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Unraveling the Link Between Antibiotics and Cancer Risk: A Literature Review

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ABSTRACT

The relationship between antibiotic use and cancer development has garnered significant attention in recent years, driven by growing concerns about the long-term impacts of antibiotic exposure on human health. This literature review aims to synthesize the existing scientific literature on the potential association between antibiotic use and the risk of developing various types of cancer. Studies have suggested that antibiotics may alter the gut microbiome, leading to dysbiosis, which in turn can influence carcinogenesis through mechanisms such as chronic inflammation, immune system modulation, and changes in metabolic pathways. Additionally, some antibiotics possess direct genotoxic effects that may contribute to cancer risk. This review examines epidemiological studies, observational research, and clinical findings to provide a comprehensive overview of the current understanding of this complex relationship. The evidence indicates a nuanced interaction, with certain antibiotics linked to increased risks for specific cancers, while others show no significant association. The review also highlights gaps in the literature, methodological limitations, and the need for further research to clarify causative pathways and establish more definitive conclusions. Understanding the intricate dynamics between antibiotic use and cancer development is crucial for informing public health policies and guiding the prudent use of antibiotics in clinical practice.

Introduction

There are more than 9.7 million cancer-related deaths worldwide [14]. Recent research has shown that there is a correlation between the health of the gut microbiome and carcinogenesis. Furthermore, antibiotics are known to disrupt the balance of the gut microbiome.

In the study of Chan et al. (2006), antibiotics are linked with the risk of breast cancer. Their study covered 18, 521 cases of women who developed breast cancer over a follow-up period of up to nine years. Based on the results, the use of antibiotics was associated with slightly elevated risk [hazard ratio (HR), 1.14; 95% confidence interval (95% CI), 1.10-1.18] but there was minimal evidence of a dose response, with HR of 1.17 (95% CI, 0.97-1.42) for >1,000 days of use versus with no use. Interestingly, they also found that when tetracyclines and macrolides are used for a long period, it display a weak association with breast cancer. However, the causal significance is still unclear. They believe that further follow-up is necessary to assess the link between lincosamides and breast cancer risk as detected in adult female patients and declared in previous reports.

Consequently, a group of doctors conducted a study on the possibility of cancer formation due to recurrent exposure to antibiotics. To further investigate the potential link between antibiotic use and cancer risk, they performed nested case-control studies on 15 common cancers using a large population-based electronic medical records database. It was found that Penicillin use was associated with higher risks of esophageal, gastric, and pancreatic cancers. Lung cancer was also elevated with the use of

penicillins, cephalosporins, or macrolides (AOR for more than five courses of penicillin: 1.4, 95% CI 1.3–1.6). Moreover, the risk of prostate cancer was modestly associated with the use of penicillins, quinolones, sulphonamides, and tetracyclines. On the other hand, breast cancer was modestly associated with the use of sulphonamide. It was also revealed that no associations were found between the use of antiviral or antifungal and cancer risk (Boursi et al., 2015).

Another study describes the possible effects of antibiotic therapies on different oncologic treatments, especially immunotherapies. The study emphasizes how antibiotic use can cause significant and long-lasting changes to the diversity of the microbial ecosystem, altering the composition of up to 30% of bacterial species in the gut microbiome. By altering the composition of the human microbiota, antibiotics can change the action of several cancer drugs, potentially reducing their efficacy and increasing their toxicity (Lopes et al., 2020)

The use of antibiotics in treating bacterial infections is central to infectious disease management, which is why understanding any link between antibiotics and cancer is crucial.

Overview of Cancer Incidence and Risk Factors

The intestinal microbiota is very critical to overall health as it plays a role in metabolism, pathogen resistance, and many other processes. Antibiotics, however, are known to disrupt these interactions and can contribute to chronic health problems.

Understanding any link between antibiotics and cancer is important as antibiotics are used to treat bacterial infections.

Antibiotics:

1. Reduce microbial diversity
2. Alter microbiota functions
3. Promote the growth of antibiotic-resistant strains
4. Makes hosts more prone to infections from harmful pathogens

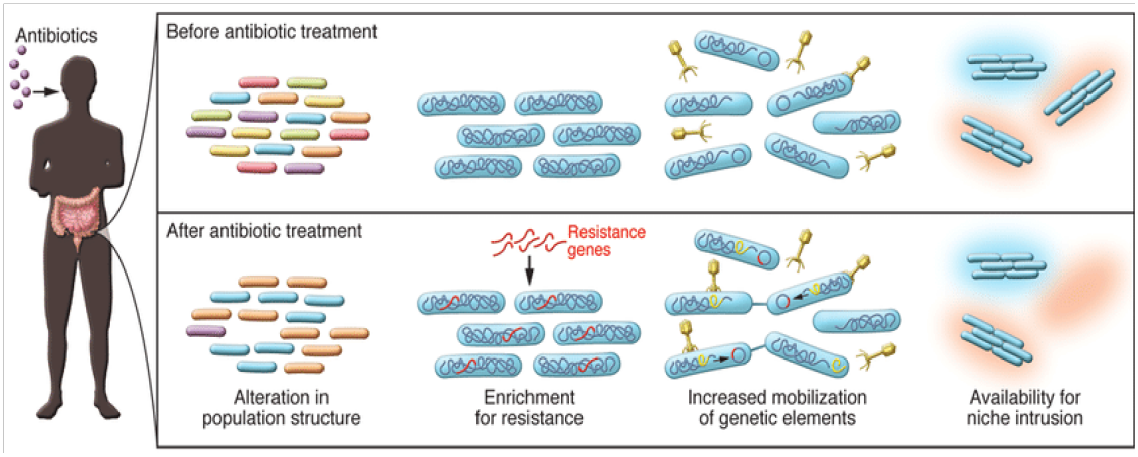

Figure 1. Illustration of some effects of antibiotics on the microbiome. Source: [15]

