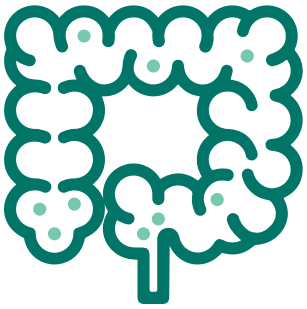
DRINKING AND COLORECTAL CANCER



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 constantly evolving, 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.

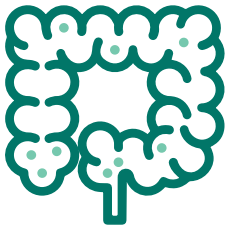
This Health Review focuses on cancer sites associated with alcohol consumption as identified by the World Cancer Research Fund and the International Agency for Research on Cancer. Due to the limited availability of national cancer statistics in many countries, U.S. data – which is publicly available 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 17.

Last literature review: July 2019

Updated 06/01/2022: Result tables have been added and content in the Biological mechanisms section has been updated.

Introduction



COLORECTAL CANCER

4%

Lifetime risk of diagnosis (U.S.)

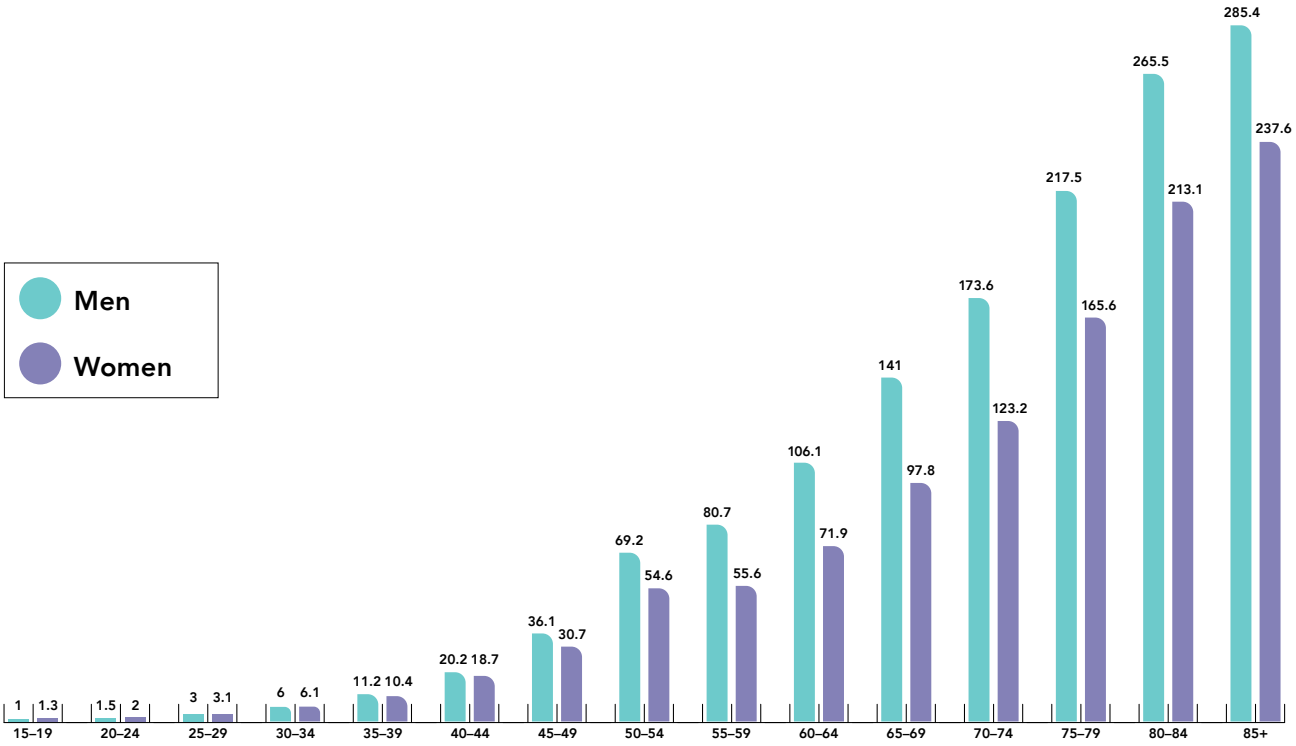
27

Global incidence per 100,000

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

Colorectal cancer is the third most common cancer in the world for men and women combined and accounts for 10% of all incident cancer cases [3]. Incidence rates vary across countries, from a high of 45.3 per 100,000 persons in Hungary to a low of 3.3 per 100,000 persons in Guinea [3]. Incidence increases with age, with 25% of new diagnoses in the U.S. among those aged from 65 and 74 years (see Figure 1) [2, 4]. In the U.S., incidence rates among men are 30% higher than in women [4].

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



Note. *Adapted from Table 6.10, Age-specific SEER incidence rates 2013-2017 [2]*

According to the World Cancer Research Fund (WCRF), alcohol consumption is a risk factor for colorectal cancer [5]. Several factors affect colorectal cancer risk, some of which may mediate or modify the relationship between alcohol consumption and colorectal cancer (see Table 1).

Table 1. Common risk factors for colorectal cancer*

Modifiable risk factors	Non-modifiable risk factors
Alcohol consumption	Adult height
Body mass index	Age
Calcium intake	Ethnicity
Dietary factors (for example, fiber, vitamin D, and red and processed meats)	Personal/family history
Length and frequency of physical activity	Race
Smoking	Type 2 diabetes

Source: *: American Cancer Society [4, 6] and The World Cancer Research Fund / American Institute for Cancer Research's Third Expert's Report 2018 [5]*

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

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

BIOLOGICAL MECHANISMS OF COLORECTAL CANCER

