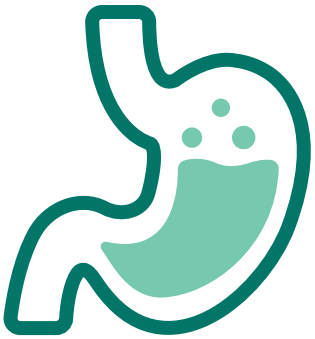
DRINKING AND STOMACH CANCER



IARD Health Reviews offer a referenced overview of recent peer-reviewed, published research on the relationship between alcohol consumption and health outcomes. They are not intended to be exhaustive representations of all scientific research on a given subject and, as research is constantlyevolving, they may not include the most recent findings. These materials do not necessarily reflect the views of IARD or its member companies. The reviews report the findings of the referenced studies and are not intended to advise individuals about their drinking. IARD and its member companies do not recommend that anyone drink alcohol for its potential health benefits and would encourage those with specific questions about their drinking to consult their healthcare professionals; together, they can determine what is best based on individual risk factors, including family history, genetics, and lifestyle. For some people, the better choice may be to not drink at all. IARD Health Reviews should be read in their entirety and not misrepresented or taken out of context.

This Health Review focuses on cancer sites associated with alcohol consumption as identified by the World Cancer Research Fund and the International Agency for Research on Cancer. Due to the limited availability of national cancer statistics in many countries, U.S. data – which is publicly available and annually updated – is sometimes used to illustrate cancer risk in this review.

A glossary of key terms used in this review can be found on page 13.

Last literature review: July 2019

Introduction

STOMACH CANCER IN MEN AND WOMEN

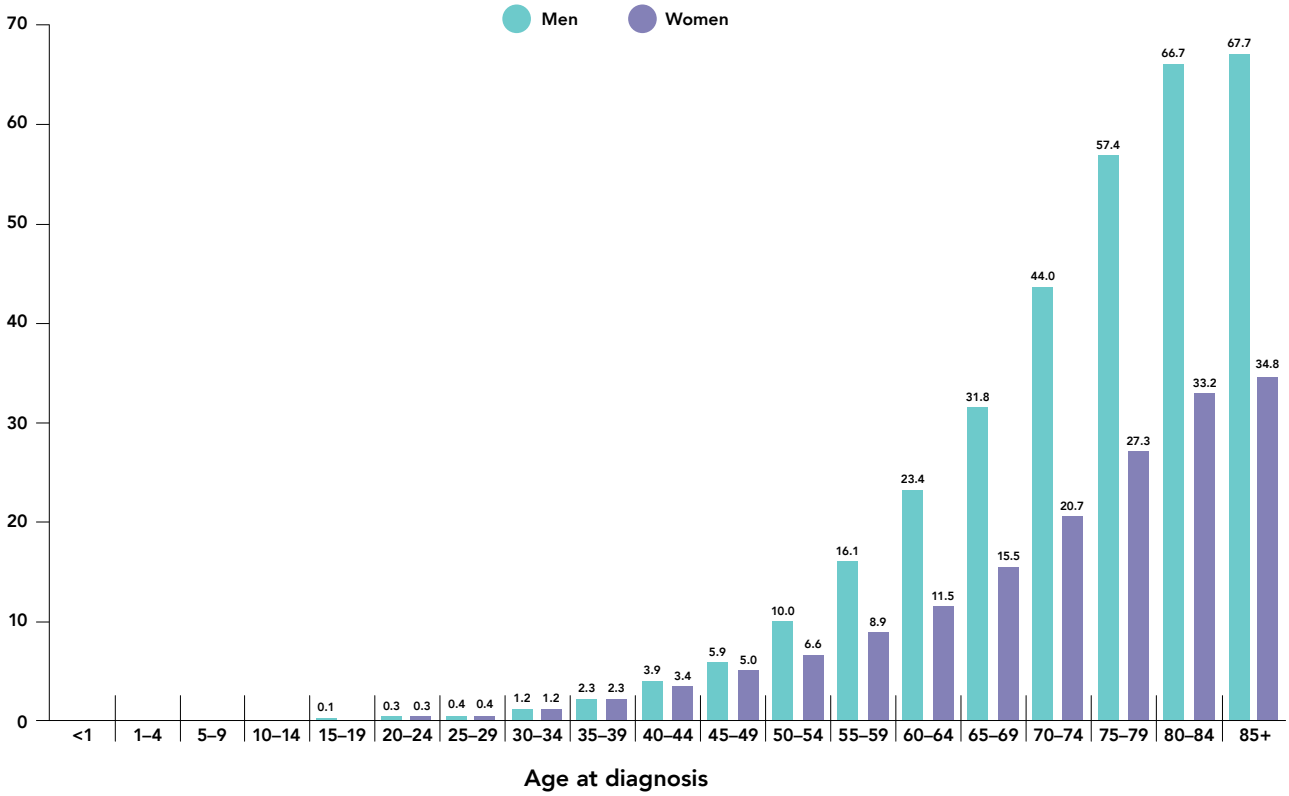
Lifetime risk of diagnosis (U.S.)

