Antidepressant use and colorectal cancer morbidity and mortality: A dose-response meta analysis

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Abstract
The risk of colorectal cancer associated to antidepressant use remains unclear. The purpose of this meta-analysis was to investigate the risk of colorectal cancer associated to antidepressant use.

Medline, Embase, Web of Science, and Cochrane Database were accessed from the dates of their establishment to October 2018, to collect study of antidepressant use and colorectal cancer morbidity and mortality. Then a meta-analysis was conducted using Stata 12.0 software.

A total of 11 publications involving 109,506 participants were included. The meta-analysis showed that antidepressant use was not associated with colorectal cancer morbidity (relevant risk (RR): 0.97; 95% confidence interval (CI): 0.94–1.01) and mortality (RR: 1.08; 95% CI: 0.99–1.17). Subgroup analysis showed selective serotonin reuptake inhibitor (RR: 0.99; 95% CI: 0.96–1.03) or serotonin norepinephrine reuptake inhibitor (RR: 1.04; 95% CI: 0.86–1.26) were not associated with colorectal cancer risk; however, TCA was associated with colorectal cancer risk decrement (RR: 0.92; 95% CI: 0.87–0.98). Furthermore, the results also showed that antidepressant use was not associated with colorectal cancer risk in Europe and North America (RR: 0.97; 95% CI: 0.92–1.02) and Asia (RR: 1.00; 95% CI: 0.95–1.26). Additionally, a dose-response showed per 1 year of duration of antidepressant use incremental increase was not associated with colorectal cancer risk (RR: 0.96; 95% CI: 0.87–1.09).

Evidence suggests that antidepressant use was not associated with colorectal cancer morbidity and mortality. The cumulative duration of antidepressant use did not utilized played critical roles.

Abbreviations:
CI = confidence interval, RRs = relevant risks, SNRI= serotonin norepinephrine reuptake inhibitor, SSRI= selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Keywords: antidepressant, colorectal cancer, dose-response relationship, meta-analysis

1. Introduction
Colorectal cancer is the third most common cancer worldwide, and fourth in cancer-related deaths.[1] At present, the effective treatment methods of colorectal cancer include surgery, radiotherapy, chemotherapy, and targeted therapy. Comprehensive treatment based on surgery is the only method that can treat colorectal liver metastases. Currently, the 5-year survival rate of colorectal liver metastases patients after surgical resection is up to 50%, but only 20% of patients have the opportunity to undergo surgical resection.[2] Neoadjuvant chemotherapy can reduce the primary tumor or metastasis focus, reduce the tumor stage, change the unresectable tumor into a resectable tumor, increase the rate of radical resection, reduce the recurrence rate, and control the microcarcinoma that exists before operation. However, the timing of surgery after neoadjuvant chemotherapy did not reach a consensus.[3] In the diagnosis and treatment of cancer, patients often undergo a series of complex psychological changes, and depression is one of the most common complications in colorectal cancer patients.

Antidepressants are widely used to cancer-related mental illness.[4–5] Three major antidepressants including selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI) and tricyclic antidepressant (TCA) treat depression. The main mechanism of these drugs is the inhibition of presynaptic monoamine reuptake and the blocking of postsynaptic Ach, H1, α1, β, and 5-HT receptors. With the further exploration of antidepressants, studies have found that antidepressants not only play a role in the treatment of mental illness, but also may be associated with the risk of colorectal cancer.[6–8]

Considering controversial evidence on the relation between antidepressants use and colorectal cancer risk and mortality, we performed a meta-analysis to summarize the relationship...
between antidepressants use and colorectal cancer risk and mortality.

2. Methods

There are no ethical issues involved in our study for our data were based on published studies, and there are no ethical issues involved in selected, assessed for quality, extracted and summarized and reported.