Researchers are continuing to explore several plausible biological mechanisms that explain the potential role of alcohol as a risk factor for colorectal cancer [5, 7], and some of these are:

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 [8, 9]. Several studies have shown that acetaldehyde is a *carcinogen* and may increase DNA damage to the epithelial cells of the colon by interfering in DNA repair, or promoting cell growth, or both [9-11]. According to some studies, alcohol may be a co-carcinogen (an agent that promotes but does not initiate cell growth) because DNA damage is an early step in carcinogenesis [8, 12, 13].

Nutritional deficiencies

The role of alcohol in colorectal cancer risk may also be related to the effect of alcohol on dietary intake or on malabsorption, or utilization of dietary nutrients [14]. The inability to support these processes may independently or jointly increase susceptibility for cancer growth [10, 15].

- Heavy alcohol consumption may be associated with deficiencies in vitamins (such as Vitamins A, C, E, folate, and thiamin) [12] and other nutrients that support the process of repairing DNA damage and neutralizing *reactive oxygen species* [16].

- Alcohol consumption may contribute to folate malabsorption and deficiency which can modify the association between colorectal cancer and alcohol [17], such that the combination of heavy alcohol consumption and low dietary folate was associated with a 31% increased risk compared to nondrinkers. Heavy alcohol consumption and high dietary folate, on the other hand, was not associated with colorectal cancer risk [17].

Microbiome imbalance

Chronic heavy alcohol consumption may result in an imbalance of the gut microbiome (the full assortment of bacteria and microbes in the gastrointestinal tract) and may weaken functioning of the gut barrier [10, 15, 18].

- The gut microbiome may mediate the relationship between alcohol consumption and colorectal cancer risk [15, 19].

- The impairment of one-carbon metabolism associated with chronic heavy drinking can lead to epigenetic changes; these are caused by folate deficiency, or byproducts of ethanol metabolism, or both, which can lead to cancer [15, 17, 20, 21].

- However, moderate consumption of some types of alcohol beverages may favorably alter the gut microbiome. *Polyphenols* found in some alcohol beverages appear to promote an increase in a type of bacteria that inhibits the growth of other types of bacteria that are associated with colon cancer [18].

