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 word 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^2statistics 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 (Table2 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. S8–18showed 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, Routy*et 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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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）

Study	Study design	Location	Time period	no. of study (case/control)	Gender/ Age（year）	Type of cancer	Exposure Definition	Measure of Exposure	Covariate adjustments	Quality assessment
Russell 2018[13]	case-control	UK	1998-2012	8762/43806	Men/ <90	prostate cancer	Antibiotics given >6 months prior to index-date	Number of prescriptions, class of antibiotic, time between the first use and event	Adjusted for civil status, education, CCI and time between first antibiotic and event	8
Ostgard 2018[14]	case-control	Denmark	1995–2013	2451/23827	Men and women/ 69.4(median)	AML	The minimum 5-year for exposure	Class of antibiotic	Adjusted for date of birth and sex.	7
Yang 2016[9]	case-control	USA	1988-2011	1159/4640	Men and women/ 10-90	Liver cancer	Antibiotic given >1 year prior to index-date	Number of prescriptions, time between the first and last	Adjusted for body mass index, smoking status, alcohol-related disorders, hepatitis B or C virus infection, diabetes, rare metabolic disorders, and use of anti-diabetic medications, paracetamol, and statins.	8
Dik 2016[8]	case–control	USA	2006–2011	4029/15988	Men and women/ ≥18	CRC	The use of antibiotics was measured in the period 1–6 years prior to CRC diagnosis, and excluded the first 1.5 years	Number of prescriptions, days of use, class of antibiotic	Adjusted for age, sex, insulin-independent diabetes, insulin-dependent diabetes, and the use of proton pump inhibitors, acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, blood lipid-lowering agents, estrogens, and immunosuppressive drugs	8
Boursi 2015[15]	case-control	USA	1995–2013	125441/490510	Men and women/ 20	15 common malignancies	Antibiotic given >1 year prior to index-date	Class of antibiotic, time between the last prescription and cancer, type of cancer	Adjusted for common cancer risk factors, reverse causality (cancer patients are at higher risk for infections), confounding by indication (infection may be a risk factor for cancer),protopathic bias (medication was prescribed due to symptom of undiagnosed cancer) and failure to account for changes in trends of antibiotic	8

							prescription over time as well as changes in antibiotic types used.

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	Measure of Exposure	Covariate adjustments	Quality assessment
Boursi 2015[16]	case-control	USA	1995–2013	20990/82054	Men and women/ ≥40	CRC	Antibiotic given >1 year prior to index-date	The total number of prescriptions, class of antibiotic, days of use	Adjusted to diabetes mellitus, ischemic heart disease, BMI, smoking history, alcohol consumption, chronic use of Aspirin/NSAIDs, and performance of screening colonoscopy	8
Wang 2014[2]	case-control	Taiwan	2000–2007	Colon 3593/14372 Rectal 1979/7916	Men and women/ 70.93± 9.40/ 69.71± 9.71	CRC	Antibiotic given >1 year prior to index-date	The total number of prescriptions, days of use, class of antibiotic	corticosteroids, antibiotics, insulin, sulfonylurea, glinides, metformin, history of cholecystectomy, number of stool occult blood tests, diuretics, number of outpatient visits, thiazolidinedione and chronic kidney disease.	7
Wirtz 2013[17]	cohort study	USA	1990-2008	1678/9112	Women/ ≥18	Breast Cancer	Antibiotic given >1 year prior to index-date	Days of use, class of antibiotic	age, incident breast cancer diagnosis year, AJCC stage, hormone receptor status, primary treatment for the initial breast cancer, endocrine therapy, BMI, smoking status, menopausal status, Charlson comorbidity score, acne and/or rosacea, COPD, UTI, and receipt of surveillance mammography.	6
Rasmussen 2012[18]	case-control	Denmark	1995–2008	13602/51.6million	Men and women/ ≥15	NHL	Antibiotic given >1 year prior to index-date	The total number of prescriptions, years since the latest prescription, class of antibiotic	Adjusted for age, sex and calendar period.	7
Tamim 2011[10]	case-control	Canada	1981–2000	1225/4900	Women / 5-82.5	Gynecological cancer:	Over a minimum of 15 years before diagnosis	Type of cancer, the total number of prescriptions, number of pills, time of exposure to	NA	6

