Antibiotic exposure is associated with an increased risk of cancer: a systematic review and meta-analysis

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Abstract

Background Several epidemiological studies have assessed the association between the use of antibiotics and cancer risk, but the results were inconsistent.

Objective The objective of this study was to perform a meta-analysis to further evaluate possible association between antibiotic exposure and the risk of cancer.

Methods We searched PubMed, Embase, Web of Science, and Chinese databases for studies on the association between antibiotic use and cancer without time restrictions. The risk estimates (hazard ratio (HR) or relative risk (RR) or Odds ratio (OR)) with their corresponding 95% confidence interval (CI) were calculated.

Results A total of 23 observational studies with 19 case-control and 4 cohort studies were included in the meta-analysis. Exposure to antibiotics significantly increased the risk of cancer with an OR of 1.20 (95% CI 1.13-1.27, P=0.000). Subgroup meta-analysis by gender showed that the effect of antibiotic use on cancer risk was greater in male (34%) compared with that in female (19%). On the other hand, the risk of cancer increased with an increasing number of antibiotic prescriptions and the increasing cumulative days of antibiotic exposure. Moreover, of the 7 antibiotic types included, the six classes of antibiotics (penicillin, macrolides, quinolones, sulfonamides, tetracycline, cephalosporins) were associated with the increased risk of cancer. Further, of the 16 separate cancers included, exposure to antibiotics increased the risk of eight common cancer types (liver cancer, colorectal cancer, stomach and small intestine cancer, lymphomas, breast cancer, lung cancer, prostate cancer, and renal and bladder).

Conclusions Exposure to common antibiotic types may increase the risk of the eight common cancer types in the studies population, especially in male, and the cancer risk increases with increasing antibiotic exposure intensity.

Background

Cancers are among the leading causes of morbidity and mortality worldwide, responsible for 18.1 million new cases and 9.6 million deaths in 2018[1]. Well-known cancer risk factors include old age, family history, smoking, inherited syndromes, inflammation, obesity, decreased physical activity, diet
and so on[2]. The hypothesis that use of antibiotics may increase risk of cancer was proposed several decades ago.

Antibiotic is an organic chemical of natural or synthetic origin that inhibits or kills pathogenic bacteria[3], and the use of antibiotics has increased dramatically all over the world in recent years. An association between antibiotic use and risk of cancer has been studied since 2004, and a study reported an increased risk of incident and fatal breast cancer[4]. Now, many observational studies in humans evaluate the possible impact of antibiotic exposure on cancer risk in the lung[5], breast[6], prostate[7], colon[8] and liver[9] with conflicting results. Some studies found that antibiotics were associated with an increased risk of cancer[9], but others showed that antibiotic exposure was associated with a decreased risk of cancer[10] or demonstrated that the evidence is insufficient to support the effect of antibiotics[5].

To better understand the relationship between exposure to antibiotics and cancer, we combined all published epidemiologic studies on this issue and conducted the meta-analysis to investigate the effect of antibiotics on cancer development. At the meantime, our other aims were to determine whether the effect of antibiotics on cancer could be different in gender, different cancers, and the specific antibiotic classes.

Methods
Following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)[11] guidelines, we performed a meta-analysis and systematic review dealing with the association between antibiotic use and cancer risk in human.

Search strategy
There is a two-step search strategy. First, a search of PUBMED/Medline, EMBASE/Web of Science and Chinese databases for articles written in English that examined exposure to antibiotics before a new diagnosis of cancer. The keywords we used were the following: (“antibiotic or penicillin or cephalosporin or tetracycline or doxycycline or fluoroquinolone or macrolide or sulfonamide or metronidazole or Nitrofuran derivates”) and (“cancer or tumor or carcinoma or melanoma or sarcoma or lymphoma or leukemia”). In the second part, we searched the bibliographies of retrieved
publications to further increase the yield of potentially relevant articles. For studies that did not report outcomes of interest, we contacted the authors via email. Two independent reviewers (Y. T.L and K. Y.H) made an initial judgment of whether the studies were eligible to be included in the analysis, and any disagreements were resolved by consulting S. H. T.