Influence of weight gain

- Indirectly, lifestyle and dietary factors (including heavy drinking) may contribute to excess weight gain and influence colorectal cancer risk through metabolic dysfunction, inflammation, *oxidative stress*, and microbiome *dysbiosis* [22].

Summary of recent colorectal 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 colorectal 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, and prospective cohort 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: colorectal 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".

COLORECTAL CANCER

In this section we present results of studies reporting relative risk estimates for colorectal cancer in general, without further classification of subtype or subgroup. The results of studies by subtype or subgroup are summarized in the next section of this review. (*Please see the Glossary on page 17 for a definition of relative risk and descriptions of magnitude of risk as weak, modest, moderate, and strong in epidemiologic research.*)

According to the WCRF, there is "convincing" evidence of an increased risk of colorectal cancer associated with alcohol consumption above 30g/day [5]. (*Please see* Background chapter *for an explanation on the WCRF definitions of strength of evidence.*)

Meta-analyses and pooled prospective cohort studies

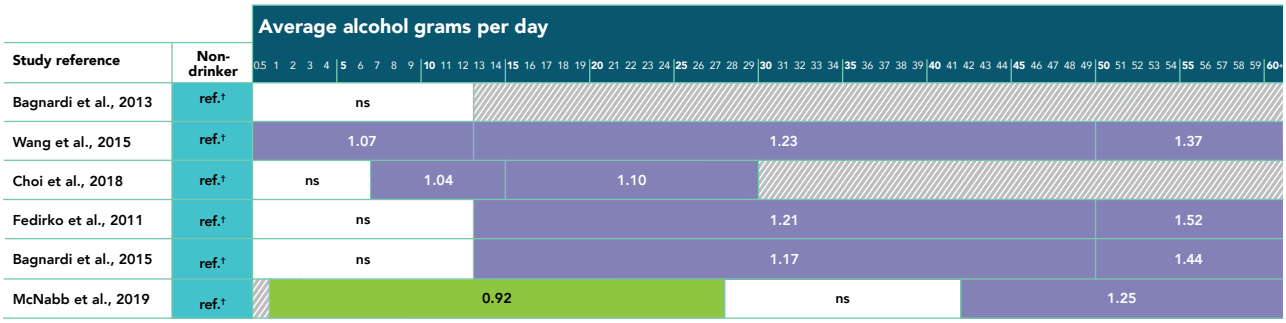
Six meta-analyses met the inclusion criteria for this review and reported on the association between colorectal cancer and alcohol consumption. Five out of six meta-analyses suggest an increased risk for colorectal cancer for men and women combined associated with alcohol consumption [23-28] (see Table 2). Compared with not drinking or occasional drinking, risk appeared to increase at different drinking levels and grow larger as alcohol intake increased starting at any alcohol consumption [27], above 6g/day [25], above 12.5g/day [23, 26], and above 42g/day [24].

- The meta-analysis conducted by McNabb et al. was the only study to report a reduced risk associated with alcohol consumption (up to 28g/day) [24].

One meta-analysis, conducted by Bagnardi et al. (2013), reported null results (no association between alcohol consumption and risk of colorectal cancer) [28].

- This study compared nondrinkers with drinkers in a light-to-moderate drinking category (up to 12.5g/day) only; drinking more than 12.5g/day was not assessed [28].

Table 2. Relative risk estimates for alcohol consumption associated with colorectal cancer for men and women combined from meta-analyses and pooled cohort studies*



* All meta-analyses and pooled cohort study designs published between January 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.
- Dashed line indicates that upper and lower limits of two drinking categories overlapped.

Results from these meta-analyses indicate that the magnitude of the risk estimate grows larger as alcohol consumption increases. Compared to nondrinkers, the lowest levels of average alcohol consumption defined by these studies (up to 12.5g/day) are associated with a 4% to 7% increase in risk (equivalent to a relative risk of 1.04 and 1.07), while the highest levels of consumption (more than 50g/day) are associated with a 37% to 52% increase in risk (equivalent to a relative risk of 1.37 and 1.52), compared to nondrinkers. Relative risk estimates of 1.04 and 1.07 are considered "weak" and 1.52 are considered "modest"; see, for example, Schoenbach and Rosamond (2000) [29] and the Glossary for additional resources.

