Review Article

Ranitidine Contaminated With N-Nitrosodimethylamine (Ndma) Link To Carcinoma: A Systematic Review And Meta-Analysis

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Abstract

Background:

Ranitidine is a generic antacid most commonly sold as Zantac. Ranitidine was popular in the United States even without a prescription until April 2020. The Food and Drug Administration (FDA) came to the conclusion that NDMA levels in ranitidine increased under ordinary storage settings, and that these thresholds increased significantly at higher temperatures. NDMA has been found to be a possible human carcinogen by independent testing, after being reported to become an efficacious carcinogen in experimental animals.

Methods:

A number of databases, such as PubMed, Cochrane Central Register and EMBASE, were searched to locate all qualified trials for Ranitidine contained NDMA, a carcinogen. In a PubMed search, 664 papers were identified till October 31, 2022, identical articles were removed, and lastly, 8 papers were included for the systemic review and meta-analysis.

Results:

Figures and tables were used to sum up Meta-regression results and the NDMA ddose-responseanalysis results. Relative Risk (R.R.) was used to assess the relationship between dietary intake of NDMA nitrates and nitrites and cancer risk. In this study, we take a look at the findings from other studies that have been done previously that showed NDMA (nitrosamines) use increased the risk of cancer by a lot. Several studies have also looked at the link between working with or eating NDMA and taking Ranitidine, which has been linked to cancers of the liver, GI tract, esophagus, pancreas, and colon.

Conclusions:

This study provided a summary of an article on dietary NDMA, including Ranitidine contamination exposure related with a significant statistical increased incidence of gastrointestinal cancers.

Introduction

The H2 antagonist Ranitidine (Zantac®) is commonly used to treat gastritis, gastro – esophageal reflux disorder (GERD), peptic ulcers, and other disorders associated with an abnormally high level of stomach acid production. And it was allowed to be sold for human consumption in the United States between 1983 and 1988; it became the world's best-selling medicine [1]. In 2004, ranitidine was also approved to be used as an over-the-counter (OTC) medicine. Recently

(in 2019), N-nitrosodimethylamine (NDMA) was identified in Ranitidine clinical studies, prompting the Food and Drug Administration (FDA) to warn of potential cancer risks connected to NDMA exposure [2]. The FDA of the United States has issued a directive requiring the withdrawal of all ranitidine products (Zantac) from the market by April 1, 2020 [3]. The FDA has found that the levels of NDMA in ranitidine increase while the drug is kept in its typical storage conditions, and those levels rise by a significantly greater amount when the drug is distributed in extremely high temperatures [4]. Recent in animals have shown that exposure to NDMA is associated with an increased risk of cancer and classed it as the most potent human carcinogen imaginable [5]. Although NDMA is not manufactured economically in the United States, it can be discharged into the air, land, and water as a byproduct of select industrial operations [6].

People may be exposed to NDMA through their diet, most frequently through the ingestion of contaminated water and/or foods containing nitrosamines (for example, cured pork) or alkylamines. Nutritional exposure to NDMA is conceivable (e.g., tea). Ingestion of NDMA is also possible through the use of cosmetic products and in industrial settings. [7]. Song et al. (2015) revealed in a meta-analysis that exposure to high intake of dietary NDMA was related Gastric cancer risk has increased by 34% [8]. Ranitidine use and gastrointestinal cancer has only been examined in a few studies. [6, 9, 10- 13]. NDMA pollution in food and industrial processes, as well as the use of Ranitidine, has been linked to an increased risk of liver and gastrointestinal cancers in several studies. [12], esophageal [14], pancreatic [15], and colorectal [16]. In addition, the period of follow-up was maybe too short to determine a connection and nonprescription medicine use was not recorded; hence, Ranitidine usage was misclassified. However, particular uses of ranitidine have been examined infrequently; hence, this constitutes a substantial gap in the literature considering the contemporary situation. The goal of this study was to examine the correlation between ranitidine use and the incidence of gastrointestinal bleeding and it may cause to gastrointestinal cancer, and the risk of developing this disease.