							antibiotics, class of antibiotic			

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	Measure of Exposure	Covariate adjustments	Quality assessment
Tamim 2010[7]	case-control	Canada	1981–2000	4052/16208	Men/ 5-82.5	Prostate cancer	Over a minimum of 15 years before diagnosis	The total number of prescriptions, number of pills, time of exposure to antibiotics, class of antibiotic	NA	6
Daniels 2009[19]	case-control	USA	1996–2006	65/195	Men/ ≥40	Prostate cancer	At least 1 year before the index date	The total number of prescriptions,	Adjusted for age group, race, years of enrollment, and number of visits.	7
Zhang 2008[5]	case-control	Spain	1995–2004	4336/10000	Men and women/ 40-84	Lung Cancer	At least 1 year before diagnosis	The total number of prescriptions, class of antibiotic	Adjusted for age group, race, years of enrollment, and number of visits.	6
Tamim 2008[6]	case-control	Canada	1991–2000	3099/12396	NA/ 5-82.5	Breast cancer	Over a minimum of 15 years before diagnosis	The total number of prescriptions, number of pills, time of exposure to antibiotics, class of antibiotic	NA	6
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)	Type of cancer, the total number of prescriptions	Adjusted with hormone replacement therapy	5
Friedman 2006[21]	cohort study	USA	1994-2003	18521/ 2130829	Women/ ≥20	Breast Cancer:	NA	Days of use, class of antibiotic	Adjusted with hormone	6
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	NA	NA	5

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	Measure of Exposure	Covariate adjustments	Quality assessment
Sorensen 2005[23]	case-control	USA	1994–2003,	2728/27280	Women/ 62(mean)	Breast cancer	NA	The total number of prescriptions, class of antibiotic	Adjusted for age at first birth, parity, and use of postmenopausal hormone replacement therapy	7
Kaye 2005[24]	case-control	USA	1987-2002	1268/6291	Women/ 40 -79	Breast cancer	At least 6 years of recorded history before their index (diagnosis) date	Days of use, class of antibiotic	Adjusting for BMI, use of hormone replacement therapy, history of benign proliferative breast disease, frequency of mammograms, and frequency of visits to general practice	8
Garcia Rodriguez 2005[25]	case-control	Spain.	1995-2001	3708/ 20000	Women/ 30–79	Breast cancer	At least 1 year before the index date	The total number of prescriptions, days of use	Adjusting for age, calendar year, body mass index, alcohol intake, hormone replacement therapy, use of nonsteroidal anti-inflammatory drugs, prior benign breast disease, utilization of health-care services, and time under observation	8
Didham 2005[26]	case-control	New Zealand	1996-2002	6678/1.2million	Men and women/	Total cancer	At least two years of prescribing and consultation data was required prior to the diagnosis of cancer	Type of cancer, class of antibiotic	Adjusting for age	7
Velicer 2004[4]	case-control	USA	1993-2001	2266 /7953	Women/ ≥19	Breast cancer	At least 1 year before their reference date	Days of use, class of antibiotic, the total number of prescriptions	Adjusted for age and for length of Group Health Cooperative enrollment.	7
Kato 2003[27]	case-control	USA	1995-1998	376/463	Men and women/ 20–79	NHL	A minimum lag period of 1 year from exposure	Days of use， class of antibiotic, the total number of prescriptions	Adjusted for age at index date, family history of hematologic cancer, college education, smoking status, average frequency of use of pain-relieving drugs, surrogate status and year of interview.	6