Global incidence per 100,000

Sources: *Global Burden Disease study 2019 (age-standardized data) [1] and the National Cancer Institute SEER Report [2]*

Stomach cancer is the fifth most common cancer in the world for men and women combined and accounts for 5.6% of all incident cancer cases [3]. Incidence rates vary across countries, from a high of 32.5 per 100,000 persons in Mongolia to a low of 0.75 per 100,000 persons in Mozambique [3]. Stomach cancer incidence increases with age [4]. In the U.S., 83% of new diagnoses occur among those aged 55 years and older; overall incidence rates across all ages are almost twice as high among men (9.7 per 100,000) than women (5.3 per 100,000) (see Figure 1). [2].

Figure 1. Age-specific incidence of stomach cancer among men and women in the U.S. per 100,000



Source: *Seer 21 Areas, Stomach SEER Incidence and U.S. Mortality Rates by Age at Diagnosis, 2014-2018 [2].*

According to the World Cancer Research Fund (WCRF), alcohol consumption is a risk factor for stomach cancer [4]. In addition, several other risk factors are associated with stomach cancer risk, some of which may mediate or modify the relationship between alcohol consumption and stomach cancer risk (see Table 1).

Table 1. Common risk factors for stomach cancers*

Modifiable risk factors	Non-modifiable risk factors
Alcohol consumption	Age
Body mass index	Common variable immune deficiency (CVID)
Diet	Epstein-Barr virus (EBV) infection
Geographical location	Genetics
Helicobacter pylori infection	Pernicious anemia
Occupational exposures	Race
Smoking	Sex

Source: *American Cancer Society [5] and The World Cancer Research Fund / American Institute for Cancer Research's Third Expert's Report 2018 [4].*

**Items are listed alphabetically and not according to importance or magnitude of risk.*

The importance (that is, the magnitude or prevalence) of any given risk factor relative to other risk factors may differ by population due to environmental, socio-economic, behavioral, or genetic differences.

BIOLOGICAL MECHANISMS OF STOMACH CANCER

Researchers are continuing to explore several plausible biological mechanisms that explain the potential role of alcohol as a risk factor in stomach cancer [4], and some of these include:

Acetaldehyde

Alcohol (ethanol) is primarily metabolized in the liver by two important families of enzymes: *alcohol dehydrogenase* (ADH) and *acetaldehyde dehydrogenase* (ALDH) and, to a lesser extent, *CYP2E1*. Alcohol is converted to *acetaldehyde* by ADH, which is then converted to acetate by ALDH [6, 7]. Several studies have shown that acetaldehyde is a *carcinogen* and may increase DNA damage to stomach cells by interfering with DNA repair, or promoting cell growth, or both [7, 8]. According to some studies, acetaldehyde may be a co-carcinogen (an agent that promotes but does not initiate cell growth) because DNA damage is an early stage in carcinogenesis [9].

- The microsomal ethanol oxidizing system, another metabolic pathway, accounts for a small percentage of ethanol metabolism but is significantly activated at chronic heavy levels of consumption (after a single week of consuming 40g/day or more) [7, 10]. The main component of this system is the enzyme CYP2E1, which breaks down alcohol into acetaldehyde and results in increased production of both acetaldehyde and *reactive oxygen species (ROS)*, which can lead to DNA damage [11-13].