Materials and Methods

In this systematic review, we examined many literatures search engine such as PubMed, the Cochrane Central Register and EMBASE, for control case studies on Ranitidine containing the carcinogen NDMA. On January 31, 2022, all searches were conducted without any limits on data or language. The search terms were "N-nitrosodimethylamine (NDMA)", "Ranitidine", "ranitidine causes cancer", and "NDMA causes cancer", "ranitidine as carcinogenic", and "NDMA carcinogenic factor." In addition to examining the reference lists of the retrieved publications, a manual search was conducted to locate any relevant research. The inclusion criteria underlying the study must satisfy the following conditions: (a) case-control design or cohort; (b) exposed to dietary NDMA, nitrates and nitrites; (c) the endpoint of relevance was cancer caused by NDMA; (d) associated 95% risk estimates with confidence intervals (95% CIs); (e) all articles that were written in English. If some of the study groups were the same or overlapped, the most thorough and important research was chosen. The literature was found and evaluated by three authors, and any differences were talked about and solved. The methodology summarized as analysis flow diagram in figure 1. The first author's name, the year of publication, information about the population, the position and time frame of the study, the sample size, the number of years of follow-up, the amount of NDMA, nitrates, and nitrites taken in, and the relative risk (R.R. or odds ratio/hazard ratio) with 95 percent confidence intervals (CI) from the most multivariable regression model with each category were all looked at. The research's quality was assessed using the Newcastle-Ottawa Scale (NOS). [17] Three criteria were used to examine each study: selection, comparison, exposure measurement, and result measurement. High-quality studies had a score of 7 or above.

Statistical Analysis

Relative Risk (R.R.) was utilized to quantify the connection between nutritional NDMA nitrates and nitrites and cancer risk. Because of the relatively low absolute chance of developing cancer, the OR and HR decided to talk to the R.R. [18] The summation of relative risk was constructed using a random-effects model (R.R.) by combining the risk estimates from each research study, taking into account differences between studies and within studies. Using the 2-based Q and I2 indexes, the statistical distribution of research was evaluated. Subgroup analyses were carried out if three or more

research on the same characteristic were available. We used Orsini et al risk trend technique to determine the dose-response relationship. [19].

Case and control participant counts, as well as person-years per case, are necessary for this method to work as well as the median amount of dietary NDMA, nitrates, or nitrites consumption during the three exposure categories. The mean or median intake of NDMA was determined for each group. Potential nonlinearity related to limited cubic splines includes four knots at percentiles of 5%, 35%, 65%, and 95% of the distributions. If linear dose-response regression did not find any heterogeneity, we utilized it directly. To investigate the model takes into account possible heterogeneity, geographic location, study design, and publication year. In addition, we carried out a sensitivity analysis to establish whether or not the results of a particular study were responsible for the overall finding. A Egger's regression asymmetry test, funnel plot, and Begg's adjusted rank correlation test were utilized in order to test for publication bias; if bias was found, the "trim and fill" strategy developed by Duval and Tweedie was utilized. [20] was applied. All analyses were conducted using version 12.0 of STATA (Stata, College Station, TX, USA). In order to be considered statistically significant, a two-sided p-value has to be less than or equal to 0.05.

Table 1. Meta-analysis features of prospective cohort studies

Authors	**Year of publication and Country**	**Cohort Size**	**No. of Cases (Age/Definition)**	**Follow-up & study Years**	**Consumption Categories**	**Adjusted Relative Risk (**Confidence interval**)**	**Changed Variables**
Galanis et. al [20],	Hawaii 1998	6297 Women & 5610 men	the Hawaii Tumor Registry 108	14.3	0-4 4-8 >9	1.0 1.28 0.85	Gender, age, education, ethnicity. smoking and alcohol use.
Van Loon, et. al[21],	Netherlands 1998	1812 Women & 1688 men	282. (the mean age was 63 years, and the standard variation was 4.1 years; self-reported, in situ cancer.	6.3	59.8 84.7 104.4 127.3 179.8	1.0 1.25 (0.84–1.86) 0.74 (0.47–1.15) 0.92 (0.59–1.44)	Age, gender, smoking status, education, coffee use
Knekt, et. al [22],	1999 Finnish	9985 men and women	Finnish Cancer Registry reported 68 cases. 18 cases were recorded for 15–49-year-olds, 28 for 50–59, and 22 for 60–99.	2.4	Quarterlies 1,2,3,4	1.0 1.03 (0.55–1.95) 0.78 (0.39–1.56) 0.75 (0.37–1.51)	Gender, age, municipality, smoking, and calorie intake affect health. .
Jakszyn, et. al[23],	2006 European	368,010 Women & 153,447 men	314 (median age of 59.2 years and an SD of 7.48)	6.6	T1 T2 T3	1.0 Zero to one (0.64–1.20). 2.0 (0,69–1,41),	gender, education, cigarette.
Larsson, et. al [24],	2006 Sweden	61,433 Women	A total of 156	1.8	<0.041 0.041–0.078 0.079–0.120 0.121–0.193	1.0 1.03 (0.61–1.77) 1.66 (1.00–2.75) 1.60 (0.93–2.76)	Age, level of education, body mass index, total energy, alcohol.