Description: Antibiotics have many harmful effects on the gut microbiome including variance in population structure, reduction in microbial diversity, an altercation in microbiota functions, promotion of antibiotic-resistant strains, increased risk of pathogenic intrusion, and increased mobilization of

genetic elements. If these mobilized genetic elements insert themselves into the DNA of somatic cells, this can directly contribute to cancers and neuropsychiatric diseases [16].

The Rationale for Investigating the Link Between Antibiotics and Cancer

Cancer is mostly seen as a disease influenced by our surroundings. Outside factors like carcinogens, pollutants, or radiation can change genetic composition as well as inside factors like metabolic, immune, or genetic deficiencies.

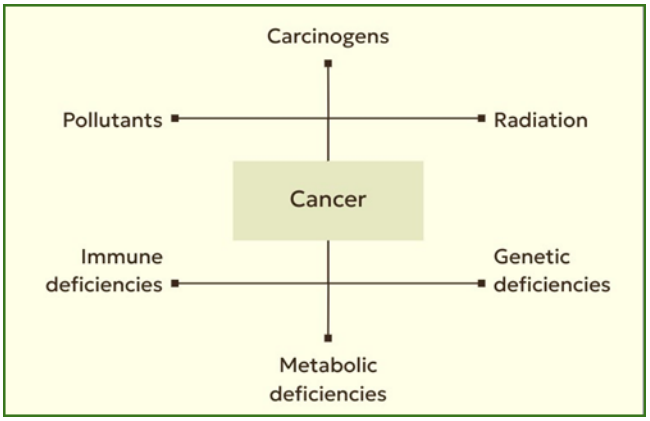

Figure 2. Diagram of outside and inside influences on cancer development. **Source:** Information received from [17]; Diagram created by Geevarghese, 2024

This is where the microbiome comes in. The gut microbiota is known to contribute to cancer development by influencing various cellular pathways in the host. Proteins, enzymes, and toxins produced by pathogenic bacteria can bind to host cells, disrupting their normal functions and leading to the promotion of different types of tumors and cancer.

Two facts emerge: one is that antibiotics save many lives annually. The other is that their use disrupts the intricate ecosystems of the gut microbiome. This disruption includes not only a reduction in the number of microorganisms in the large intestine but also a decrease in their variety. Your microbiome is unique to you as it includes diverse and complex colonies that work with your body. Antibiotics not only reduce microbial diversity, but they also alter microbiota functions, and promote the growth of antibiotic-resistant strains, making hosts more prone to infections from harmful pathogens. [11]

Background of Microbiome

The microbiome is the genome of all our microbes. Most of our microbes dwell in our gut, and the human microbiome has around 100 trillion microbes—the functions of the human microbiome range from developing our immune system to influencing our behavior. [11]

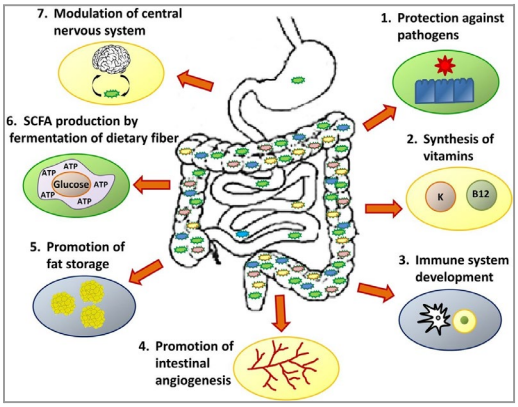

Figure 3. The human microbiome. Source: Image retrieved from [11]

Description: The human microbiome is in control of various vital homeostatic mechanisms. This also includes improving metabolism, prevention against autoimmunity, and strengthening against infection and inflammation.

Composition of Microbiome

The microbiome is dynamic and changes based on certain factors such as diet and antibiotic usage. According to Amon and Sanderson [11], "A healthy human gut can house at least 1000 different species of bacteria, comprising two major phyla, namely Bacteroidetes and Firmicutes." Other microbes such as viruses, fungi, and archaea also live in the gut.

While much still has to be learned about the association between changes in the microbiome composition and disease pathogenesis, many studies indicate that therapies aimed at restoring the balance of gut microbiota successfully treat specific human illnesses [11].