- Clinical research has demonstrated that individuals with certain gene mutations in ADH, ALDH, and CYP2E1 accumulate higher levels of acetaldehyde in the liver, stomach, and other tissues during alcohol metabolism than individuals without these mutations [13, 14].

- Epidemiologic research has found that individuals who carry these genetic mutations have an increased risk of certain cancers [15-21].

Nutritional deficiencies

The role of alcohol in stomach cancer risk may also be related to the effect of alcohol on dietary intake, or on malabsorption, or utilization of dietary nutrients [22]. The inability to support these processes may independently or jointly increase susceptibility for cancer growth [8, 23].

- Heavy alcohol consumption may be associated with certain nutrient deficiencies (such as vitamins A, B9 (folate), C, and E, glutathione, and zinc) [14, 24-26] as well as deficiencies in other nutrients that support the processes of repairing DNA damage and neutralizing ROS [27].

Tissue integrity

- Alcohol may act as a solvent by changing the proteins involved in maintaining tissue integrity, which could lead to increased invasiveness of carcinogens such as tobacco and *Helicobacter pylori (H. pylori)* into stomach tissue [12, 15, 26, 28].

Interaction with Helicobacter pylori

The process by which stomach cancer develops may or may not be related to the joint effect of alcohol consumption and H. pylori infection. H. pylori bacteria is a known risk factor for stomach cancer.

- Some studies have shown that alcohol consumption will induce stomach mucosa injury [29, 30], which results in inflammation that can prevent the elimination of H. pylori bacteria [30].

- Other studies have shown that alcohol may kill bacteria such as H. pylori [30] and may increase stomach acid secretion, making the environment unsuitable for bacterial growth and reducing the risk of stomach cancer [29, 30].

Summary of recent stomach cancer research

This chapter of the *IARD Health Review: Drinking and Cancer* includes studies that examine the association between alcohol consumption and risk of being diagnosed with stomach cancer.

For this chapter, the following criteria were used to select studies following a literature search using the IARD Research Database and PubMed.

Study designs: meta-analyses (a type of study that pools data from multiple studies), pooled cohort studies, pooled case-control studies, prospective cohort studies, and case-control studies; systematic reviews were excluded from the summary of results section because of the absence of new or pooled risk estimates
Publication dates: from 2007 through June 2019
Outcomes: stomach cancer incidence; combined incidence and mortality (for meta-analyses only)
Exposure: at least three quantified levels of alcohol consumption; or at least two quantified levels of alcohol consumption if a study examined a limited range of alcohol consumption (for example, up to one drink per day only)
Sample size: 1,000+

When multiple analyses were presented in a study, we included results from models that were fully adjusted, used a lifetime alcohol consumption assessment (versus a single assessment), and separated former drinkers from lifetime abstainers. Results of meta-analyses and pooled cohort studies are presented first, followed by results of individual studies to allow comparison of risk estimates across both types of study designs.

Note: The time frame of alcohol exposure assessment varies from study to study (for example, researchers could assess a study participant's lifetime, recent past, or current consumption), making it difficult to determine whether risk estimates reflect recent drinking patterns or the accumulation of drinking patterns over a lifetime. *This topic is discussed in the chapter "**Discussion of conceptual and methodological issues**".*

STOMACH CANCER, UNSPECIFIED

In this section we present results of studies reporting *relative risk* estimates for stomach cancer in general, without further classification of subsites. The results of studies by subsites are summarized in the next section of this review. (*Please see the Glossary on page 15 for a definition of relative risk (RR) and descriptions of magnitude of risk as weak, modest, moderate, and strong in epidemiologic research.)*

According to the WCRF, there is "probable" evidence of an increased risk of stomach cancer associated with alcohol consumption above 45g/day [4]. *(Please see **Background chapter** for an explanation on the WCRF definitions of strength of evidence.)*

Meta-analyses

Four meta-analyses met the inclusion criteria for this review and reported on the association between stomach cancer in general and alcohol consumption [31-34] (see Table 2).

