with adjusted estimates (OR: 1.14; 95% CI 1.00–1.30), and by 10% in studies with unadjusted estimates (OR: 1.10; 95% CI 1.05–1.15) (Table 1, Supplemental Figs. 3–7). Similar results were found for studies conducted after 2020 (OR: 1.10; 95% CI 1.04–1.16) and before 2020 (OR: 1.14; 95% CI 1.00–1.30), in studies with NOS comparability of 2 (OR: 1.17; 95% CI 1.04–1.32), and in studies with a follow-up > 5 years (OR: 1.14; 95% CI 1.01–1.29) (Table 1, Supplemental Fig. 8–10). Antibiotic use increased the risk of colorectal tumors by 17% in studies with a duration of antibiotic use > 14 days (OR: 1.17; 95% CI 1.01–1.36) (Table 1, Supplemental Fig. 11). Antibiotic use also increased the risk of colorectal tumors by 21% in studies with one to four antibiotic prescriptions (OR: 1.21; 95% CI 1.00–1.45), by 72% in studies with five to 10 antibiotic prescriptions (OR: 1.72; 95% CI 1.03–2.88), and by 103% in studies with > 10 antibiotic prescriptions (OR: 2.03; 95% CI 1.91–2.15) (Table 1, Supplemental Fig. 12).

Subgroup analysis demonstrated consistent results. The pooled estimate using only adjusted ORs was 1.14 (95% CI 1.00–1.30), while the estimate for the analysis restricted to unadjusted ORs was 1.10 (95% CI 1.05–1.15). Both findings showed high concordance with the overall analysis result (OR: 1.13; 95% CI 1.04–1.22).

Sensitivity analyses

Compared with no antibiotic exposure, antibiotic use significantly increased the risk of colorectal tumors in sensitivity analyses in studies with a large sample size, in Western countries, early-onset tumors, antibiotic combinations, adjusted estimates, cohort studies, studies conducted between 2014–2024, nationwide databases, NOS scores ≥ 7, NOS comparability = 2, and follow-up > 3 years. In addition, sensitivity analyses using the leave-one-out method achieved consistent ORs, ranging from 1.09 (95% CI 1.04–1.14) to 1.14 (95% CI 1.06–1.23)