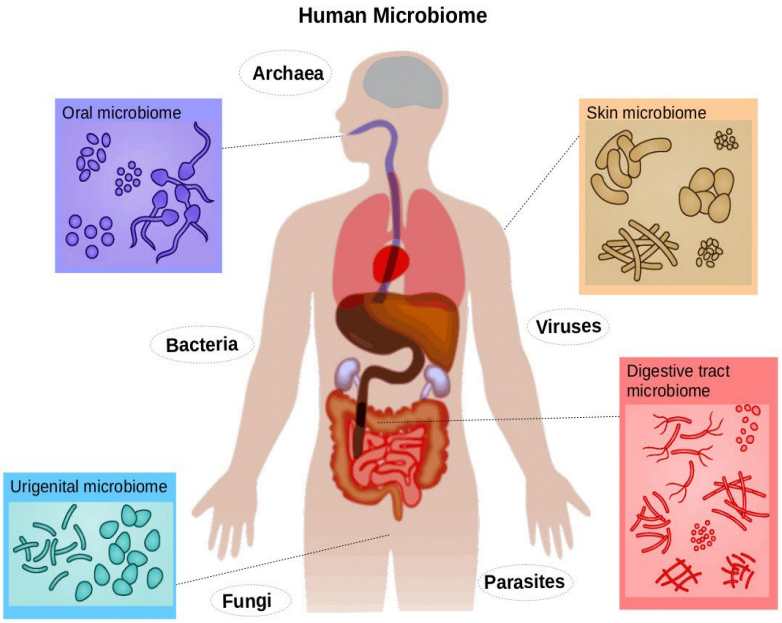

Figure 4. The Microbiota of the Microbiome . Source: Image retrieved from [18]

Description: Microbial cells - including archaea, bacteria, fungi, viruses, and parasites - live on and in us.

Methods

This study is a literature review that concludes the effect of antibiotics on tumorigenesis and discusses the extent to which this conclusion can be accepted and generalized.

Study design:

1. Literature search

A comprehensive literature search will be conducted in the following electronic databases:

- PubMed
- Embase
- Cochrane Library
- Scopus
- Web of Science

The search strategy will include keywords and Medical Subject Headings (MeSH) such as: ● "Antibiotics"

- "Antimicrobial agents"
- "Cancer"
- "Neoplasms"
- "Oncogenesis"
- "Risk factors"

2. Study Selection Process

a) Title and Abstract Screening: Two reviewers will independently screen titles and abstracts for relevance. Disagreements will be resolved by consensus or by consulting a third reviewer.

b) Full-Text Review: The same two reviewers will retrieve and assess texts of potentially eligible studies independently. Any disagreements will be resolved through discussion or third-party adjudication.

3. Data Extraction

A standardized data extraction form will be used to collect the following information from each included study:

- Study characteristics: Author, year, country, study design, sample size.
- Participant characteristics: Age, sex, health status.
- Antibiotic exposure: Type, dose, duration, frequency.
- Outcome measures: Type of cancer, method of diagnosis, follow-up duration.
- Statistical analyses: Risk estimates (e.g., odds ratios, relative risks, hazard ratios) with confidence intervals.
- Adjustments for confounders: Variables controlled for in the analysis.

4. Risk of Bias Assessment

The risk of bias for included studies will be assessed using appropriate tools:

- Cohort and Case-Control Studies: Newcastle-Ottawa Scale (NOS).
- Randomized Controlled Trials: Cochrane Risk of Bias Tool.

Discussion

Population Characteristics

Aromaa et al. [4] conducted a study on a population of 3,112,624 Finnish individuals aged 30-79 years, selected from the Population Register, which maintains demographic data for all Finnish citizens. Participants were alive and cancer-free as of January 1, 1995, and had no history of cancer diagnoses between 1953 and 1997. Additionally, individuals who died between January 1, 1995, and December 31, 1997, were excluded. The cohort included 1,492,984 men and 1,619,640 women. Data on antibiotic use from 1995 to 1997 was obtained from the Drug Prescription Registry. During the follow-up period from 1998 to 2004, 134,070 cancer cases were recorded in the Finnish Cancer Registry. The study employed Cox proportional hazards regression to estimate relative risks (RRs) and 95% confidence intervals (CIs) for cancer development, revealing that higher antibiotic use was associated with an increased risk of various cancers.

Boursi et al's [5] study included 125,441 individuals with 15 distinct types of cancer and 490,510 matched controls. Among the cases, the most frequent cancers were breast cancer in females (31,131 cases) and prostate cancer in males (27,212 cases). Penicillin emerged as the most frequently prescribed antibiotic during the follow-up period, with over 45% of the participants (279,777 individuals) receiving at least one prescription. This comprehensive dataset allowed for a detailed examination of the relationship between antibiotic use and the incidence of various cancers, shedding light on potential correlations between antibiotic consumption and cancer development.

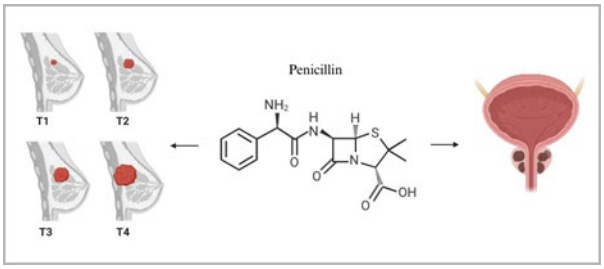

Figure 5. Risk of Penicillin. **Source:** Information received from [5], image created by Geevarghese, 2024

Description: Penicillin may increase the risk of breast cancer development and prostate cancer development.