- Four studies reported an increased risk associated with alcohol consumption starting at more than 0g/day [32], 12g/day [33], 24g/day [34], or 50g/day [31] compared to nondrinkers.

- One of the four studies stratified by sex and found that results for men and women combined held true for men only; for women, results indicated a reduced risk in stomach cancer associated with alcohol consumption up to 12g/day [34].

Individual prospective cohort studies

Twenty-one individual prospective cohort or case-control studies met the review criteria and reported on the association between stomach cancer risk and alcohol consumption (see Table 3) [15, 17-21, 35-49].

- Eight out of 13 studies reporting a risk estimate for men and women combined found an increased risk of stomach cancer associated with alcohol consumption, of which five reported an increase starting at less than 45g/day [36, 37, 47-49] and three reported an increase starting at greater than 45g/day [15, 19, 35]. Five studies reported no association between stomach cancer risk and any level of consumption [17, 18, 20, 21, 38].

- Eleven individual prospective cohort or case-control studies reported risk estimates for men and women separately; eight for men [20, 21, 37, 39-43] and seven for women [20, 21, 37, 39, 44-46].

- Among men, four of eight studies reported an increased risk of stomach cancer associated with alcohol consumption starting at more than 0g/day [37], 2g/day [41], 14g/day [42] and 25g/day [43], and four reported no association [20, 21, 39, 40].

- Among women, one of seven studies reported an increased risk of stomach cancer associated with alcohol consumption starting at 3g/day [20], one study found a reduced risk between 10 and 21g/day [46] and five studies reported no association [21, 37, 39, 44, 45].

Table 2. Relative risk estimates for alcohol consumption associated with stomach cancer from meta-analyses*

Study reference	Nondrinker	Average alcohol grams per day
Combined sexes		
Ma et al., 2017	ref.†	1.3 (0.5–59.9) | 1.58 (60–70+)
Ferro et al., 2018	ref.†	ns (0.5–4.9) | 1.13 (5–49.9) | 1.37 (50–70+)
He et al., 2017	ref.†	ns (0.5–4.9) | ns (5–24.9) | 1.13 (25–70+)
Tramacere et al., 2012	ref.†	1.20 (50–70+)
Men		
He et al., 2017	ref.†	ns (0.5–4.9) | ns (5–24.9) | 1.13 (25–70+)
Women		
He et al., 2017	ref.†	0.74 (0.5–4.9) | ns (5–24.9) | ns (25–70+)