2.1. Search strategy

Medline, Embase, Web of Science, and Cochrane database were electronically searched from inception to October 2018. In addition, references to published studies were traced back to include other relevant literature. Two reviewers independently screened literature, extracted the data, and assessed the risk of bias in the included studies. The search was performed by means of a combination of academic and non-academic words, and appropriate adjustments were made depending on the database. The search terms included: “Antidepressive agents” or “Antidepressive drugs” or “Amitriptyline” or “Amoxapine” or “Benactyzine” or “Bupropion” or “Citalopram” or “Clopyrine” or “Clovoxamine” or “Deanol” or “Desipramine” or “Dothiepin” or “Doxepin” or “Fluoxetine” or “Fluvoxamine” or “Imipramine” or “Ipripdone” or “Lofezpramine” or “Mianserin” or “Nialamide” or “Nortripyline” or “Opipramol” or “Paroxetine” or “Phenelzine” or “Pizofylamine” or “Vilazdone Hydrochloride” or “Viloxazine” or “Sulpiride” or “Sertraline” or “Ropipram” and “Colorectal neoplasms” or “Colorectal tumors” or “Colorectal cancer” or “CRC”.

2.2. Inclusion criteria

Then, in selection of the study design, we only included observational study. As for the interventions, the content of selected articles must be related to the effect of antidepressant use on the risk or mortality of colorectal cancer. Two researchers independently screened the literature and extracted and cross-checked the data. If there is any disagreement, a third author was consulted to reach a consensus. When reading the literature, first read the questions and abstracts. After excluding the clearly unrelated documents, read the full text to determine whether the final inclusion.

2.3. Exclusion criteria

We exclude literature with obvious errors, defects, unknown information provided by relevant queries in the trial design, and literature in which baseline data are not comparable without inter-group equilibrium comparison. We also exclude review literature such as meta-analysis, newsletters, research progress, conference abstracts, and animal experiments.

2.4. Data extraction and methodological quality evaluation

According to the inclusion and exclusion criteria, the titles and abstracts of the literature were screened by 2 independent researchers. Then through reading the full text, exclude the literature that does not accord with this research scheme and record the reasons and quantity of exclusion. Finally, the selected literature was cross-checked by 2 researchers, and the disagreement was resolved through discussion or consultation with a third researcher. Extracted data included basic information regarding the study, including the first author and publication time, study design, number of participants, and the average age. Quality assessment was performed according to the Newcastle–Ottawa scale.[9]

2.5. Statistical analysis

Stata 12.0 software was used for statistical analysis. The relative risk (RR) was calculated for the counts, and the 95% confidence interval (CI) was calculated to estimate the effect size. A P-value < .05 was considered statistically significant. Heterogeneity among the included studies was analyzed with the chi2 test (test level is α=0.10), and the size of heterogeneity was quantified by combining I2. If I2 < 50%, it indicated that there was homogeneity among the studies, which could be directly combined and analyzed by fixed effect model. If I2 ≥ 50%, the heterogeneity of each study is indicated, and the random effect model is used for statistical analysis.[10]

3. Results

3.1. Literature search results

A total of 631 related articles were obtained with the initial inspection. By reading the summary of the title and the full text, according to the established inclusion, the exclusion criteria gradually screened the literature that met the criteria, and finally 11 articles were included (Tables 1 and 2).[11–21] The retrieval process is shown in Figure 1.