**Inclusion and exclusion criteria**

The inclusion criteria were required as follows. (1) The original articles in English and Chinese languages were cohort studies and case-control studies that provided data on antibiotic exposure before new diagnoses of cancer. (2) Antibiotic exposure was determined by either medication prescription records or by patient survey. (3) Studies reported the risk estimates (hazard ratio (HR) or relative risk (RR) or Odds ratio (OR)) with their corresponding 95% confidence interval (CI) or original data allowing us to compute them were available. Studies were excluded if they did not report data on antibiotic exposure or did not have a control group. Duplicate reports, abstracts and review articles were also excluded in this analysis.

**Data extraction and Quality assessment**

Data extraction from each study included the name of the first author, study design, publication year, study region, study period, total number of sample size, type of cancer, adjustments, exposure definition, and measure of exposure. Two investigators (Y. T.L and K. Y.H) independently extracted the data, and discrepancies were resolved through consensus.

The methodological quality of included studies was evaluated based on the Newcastle-Ottawa Scale (NOS)[12] for assessing the quality of case-control studies and cohort studies in meta-analysis. A star system of the NOS ranges from 0 to 9 and is composed of the three categories: selection, comparability, and exposure. The score of 7 or higher in case-control studies and cohort studies was considered as the high-quality studies. Study quality was assessed independently by two of the investigators (C. X.Z and L.Z), and any discrepancies were addressed by a joint reevaluation of the original article.

**Definition of antibiotic exposure intensity**

Based on the different total number of antibiotic prescriptions reported in the included studies for
each participant before tumor occurrence, we classified the total number of antibiotic prescriptions into three groups. Higher use of antibiotics was defined as use of the total number of prescriptions of no less than 10 times, moderate use of antibiotics was defined as use of the total number of prescriptions of 5–10 times, and lower use of antibiotics was defined as use of the total number of prescriptions of no more than 5 times. On the other hand, according to the different cumulative days of antibiotic use, we classified them into two group: ≤50days and >50days.

**Statistical analysis**

Statistical analysis was performed using STATA version 12.0. The results were expressed in terms of OR and 95%CI, and P<0.05 was considered statistically significant. To assess the heterogeneity in results of individual studies, $I^2$ statistics were used. If $I^2$>50%, we considered to indicate substantial heterogeneity between studies and a random-effects models was used. Conversely, a fixed-effects model was used. Then, subgroup analysis and sensitivity analysis by omitting one study each time and recalculating the pooled OR was performed. Publication bias was evaluated with the use of funnel plots and Egger’s test for asymmetry. When the P values is less than 0.05 by Egger’s test, publication bias exists.

**Results**

**Search results and study characteristics**

Figure 1 shows the detailed selection process. A total of 5973 potentially relevant articles were initially retrieved using our database search strategy, and 3749 duplicate articles were excluded. After screening the title and assessing the abstract, 41 articles were remained for full text review. Among them, 18 articles were excluded (9 were not relevant to our analysis, 6 were review articles, 2 did not provide insufficient data, and 1 did not have a control group). In the end, a total of 23[2, 4–10, 13–27]eligible articles were included in our meta-analysis: 19 case-control[2, 4–10, 13–16, 18, 19, 23–27] and 4 cohort studies[17, 20–22].

Table 1 shows the general characteristics of the studies included in the analyses. A total of 23 included studies published between 2003 and 2018 had 529527210 participants, including 366721 case and 529160489 controls. 16 common cancers involved liver cancer, colorectal cancer, stomach
and small intestine cancer, lymphomas, breast cancer, lung cancer, prostate cancer, renal and bladder, leukemia, esophageal cancer, gallbladder cancer, pancreas cancer, cervical cancer, ovarian cancer, corpus uteri cancer, and melanoma can be found in this analysis. Of the studies, seven were conducted in Europe (1 in UK, 2 in Denmark, 2 Spain, 1 in Finland, and 1 in Sweden), fourteen in North America (11 in USA and 3 in Canada), one in Asia (Taiwan), and one in Oceania (New Zealand). The quality on the basis of the NOS score were described in Table 1. The range of quality scores was 5 to 8. 14 studies were deemed to be of high quality on the basis of the NOS score, and the other 9 studies were low quality.

**Antibiotic use and cancer risk**

For the primary outcome of cancer occurrence, a meta-analysis was conducted with the data from the 23 heterogeneous studies ($I^2 = 92.9\%$), showing exposure to antibiotics significantly increased the risk of cancer with an OR of 1.20 (95% CI 1.13–1.27, $P = 0.000$; Fig.2). Subsequently, we conducted a sensitivity analysis by omitting one study each time and recalculating the pooled OR, and the results showed the pooled risk estimates did not change significantly (Additional file 1: TableS1). There was a symmetric funnel plot and no evidence of significant publication bias from Begg’s test ($P = 0.196$) of the 23 studies.