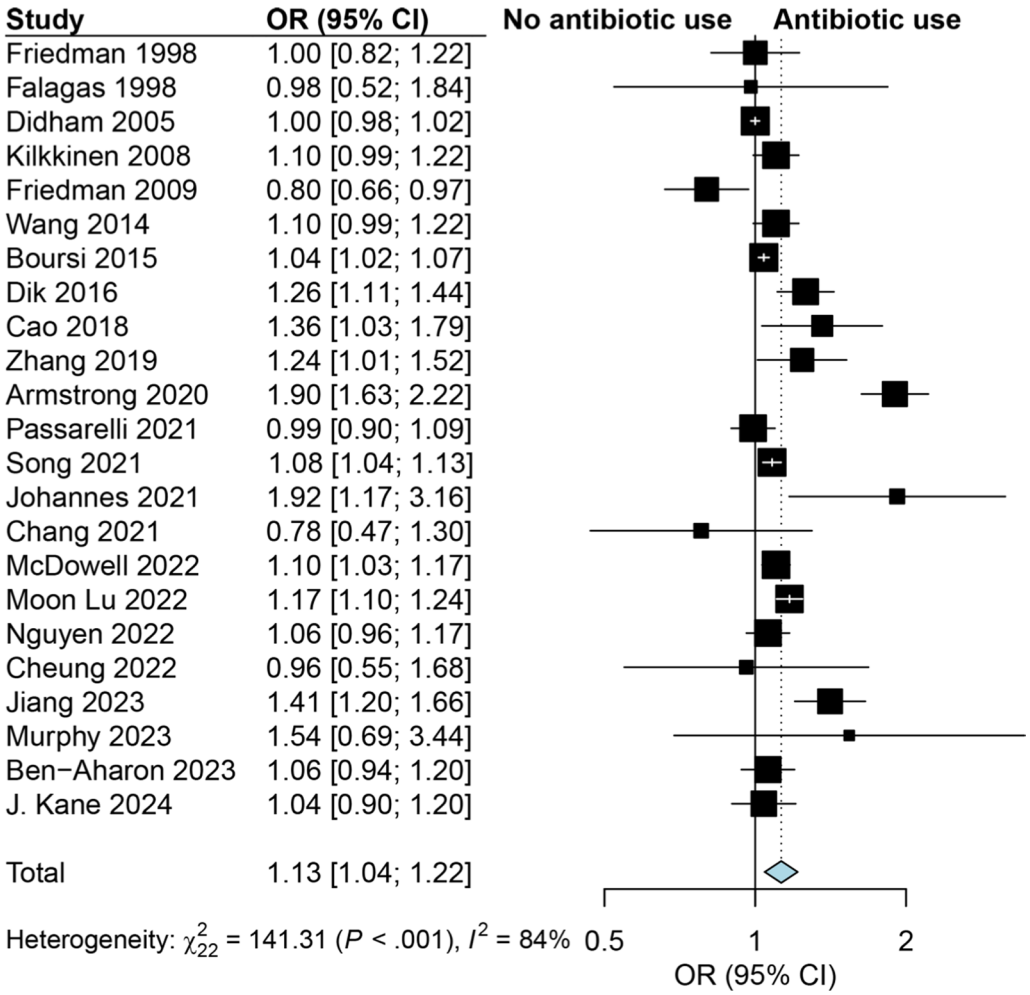

Fig. 2 Forest plot of relationship between antibiotic exposure and the risk of colorectal tumors

(Table 2) (Supplemental Figs. 13–24), indicating that the current findings were robust.

To address potential concerns regarding article quality, we performed sensitivity analyses for all the subgroup analyses by including only articles with an NOS score ≥7. The risks of malignant (OR: 1.13; 95% CI 1.03–1.24) and benign colorectal tumors (OR: 1.13; 95% CI 1.00–1.27) were both significantly increased by 13% after antibiotic use compared with no antibiotic use (Supplemental Table 5, Supplemental Fig. 25). Antibiotic use significantly increased the risk of colon tumors by 13% compared with no antibiotic exposure (OR: 1.13; 95% CI 1.02–1.25) (Supplemental Table 5, Supplemental Fig. 26). Antibiotic use also increased the risk of colorectal tumors by 16% in studies with a sample size >5000 (OR: 1.16; 95% CI 1.00–1.26), by 13% in studies from Western countries (OR: 1.13; 95% CI 1.04–1.23), by 16% in studies with combined antibiotics (OR: 1.16; 95% CI 1.07–1.25), by 11% in case–control studies (OR: 1.11; 95% CI 1.02–1.21), by 23% in cohort studies (OR: 1.23; 95% CI 1.06–1.42), and by 13% in studies with unadjusted estimates (OR: 1.10; 95% CI 1.05–1.15) (Supplemental Table 5, Supplemental Figs. 27–31). Similar results were found for studies conducted after 2020 (OR: 1.10; 95% CI 1.04–1.16) and before 2020 (OR: 1.16; 95% CI: 1.00–1.34), in studies with NOS comparability of 2 (OR: 1.17; 95% CI 1.04–1.32), and in studies with a follow-up >5 years (OR: 1.14; 95% CI 1.01–1.29) (Supplemental Table 5, Supplemental Figs. 32–34).