					>0.194	1.96 (1.08–3.58)	
Keszei, et. al [25],	2013 the Netherlands	120,852 men and women	Women, mean: 62.6 years, SD: 4.3; 663 (Women, mean: 62.6 years, SD: 4.2; Men, mean: 62.4 years, SD: 4.0/through linkage to the Men, mean: 61.4 years, SD: 4.1;	3.6	Men sample 0.08, women sample 0.04 points lower. Men 0.25women, 0.07	Men 0.94 (0.59–1.49) 1.00 (0.64–1.56) 1.0 (Referent) Men, Non-cardia 1.31 (0.95–1.81) 1.09 (0.79–1.50) 1.0 (Referent) Women, Cardia 1.02 (0.33–3.14) 0.97 (0.34–2.78) 1.0 (Referent) Women, Non-cardia 0.90 (0.58–1.42) 1.37 (0.92–2.02) 1.0 (Referent)	Age, smoking beer, vegetable and fruit intake, educational level, and non-workplace physical activity are some of the factors that go into a person's health.
Anton Pottegård et. al [31],	2018 Denmark	5150 men and women	Men, mean: 61.5 years, SD: 4.0/through linkage to the Men, mean: 60.4 years, SD: 4.3; Women, mean: 61.6 years, SD: 4.2; 625 (Women, mean: 60.8 years, SD: 4.5;	4.6	Q1 Q2 Q3 Q4	(95% confidence interval 0.85 to 1.41) (hazard ratio 1.46, 95% confidence interval 0.79 to 2.73)	Age, smoking history, the quantity of cigarettes smoked daily.
Ilijana Sedlo et. al [32],	2021 Croatia	5150 men and women	314 (mean: 62.2 years, SD: 3.24/ backed up by a team of pathologists)	1.7	T1:men0.01 women,0.02 T2: men0.06 women,0.03; T3:men0.20 women,0.05	NA	combinations of amines and nitrogen compounds and the use of specific catalysts and reagents.
Hedetomo Yooko et. al [33],	2021 Japan	NA	Ranitidine hydrochloride and its impurities have been subjected to heat degradation investigations.	1.2	Q2	NA	examination of impurities (Imps. A through K) is considered.

Table 2. The meta-case-control analysis's study

Authors	Year of publication and Country	Number of Cases (Age/Definition)	Number and Type of Controls	Duration of Study	Content Values Nutrient	Consumption Categories	Accustomed OR (Confidence Interval)	Accustomed Variables
Pobel, et. al[26],	1995 France	92 (mean: 66.6 years, SD: 10.4)	129 Based on hospital	From 1985 to 1988	dairy,meats,eggs, fish, wheat,fruitsand beverages.	T1 T2 T3	7.00 (1.85–26.46) 4.13 (0.93–18.27) 1.0	Age, Gender, job title, and daily caloric intake
La Vecchia, et. al1995 [27],	1995 Italy	746 (19 to74 years/ confirmed by histologically)	2053 Based on the Hospital	From 1985 to 1993	comparing foods from survey with selected foods or from published sources	<0.13 0.13–0.19 >0.19	1.0 (Referent) 1.11 (0.90–1.40) 1.37 (1.10–1.70)	Age, gender, education, family history of stomach cancer, , beta-carotene and vitamin C intake,
De Stefani, et. al [28],	1998 Uruguay	340 (25-84/Microscopic)	698 Based on the hospital	From 1993 to 1996	existing literature data, generated from fried, broiled, or salted flesh	<0.14 0.15–0.18 >0.27 0.19–0.2	1.0 2.07 (1.36–3.18) 3.23 (2.13–4.89) 3.62 (2.38–5.51)	Age, sex, residence, urban/rural status, tobacco duration, total alcohol consumption
Palli, et. al [29],	2001 Italy	130 cases; > 64 years, 222 382 cases (less than 50 years old, 30; 50–64 years old, cases; histologically confirmed)	561 population based	From 1985 to 1987	Determined by food items from the FFQ and tables that contain food composition	0.12 0.20 0.33	1.0 (Referent) 1.10 (0.80–1.60) 1.10 (0.80–1.50)	age, gender, social status, family history of stomach cancer, location, BMI.