Then, a subgroup analysis was conducted by sex. In the male group, the result from 8 articles[2, 5, 7, 13, 14, 19, 20, 22] showed that antibiotic use was associated with a 34% increased risk of cancer (OR = 1.34 95%CI: 1.15–1.56; $P = 0.000$; Table 2 and Fig.3) using random effect model. However, in the female group, the 12 heterogeneous studies[2, 4, 5, 10, 14, 17, 20–25] were included in the analysis, only showing a 19% increased risk of cancer in relation to antibiotic use (OR = 1.19 95%CI: 1.09–1.3; $P = 0.000$) with random effect model.

**The classes of antibiotic use and cancer risk**

We pooled data on the classes of antibiotics, and 17 studied[2, 4–8, 10, 13, 15–18, 21, 23, 24, 26, 27] reported on the risk associated with specific antibiotics. Sufficient data were available on seven antibiotic classes including penicillin, macrolides, quinolones, sulfonamides, tetracycline, cephalosporins, and nitrofuran derivates. We found that, with the exception of nitrofuran derivates,
the other six classes of antibiotics were associated with the increased risk of cancer (Table 2 and Additional file 2: Fig.S1–7). Then, a sensitive analysis was conducted and indicated that no individual studies could change the pooled results (Additional file 1: TableS2–8).

The intensity of antibiotic exposure and cancer risk

When combining 12 studies[4–9, 13, 16, 18, 20, 23, 25] that provided total number of antibiotic prescriptions for each participant, we additionally examined antibiotic use by the number of prescriptions. The meta-analysis indicated that the risk of developing cancer increased with an increasing number of antibiotic prescriptions, and the pooled OR was 1.22 (95%CI: 1.13–1.33, P = 0.000) for lower use, 1.39 (95%CI:1.20–1.61, P = 0.000) for moderate use, and 1.40 (95%CI:1.11–1.76, P = 0.005) for higher use (Table 2 and Fig.4). Furthermore, we calculated the cumulative days of antibiotic exposure. The combined analysis (Table 2 and Fig. 5) from 8 heterogeneous studies[4, 8, 16, 17, 21, 24, 25, 27] showed a greater increased risk of cancer(25%) in the group with the cumulative >50days of antibiotic use (OR = 1.25 95%CI: 1.09–1.42, P = 0.001) compared with the group with the cumulative ≤50days(13%) (OR = 1.13 95%CI: 1.05–1.21, P = 0.001).

Antibiotic use and different cancers

Table 2 and Additional file 2: Fig. S8–18 showed the ORs for the 16 separate cancers that we assessed. The exposure to antibiotics was associated with an elevated risk of eight common cancer types, namely, liver cancer (OR = 1.22, 95%CI:1.08–1.38, P = 0.001), colorectal cancer (OR = 1.09, 95%CI:1.02–1.18, P = 0.015), stomach and small intestine cancer (OR = 1.12, 95%CI:1.04–1.21, P = 0.002), lymphomas (OR = 1.26, 95%CI:1.10–1.46, P = 0.001), breast cancer (OR = 1.31, 95%CI:1.05–1.22, P = 0.001), lung cancer(OR = 1.18, 95%CI:1.08–1.29, P = 0.000), prostate cancer(OR = 1.26, 95%CI:1.06–1.50, P = 0.009), renal and bladder (OR = 1.20, 95%CI:1.02–1.42, P = 0.03). However, there was no significant association between antibiotic use and the risk of the other eight cancer types, namely, leukemia(P = 0.06), esophageal cancer(P = 0.813), gallbladder cancer(P = 0.345), pancreas cancer(P = 0.118), cervical cancer(P = 0.134), ovarian cancer(P = 0.391), corpus uteri cancer(P = 0.507), and melanoma(P = 0.288).