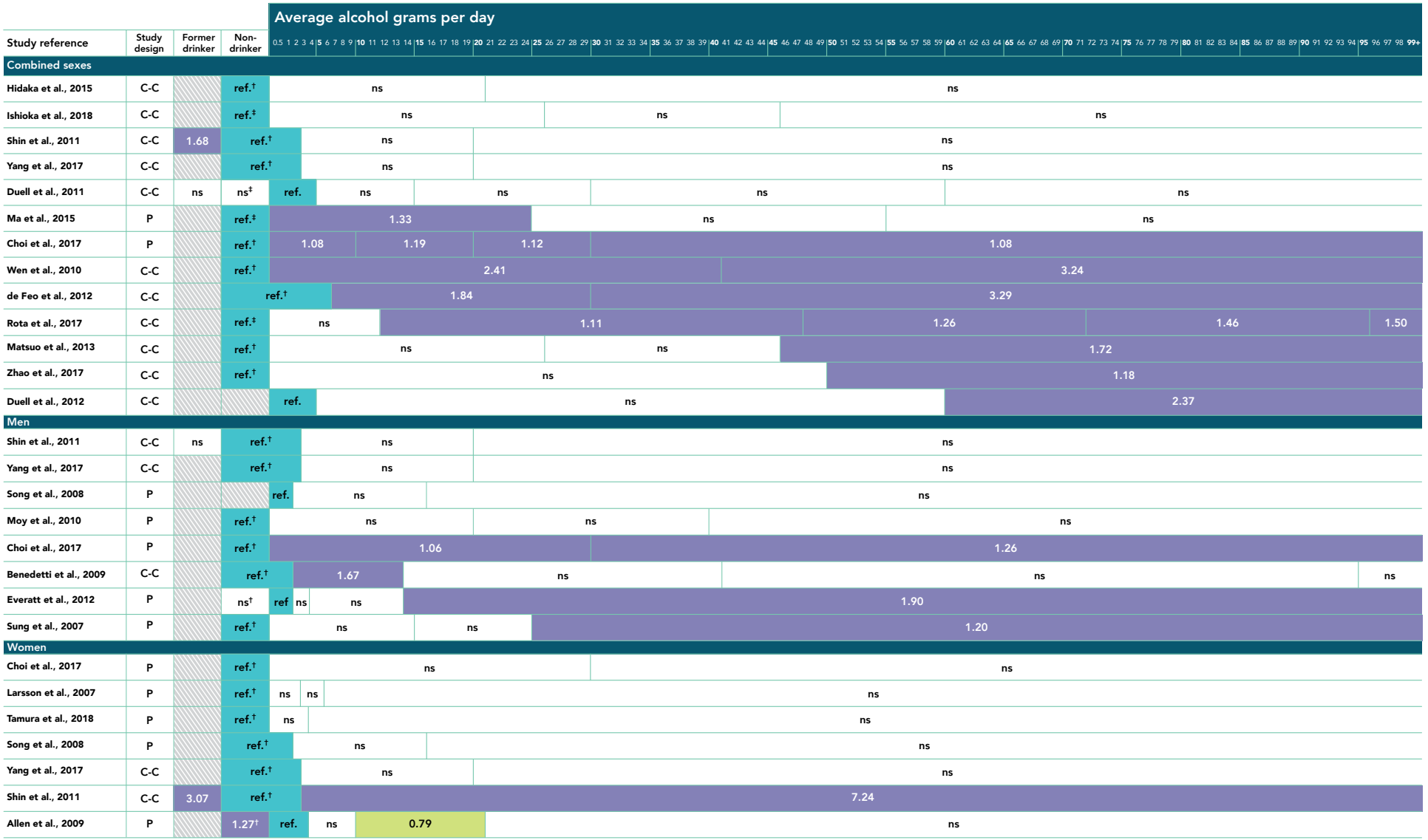
*All meta-analysis study designs published between 2007 and June 2019 and reporting risk estimates for drinking at multiple drinking levels were included in this table.

† Nondrinker (may include former or occasional drinkers or both)

Table Notes:

- Vertical bars correspond to the lower and upper limits of each drinking level as defined by the study, converted, if necessary, to grams of pure alcohol per day.
- Purple shading indicates a statistically significant increase in relative risk compared to the reference group.
- Green shading indicates a statistically significant decrease in relative risk, compared to the reference group.
- Grey shading indicates that the study did not assess risk at this drinking level.
- "ns" indicates that risk for that drinking level was not statistically different from risk for the reference group.
- Under the "Study Designs" column, "P" indicates prospective studies and "C-C" indicates case-control studies (Table 3–4 and 6 only).

Table 3. Relative risk estimates for alcohol consumption associated with stomach cancer from individual prospective cohort and case-control studies*



* All individual prospective cohort study and case-control study designs published between 2007 and June 2019 and reporting risk estimates for drinking at multiple drinking levels were included in this table.

† Nondrinker (may include former or occasional drinkers or both)

‡ Nondrinker (lifetime abstainers)

Results from these studies indicate that the magnitude of the risk estimates measuring the association between alcohol consumption and stomach cancer appears to range from a "weak" to "modest" increase in risk as alcohol consumption increases among combined sexes. Compared to nondrinkers, the lowest categories of average alcohol consumption as defined by these studies (up to 10g/day) are associated with an 8% increase in risk (equivalent to a relative risk of 1.08), while the highest levels of consumption (more than 96g/day) are associated with an 50% increase in risk (equivalent to a relative risk of 1.50), compared to nondrinkers. Relative risk estimates of 1.08 are considered "weak" and 1.50 are considered "modest"; see, for example, Schoenbach and Rosamond (2000) [50] and the Glossary for additional resources.