Publication bias

The 23 studies included in the quantitative meta-analysis showed no evidence of publication bias based on Begg's test (P =0.8119) (effect size: 3.05; 95% CI 2.81–3.31) (Fig. 3A). Furthermore, trim-and-fill analysis revealed that six potential studies were absent. After filling, the refitted data (effect size: 2.82; 95% CI

Table 1 Subgroup analyses of relationships between sometime antibiotic exposure and future risks of benign and malignant colorectal tumors

Group/subgroup	No. studies	Test of heterogeneity		OR (95% CI)
		I^2 value	*P* value	
Patient types				
Malignant	20	85%	< 0.01	1.13 (1.03–1.23)
Benign	5	72%	< 0.01	1.13 (1.00–1.27)
Location				
Colon	9	76%	< 0.01	1.13 (1.03–1.25)
Rectum	7	87%	< 0.01	0.96 (0.83–1.10)
Mix (colon and rectum)	14	88%	< 0.01	1.18 (1.04–1.33)
Sample size				
> 5000	18	84%	< 0.01	1.17 (1.07–1.27)
< 5000	5	0%	0.92	1.00 (0.98–1.02)
Country				
Western	21	86%	< 0.01	1.13 (1.04–1.23)
Eastern	2	0%	0.64	1.09 (0.99–1.21)
Antibiotics type				
Combination antibiotics	20	86%	< 0.01	1.15 (1.07–1.24)
Single antibiotic	3	21%	0.28	0.90 (0.74–1.09)
Study design				
Case–control study	17	87%	< 0.01	1.11 (1.02–1.21)
Cohort study	6	42%	0.13	1.23 (1.06–1.42)
Adjusted estimates				
Yes	13	91%	< 0.01	1.14 (1.00–1.30)
No	10	39%	0.1	1.10 (1.05–1.15)
Study period				
After 2020	12	59%	< 0.01	1.10 (1.04–1.16)
Before 2020	11	90%	< 0.01	1.14 (1.00–1.30)
NOS comparability				
= 2	12	83%	< 0.01	1.17 (1.04–1.32)
< 2	11	75%	< 0.01	1.07 (0.99–1.15)
Follow-up period				
≥ 5 years	11	88%	< 0.01	1.14 (1.01–1.29)
< 5 years	3	41%	0.18	1.05 (0.96–1.14)
Not reported	9	74%	< 0.01	1.15 (1.00–1.31)
Duration of antibiotic use				
> 14 days	3	68%	0.04	1.17 (1.01–1.36)
≤ 14 days	3	60%	0.08	1.08 (0.97–1.20)
Others	20	86%	< 0.01	1.13 (1.03–1.23)
Number of prescriptions				
1–4	2	39%	0.2	1.21 (1.00–1.45)
5–10	2	93%	< 0.01	1.72 (1.03–2.88)
> 10	2	0	0.83	2.03 (1.91–2.15)
Others	21	74%	< 0.01	1.08 (1.04–1.13)

CI confidence interval, *No.* number, *OR* odds ratio

2.52–3.15) remained consistent with the above findings (Fig. 3B), suggesting no evidence of publication bias in the study.

Comparison with previous studies

The current study provides novel findings compared with previous meta-analyses. Our findings contradict those of a previous meta-analysis, which concluded that antibiotic exposure was not significantly associated with the risk of colorectal adenoma or cancer (OR: 1.06; 95% CI 0.93–1.22) [8], while our updated analysis, which incorporated 15 additional studies and employed more stringent subgroup and sensitivity analyses, demonstrated a significant association between antibiotic exposure and the risks of both benign and malignant colorectal tumors. This discrepancy may be attributed to the inclusion of the 15 additional recent studies, which provided updated evidence on the association between antibiotics and colorectal tumors. In addition, our subgroup and sensitivity analyses substantially reduced heterogeneity, thereby enhancing the robustness of our conclusions.

Unlike previous meta-analyses that exclusively examined malignant tumors [7, 9, 10], the current study specifically evaluated the impact of antibiotic exposure on benign colorectal tumors. The results indicated that antibiotic exposure was associated with increased risks of both malignant and benign colorectal tumors. This finding suggests that the long-term effects of antibiotics may already manifest during the benign stage, for instance, by inducing gut microbiota dysbiosis, thereby influencing the development of benign tumors and their progression to colorectal cancer. This finding highlights the need for more stringent clinical evaluation of prolonged antibiotic use and supports enhanced endoscopic surveillance in individuals with long-term antibiotic exposure.