Gary et al. [6] studied 2,130,829 adult female subscribers of a healthcare program, focusing on their Dik et al. [7] studied 4,029 CRC cases (47% male, average age 71 ± 11 years) and 15,988 controls. Antibiotics were prescribed to 65.3% of cases and 64.0% of controls, with no significant difference ($p = 0.13$). A much more diversified study has been conducted by Mohammed et al. [8] among a population of 40,548 people and all the details regarding the different characteristics and the number of people belonging to that are also given. This was a comprehensive study with more clarity and diversification

McDowell et al. [10] classified the population into two groups, a smaller group of 445 people who are below 50 years and a larger group of 7,458 people who are above 50 years old. The palliative data collected made the biases in the second data. Males are slightly higher than females in the two data groups. The population selected for the study is diverse and different areas of the world are also

taken. Some included people from Sweden, some from Britain, some from the USA. Different age groups and genders were also selected.

Paper	Country	Number of people	Number of males	Number of females	Age group
The role of the microbiome in cancer development and therapy	N/a	N/a	N/a	N/a	N/A
Use of Antibiotics and Risk of Cancer: A Systematic Review and Meta-Analysis of Observational Studies	Western countries	7,947,270	N/a	N/a	N/a
Antibiotics for cancer treatment: A double-edged sword	N/a	N/a	N/a	N/a	N/a
Antibiotic use predicts an increased risk of cancer	Finland	3,112,624	N/a	N/a	30-79
Recurrent antibiotic exposure may promote cancer formation – Another step in understanding the role of the human microbiota?	UK	490,510	148,063	342,447	Adult
Antibiotics and Risk of Breast Cancer: Up to 9 Years of Follow-up of 2.1 Million Women	USA	2,130,829	0	2,130,829	Adults 20+ years
Frequent Use of Antibiotics Is Associated with Colorectal Cancer Risk: Results of a Nested Case-Control Study	Netherlands	15,988	7,527	8,461	Adults 18+ years Mean age 71.4
Antibiotics Use and Subsequent Risk of Colorectal Cancer: A Swedish Nationwide Population-Based Study	Sweden	202,720	107,285	95,435	Adults(18+)
Antibiotics, cancer risk, and oncologic treatment efficacy: a practical review of the literature	N/a	7,947,270	N/a	N/a	N/a
Oral antibiotic use and early-onset colorectal cancer: findings from a case-control study using a national clinical database	Scotland	30,418	16,995	13,423	Adults Two sections One group <50 years Other >50 years

Antibiotic Exposure

The exposure to different antibiotics for different time periods of exposure is analyzed in each paper. Antibiotic exposure has been extensively studied to understand its association with cancer risk and its impact on oncologic treatments. Various studies have explored different antibiotics, exposure durations, and patient demographics. Bhatt et al. [1] conducted their study using a mouse model to analyze antibiotics targeting gram-positive bacteria in combination with chemotherapeutic agents like oxaliplatin and cyclophosphamide.

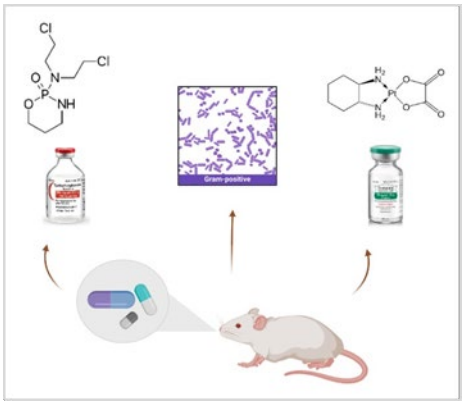

Figure 6. Antibiotic Targets. Source: Information received [1], image created by Geevarghese, 2024

Description: Antibiotics can target gram-positive bacteria and chemotherapeutic agents like oxaliplatin and cyclophosphamide

Petrelli et al. [2] did a systematic review and meta-analysis of observational studies involving 7,947,270 individuals who examined a variety of antibiotics, including nitroimidazoles, penicillins, tetracyclines, macrolides, quinolones, cephalosporins, and sulfonamides, over a 1-5 year period. Gao et al. [3] highlighted the use of anticancer antibiotics such as daunorubicin, epirubicin, and mitoxantrone, though the exposure term was not mentioned. Research involving 3,112,624 individuals indicated that unspecified antibiotics predicted an increased cancer risk over 1-3 years.

Aromaa et al. [4] studied 125,441 participants and found that recurrent exposure to antibiotics like penicillins, cephalosporins, macrolides, tetracyclines, sulfonamides, quinolones, and nitroimidazoles, with greater than one year of exposure, might promote cancer formation. Further, a follow-up of 2.1 million women for up to 9 years revealed a weaker association, in comparison to the other tested antibiotics, between the use of tetracyclines and macrolides and breast cancer risk. Boursi et al. [5] did a case-control study with 490,510 cases and found that frequent use of various antibiotics, including tetracyclines, amphenicols, penicillins, cephalosporins, sulfonamides, macrolides, aminoglycosides, quinolones, imidazoles, and nitrofuran derivatives, was associated with colorectal cancer risk over 1-6 years. Mohammed et al. [8] who did a Swedish nationwide study of 40,545 individuals, indicated a correlation between antibiotics under the Anatomical Therapeutic Chemical codes J01 and J04 and colorectal cancer risk over a one-year period. A practical review of the literature on nearly 8 million people highlighted the potential risks associated with antibiotic use over 1-5 years. Lastly, a study of 7,903 cases explored the link between oral antibiotic use and early-onset colorectal cancer, noting a 6.9-8-year exposure period to anti-anerobic antibiotics and any antibiotics.