Discussion
This present meta-analysis, which was based on twenty-three observational studies involving 529527210 participants, was designed to investigate the association between antibiotic use and the risk of cancer. Though many studies have explored the association, there is still no consistent conclusion. To our knowledge, this is the first meta-analysis investigating the relationship between antibiotic exposure and cancer risk. Our results revealed that exposure to antibiotics increased the risk of cancer. Subgroup meta-analysis by gender showed that the effect of antibiotic use on cancer risk seemed to be greater in the male group (34%) compared with the female group (19%). On the other hand, the risk of cancer increased with an increasing number of antibiotic prescriptions and the increasing cumulative days of antibiotic exposure. Moreover, of 7 common antibiotic types, the six classes of antibiotics (penicillin, macrolides, quinolones, sulfonamides, tetracycline, cephalosporins) were associated with the increased risk of cancer, whereas no significant association was found between nitrofuran derivates and cancer risk. Further, of 16 separate cancers, exposure to antibiotics increased the risk of eight common cancer types (liver cancer, colorectal cancer, stomach and small intestine cancer, lymphomas, breast cancer, lung cancer, prostate cancer, and renal and bladder), but no significant association was found between antibiotic exposure and the other 8 cancer types (leukemia, esophageal cancer, gallbladder cancer, pancreas cancer, cervical cancer, ovarian cancer, corpus uteri cancer, and melanoma).

Although it is impossible to draw causal links on the basis of these data, there are several possible explanations for the increased risk of cancer with the use of antibiotics. First, since antibiotic has no known direct carcinogenic effect, our main hypothesis focuses on the effect of antibiotic use on the composition of the human microbiota. The microbiome can induce chronic inflammation[28], influence human metabolism by activating genes that are related to both insulin resistance and cell proliferation[16], and affect the immune-system response against cancer[29]. Studies in germ-free animals reveal evidence for tumor-promoting effects of the microbiota in spontaneous, genetically-induced and carcinogen-induced cancers in various organs, including the skin, colon, liver, breast and lung[30]. The repeated antibiotic exposure could cause a lasting change in bacterial diversity and taxonomic richness[31]. Further, metaproteomic analysis also demonstrates that antibiotics reduce
the abundance and diversity of microbiome and negatively affect the overall metabolic status of the gut microbiome[32]. In addition, studies have shown antibiotics resistance can persist for longer periods of time than previously recognized[33]. The effect isn’t unique only to the gut microbiota, and it can occur by microbiota of other organs as well, such as liver and blood system. Josefsdottir et al[34] showed microbiome depletion as a result of broad-spectrum antibiotic treatment disrupts basal Stat1 signaling and alters T-cell homeostasis, leading to impaired progenitor maintenance and granulocyte maturation. Schwabe et al[30] suggested antibiotic-induced disturbance of commensal microbiota and subsequent dysbiosis might result in increased hepatic exposure to bacterial products and metabolites that could be carcinogenic.

Another plausible mechanism connecting the use of antibiotics to the increased risk of cancer may be involved in detrimental effects on immune defense, especially long-term and repeated treatment. Commensal bacteria are crucial to maintain immune homeostasis in mucosal tissues and disturbances in their ecology can affect disease susceptibility. Antibiotics could destroy the commensal bacteria and the antibiotic-treated mice were more susceptible to development of engrafted B16/F10 melanoma and Lewis lung carcinoma, suggesting the deleterious effects of antibiotic treatment on cancer susceptibility and progression[29]. Antibiotics can also affect the immune system by disturbing the gut microbiota, which plays an important role in maintaining a healthy immune system[35]. What’s more, Routyet al showed antibiotic inhibited the clinical benefit of immune checkpoint inhibitors in patients with cancer[36]. Therefore, antibiotics could affect the weaken immune system and exposure to antibiotics are more susceptible for developing cancer.