CANCER SUBSITES

Stomach cancers can be divided into two subsites: the stomach cardia, which refers to the top part of the stomach that also encompasses the esophageal gastric junction, and the stomach non-cardia, which refers to the remaining portion of the stomach.

Cardia stomach cancer

One study reported no association between alcohol consumption 50g/day or more and cardia stomach cancer (CSC) when compared to nondrinkers; however, consumption less than 50g/day was not analyzed [31].

Individual prospective cohorts and case-control studies

Six individual prospective cohort or case-control studies that met the review criteria reported on the association between CSC and alcohol consumption (see Table 4). Two of four studies reported a reduced risk up to 5g/day [51] and from 5g/day up to 15g/day [38] and two studies found no association [52-54].

- Three studies stratified by sex and found no association between alcohol consumption and CSC for either sex [43, 53, 55].

Four individual prospective cohort or case-control studies that met the review criteria reported on the association between NCSC and alcohol consumption (see Table 6). Two of four studies reported an association between current alcohol consumption and NCSC; one found an increased risk starting at 60g/day [38] and one found a reduced risk associated with consuming up to 14g/day [53].

- The combined sexes results for Wang et al., 2018, did not hold when stratified by sex. No association was reported for men or women separately [53].

Non-cardia stomach cancer

Meta-analyses

Three meta-analyses that met the review criteria reported on the association between non-cardia stomach cancer (NCSC) and alcohol consumption. One study found an increased risk associated with alcohol consumption starting at 50g/day [56] and the other two found no association between NCSC and alcohol consumption [31, 57] (see Table 5).

- Two studies exclusively examined drinking levels 50g/day or more [31] and 30g/day or less [57].

- When stratified by sex, two studies reported no association between alcohol consumption and NCSC for men and women separately [56, 57].

Table 4. Relative risk estimates for alcohol consumption associated with cardia stomach cancer from individual prospective cohort and case-control studies*

Study reference	Study design	Nondrinker	Average alcohol grams per day
Combined sexes			
Freedman et al., 2007	P	ns†	ref. 0.5–24 | ns 25–70+
Wang et al., 2018	P	ref.†	ns 0.5–39 | ns 40–70+
Steevens et al., 2010	P	ref.†	0.46 0.5–4 | ns 5–14 | ns 15–34 | ns 35–70+
Duell et al., 2011	C-C	ns†	ref. 0.5–4 | 0.57 5–14 | ns 15–34 | ns 35–59 | ns 60–70+
Men			
Sung et al., 2007	P	ref.†	ns 0.5–19 | ns 20–29 | ns 30–70+
Wang et al., 2018	P	ref.†	ns 0.5–39 | ns 40–70+
Song et al., 2014	C-C	ref.†	ns 0.5–4 | ns 5–70+
Women			
Wang et al., 2018	P	ref.†	ns 0.5–39 | ns 40–70+

*All individual prospective cohort and case-control studies published between 2007 and June 2019 and reporting risk estimates for drinking at multiple drinking levels were included in this table.
† Nondrinker (may include former or occasional drinkers or both)

Table 5. Relative risk estimates for alcohol consumption association with stomach non-cardia stomach cancer from meta-analyses*

Study reference	Nondrinker	Average alcohol grams per day
Combined sexes		
Tramacere et al., 2012	ref.†	ns 50–70+
Choi et al., 2018†	ref.†	ns 0.5–19 | ns 20–29 | ns 30–44
Bagnardi et al., 2015†	ref.†	ns 0.5–24 | ns 25–49 | 1.21 50–70+
Men		
Choi et al., 2018†	ref.†	ns 0.5–19 | ns 20–29 | ns 30–44
Bagnardi et al., 2015†	ref.†	ns 0.5–24 | ns 25–49 | ns 50–70+
Women		
Choi et al., 2018†	ref.†	ns 0.5–19 | 20–44
Bagnardi et al., 2015†	ref.†	ns 0.5–24 | ns 25–49 | ns 50–70+

* All meta-analysis study designs published between 2007 and June 2019 and reporting risk estimates for drinking at multiple drinking levels were included in this table.
† Nondrinker (may include former or occasional drinkers or both)

Individual prospective cohorts and case-control studies

Four individual prospective cohort or case-control studies that met the review criteria reported on the association between NCSC and alcohol consumption (see Table 6). Two of four studies reported an association between current alcohol consumption and NCSC; one found an increased risk starting at 60g/day [38] and one found a reduced risk associated with consuming up to 14g/day [53].