An additional four meta-analyses and one pooled cohort study were included in the literature review but excluded from the summary above. These studies reported risk estimates comparing highest to lowest consumption categories, without defining those categories in number of drinks or grams of alcohol and potentially combining light drinkers with nondrinkers [30-34].

Individual prospective cohort studies

Twelve individual prospective cohort studies that met the review criteria reported results for men and women combined, some of which are included in the meta-analyses mentioned above, and mostly indicate an increase in risk starting at more than 30g/day (see Table 3).

Ten studies found an association between some level of alcohol consumption and increased colorectal cancer risk [17, 35-43], and a minority (two) reported no association (null results) [44, 45].

- Seven studies reported an increased risk starting at 30g/day [17, 35, 37, 43], 40g/day [40, 41], and 60 g/day [39].
- One study found an association at any level of alcohol consumption and increased risk of colorectal cancer [38].
- Two studies reported an increase in risk at 15–16g/day. However, these two studies defined their drinking categories such that all alcohol consumption greater than 15 or 16g/day was grouped together, making it impossible to discern the association between more precise levels of alcohol consumption and the risk of colorectal cancer [36, 42].

These results are consistent with the findings of the WCRF Report on Diet and Cancer, which finds an association between drinking 30g or more per day and an increased risk of colorectal cancer [5].

As with the findings from meta-analyses and pooled cohort studies, the magnitude of risk for drinkers compared to nondrinkers ranged from a "weak" to "modest" association, as described by Schoenbach and Rosamond [29]. For example, results from the ten prospective cohort studies described above included risk estimates ranging from 1.08 to 1.53.

Note that the drinking level categories from meta-analyses in Table 2 are generally broader than the categories from individual cohort studies in Table 3. Broader drinking categories may be necessary when pooling data from various sources with various drinking level definitions, but they cannot distinguish differences in risk between more narrowly defined drinking categories. For example, the Bagnardi (2015) "moderate" drinking category in Table 2 includes the range from 12.5g to <50g/day as a single category, which cannot improve understanding of whether there is a difference in risk between drinking one, two, three, or four drinks per day. This topic is discussed further in the chapter "Discussion of conceptual and methodological issues"*.*

Table 3. Relative risk estimates for alcohol consumption associated with colorectal cancer from prospective studies with combined estimates for men and women*

Study reference	Former drinker	Non-drinker	Average alcohol grams per day
Park et al., 2009		ref.†	ns (0.5–14) | ns (15–19) | ns (20–24) | ns (25–70+)
Kunzmann et al., 2018		ref.‡	ns (0.5–1) | ns (2–4) | ns (5–9) | ns (10–14) | ns (15–29) | ns (30–39) | ns (40–70+)
Choi et al., 2017		ref.†	1.08 (0.5–9) | 1.25 (10–19) | 1.10 (20–24) | 1.04 (25–70+)
Nishihara et al., 2014		ref.†	ns (0.5–14) | 1.28 (15–70+)
Bradbury et al., 2020			ref. (0.5–1) | ns (2–9) | ns (10–19) | 1.21 (20–70+)
Nan et al., 2013		ref.†	ns (0.5–9) | ns (10–14) | ns (15–24) | 1.35 (25–70+)
Cho et al., 2012		ref.†	ns (0.5–9) | ns (10–14) | ns (15–24) | 1.36 (25–70+)
Park et al., 2018		ref.†	ns (0.5–9) | ns (10–24) | 1.24 (25–70+)
Bongaerts et al., 2008		ref.†	ns (0.5–9) | ns (10–24) | 1.53 (25–70+)
Jayasekara et al., 2017		ref.‡	ns (0.5–19) | ns (20–24) | ns (25–39) | 1.50 (40–70+)
Klatsky et al., 2015	ns	ref.‡	ns (0.5–14) | ns (15–39) | 1.40 (40–70+)
Ferrari et al., 2007		ns‡	ref. (0.5–9) | ns (10–24) | ns (25–54) | 1.98 (55–70+)