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	Heterogeneity I^2
All[2, 4-10, 13-27]	23	1.20(1.13,1.27)	0.000	92.9%
Antibiotic class				
Penicillin [2,4-8,10,13,15-18,21,23,24,26,27]	17	1.15(1.09,1.21)	0.000	89.7%
Macrolides [4-8,10,15,16,18,21, 23,24,26]	14	1.14(1.08,1.20)	0.000	85.1%
Quinolones [2,4,5,8,13,15-18,21, 23]	11	1.16(1.06,1.26)	0.001	86.2%
Sulfonamides [4-8,10,13,15-17, 21,23,26,27]	14	1.14(1.06,1.22)	0.000	90.4%
Tetracycline [4-8,10,13,15-18,21,23,24,26,27]	16	1.10 (1.05,1.16)	0.000	84.0%
Cephalosporins [2,4-7,10,13,15-17,21,23,24, 26,27]	15	1.19 (1.10,1.28)	0.000	88.6%
Nitrofuran derivates [8,13,15,16,21,26]	6	1.11 (0.97,1.27)	0.130	95.0%
Type of cancer				
Prostate [7,13,15,19,20,26]	6	1.26(1.06,1.50)	0.009	98.3%
Leukemia [14,20,26]	3	1.19(0.99,1.42)	0.060	92.2%.
Lymphomas [18,20,26,27]	4	1.26(1.10,1.46)	0.001	94.9%.
Lung [5,15,20,26]	4	1.18(1.08,1.29)	0.000	78.9%
Liver cancer [9,15,20]	3	1.22(1.08,1.38)	0.001	49.3%
Colorectal cancer [2,8,16,20,26]	5	1.09(1.02,1.18)	0.015	89.2%
Esophagus [15,20,26]	3	1.01(0.91,1.12)	0.813	66.7%
Stomach and small intestine [15,20,22,26]	4	1.12(1.04,1.21)	0.002	72.6%
Gallbladder [15,20]	2	1.12(0.89,1.40)	0.345	0%
Pancreas [15,20]	2	1.24(0.95,1.61)	0.118	85.1
breast cancer [4,6,15,17,20,21,23-26]	10	1.31(1.05,1.22)	0.001	95.5%
Cervix [10,15,20]	3	0.73(0.49,1.10)	0.134	96.5%
Ovary [10,20]	2	0.97(0.90,1.04)	0.391	0%
Corpus uteri [10,20]	2	1.06(0.89,1.28)	0.507	69.5%
Renal and bladder [15,20,26]	3	1.20(1.02,1.42)	0.030	96.5%
Melanoma [15,20,26]	3	1.07(0.95,1.21)	0.288	92.5%
The total number of antibiotics prescriptions				
Low [5-9,13,16,18,20]	9	1.22(1.13,1.33)	0.000	88.8%
Intermediate [5,7-9,13,16,18,20]	8	1.39(1.20,1.61)	0.000	96.7%
High [4-7,9,13,16,23,25]	9	1.40(1.11,1.76)	0.005	96.9%
The cumulative days of antibiotic use				
≤50days [4,8,16,17,21,24,25,27]	8	1.13(1.05,1.21)	0.001	75.9%
>50days [4,8,16,17,21,24,25,27]	8	1.25(1.09,1.42)	0.001	90.7%
Sex				
Male [2,5,7,13,14,19,20,22]	8	1.34(1.15,1.56)	0.000	93.1%
Female [2,4,5,10,14,17,20-25]	12	1.19(1.09,1.31)	0.000	92.8%