- The combined sexes results for Wang et al., 2018, did not hold when stratified by sex. No association was reported for men or women separately [53].

JOINT EFFECT OF ALCOHOL AND H. PYLORI

The WCRF and other organizations, such as the American Cancer Society, have identified H. pylori infection as a risk factor for stomach cancer, specifically NCSC [4, 5]. Several studies that investigate the relationship between alcohol consumption and stomach cancer included in this review adjust for H. pylori infection in their multivariate analysis [17-21, 36, 40].

Although a full analysis of studies examining the joint effect and magnitude of risk was outside the scope of this review, three studies included in this review examined the joint effect [21, 36, 48]. *(Please see the Glossary on page 15 for a definition of relative risk (RR) and descriptions of magnitude of risk as weak, modest, moderate, and strong in epidemiologic research.)* One study reported a strong joint effect of a negative H. pylori infection status and heavy alcohol consumption (55g/occasion or more) on the increased risk of stomach cancer [RR = 3.27; 95%CI (1.05-10.56)] [36]. Two studies reported a "modest" joint effect of a positive H. pylori infection status and heavy alcohol consumption of 20g/day or more [RR = 1.50; 95%CI (1.04-2.16)] [21] and 48g/day or more [RR= 1.52; 95%CI (1.16-2.00)] [48] on the increased risk of stomach cancer but one study found a reduced risk at light consumption levels of up to 12g/day [RR = 0.77; 95%CI (0.63-0.96)] [48]. This inconsistency may be explained by potential opposing mechanisms. *(Please see also the Biological mechanisms section for a discussion of the effect of alcohol consumption and H. pylori infection on stomach cancer risk.)*

FUTURE RESEARCH

Further research is needed to understand the joint effect of alcohol and H. pylori on the risk of stomach cancer. In addition, more research is needed to understand how a cluster of modifiable risk factors can impact stomach cancer risk. For example, Buckland et al. (2015), found that having a healthy index score (never smoking, no or low alcohol intake, high Mediterranean diet score, and normal BMI) of 3 was associated with a 51% reduced risk of stomach cancer, compared to a score of 0 [58].

This review did not evaluate risk of bias or overall study quality as this was out of the scope of the review, and instead left interpretation of study quality and findings to the reader. However, future systematic reviews could contribute to a greater understanding of the relationship between alcohol consumption and stomach cancer risk by assessing study quality. Such an exercise may help readers interpret individual study results in the context of other published research and assess the overall quality of evidence from the existing body of research.

Table 6. Relative risk estimates for alcohol consumption associated with non-cardia stomach cancer from individual prospective cohort and case-control studies*

Study reference	Study design	Nondrinker	Average alcohol grams per day
Combined sexes			
Steevens et al., 2010	P	ref.†	ns
Freedman et al., 2007	P	ns†	ref.
Duell et al., 2011	C-C	1.61†	ref.
Wang et al., 2018	P	ref.†	0.81
Men			
Wang et al., 2018	P	ref.†	ns
Women			
Wang et al., 2018	P	ref.†	ns

Study reference	0.5 1 2 3 4	5 6 7 8 9	10 11 12 13 14	15 16 17 18 19	20 21 22 23 24	25 26 27 28 29	30 31 32 33 34	35 36 37 38 39	40 41 42 43 44	45 46 47 48 49	50 51 52 53 54	55 56 57 58 59	60 61 62 63 64	65 66 67 68 69	70+
Steevens et al., 2010	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Freedman et al., 2007	ref.	ref.	ref.	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Duell et al., 2011	ref.	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	2.90	2.90	2.90
Wang et al., 2018	0.81	0.81	0.81	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Wang et al., 2018	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Wang et al., 2018	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns

*All individual prospective cohort and case-control studies published between 2007 and June 2019 and reporting risk estimates for drinking at multiple drinking levels were included in this table.