These studies collectively underscore a potential link between antibiotic use and increased cancer risk, particularly with extended exposure periods, necessitating further targeted research to elucidate the mechanisms and causal relationships.

Paper	Number of people/sample size	Antibiotic(s) mentioned	Term of exposure
The role of the microbiome in cancer development and therapy[1]	Used mouse model for analysis	Antibiotics targeting gram-positive bacteria used in combination with specific chemotherapeutic agents like oxaliplatin and cyclophosphamide.	N/a
Use of Antibiotics and Risk of Cancer: A Systematic Review and Meta-Analysis of Observational Studies [2]	7,947,270	A variety of antibiotics including Nitroimidazoles, penicillins, tetracyclines, macrolides, quinolones, cephalosporins, sulfonamides	1-5 years review of different papers
Antibiotics for cancer treatment: A double-edged sword[3]	N/a	Anticancer antibiotics like Daunorubicin, Epirubicin, Mitoxantrone and others	Not mentioned
Antibiotic use predicts an increased risk of cancer[4]	3,112,624	Not specified.	1-3 years
Recurrent antibiotic exposure may promote cancer formation – Another step in understanding the role of the human microbiota?[5]	490,510	Penicillin, cephalosporins, macrolides, tetracyclines, sulphonamides, quinolones, and nitroimidazole	0, 1, 2–5, and >5 courses) Greater than 1 year
Antibiotics and Risk of Breast Cancer: Up to 9 Years of Follow-up of 2.1 Million Women[6]	2,130,829	Tetracyclines and Macrolides groups	100 to 1000 days
Frequent Use of Antibiotics Is Associated with Colorectal Cancer Risk: Results of a Nested Case-Control Study[7]	15,988	Tetracyclines (ATC codes J01A), amphenicols (ATC codes J01B), penicillins (ATC codes J01C), cephalosporins (ATC codes J01D), sulfonamides and trimethoprim (ATC codes J01E), macrolides (ATC codes J01F), aminoglycosides (ATC codes J01G), quino lones (ATC codes J01M), imidazoles (ATC codes J01XD), nitrofuran derivates (ATC codes J01XE), and others (ATC codes J01XA, J01XB, J01XC, J01XX).	1-6 years

Antibiotics Use and Subsequent Risk of Colorectal Cancer: A Swedish Nationwide Population-Based Study[8]	202,720	Antibiotics under Anatomical Therapeutic Chemical codes J01 and J04 (anti-infective agents for systemic use)	1 year
Antibiotics, cancer risk and oncologic treatment efficacy: a practical review of the literature[9]	7,947,270	Not specified	1-5 years
Oral antibiotic use and early-onset colorectal cancer: findings from a case-control study using a national clinical database[10]	30,418	Antianaerobic antibiotics and any antibiotics	6.9-8 years

Cancer Outcomes

The outcomes of cancer investigations from the listed studies offer a diverse panorama of insights into antibiotic exposure and its implications. Petrelli et al. [2] did a systematic review and meta-analysis involving over 7.9 million individuals exploring the association between antibiotic use and various cancers, including gastric, colorectal, and skin cancers, over a review period spanning 1 to 5 years. A study examining antibiotic use's dual role in cancer treatment, by Gao et al. [3] highlighted lung, colon, and skin cancers without specifying the number affected. Notably, a cohort study[4] involving 3.1 million participants found an increased risk of prostate, breast, lung, and colon cancers over 1 to 3 years, suggesting a potential link between antibiotic use and cancer development. Conversely, investigations into recurrent antibiotic exposure on cancer formation, encompassing gastrointestinal, genitourinary, and lung cancers among 125,441 individuals, implied a nuanced understanding of antibiotic courses ranging from 0 to >5, emphasizing the complexity of such associations [5]. Furthermore, a comprehensive follow-up of 2.1 million women over 100 to 1000 days identified a notable incidence of breast cancer, underlining the need for prolonged surveillance[6]. Moreover, a nested case-control study on colorectal cancer risk among 15,998 individuals found an association with frequent antibiotic use over a period greater than one year, while a Swedish nationwide study highlighted a similar risk among 202,720 individuals over 100 to 1000 days [8]. A literature review on nearly 8 million individuals explored the implications for genitourinary and pancreaticobiliary cancers over 1 to 6 years. Finally, a case-control study investigating early-onset colorectal cancer among 30,418 individuals provided insights into the potential link between oral antibiotic use and colorectal cancer risk over one year [10]. These studies collectively underscore the multifaceted interplay between antibiotic exposure and cancer outcomes, prompting further research into elucidating the underlying mechanisms and clinical implications.