* All individual prospective cohort study designs published between January 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)

COLORECTAL CANCER, BY SEX

Recent research has suggested that the association between alcohol consumption and colorectal cancer risk may differ by sex [4, 46, 47]. Some studies and cancer research organizations suggest that, in addition to different drinking patterns, differences in sex hormones (estrogen or progesterone) and levels of ADH may be contributors to this dissimilarity between sexes.

Research has shown that an increase of estrogen either endogenously (for example, menstrual start or pregnancy) or exogenously (for example, oral contraceptives or hormone replacement therapy) may provide a protective effect against colorectal cancer among women [48-50]. When estrogen binds to certain hormone receptors in the colon it may help mitigate cancer growth [49, 51].

Other studies have shown that activity levels of ADH in the stomach and liver are higher in men than women [52-54]. Higher ADH activity could indicate that men may be exposed to higher levels of acetaldehyde (see Biological Mechanisms section for an explanation of the role of acetaldehyde), which may increase cancer risk [52].

However, research on the role of sex hormones and ADH enzyme levels in the relationship between alcohol consumption and colorectal cancer is ongoing and the existing research is currently inconclusive.

Men

Meta-analyses and pooled prospective cohort studies

Seven meta-analyses that met the inclusion criteria for this review reported on the association between colorectal cancer risk for men and alcohol consumption. Six out of seven meta-analyses suggest an increase in colorectal cancer risk for men associated with alcohol consumption [23-28, 55] (see Table 4). These studies reported no increase in risk for their lightest drinking categories compared with nondrinkers but reported a statistically significant increase starting at above 6g/day [25], 12.5g/day [23, 26, 27], 23g/day [55], and 42g/day [24].

- One study reported no association between drinking and colorectal cancer risk for men [28]. However, it only compared nondrinkers to drinkers who consumed up to 12.5g/day and did not include higher consumption categories [28].

One meta-analysis included in the literature review reported risk estimates comparing highest to lowest consumption categories but was excluded from the summary above because it did not quantify those categories in number of drinks or grams of alcohol and may have combined light drinkers with nondrinkers [31].

Table 4. Relative risk estimates for alcohol consumption associated with colorectal cancer for men from meta-analyses and pooled cohort studies*

Study reference	Occasional drinker	Non-drinker	Average alcohol grams per day
Bagnardi et al., 2013		ref.†	ns (0.5–14)
Choi et al., 2018		ref.†	ns (0.5–4)	1.06 (5–14)	1.19 (15–29)
Wang et al., 2015		ref.†	ns (0.5–14)	1.28 (15–49)	1.38 (50–100+)
Bagnardi et al., 2015		ref.†	ns (0.5–14)	1.21 (15–49)	1.53 (50–100+)
Fedirko et al., 2011		ref.†	ns (0.5–14)	1.24 (15–49)	1.62 (50–100+)
Mizoue et al., 2008	ns	ref.†	ns (0.5–24)	1.42 (25–39)	1.95 (40–54)	2.15 (55–74)	2.96 (75–100+)
McNabb et al., 2019		ref.†	ns (0.5–29)	ns (30–34)	1.32 (35–100+)

* All meta-analyses and pooled cohort studies study designs published between January 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 cohort studies

Nineteen prospective cohort studies that met the review inclusion criteria provided separate risk estimates for men, many of which are included in the meta-analyses mentioned above, and found similar results to those of the meta-analyses [17, 35-38, 40, 42-44, 47, 56-64].