Figures

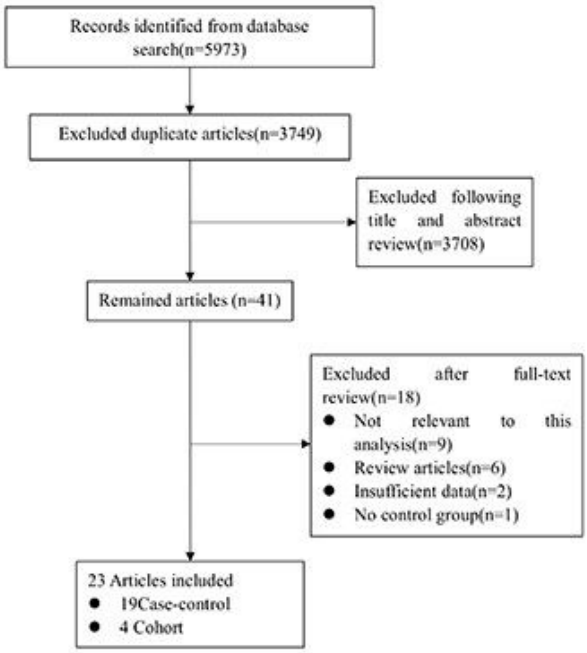

Figure 1

Flow diagram of literature search and study selection

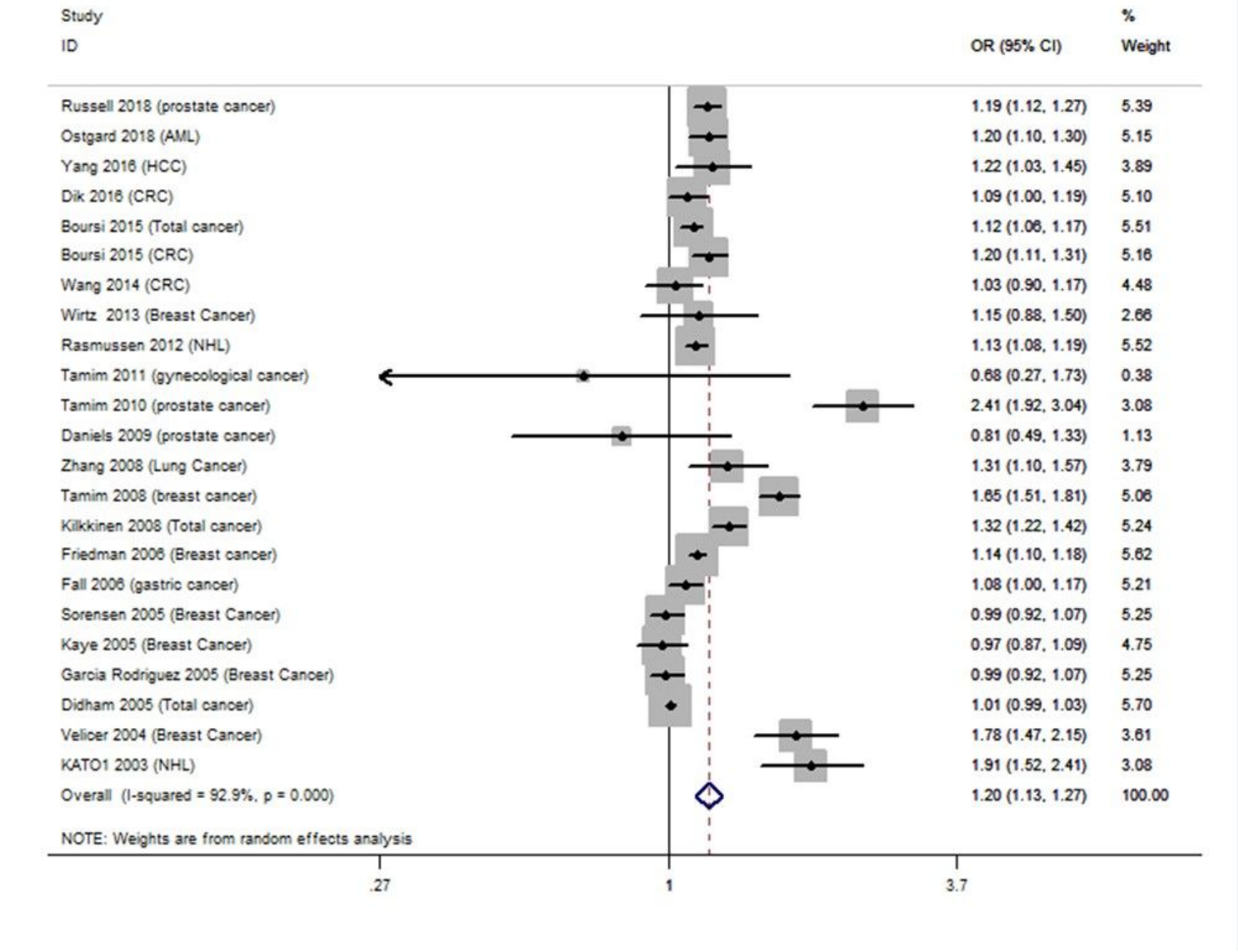