These mechanisms may explain the part effects of antibiotic use on tumor, but as for the time being the causal or confounding nature of antibiotics and cancer relationship has not been established. Here, it is important that the association in our analysis deserves attention. This highlights the fact that antibiotics may have negative effects on patients (increase the risk of cancer, for example) when treating or preventing the human infectious diseases, and thus they should be reasonably used. Of course, the findings in our analysis still needs for further biochemical investigations and confirmation. Our meta-analysis has to be interpreted with caution in view of some limitations. Firstly, studies
included in this analysis are observational epidemiological studies such as case-control and cohort studies. In general, case-control studies are more susceptible to biases, such as selection bias and recall bias. Also, case-control studies and cohort studies have a lower level of evidence than randomized controlled trials. However, to our knowledge, by reason of the low incidence of cancer, it is difficult to complete a large randomized controlled trial within a finite time horizon. Secondly, there was significant heterogeneity among the studies when all were grouped together. The heterogeneity appeared to be due to the different standards to measure antibiotic use and cancer risk. However, omitting one study each time in sensitivity analysis affected the magnitude but did not affect the statistical significance of our results. Thirdly, a small part of studies didn’t adjust some confounders such as age, smoking, alcohol drinking, and other cancer risk factors. Fourthly, all the studies measured antibiotic use by prescription based on health-care system or databases. Therefore, it is possible that some recorded antibiotics were not used. The last limitation is that the included study populations mainly come from Europe and North America, thus the study coverage in the world was limited because of absence of studied from Africa, Asia, and Australia. Therefore, the value of our results is limited for other areas except the countries involved in the study.

Conclusion
Our study demonstrated that exposure to common antibiotic types may increase the risk of the above eight common cancer types in the studies population, especially in the male population, and the cancer risk increases with increasing antibiotic exposure intensity. More large and precise studies are required to further assess the association and the underlying mechanisms between antibiotic use and cancer risk.

Abbreviations
AML: acute myeloid leukemia; CRC: colorectal cancer; CI: confidence interval; HR: hazard ratios; HCC: hepatocellular carcinoma; NHL: non-Hodgkin lymphomas; OR: odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR: relative risks.

Declarations

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meta-analysis.

Authors’ contributions
Y. T.L: study design, data collection, data analysis and interpretation, and writing and editing the paper; K. Y.H: study design, data collection, data analysis and interpretation, reviewed drafts of the paper; C. X.Z: data collection, and data analysis; L.Z: data analysis and interpretation; S. H.T: study design, critical revision of the manuscript for important content.

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Availability of data and materials
All data are included in this paper and its supplementary information

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Competing of interest
Authors declare that they have no conflict of interest.

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Tables

Table 1. General characteristics of included studies n=23

14
| Study       | Study design | Location | Time period | no. of study (case/control) | Gender/ Age/year | Type of cancer | Exposure Definition |
|-------------|--------------|----------|-------------|----------------------------|-----------------|----------------|---------------------|
| Russell 2018[13] | case-control | UK       | 1998-2012   | 8762/43806                 | Men/ <90        | prostate cancer  | Antibiotics given > prior to index-date |
| Ostgard 2018[14] | case-control | Denmark  | 1995-2013   | 2451/23827                 | Men and women/ 69.4(median) | AML            | The minimum 5-yr exposure |
| Yang 2016[9] | case-control | USA      | 1988-2011   | 1159/4640                  | Men and women/ 10-90 | Liver cancer    | Antibiotic given >1 to index-date |
| Dik 2016[8]  | case-control | USA      | 2006-2011   | 4029/15988                 | Men and women/ ≥18 | CRC            | The use of antibiotics measured in the periods prior to CRC and excluded the first 1.5 years |
| Boursi 2015[15] | case-control | USA      | 1995-2013   | 125441/490510              | Men and women/ 20 | 15 common malignancies | Antibiotic given >1 to index-date |

Table 1. General characteristics of included studies n=23 Continued
| Study          | Study design | Location  | Time period | no. of study (case/control) | Gender/ Age/year | Type of cancer | Exposure Definition |
|---------------|-------------|-----------|-------------|----------------------------|------------------|-----------------|---------------------|
| Boursi 2015[16] | case-control | USA       | 1995-2013   | 20990/82054                | Men and women/ 40 | CRC             | Antibiotic given >1 to index-date |
| Wang 2014[2]   | case-control | Taiwan    | 2000-2007   | Colon 3593/14372           | Men and women/ 70.93± 9.40/69.71± 9.71 | CRC             | Antibiotic given >1 to index-date |
| Wirtz 2013[17]| cohort study | USA       | 1990-2008   | 1678/9112                  | Women/ ≥18        | Breast Cancer   | Antibiotic given >1 to index-date |
| Rasmussen 2012[18] | case-control | Denmark    | 1995-2008   | 13602/51.6million          | Men and women/ ≥15 | NHL             | Antibiotic given >1 to index-date |
| Tamim 2011[10] | case-control | Canada    | 1981-2000   | 1225/4900                  | Women / 5-82.5    | Gynecological cancer: Over a minimum of 15 years before diagnosis |