Our research demonstrated other novel findings. Combined antibiotic therapy was associated with a higher risk of colorectal neoplasia compared with monotherapy, while the risk of colorectal tumors was increased by antibiotic usage for >14 days (OR: 1.17; 95% CI 1.01–1.36) and by an increase in the number of prescriptions. The risk of colorectal tumors increased with increasing cumulative antibiotic prescriptions, with the highest risk in patients with >10 prescriptions (OR: 2.03; 95% CI 1.91–2.15), followed by five to 10 (OR: 1.72; 95% CI: 1.03–2.88) and one to four prescriptions (OR: 1.21; 95% CI 1.00–1.45). The specific details for comparison with previous meta-analyses are provided in Supplementary Table 6.

Table 2 Sensitivity analyses of relationships between sometime antibiotic exposure and future risks of benign and malignant colorectal tumors

Subgroup	No. of studies	Test of heterogeneity		OR (95% CI)
		I^2 value	*P* value	
Sample size > 1000	19	83%	< 0.01	1.15 (1.06–1.26)
Western country	21	86%	< 0.01	1.13 (1.04–1.23)
Early-onset tumors	3	76%	0.02	1.25 (1.02–1.53)
Antibiotic combination	20	86%	< 0.01	1.15 (1.07–1.24)
Adjusted odds ratio	12	91%	< 0.01	1.15 (1.00–1.33)
Cohort study	6	42%	0.13	1.23 (1.06–1.42)
Study period during 2014–2024	18	83%	< 0.01	1.17 (1.08–1.27)
Nation-wide database	12	91%	< 0.01	1.20 (1.08–1.33)
NOS score ≥ 7	20	82%	< 0.01	1.13 (1.04–1.22)
NOS comparability = 2	12	83%	< 0.01	1.17 (1.04–1.32)
Follow-up longer than 3 years	13	86%	< 0.01	1.13 (1.02–1.25)

CI confidence interval, *No.* number, *OR* odds ratio

Discussion

This meta-analysis evaluated the correlation between sometime antibiotic exposure and the risk of future benign or malignant colorectal tumors. This study revealed that people who had ever used antibiotics had a 13% higher risk of developing either benign or malignant colorectal tumors compared with those without antibiotic use. The influence of antibiotic use on colorectal tumor risk remained consistent and robust across various subgroups. A comprehensive compilation of 23 studies was integrated into the present study to conduct enriched subgroup and rigorous sensitivity analyses. Despite heterogeneity in adjustment statuses across primary studies, multiple subgroup and sensitivity analyses confirmed that this variation did not significantly affect the pooled effect size, thereby enhancing the robustness of the conclusions. The findings of this meta-analysis thus demonstrated enhanced reliability and robustness compared with previous meta-analyses [7–10].

We found that current or past antibiotic use was associated with an increased risk of colon cancer, rather than rectal cancer. This discrepancy may be closely linked to differences in microbiota concentrations between the colon and rectum, with higher microbial density and metabolic activity in the colon [37, 38]. The type of antibiotic regimen was also a significant factor affecting tumor risk, with combined, but not single antibiotic use correlated with an elevated tumor risk. This could be attributed to the broader antibacterial spectrum of combination therapies, which can excessively disrupt gut microbiota and undermine anti-inflammatory microbial functions, thus increasing pathogenic bacteria and facilitating tumorigenesis [39, 40].

Regarding the follow-up duration after antibiotic exposure, analyses with periods > 5 years were significantly correlated with tumor risk, whereas shorter follow-up periods were not significantly correlated, possibly because of the estimated 8–10-year latency period of colorectal tumors [27]. An inadequate follow-up period may prematurely truncate the findings, leading to a higher incidence of negative outcomes and thus affecting the study conclusions; however, further studies are needed to assess the influence of body mass index within the subgroup analysis and to assess the association between sex and tumor risk.