CI: confidence interval; NDMA: N-nitrosodimethylamine; BMI: body mass index; RR: relative risk; SD: standard error; NA: Not Applicable FFQ: food frequency questionnaire

Flow chart literature review process

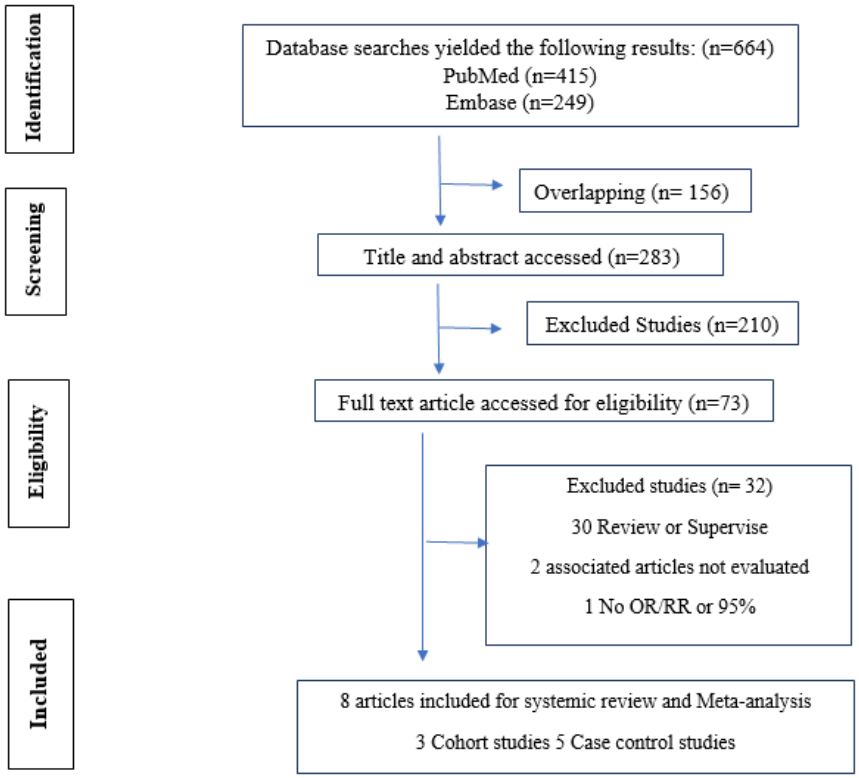

Figure 1 - PRISMA Systematic review and meta-analysis flow diagram showing the literature review process

Results

NDMA Cancer Risk Associated with Alcohol Consumption

Combining the results of six case-control studies and eight cohort studies [21, 22] where researchers to assess the connection between NDMA consumption and the risk of developing cancer are summarized in Figure 2 and table 3.

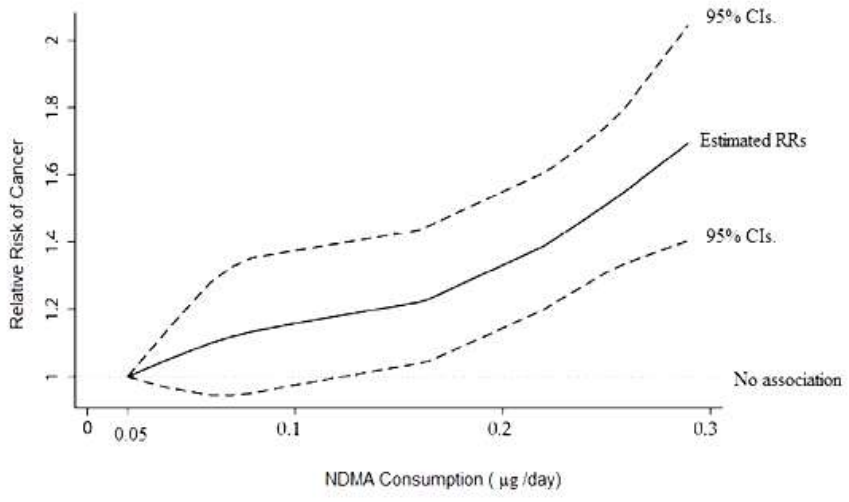

Figure 2- This depicts the daily NDMA consumption and cancer risk. All NDMA-relative hazards were evaluated using the lowest reference interval (0.05g/day)