Table 1

| Author (yr) | Study design | Country | Age (yr) | No. of participants | Endpoints (cases) | Type of drugs | Quality score |
|------------|--------------|---------|----------|---------------------|-------------------|---------------|--------------|
| Boursi et al (2015) | Case-control | UK | 55.1 ± 0.5 | 108521 | CRC risk (22163) | SSRI, SNRI, TCA | 6 |
| Chubak et al (2011) | Case-control | USA | 70.0 ± 12.0 | 1305 | CRC risk (649) | SSRI, TCA | 7 |
| Coogan et al (2009) | Case-control | USA | 18.0–79.0 | 2484 | CRC risk (529) | SSRI, TCA | 7 |
| Cronin-Fenton et al (2011) | Case-control | Denmark | >18.0 | 109769 | CRC risk (9979) | SSRI, TCA | 6 |
| Lee et al (2017) | Case-control | China | >18.0 | 290327 | CRC risk (49342) | SSRI, SNRI, TCA | 6 |
| Walker et al (2011) | Case-control | UK | 72.5 | 93544 | CRC risk (6232) | SSRI, TCA | 7 |
| Xu et al (2006) | Case-control | Canada | 5.0–85.0 | 16507 | CRC risk (3306) | SSRI | 7 |
| Haukka et al (2011) | Cohort | Finland | 35.0–58.0 | 418588 | CRC risk (153) | SSRI | 7 |
| Khan et al (2010) | Cohort | UK | >18.0 | 26213 | CRC mortality (5061) | SSRI | 8 |
| Keely et al (2012) | Cohort | Canada | >18.0 | 5726 | CRC mortality (3501) | SSRI | 7 |
| Walker et al (2012) | Cohort | UK | 70.6 | 22524 | CRC mortality (6004) | TCA | 7 |

CRC = colorectal cancer, SNRI = serotonin-norepinephrine reuptake inhibitors, SSRI = selective serotonin reuptake inhibitors, TCA = tricyclic antidepressants.
3.2. Antidepressant use and colorectal cancer morbidity

Figure 2 displays the results of antidepressant use and the risk of colorectal cancer. Eight studies including 1 cohort study and 7 case-control studies were included in this meta-analysis to evaluate the risk of colorectal cancer and antidepressant use. The results showed antidepressant use was not associated with colorectal cancer morbidity (RR: 0.97; 95% CI: 0.94–1.01) and mortality (RR: 1.08; 95% CI: 0.99–1.17). Subgroup analysis showed SSRI (RR: 0.99; 95% CI: 0.96–1.03) or SNRI (RR: 1.04; 95% CI: 0.86–1.26) were not associated with the risk of colorectal cancer, however, TCA was associated with colorectal cancer risk decrement (RR: 0.92; 95% CI: 0.87–0.98). Furthermore, antidepressant use was not associated with colorectal cancer risk decrement in Europe and North America (RR: 0.97; 95% CI: 0.92–1.02) and Asia (RR: 1.00; 95% CI: 0.95–1.26) (Table 3).

3.3. Antidepressant use and colorectal cancer mortality

Figure 3 displays the results of antidepressant use and the mortality of colorectal cancer. Three cohort studies were included in this meta-analysis to evaluate the association between antidepressant use and the mortality of colorectal cancer. The results showed antidepressant use was not associated with colorectal cancer mortality (RR: 1.08; 95% CI: 0.99–1.17).

3.4. Dose-response meta-analyses between antidepressant use and colorectal cancer risk

Five studies were included in the dose-response meta-analyses to evaluate the association between antidepressant use and colorectal cancer risk. A dose-response showed per 1 year of duration of antidepressant use incremental was not associated with the risk of colorectal cancer (RR: 0.96; 95% CI: 0.87–1.09) (Fig. 4).

3.5. Publication bias

Most of points are evenly distributed on both sides of the inverted funnel plot, suggesting that there is less likelihood of publication bias (Fig. 5). Publication bias of antidepressant use and colorectal
cancer morbidity and mortality was evaluated with Egger’s test. 
\( P > .05 \) showed that there is less likelihood of publication bias
(supplementary Table 1, http://links.lww.com/MD/E288).