This study had some limitations. First, there was substantial heterogeneity among the included studies, possibly attributable to differences in study designs, confounding factors, adjusted and unadjusted estimates, antibiotic types and doses, antibiotic duration and frequency, and the timing of antibiotic exposure. Second, the trim-and-fill funnel plot suggested that six potential studies were absent; however, it is hard to rule out the existence of publication bias. Third, none of the included studies reported data on antibiotic dose and exposure timing, and we were therefore unable to analyze their impacts. Further studies are required to investigate these factors. Although the above limitations may have affected the findings, multiple subgroup and sensitivity analyses demonstrated the robustness of the main findings.

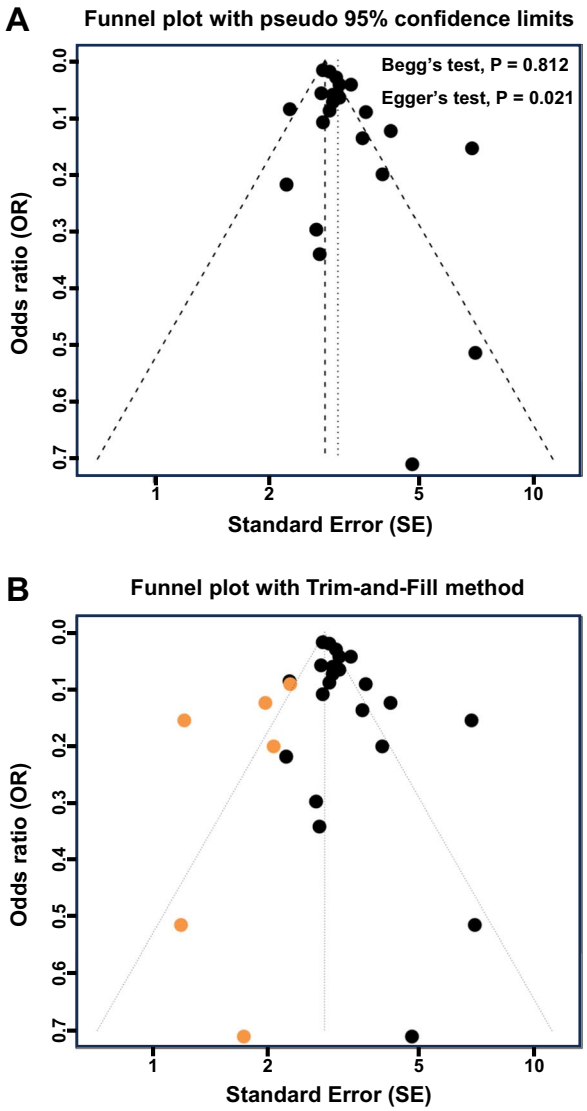

Fig. 3 **A** Funnel plot for publication bias of association between antibiotic exposure and the risk of colorectal tumors. **B** Funnel plot for publication bias after processing trim-and-fill analysis

Conclusion

Past or present antibiotic use increased the risk of colorectal tumors by 13% compared with individuals with no antibiotic use, suggesting that antibiotic exposure may increase the risks of both benign and malignant colorectal tumors. These results highlighted the need for clinicians to prescribe antibiotics appropriately and with caution to avoid antibiotic overuse.

Abbreviations

OR	Odds ratio
PROSPERO	Prospective Register of Systematic Reviews
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
HR	Hazard ratio
RR	Risk ratio
NOS	Newcastle–Ottawa Scale
CI	Confidence interval

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

The conceived and designed the study: Y.-C.L., X.-Y.T., and C.-D.Z.: conceived and designed the study; Y.-C.L., X.-Y.T., and Y.C: analyzed the data; X.-Y.T., and Y.-C.L.: contributed reagents/materials/analysis; Y.-C.L., X.-Y.T., J.-X.L., Y.Q., X.-Y.L., Y.C., and C.-D.Z.: wrote the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

The data supporting the main findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

None reported.

Consent for publication

All the authors have signed the form of consent for publication.

Competing interests

The authors declare no conflict of interest.

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