The pooled R.R. A 95 percent confidence interval (CI) ranging from 1.03–1.77 showed that there was clear evidence of heterogeneity in the results when comparing high vs low intake: (I 2 = 75.8 percent, Figure 2: p 0.001). These R-R estimations from these subgroups revealed no meaningful correlation (Table 3). In addition, a modest correlation was found in studies of a very good quality (rating 7 stars; relative risk, 1.30; 95 percent confidence interval, 0.97–1.75).

Analysis of NDMA Dose-Response

It was determined that NDMA has a dose-dependent effect on the body [25, 27, 28]. As NDMA intake increases, a nonlinear trend towards cancer risk ($p_{non\_linearity} < 0.001$) was identified (following graph), which demonstrates an NDMA use with a daily dose of 0.15 g or more is associated with an increased risk. (Figure 2).

Meta-Regression of NDMA

The overall heterogeneity, as shown in Table 3, appears to be influenced by research design, with the majority of them being linked to NDMA consumption and cancer risk. Unadjusted between-study variation (0.028/0.046) may be explained by study design alone in univariate meta-analysis regressions (T2). T2 for NDMA dropped from 0.14 to 0.023 in the meta-regression model when all variables were considered. (Study pattern, publication year, and geographic zone) were included. The research type was revealed to be the predominant source of variability for NDMA, accounting for 84.86 percent of the T2 It's possible to explain 92.3 percent of T2 for NDMA with geographic region, but the subgroups' conformity to it still has non-negligible variability.

Variable	Co-efficient	95% CI	p-Value
Study pattern	0.210	_0.287 to 0.688	0.365
Geographic Area	0.919	_0.039 to 1.865	0.062
Year of publication	0.109	_0.805 to 0.998	0.812

Table 3 - NDMA's meta-regression study

NDMA Sensitivity Analysis

We performed a sensitivity analysis to check for uniformity in the correlations between NDMA consumption and cancer risk. After excluding individual studies, the NDMA R.Rs ranged from 0.97 to 1.89. The study of La Vecchia et al. appears to be the root source of the variation. [28] For this study, the Galbraith plot phenomenon provided supporting evidence. When De Stefani et al. case-control study was excluded, the combined statistics for the entire association about NDMA consumption and stomach carcinoma decreased by 95 percent confidence intervals (0.79, 0.66-0.95), resulting in a lower summary R.R.s value (I2 = 8.8%, p = 0.349). This research findings heterogeneity was still not distinguished (p = 0.349, I2 = 8.8%). RR was 1.18 (95% CI, 0.97–1.43) when this trial was eliminated, with considerable heterogeneity (I2 = 46.7%, p = 0.050).