† Nondrinker (may include former or occasional drinkers or both).

Glossary

- **Acetaldehyde** is a product of the metabolism of ethanol, which begins in the mouth and digestive tract but takes place primarily in the liver. Acetaldehyde is a carcinogen and can damage DNA and increase cell proliferation.

- **Acetaldehyde dehydrogenase (ADH)** is an enzyme that breaks down acetaldehyde into smaller molecules such as acetate, which are further broken down into carbon dioxide and water molecules.

- **Alcohol dehydrogenase (ALDH)** is an enzyme involved in metabolism of ethanol which breaks down alcohol

- **Carcinogen** is any agent or substance that can cause cancer.

- **CYP2E1** is a protein that is induced by ethanol, diabetes, and starvation and metabolizes ethanol and other endogenous and exogenous substances.

- **Reactive oxygen species (ROS)** are a group of highly-reactive molecules containing oxygen that, at low levels, are an important part of metabolism and inflammatory response. An excess of reactive oxygen species can damage cellular proteins, lipids, or DNA, and has been linked with chronic diseases, such as cancer, diabetes, and cardiovascular disease.

- **Relative risk (RR)** is a measure that compares the probability of a given outcome (for example, breast cancer) among a group of people with a given risk factor (for example, alcohol consumption) with the probability of that outcome among a group of people without the risk factor (for example, nondrinkers). A risk estimate above one (RR>1) indicates an increased risk of the outcome associated with the exposure and a risk estimate below one (RR<1) indicates a reduced risk of the outcome associated with the exposure. If the risk estimate is equivalent to one (RR=1) then there is no association between the outcome and the exposure.

    - The magnitude of relative risk describes the strength of the association between the exposure and outcome of interest, or the relative risk estimate. There are several terms used to describe or interpret different relative risk estimates. Some commonly used descriptors are weak, small, moderate, medium, strong, or large [50, 59-62], however, the risk estimates associated with each term may differ or overlap (see Figures 2A–C). For example, according to Schoenbach and Rosamond 2000 [50], a moderate risk is equivalent to a relative risk of 1.8 to 3.0, while Craun and Calderon 200, states that moderate to strong risk is equivalent to a relative risk greater than 1.5 [59, 60].

Figure 2A. Descriptions of magnitude of risk

1.0	No association (null value)
1.1–1.3	Weak
1.4–1.7	Modest
1.8–3.0	Moderate
3–8	Strong
For inverse associations (risk ratio is less than 1.0), take the reciprocal and look in above table, for example, the reciprocal of 0.5 is 2.0, which corresponds to a "moderate" association.	

Source: *Schoenbach and Rosamond 2000 [50]*

Figure 2B. Descriptions of magnitude of risk

	Trivial	Small	Moderate	Large	Very Large	Nearly perfect	Perfect
Correlation	0.0	0.1	0.3	0.5	0.7	0.9	1
Diff. in means	0.0	0.2	0.6	1.2	2.0	4.0	infinite
Freq. diff.	0	10	30	50	70	90	100
Rel. risk	1.0	1.2	1.9	3.0	5.7	19	infinite
Odds ratio	1.0	1.5	3.5	9.0	32	360	infinite

Source: *Hopkins 2002 [61]*

Figure 2C. Descriptions of magnitude of risk

Effect size: Interpretation suggestions for social science data

Type of effect size estimate	Included indices	RMPE	Moderate effect	Strong effect
Group difference	d, Δ, g	0.41	1.15	2.70
Strength of association	r, R, ϕ, p, partial r, β, r_{pb}, tau	0.2	0.5	0.8
Squared association indices	r^2, R^2, η^2, adjusted R^2, ω^2 ε^2	0.04	0.25	0.64
Risk estimates	RR, OR	2.0*	3.0	4.0

Note. RMPE = recommended minimum effect size representing a "practically" significant effect for social science data. For effects with highly valid dependent measures (e.g., death) and using rigorous controlled outcomes trials, lower values may have practical value. RR = relative risk; OR = odds ratio.
*These are not anchored to *r* and should be interpreted with caution

Source: *Ferguson 2016 [62]*

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