Data Analysis

7,947,270 participants (n = 25 studies).
In general, the use of antibiotics was identified as an independent risk factor for developing cancer

Type of cancer	OR (Odds Ratio)	95% Confidence Interval	Probability
Overall	1.18	1.12 - 1.24	p < 0.001
Lung cancer	1.29	1.03 - 1.61	p = .02
Lymphomas	1.31	1.13 - 1.51	p < 0.001
Pancreatic Cancer	1.28	1.04 - 1.57	p = 0.019
Renal Cell Carcinoma	1.28	1.1 - 1.5	p = 0.001
Multiple Myeloma	1.36	1.18 - 1.56	p < 0.001

Figure 7. Use of Antibiotics and Risk of Cancer Source: Data source from Petrelli et al., 2019; Table created by Geevarghese, 2024

Description: This table summarizes data showing that the risk of cancer development increases by 12 to 24 percent overall.

Here we see that we are getting moderate odds ratio values. Overall, people who take antibiotics are 18% more likely to develop cancer.

Because the confidence intervals do not include 0 and the probabilities are all less than a significance level of .05, we can accept the alternative hypothesis that there is an association between cancer and antibiotic cancer. There is moderate evidence that suggests prolonged or excessive antibiotic use throughout a person's lifetime is linked to a slight increase in the risk of various cancers.

Paper	Number of people/samples	Number of people affected by cancer	The type of cancers discussed	Term of exposure to antibiotics
The role of the microbiome in cancer development and therapy[1]	Used mouse model for analysis	N/a	N/a	N/a
Use of Antibiotics and Risk of Cancer: A Systematic Review and	7,947,270	N/a	Gastric, colorectal, skin, etc. A wide variety of cancers	1-5 years review of different papers
Meta-Analysis of Observational Studies[2]				
Antibiotics for cancer treatment: A double-edged sword[3]	N/a	N/a	Lung cancer, colon cancer, skin cancer, etc	Not mentioned

Antibiotic use predicts an increased risk of cancer[4]	3,112,624	134,070	Prostate, breast, lung and colon	1-3 years
Recurrent antibiotic exposure may promote cancer formation – Another step in understanding the role of the human microbiota?[5]	490,510	125,441	gastro-intestinal, genito-urinary, and lung cancers	0, 1, 2–5, and >5 courses)
Antibiotics and Risk of Breast Cancer: Up to 9 Years of Follow-up of 2.1 Million Women[6]	2,130,829	18,521	Breast cancer	100 to 1000 days
Frequent Use of Antibiotics Is Associated with Colorectal Cancer Risk: Results of a Nested Case-Control Study[7]	15,998	4,098	Colorectal Cancer	Greater than 1 year
Antibiotics Use and Subsequent Risk of Colorectal Cancer: A Swedish Nationwide Population-Based Study[8]	202,720	40,545	Colorectal Cancer	100 to 1000 days
Antibiotics, cancer risk and oncologic treatment efficacy: a practical review of the literature[9]	7,947,270	N/a	genitourinary and pancreaticobiliary cancer	1-6 years
Oral antibiotic use and early-onset colorectal cancer: findings from a case-control study using a national clinical database[10]	30,418	7,903	colorectal cancer	1 year

Summary of Findings

Associations with Antibiotic Use and Breast Cancer

Multiple studies have examined the link between antibiotic use and breast cancer risk. A large-scale study involving 2,130,829 women over up to 9.4 years found a slight increase in breast cancer risk associated with antibiotic use, with a hazard ratio (HR) of 1.14 (95% CI, 1.10-1.18). The association was observed across different antibiotic classes, though the overall risk increase was modest and could be influenced by underlying conditions like acne or rosacea. Another study demonstrated a trend of increasing breast cancer risk with higher cumulative days of antibiotic use. For categories of increasing use (0, 1-50, 51-100, 101-500, 501-1000, and >1000 days), the odds ratios for breast cancer ranged from 1.45 to 2.07, with a significant trend ($P < .001$). The highest risk was seen with more than 500 days of use.

Associations with Antibiotic Use and Colorectal Cancer

Several large studies have indicated a link between antibiotic use and an increased risk of colorectal cancer. A study utilizing data from a health insurance database found that higher antibiotic usage was associated with a higher risk of CRC. For instance, those with eight or more prescriptions had a 26% increased risk (OR 1.26, 95% CI 1.11–1.44). Another population-based case-control study from Sweden involving over 40,000 CRC cases and 200,000 controls showed that frequent antibiotic use was associated with a higher risk of proximal colon cancer (OR 1.17, 95% CI 1.05-1.31). The study found an inverse association with rectal cancer, particularly in women.

Surprisingly for all the papers that related to colonel cancer, the cancer occurrence was 20-26%. The is much larger compared to breast cancer and other cancers which had an occurrence rate of 0.8 to 4%. This is notable as the colon harbors the most densely populated microbial community found in humans, with microbial counts ranging from 10^{10} to 10^{11} cells per gram of intestinal content [11]. The use of antibiotics thus greatly disrupts the balance of microbial cells, consequently leading to a higher rate of cancer occurrence. We can conclude that the occurrence of cancer is also high in those areas where the bacteria have a symbiotic relationship with the body.

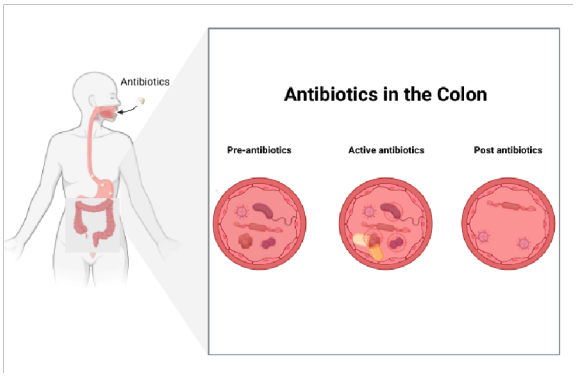

Figure 8. Effects of Antibiotics on the Microbiota of the Colon. Source: Information retrieved from [11], image created by Geevarghese, 2024.