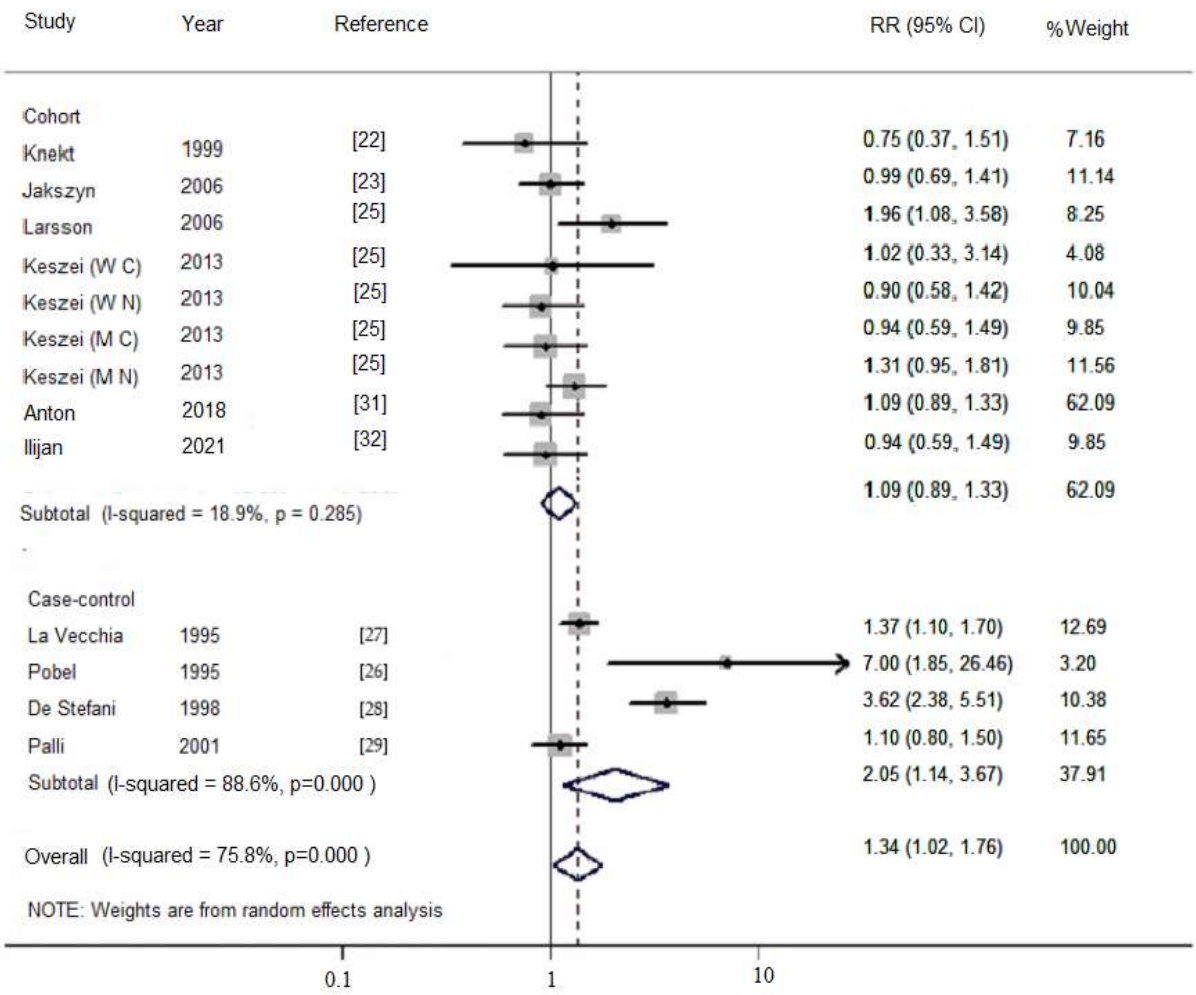

Figure 3 - Risk of cancer-based on NDMA intake from higher to lowers categories

Bias in Publication

As depicted, in Figure 4, the Risk of bias assessments was examined that use the Newcastle Ottawa Scale for experiments; there were no obvious asymmetry markers in these funnel plots. Furthermore, the Egger and Begg test found significant corroborating evidence in favor of bias NDMA (Begg, p = 1.000; Egger, p = 0.842). The trim and fill technique, which was utilized in an effort to adjust for the possible publication bias for NDMA, did not have any impact on the results. (R.R.: 0.765; 95 percent CI, 0.652–0.832; Figure 3).

Low Potential for Bias	
Moderate to unknown risk of Bias	
Significant Potential for Bias	

Study	Is the problem adequately described?	Instance Representation	Controls selected	Control definition	Case Comparison and Case Control	Exposure Determinations	The identical case/control ascertainment approach	Overall rating
Galanis et al.,**1998**[20],	1	0	1	1	2	0	1	7
Van Loon et al.,**1998**[21],	1	0	1	1	2	0	1	7
Knekt et al., **1999**[22],	1	0	1	1	2	0	1	7
Jakszyn et al.,**2006**[23],	1	0	0	1	2	0	1	6
Larsson et al.,**2006**[24],	1	0	1	1	2	1	1	6
Keszei et al.,**2013**[25],	1	0	1	1	2	0	1	8
Pobel et al.,**1995**[26],	1	0	1	1	2	0	1	7
La Vecchia et al.,**1995** [27],	1	0	0	1	2	0	1	6
De Stefeni et al.,**1998** [28],	1	0	1	1	2	1	1	6
Russo et al.,**2001**[29],	1	0	1	1	2	0	1	8
Anton Pottegård et al.,**2018.**[31],	1	0	0	1	2	0	1	7
Ilijana Sedlo et al.,**2021.**[32],	1	0	1	1	2	0	1	6
Hedetomo Yooko et al.,**2021.**[33],	1	0	1	1	2	0	1	7

Figure 4 - The Newcastle-Ottawa Scale is a tool that is utilized in case-control research in order to evaluate the potential for bias.