Figure 2

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

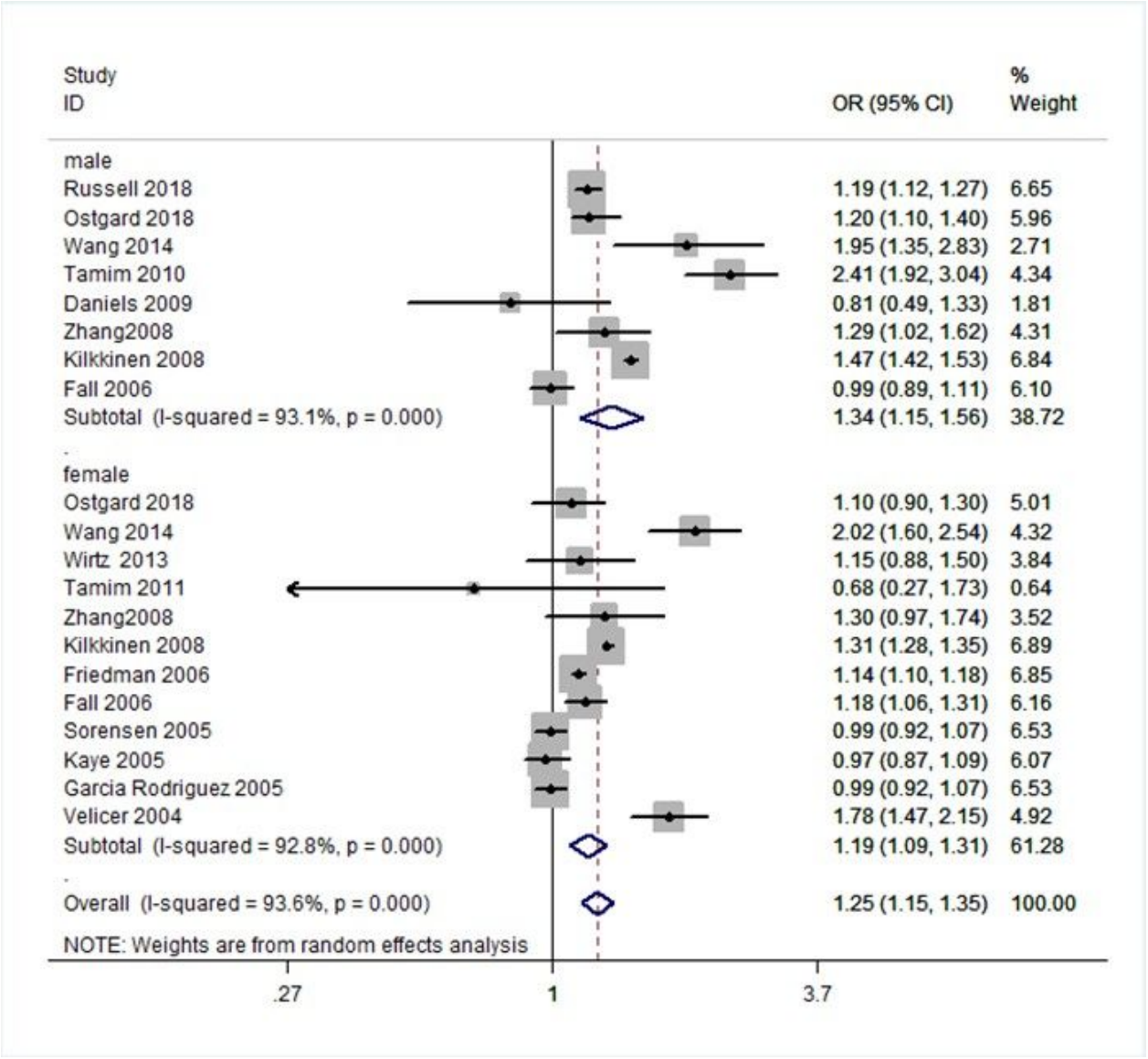

Figure 3

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