Description: As the colon holds a very big population of diverse microbiota, antibiotics really disrupt the colonic system by decreasing variance, population structure, and functions of microbial cells.

Mechanisms and Confounding Factors

Antibiotics can disrupt the gut microbiota, leading to dysbiosis, which may promote colorectal carcinogenesis through various mechanisms such as inflammation, production of carcinogenic metabolites, and immune modulation. Observational studies have inherent limitations in establishing causality due to potential confounders. For instance, infections requiring antibiotics might be linked to inflammation, which in turn could contribute to cancer development. Thus, the indication for antibiotic use itself could be a confounding factor.

Studies have suggested that the risk varies by the type of antibiotic and cancer location within the colon. For example, quinolones and sulfonamides/trimethoprims have been associated with a higher risk of proximal colon cancer, while no significant association was found with methenamine hippurate, a urinary tract antiseptic that does not affect the gut microbiota. Experimental models, such as

gnotobiotic mice, have demonstrated that specific microbiota can affect cancer susceptibility and progression through mechanisms like modulating inflammation and inducing DNA damage. These findings highlight the complex interplay between antibiotics, microbiota, and cancer risk.

Other Cancer Risk Areas

Antibiotic use is associated with an increased risk of several cancers, including prostate, lung, breast, and colon cancers. Frequent courses of certain antibiotics, like penicillin, are linked to higher risks of esophageal, gastric, and pancreatic cancers. Increased risk of lung cancer is observed with the use of penicillin, cephalosporins, and macrolides

Strengths and Limitations of the Included Studies

Our understanding of antibiotic-associated disturbance of the microbiota has been limited by the poor sensitivity, inadequate resolution, and significant cost of current research methods.

Strength of The Included Studies

1. Large Sample Sizes :
    - Many of the studies included large populations, providing robust statistical power and enhancing the reliability of the findings.
2. . Long Follow-Up Periods :
    - Extended follow-up periods (up to 9.4 years in some studies) allow for a more comprehensive observation of the long-term effects of antibiotic use on cancer risk.
3. Diverse Populations :
    - Studies covered diverse populations from different regions, enhancing the generalizability of the findings. While not all populations were covered, a good majority were.
4. Detailed Prescription Records :
    - Use of comprehensive health insurance databases and prescription records ensures accurate tracking of antibiotic use.
5. Controlled for Confounding Factors :
    - Many studies adjusted for various confounders such as age, sex, comorbidities, and hormone use, which helps isolate the effect of antibiotic use on cancer risk.
6. Subgroup Analyses :
    - Some studies conducted subgroup analyses by antibiotic class, cancer type, and specific conditions (e.g., acne or rosacea), providing more detailed insights into the associations.

Limitations of The Included Studies

1. Observational Nature :
    - Most studies are observational, which limits the ability to establish causality between antibiotic use and cancer risk. Confounding by indication (the reason for antibiotic use) may influence results.
2. Residual Confounding :
    - Despite adjustments, residual confounding factors (unmeasured variables) may still impact the associations observed.
3. Self-Reported Data :

- Some studies may rely on self-reported antibiotic use, which can introduce recall bias and inaccuracies.

4. Lack of Randomized Controlled Trials (RCTs) :
   - The absence of RCTs limits the ability to definitively determine the causal relationship between antibiotics and cancer risk.
5. Variation in Antibiotic Types and Doses :
   - Differences in types and doses of antibiotics used across studies can lead to inconsistent findings and complicate comparisons.
6. Potential for Reverse Causation :
   - Reverse causation is a concern where underlying conditions (e.g., infections or inflammations) that necessitate antibiotic use might themselves be linked to increased cancer risk.
7. Population-Specific Findings :
   - Results from studies in specific populations or regions may not be generalizable to other groups.
   - The studies are from different countries. However, the data from other continents like Asia and Africa are not analyzed. This needs to be done so that an idea about the diets could also be included.
8. Limited Mechanistic Insights :
   - Observational studies typically do not provide mechanistic insights into how antibiotics may influence cancer development, necessitating further experimental research.

The strengths of these studies lie in their large sample sizes, long follow-up periods, and detailed data collection, which provide robust evidence for an association between antibiotic use and cancer risk. However, their observational nature, potential for residual confounding, and lack of RCTs limit the ability to draw definitive causal conclusions. Further research, including mechanistic studies and randomized trials, is necessary to better understand the relationship between antibiotic use and cancer development.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Studies investigating the association between antibiotic use and the risk of cancer in human populations.
- Studies of any design (e.g., randomized controlled trials, cohort studies, case-control studies).
- Studies published in peer-reviewed journals.
- Studies available in the English language, due to limitations in translation resources.
- Studies reporting original data, not reviews, meta-analyses, or editorials.
- Studies with a clear definition of antibiotic exposure, including type, duration, and dosage.
- Studies reporting cancer incidence or prevalence as an outcome measure.
- Studies with a follow-up period long enough to assess the development of cancer following antibiotic exposure.
- Studies with sufficient data to calculate effect estimates (e.g., relative risks, odds ratios) or provide relevant information for qualitative synthesis.