- Fifteen of these studies found an increased risk associated with alcohol consumption starting at various drinking levels compared with nondrinkers or drinking <0.5g/day, with half of the studies reporting an increased risk associated with drinking levels starting below 28g/day [36, 38, 42, 43, 61, 62, 64] and half reporting risk increasing at levels at or above 28g/day [17, 35, 37, 47, 56, 57, 59, 63]
    - One study used a drinking category between 0 and 28g/day as the reference group, making it difficult to compare the results with the other studies. In this study, drinking between 29 and 55g/day and more than 56g/day were both associated with an increased risk compared with drinking less than 28g/day [57].
- Four studies found no association between alcohol consumption and colorectal cancer risk among men [40, 44, 58, 60].

Table 5: Relative risk estimates for alcohol consumption associated with colorectal cancer for men from prospective studies with estimates*

Study reference	Former drinker	Non-drinker	Average alcohol grams per day
Park et al., 2009		ref.†	ns | ns | ns | ns
Jayasekara et al., 2017		ref.‡	ns | ns | ns | ns
de Vogel et al., 2008		ref.†	ns | ns
Betts et al., 2018		ref.†	ns | ns | ns
Choi et al., 2017		ref.†	1.18 | 1.40
Everatt et al., 2013		ns†	ref. | 1.46 | ns | ns | ns
Hippisley-Cox et al., 2015		ref.†	ns | 1.14 | 1.30 | 1.62 | 1.56
Bradbury et al., 2020			ref. | ns | 1.23 | 1.45
Nishihara et al., 2014		ref.†	ns | 1.39
Park et al., 2018		ref.†	ns | ns | 1.16 | 1.28
Toriola et al., 2008			ref. | ns | ns | ns | 3.50
Akinyemiju et al., 2017			ref. | 2.02 | 1.42
Cho et al., 2015	ns	ref.†	ns | ns | 2.24
Nan et al., 2013		ref.†	ns | ns | ns | ns | 1.38
Cho et al., 2012		ref.†	ns | ns | ns | ns | 1.40
Offermans et al., 2018		ref.†	ns | 1.58
Bongaerts et al., 2008		ref.†	ns | 1.61
Thygesen et al., 2008	ns	ref.‡	ns | ns | ns | ns | 1.56 | 1.59
Akhter et al., 2007		ref.†	ns | ns | 1.91

* All individual prospective cohort study designs published between January 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)

Women

Meta-analyses and pooled prospective cohort studies

The same seven meta-analyses and pooled cohort studies that analyzed sex-specific risk estimates for men reported risk estimates for women [23-28, 55] (see Table 6). The results of these meta-analyses and the 17 individual prospective cohort studies for women that met the review inclusion criteria were mixed.

Table 6. Relative risk estimates for alcohol consumption associated with colorectal cancer for women from meta-analyses and pooled cohort studies*

Study reference	Occasional drinkers	Non-drinker	Average alcohol grams per day
Bagnardi et al., 2015		ref.†	ns ns ns
Choi et al., 2018		ref.†	ns ns ns
Fedirko et al., 2011		ref.†	ns 1.08 1.54
Wang et al., 2015		ref.†	ns 1.14 ns
Mizoue et al., 2008	ns	ref.†	ns 1.57
Bagnardi et al., 2013		ref.†	0.93
McNabb et al., 2019		ref.†	0.88 ns ns

* All meta-analyses and pooled cohort studies study designs published between January 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)

Three of the seven meta-analyses and pooled cohort studies reporting risk estimates for women found an increased risk associated with alcohol consumption categories starting above 12.5g/day [26, 27] and above 22g/day [55], and two studies reported no association [23, 25].

- However, the Choi et al. meta-analysis limited to comparing nondrinkers to drinkers who consumed up to 30g/day; there are no risk estimates for categories of drinkers above 30g/day [25].

Two studies found a reduced risk associated with alcohol consumption at or below 12.5g/day [28] and 28g/day [24] and no increased risk at any level of consumption.