4. Discussion

Depressive disorder is a kind of mental disease with low mood,
loss of interest, and low energy. It has the characteristics of high
prevalence, high disability rate, and high mortality. According to
WHO, patients with all types of depression account for 3% to
5% of the global population. By 2020, the percentage of
neuropsychiatric disorders in the disability-adjusted health years
of the global disease burden will rise to 15%, and depression will
be the first of them. Depression will surpass cancer, become the
second most common disease in the world, and become the
second leading cause of disability in humans after cancer. \(^{125}\) In
addition, the incidence of emotional disorders in patients with
malignant tumors is high, with depressive disorders being the
most common. Depression, as one of the most common
psychological damage in patients with malignant tumor, directly
affects the occurrence, development and prognosis of the tumor,
and reduces the quality of life of the patients. \(^{23,24}\)

With the understanding of the neurobiological mechanism of
depressive disorder, more attention has been paid to the use
of drugs to treat depression in malignant tumor patients. A
number of in vitro simulation experiments have suggested that
antidepressant can inhibit the development of cancer, angiogen-
esis, proliferation, and metastasis. \(^{25,26}\) What really caught the
attention of the medical community to the safety of these drugs
was a meta-analysis by Ostuzzi et al in 2015. Ostuzzi et al
included 19 randomized controlled trials with a short follow-up
period showed that antidepressant use can decrease the risk of
cancer. \(^{24}\) However, the latest meta-analysis in 2018 showed
different conclusions. Huo et al included 8 observational studies
showed that antidepressant use was not associated with the risk
of ovarian cancer. \(^{27}\) To further clarify the relationship between
antidepressant use and colorectal cancer risk and mortality, we
included 11 publications in this meta-analysis. The result showed
that antidepressant use was not associated with colorectal cancer
morbidity and mortality. Subgroup analysis showed SSRI or
SNRI were not associated with colorectal cancer risk, however,
TCA was associated with colorectal cancer risk decrement.
Simultaneously, the potency and the cumulative duration of
antidepressant use was not play critical roles.

The main TCA currently used in clinical are clomipramine,
amitriptyline, and doxepin. Compared with SSRI, TCAs have
better clinical effect. \(^{28}\) Tumor patients with depressive disorder
have a good effect of low dose TCAs, and most of them are also
better tolerated by TCAs. \(^{29}\) The main mechanism of TCAs are
the inhibition of presynaptic monoamine reuptake and the
blocking of postsynaptic Ach, H1, \( \alpha_1, \beta, 5-HT \) receptors. \(^{30}\)
Therefore, these drugs are characterized by broad spectrum of

![Flow diagram of the study selection process.](http://links.lww.com/MD/E288)
Figure 2. Forest plot showing the pooled effects of antidepressant use on the risk of colorectal cancer. Solid diamonds and horizontal lines represent relevant risks (RRs) (95% confidence interval (CIs) for the outcome of interest. Solid circles and horizontal lines represent RRs (95% CIs); the gray boxes reflect the statistical weight of the study. The dotted vertical line denotes the point estimate for the pooled RRs and the solid vertical line indicates the line of no effect. The open diamond represents the pooled RR with its 95% CI.

| Table 3 | Main results of eligible studies evaluating antidepressant use and risk of colorectal cancer. |
|---------|--------------------------------------------------------------------------------------------------|
|         | No. of studies | Odds ratio (95% CI) | P for test | Heterogeneity | Model |
| Type of drugs | | | | P value | I² (%) |
| SSRI | 8 | 0.99 (0.96–1.03) | .742 | .219 | 27.5% | Fixed-effects model |
| SNRI | 2 | 1.04 (0.86–1.26) | .669 | .416 | 0.0% | Fixed-effects model |
| TCA | 7 | 0.92 (0.87–0.98) | .010 | .360 | 8.8% | Fixed-effects model |
| Study location | | | | | |
| Europe and North America | 14 | 0.97 (0.92–1.02) | .278 | .095 | 37.1% | Fixed-effects model |
| Asia | 3 | 1.00 (0.95–1.26) | .991 | .989 | 0.0% | Fixed-effects model |
| Study design | | | | | |
| Case-control | 14 | 0.97 (0.94–1.01) | .107 | .132 | 30.5% | Fixed-effects model |
| Cohort | 3 | 1.11 (0.56–2.12) | .241 | .219 | 13.5% | Fixed-effects model |
| Study quality | | | | | |
| Score ≥7 | 7 | 0.92 (0.82–1.03) | .461 | .674 | 0.0% | Fixed-effects model |
| Score <7 | 10 | 0.99 (0.96–1.03) | .730 | .803 | 0.0% | Fixed-effects model |
| No of participants | | | | | |
| ≥10,000 | 4 | 0.79 (0.58–1.07) | .127 | .361 | 6.4% | Fixed-effects model |
| <10,000 | 13 | 0.98 (0.95–1.01) | .148 | .183 | 27.4% | Fixed-effects model |
| No of cases | | | | | |
| ≥1000 | 10 | 0.98 (0.94–1.01) | .144 | .135 | 34.1% | Fixed-effects model |
| <1000 | 7 | 0.83 (0.63–1.10) | .204 | .404 | 0.3% | Fixed-effects model |