Exclusion Criteria

- Animal studies, in vitro studies, and ecological studies.
- Studies focus solely on microbial or cellular mechanisms without assessing cancer outcomes in humans.
- Studies with inadequate control for confounding factors (e.g., age, smoking, comorbidities) that may influence the relationship between antibiotics and cancer risk.
- Studies assessing the impact of antibiotics as part of cancer treatment (e.g., prophylactic antibiotics for chemotherapy-induced neutropenia).
- Studies assessing antibiotics used specifically for the treatment of cancer-related infections (e.g., prophylaxis for febrile neutropenia).
- Studies lacking sufficient detail on antibiotic exposure or outcome assessment.
- Studies with a high risk of bias or methodological limitations (e.g., incomplete follow-up, inadequate adjustment for confounders).
- Duplicate publications or redundant data from the same study population.
- Conference abstracts, posters, and unpublished data due to potential lack of peer review and limited detail.

Conclusion

The study highlights a potential association between antibiotic use and an increased risk of various cancers, such as breast and colorectal cancers. The evidence suggests that frequent and prolonged use of antibiotics may contribute to cancer risk, most likely due to alterations in the gut microbiota and immune system functions. While the correlations identified are relatively weak, they point to the need for cautious use of antibiotics and reinforce the importance of antibiotic stewardship in clinical practice. These findings emphasize the need for healthcare providers to carefully consider the long-term implications of antibiotic prescriptions, balancing immediate therapeutic benefits against potential future risks.

Future research should focus on elucidating the mechanisms by which antibiotics influence cancer risk, particularly through changes in the gut microbiome and its impact on immune regulation and inflammation. Longitudinal studies and randomized controlled trials are essential to establish causality and understand the specific conditions under which antibiotics may increase cancer susceptibility. Additionally, investigations into the role of individual antibiotic classes and their differential effects on various cancer types will provide more nuanced insights. Such research will ultimately contribute to more informed guidelines for antibiotic use and strategies for mitigating potential adverse effects, enhancing both cancer prevention and overall patient health.

Clinical Implications

Clinicians should be judicious in prescribing antibiotics, avoiding unnecessary or prolonged courses to minimize potential long-term health risks, including cancer. Implementing and reinforcing antibiotic stewardship programs is essential to ensure antibiotics are used appropriately and only when necessary. Educating patients about the potential long-term risks associated with antibiotic use, including the possible increased risk of cancer, and emphasizing the importance of adhering to prescribed courses only when necessary, is crucial. Patients with extensive or frequent antibiotic use should be monitored more closely for potential long-term health effects, including regular screenings for cancer as part of their healthcare management. When appropriate, consider alternative treatments for conditions that do not necessarily require antibiotics, thereby reducing exposure to antibiotics. Additionally, encouraging

ongoing research to further elucidate the relationship between antibiotic use and cancer risk, and updating clinical guidelines accordingly based on emerging evidence, is necessary. Collaboration between oncologists, infectious disease specialists, and primary care providers would serve as beneficial to developing comprehensive care strategies that balance the immediate benefits of antibiotic use with potential long-term risks. Furthermore, developing and advocating for policies that limit the overuse of antibiotics in both clinical and agricultural settings, considering the broader implications for public health, would help to regulate overuse. Recognizing the role of gut microbiota in overall health and considering the impact of antibiotics on microbiota composition is also essential as probiotic therapy or other measures to maintain or restore healthy microbiota could be integrated into patient care.

Recommendations for Further Research

Research in the field of colorectal cancer (CRC) and antibiotic use should focus on elucidating the underlying mechanisms driving the observed association. Specifically, prospective cohort studies with long-term follow-up are warranted to establish a causal relationship between antibiotic exposure and CRC risk. These studies should account for potential confounding factors such as diet, lifestyle, and comorbidities to provide more robust evidence.

The diet of each person will also aid in the destruction of gut bacteria or colon cancer. This needs to be addressed and a more diverse study should be conducted in terms of race and the continents including Asia and Africa. Another recommendation is to foster interdisciplinary collaboration among microbiologists, oncologists, epidemiologists, and pharmacologists to develop comprehensive research frameworks addressing the multifaceted nature of antibiotic use and cancer risk.

Mechanistic studies at the molecular and cellular levels are needed to understand how antibiotics may influence gut microbiota composition and function, leading to CRC development. Moreover, the dose-response relationship should be explored in more detail to understand how different durations and intensities of antibiotic use affect cancer risk across various populations and cancer types. To understand better which cancers are most affected, future research should investigate the association between antibiotic use and specific cancer subtypes, including site-specific colorectal cancers (e.g., proximal vs. distal colon). In response to the connection between antibiotics and carcinogenesis, interventional studies to test whether modifying antibiotic use or incorporating probiotics and other microbiota-targeted therapies can mitigate cancer risk should be designed. Lastly, randomized controlled trials evaluating the impact of antibiotic stewardship programs on CRC incidence could help inform guidelines for antibiotic prescribing practices and potentially mitigate CRC risk associated with antibiotic use.

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