Table 1. General characteristics of included studies n=23 Continued
| Study          | Study design | Location  | Time period | no. of study (case/control) | Gender/ Age/year | Type of cancer | Exposure Definition                      |
|---------------|--------------|-----------|-------------|-----------------------------|------------------|----------------|------------------------------------------|
| Tamim 2010[7] | case-control | Canada    | 1981–2000   | 4052/16208                  | Men/ 5-82.5      | Prostate cancer | Over a minimum of 15 years before diagnosis |
| Daniels 2009[19] | case-control | USA       | 1996–2006   | 65/195                      | Men/ ≥40         | Prostate cancer | At least 1 year before the index date     |
| Zhang 2008[5]  | case-control | Spain     | 1995–2004   | 4336/10000                  | Men and women/ 40-84 | Lung Cancer | At least 1 year before diagnosis          |
| Tamim 2008[6]  | case-control | Canada    | 1991–2000   | 3099/12396                  | NA/ 5-82.5       | Breast cancer | Over a minimum of 15 years before diagnosis |
| Kilkkinen 2008[20] | cohort study | Finland  | 1998–2004   | 134070/ 3112624             | Men and women/ 30–79 | Total cancer | Covering each time window (i.e. 1995–1997, 1998–2000 and 2001–2003) |
| Friedman 2006[21] | cohort study | USA      | 1994–2003   | 18521/ 2130829             | Women/ ≥20       | Breast cancer: | NA                                       |
| Fall 2006[22]   | cohort study | Sweden    | 1970–2003   | 645/ 5914225               | Men and women/ 40.6(mean) | Gastric cancer | Exclusion of the first year of follow-up |

Table 1. General characteristics of included studies n=23 Continued
| Study             | Study design | Location | Time period       | no. of study (case/control) | Gender/ Age/year | Type of cancer          | Exposure Definition                                                                 |
|------------------|--------------|----------|-------------------|-----------------------------|------------------|------------------------|------------------------------------------------------------------------------------|
| Sorensen 2005[23] | case-control | USA      | 1994-2003,        | 2728/27280                  | Women/ 62(mean)  | Breast cancer           | NA                                                                                |
| Kaye 2005[24]     | case-control | USA      | 1987-2002         | 1268/6291                   | Women/ 40 -79    | Breast cancer           | At least 6 years of history before their (diagnosis) date                           |
| Garcia Rodriguez 2005[25] | case-control | Spain    | 1995-2001         | 3708/20000                  | Women/ 30–79     | Breast cancer           | At least 1 year before index date                                                  |
| Didham 2005[26]   | case-control | New Zealand | 1996-2002        | 6678/1.2million             | Men and women/  | Total cancer            | At least two years prescribing and coding data was required before diagnosis of cance |
| Velicer 2004[4]   | case-control | USA      | 1993-2001         | 2266 /7953                  | Women/ ≥19       | Breast cancer           | At least 1 year before reference date                                              |
| Kato 2003[27]     | case-control | USA      | 1995-1998         | 376/463                     | Men and women/ 20–79 | NHL                    | A minimum lag period from exposure                                                |