SNRI = serotonin-norepinephrine reuptake inhibitors, SSRI = selective serotonin reuptake inhibitors, TCA = tricyclic antidepressants.
Figure 3. Forest plot showing the pooled effects of antidepressant use on colorectal cancer mortality. Solid diamonds and horizontal lines represent relevant risks (RRs) (95% confidence interval (CI)) for the outcome of interest. Solid circles and horizontal lines represent RRs (95% CIs); the gray boxes reflect the statistical weight of the study. The dotted vertical line denotes the point estimate for the pooled RRs and the solid vertical line indicates the line of no effect. The open diamond represents the pooled RR with its 95% CI.

Figure 4. Dose-response analysis between antidepressant use and colorectal cancer risk. The solid line represents point estimates of the association of antidepressant use and colorectal cancer risk with the use of a restricted cubic splines model, and the dashed lines indicate 95% confidence intervals. lwthref: log (lb); ubwithref: log(ub); rwithref: log(n); rr_lin: predicted rr.
antidepressants and strong effects. Weinbach et al. found that TCAs could induce apoptosis of colorectal cancer cells by inhibiting the activity of mitochondrial complex III, resulting in the decrease of mitochondrial membrane potential.\(^{[31]}\)

Meta-analysis is a descriptive quadratic analysis, which has some defects. First, different doses and administration schemes and patients of different age were included, resulting in clinical heterogeneity. Second, although systematic literature retrieval has been carried out, only 11 studies have been included in meta-analysis, the size of the sample may have impact the results. Third, there are differences in the inclusion conditions of each study, resulting in incomplete or inaccurate collection of some data, and it is not possible to clearly explain when antidepressants should be used, the relationship between the dosage and the incidence of colorectal cancer. Moreover, the language of the retrieval is limited to English published articles, which may ignore the unpublished articles and cause the deviation of the language. Finally, since the economic evaluation indicators were not retrieved, and cost benefit analysis was not performed, future research is warranted.

In summary, based on this study, the results of the present meta-analysis showed that antidepressant use was not associated with colorectal cancer morbidity and mortality. SSRI or SNRI were not associated with colorectal cancer risk, however, TCA was associated with colorectal cancer risk decrement. The cumulative duration of antidepressant use did not play critical roles. These findings that the use of antidepressants, except TCA, did not increase the risk of colorectal cancer would have significant public health implications. In the future, large, multicenter, high-quality randomized controlled trials should be included, and long-term follow-up mechanisms should be established, as far as possible, in order to obtain high-quality, more convincing clinical studies, to provide more evidence-based medical evidence for scientific research and clinical practice.

**Author contributions**

Data curation: Lin Chen, Xun Li, Chuanxin Zou.
Formal analysis: Lin Chen, Xun Li.
Methodology: Chuanxin Zou.
Software: Xun Li, Chengbin Li.
Validation: Chengbin Li.

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