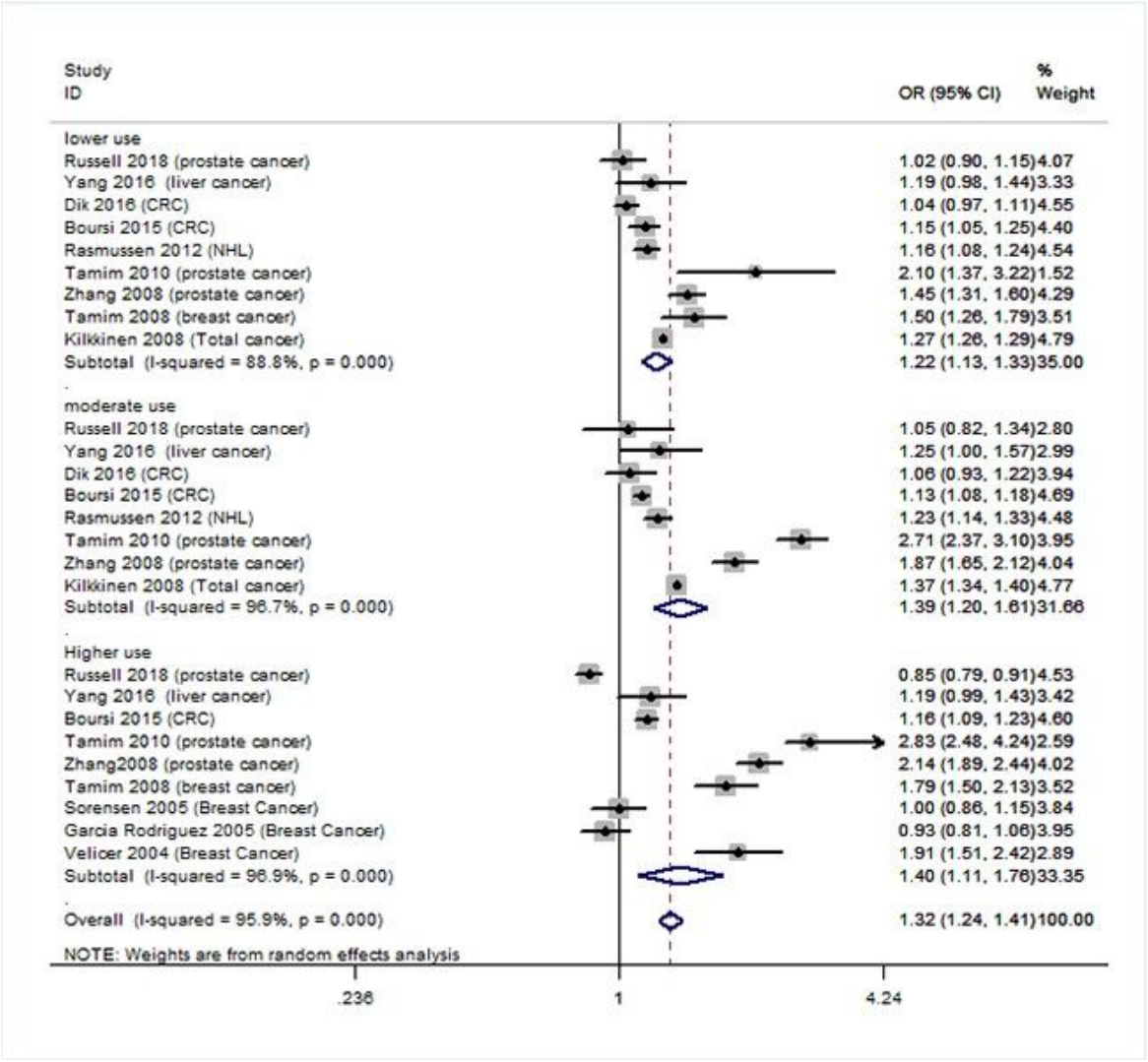

Figure 4

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

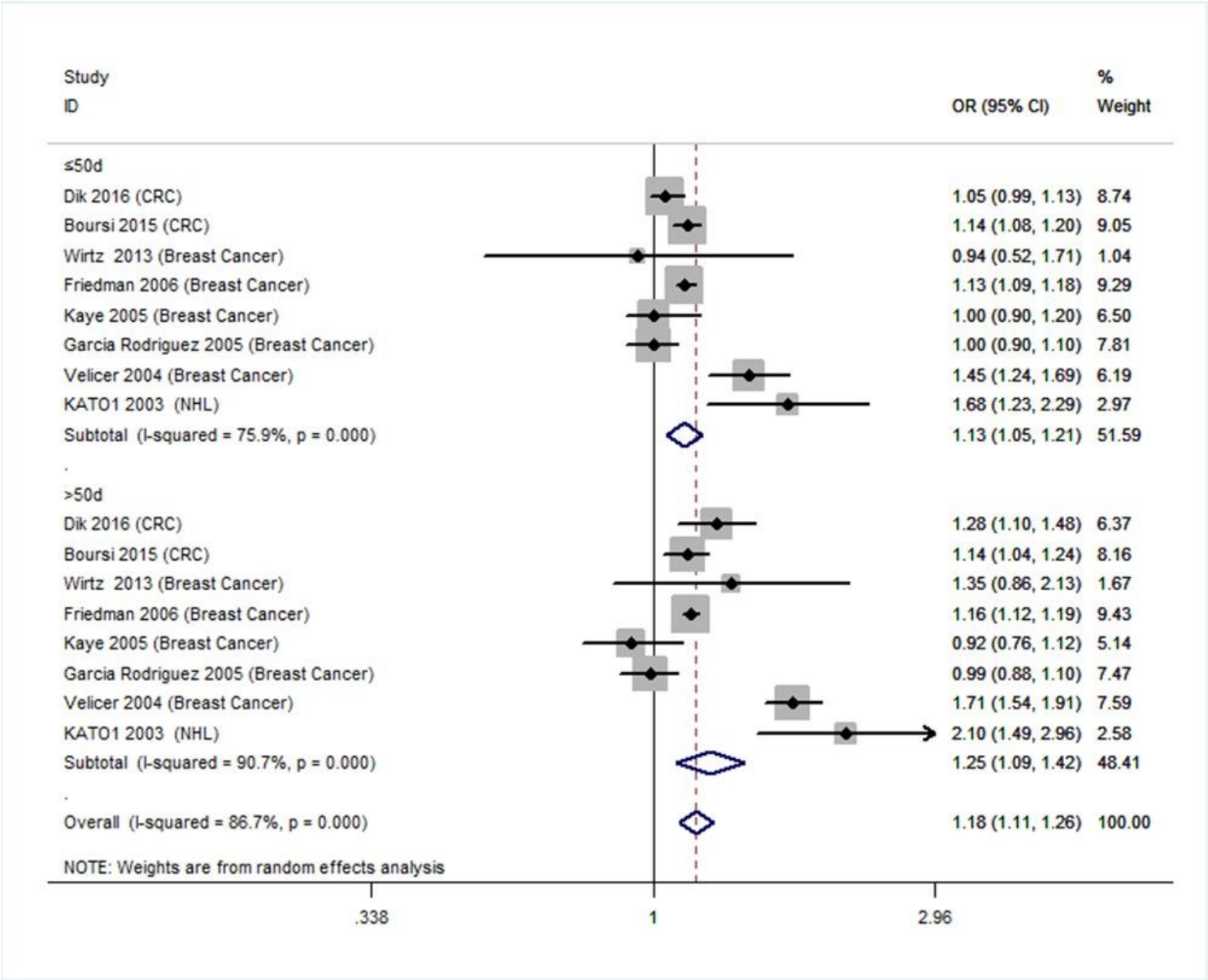

Figure 5

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

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile2.docx
- Additionalfile1.docx