CRC: colorectal cancer; NHL: non-Hodgkin lymphomas

Table 2. antibiotics use and the risk of cancer in the subgroup analysis by various factors
| Factors                                      | Number of studied | Pooled OR (95%CI)           | P value |
|---------------------------------------------|-------------------|----------------------------|---------|
| All [2, 4-10, 13-27]                        | 23                | 1.20 (1.13, 1.27)           | 0.000   |
| Antibiotic class                            |                   |                            |         |
| Penicillin [2, 4-8, 10, 13-15, 18, 21, 23, 24, 26, 27] | 17                | 1.15 (1.09, 1.21)           | 0.000   |
| Macrolides [4-8, 10, 15, 16, 18, 21, 23, 24, 26] | 14                | 1.14 (1.08, 1.20)           | 0.000   |
| Quinolones [2, 4, 5, 8, 13, 15-18, 21, 23]   | 11                | 1.16 (1.06, 1.26)           | 0.001   |
| Sulfonamides [4-8, 10, 13, 15-17, 21, 23, 26, 27] | 14                | 1.14 (1.06, 1.22)           | 0.000   |
| Tetracycline [4-8, 10, 13, 15-18, 21, 23, 24, 26, 27] | 16                | 1.10 (1.05, 1.16)           | 0.000   |
| Cephalosporins [2, 4-7, 10, 13, 15-17, 21, 23, 24, 26, 27] | 15                | 1.19 (1.10, 1.28)           | 0.000   |
| Nitrofurans derivates [8, 13, 15, 16, 21, 26] | 6                 | 1.11 (0.97, 1.27)           | 0.130   |
| Type of cancer                              |                   |                            |         |
| Prostate [7, 13, 15, 19, 20, 26]             | 6                 | 1.26 (1.06, 1.50)           | 0.009   |
| Leukemia [14, 20, 26]                        | 3                 | 1.19 (0.99, 1.42)           | 0.060   |
| Lymphomas [18, 20, 26, 27]                   | 4                 | 1.26 (1.10, 1.46)           | 0.001   |
| Lung [5, 15, 20, 26]                         | 4                 | 1.18 (1.08, 1.29)           | 0.000   |
| Liver cancer [9, 15, 20]                     | 3                 | 1.22 (1.08, 1.38)           | 0.001   |
| Colorectal cancer [2, 8, 16, 20, 26]         | 5                 | 1.09 (1.02, 1.18)           | 0.015   |
| Esophagus [15, 20, 26]                       | 3                 | 1.01 (0.91, 1.12)           | 0.813   |
| Stomach and small intestine [15, 20, 22, 26] | 4                 | 1.12 (1.04, 1.21)           | 0.002   |
| Gallbladder [15, 20]                         | 2                 | 1.12 (0.89, 1.40)           | 0.345   |
| Pancreas [15, 20]                            | 2                 | 1.24 (0.95, 1.61)           | 0.118   |
| Breast cancer [4, 6, 15, 17, 20, 21, 23-26]  | 10                | 1.31 (1.05, 1.62)           | 0.001   |
| Cervix [10, 15, 20]                          | 3                 | 0.73 (0.49, 1.10)           | 0.134   |
| Ovary [10, 20]                               | 2                 | 0.97 (0.90, 1.04)           | 0.391   |
| Corpus uteri [10, 20]                        | 2                 | 1.06 (0.89, 1.28)           | 0.507   |
| Renal and bladder [15, 20, 26]               | 3                 | 1.20 (1.02, 1.42)           | 0.030   |
| Melanoma [15, 20, 26]                        | 3                 | 1.07 (0.95, 1.21)           | 0.288   |
| The total number of antibiotics prescriptions|                   |                            |         |
| Low [5-9, 13, 16, 18, 20]                    | 9                 | 1.22 (1.13, 1.33)           | 0.000   |
| Intermediate [5, 7-9, 13, 16, 18, 20]        | 8                 | 1.39 (1.20, 1.61)           | 0.000   |
| High [4-7, 9, 13, 16, 23, 25]                | 9                 | 1.40 (1.11, 1.76)           | 0.005   |
| The cumulative days of antibiotic use        |                   |                            |         |
| ≤50 days [4, 8, 16, 17, 21, 24, 25, 27]      | 8                 | 1.13 (1.05, 1.21)           | 0.001   |
| >50 days [4, 8, 16, 17, 21, 24, 25, 27]      | 8                 | 1.25 (1.09, 1.42)           | 0.001   |
| Sex                                          |                   |                            |         |
| Male [2, 5, 7, 13, 14, 19, 20, 22]           | 8                 | 1.34 (1.15, 1.56)           | 0.000   |
| Female [2, 4, 5, 10, 14, 17, 20-25]          | 12                | 1.19 (1.09, 1.31)           | 0.000   |

**Figures**

[Diagram of the search process and article exclusion criteria]
Figure 1

Flow diagram of literature search and study selection
Figure 2

Risk of cancer with antibiotic exposure across all studies. Forest plot showing the summary odds ratio (OR). Weights are from random-effects analysis.
Figure 3

Risk of cancer with antibiotic exposure by gender. Forest plot showing the summary odds ratio (OR). Weights are from random-effects analysis.
Figure 4

Risk of cancer with the total number of antibiotics prescriptions. Forest plot showing the summary odds ratio (OR). Weights are from random-effects analysis.
Figure 5

Risk of cancer with the cumulative days of antibiotic use. Forest plot showing the summary odds ratio (OR). Weights are from random-effects analysis.

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