Discussion

Several studies have investigated the possible link between NDMA and nitrosamine consumption and several types of cancer. In this review, we found that NDMA consumption was linked to an increased risk of cancer. These results were replicated in a second case-control study, and the carcinogenicity of NDMA was validated by cohort studies. [11, 14]. When the daily NDMA consumption approached 0.15 mg, the cancer-causing and negative effects on humans were more obvious, according to the dose response analysis [15]. NDMA's chemical and biological features can be explained by its methods of action. Processing meats and other exposing foods to temperatures that are too high can cause the development of nitrosamines. The carcinogenicity of these chemicals was investigated in animal models. Nitrates were not shown to be carcinogenic to animals in 2010, discussing with the International Agency for Research on Cancer (IARC) [30]. The FDA became aware of the possible health concerns connected with NDMA exposures to the general population, including cancer [2]. Associating with amines or amides caused cancer in humans. Most nitrosamines have been shown to cause adenocarcinoma by genetic mutation and DNA adduction, according to research. These compounds' animal toxicity was detailed in an illustrated systematic review by Bryan et al., based on earlier investigations [31]. Hedetomo Yooko et al. discovered in 2021 that Ranitidine hydrochloride's amorphous impurities, which may cause cancer, were generated by the heat breakdown of the drug. [32]. A new investigation into the occurrence of nitrosamine contaminants in medical items was conducted in 2021 by Ilijana Sedlo et al. According to data from prospective cohort studies [21,23], Dietary NDMA consumption does not appear to be linked to an increased risk of cancer. Since a single study might not be sufficient to detect a trend, a Meta-analysis is necessary. This conclusion must be backed up by studies that employ established methods to evaluate the source of consuming in the diet to the greatest extent practical. Our NDMA meta-analysis included data from a sizable patient population (698,678 in total), showed variability in the dose-response relationship, was based on credible sources, and yielded stable stability analysis results. The following are little bit of the drawbacks to this approach:

Numerous studies were lacking from the cancer stratification analysis and the dose-response study. Research with unique clinical aspects is needed to address these issues. Stratified analysis nevertheless revealed large variations in NDMA concentrations between subgroups, suggesting that this variation was not eliminated during the process. Distal stomach cancer is more likely to occur in those who are infected with the Helicobacter pylori bacteria. This meta-analysis comprised just three case-control studies [34, 35]. Due to advancements in food processing technologies, the concentration of nitrosamines in foodstuffs has altered over time in cohort studies. In addition, it's possible that people have altered their eating patterns. As a result, more prospective studies utilizing full questionnaires and regular updates to diet information are needed.

It is possible to enhance health and even reduce the risk of cancer with nutrition, which is a multidimensional exposure variable. As previously stated by WCRF/AICR [36], non-starchy fruits and vegetables with rich in the substance of antioxidants, ascorbic acid and fiber, and may have a substantial impact on stomach cancer. On the other side, there is evidence that links cancer to salt and foods that are preserved with salt. There is some evidence to suggest that consuming NDMA may increase the chance of developing cancer. A review of past research supports the idea that NDMA use increases risk, whereas most of the research comprises better-conducted and planned studies that consider NDMA as a possible human carcinogen [33]. Our stratified analysis of data from a sample size and rankings yielded these findings. Ranitidine exposure raises the risk of cancer, according to the data we gathered.

Conclusions

The findings of this meta-analysis revealed that indulging in activities that involved the use of ranitidine and NDMA related to an elevated chance of developing gastric cancer. To further understand the role that these drugs play in the genesis of gastric cancer, we need to conduct additional large prospective studies that are properly planned.

Conflict of Interest: None of the writers have disclosed any competing interests.

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