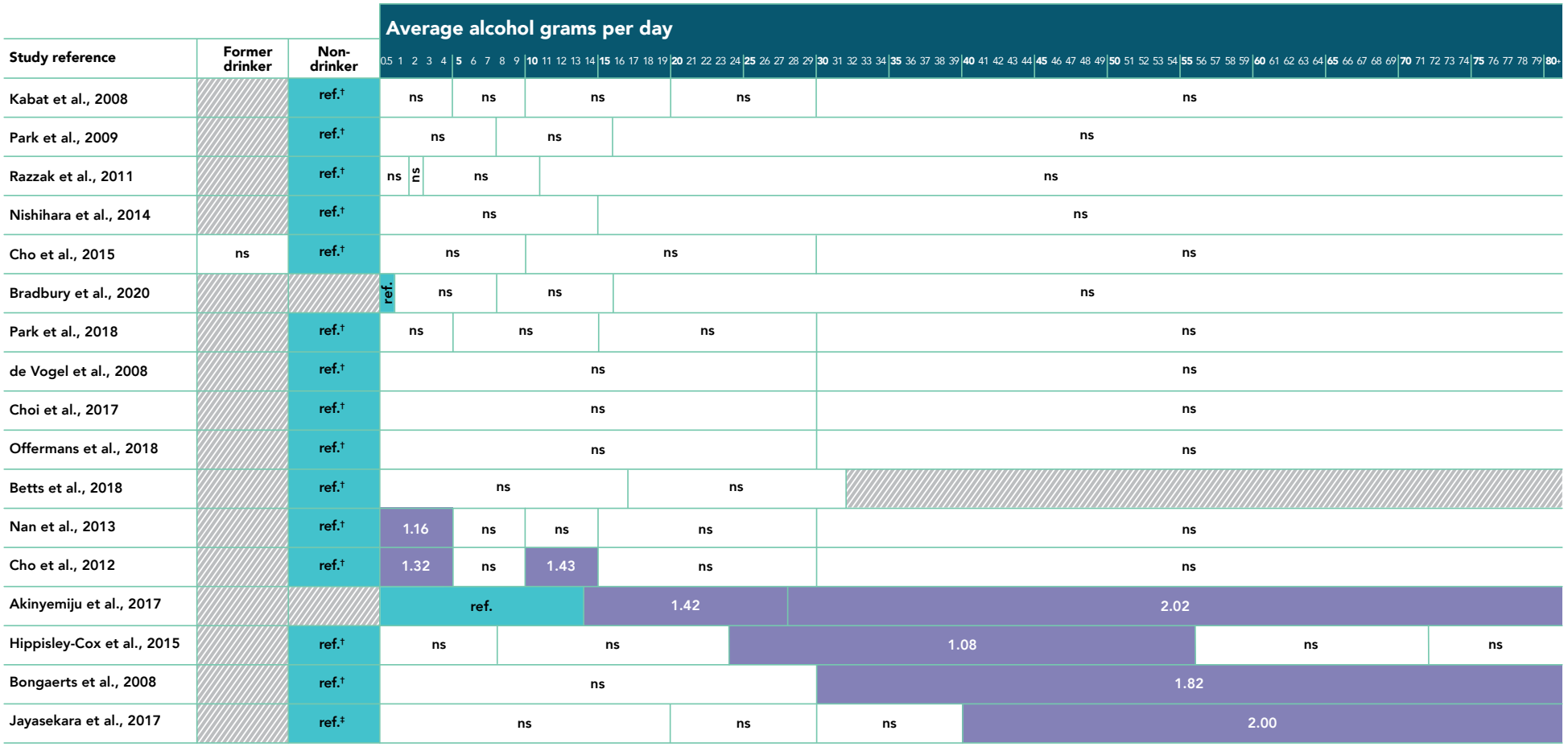
- However, Bagnardi et al. (2013) is a meta-analysis limited to comparing nondrinkers to light-to-moderate drinkers (up to 12.5 g/day) only; there are no risk estimates for categories of drinkers above 12.5g/day.

One meta-analysis included in the literature review reported risk estimates comparing highest to lowest consumption categories but was excluded from the summary above because it did not quantify those categories in number of drinks or grams of alcohol and potentially combining light drinkers with nondrinkers [31].

Individual prospective cohort studies

The results from 17 individual prospective cohort studies, many of which are included in the meta-analyses described above, reported risk estimates for women (see Table 7).

Table 7: Relative risk estimates for alcohol consumption associated with colorectal cancer from prospective studies with estimates for women*



* All individual prospective cohort study designs published between January 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)

Eleven studies reported no association between alcohol and colorectal cancer at any level of consumption [36, 38, 42-44, 47, 58-60, 65, 66] and a minority (six) reported an increased risk [17, 35, 37, 40, 57, 62], most often associated with drinking 24g/day or more [35, 40, 57, 62].

- However, two studies found an increased risk at lower levels of alcohol consumption, less than 5g/day and between 10 and 15g/day, but no increase in risk associated with heavier drinking [17, 37].

A comparison of the results from all the individual cohort studies (the meta-analyses and individual prospective cohorts) that reported sex-specific estimates highlights a difference between men and women in the consistency of statistically significant results.

- Of the individual studies referenced above, 41% of studies among women found an increased risk at any level of drinking. Conversely, 84% of studies among men found an increase in colorectal cancer risk associated with drinking and this was mostly above 28g/day.

- In general, for both men and women, risk appears to increase as drinking levels increase, and the magnitude of risk ranges from a "weak" association to a "modest" association, as described by Schoenbach and Rosamond (2000) [29]. For example, results from the meta-analyses show a range of increased risk estimates across alcohol consumption categories, from 1.06 to 2.96 for men and 1.08 to 1.57 for women.

Future Research

Some studies have focused on examining the joint effect of modifiable behavioral risk factors that people tend to adopt collectively by comparing the presence or absence of multiple risk factors combined. While threshold values defining risk may vary from study to study (for example, 14 or fewer UK units per week [67] or up to 24g/day for men and 12g/day for women [68]), modifiable risk factors commonly included in joint effect analyses for colorectal cancer are [57, 67-71]:

- Alcohol consumption
- Body mass index
- Dietary patterns
- Physical activity levels
- Smoking patterns
- Waist circumference

Collectively, these modifiable risk factors may have a larger effect than individually [68, 70]. A complete analysis of studies examining multiple risk factors simultaneously was outside the scope of this review, but the results of recent studies have shown that adherence to the "healthier" levels of at least four or five of these modifiable risk factors (as defined by each study) was associated with a 25% to 77% reduced risk for colorectal cancer compared to adherence to only one or none [67-70]. Similarly, other studies have found increased risk of 106% [57] and 291% [71] associated with adopting only one or no healthy behaviors compared to adherence to four or five healthy behaviors (same concept as above but opposite reference categories). Further research is needed to understand the joint effect of multiple risk factors on colorectal cancer risk.

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 colorectal 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.

Glossary

- **Acetaldehyde** is a product of ethanol metabolism, which takes place in the liver and can lead to DNA damage.
- **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 into acetaldehyde molecules.
- **Carcinogen** is any agent or substance that can cause cancer.
- **Dysbiosis** is an imbalance in the gut's population of microbes.
- **Oxidative stress** occurs when there is an imbalance between the accumulation of reactive oxygen species (see below for definition) and the body's ability to detoxify and eliminate these molecules through an antioxidant (for example, glutathione, vitamin C, vitamin E) defense.
- **Polyphenols** are micronutrients found in plant-based foods that contain antioxidants and have many health benefits.
- **Reactive oxygen species** 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** 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 [29, 72-75], however, the risk estimates associated with each term may differ or overlap (see Figure 2A-C). For example, according to Schoenbach and Rosamond 2000 [29], 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 [72, 73].

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 asociations (risk ratio is less than 1.0), take the reciprocal and look in above table, for example, reciprocal of 0.5 is 2.0, which corresponds to a "moderate" association.	

Note. *Schoenbach and Rosamond 2000 [29]*

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

Note. *Hopkins 2002 [74]*

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, rh, 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 [75]*

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