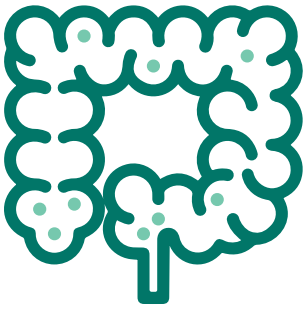
DRINKING AND COLORECTAL CANCER



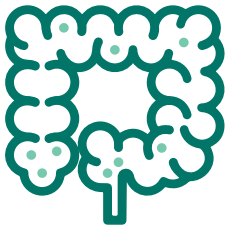
IARD Health Reviews offer a referenced overview of recent peer-reviewed, published research on the relationship between alcohol consumption and health outcomes. They are not intended to be exhaustive representations of all scientific research on a given subject and, as research is constantly evolving, 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. People with specific questions about their drinking are encouraged to consult a healthcare professional; 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 Foundation 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 11.

Last literature review: July 2019

Introduction



COLORECTAL CANCER

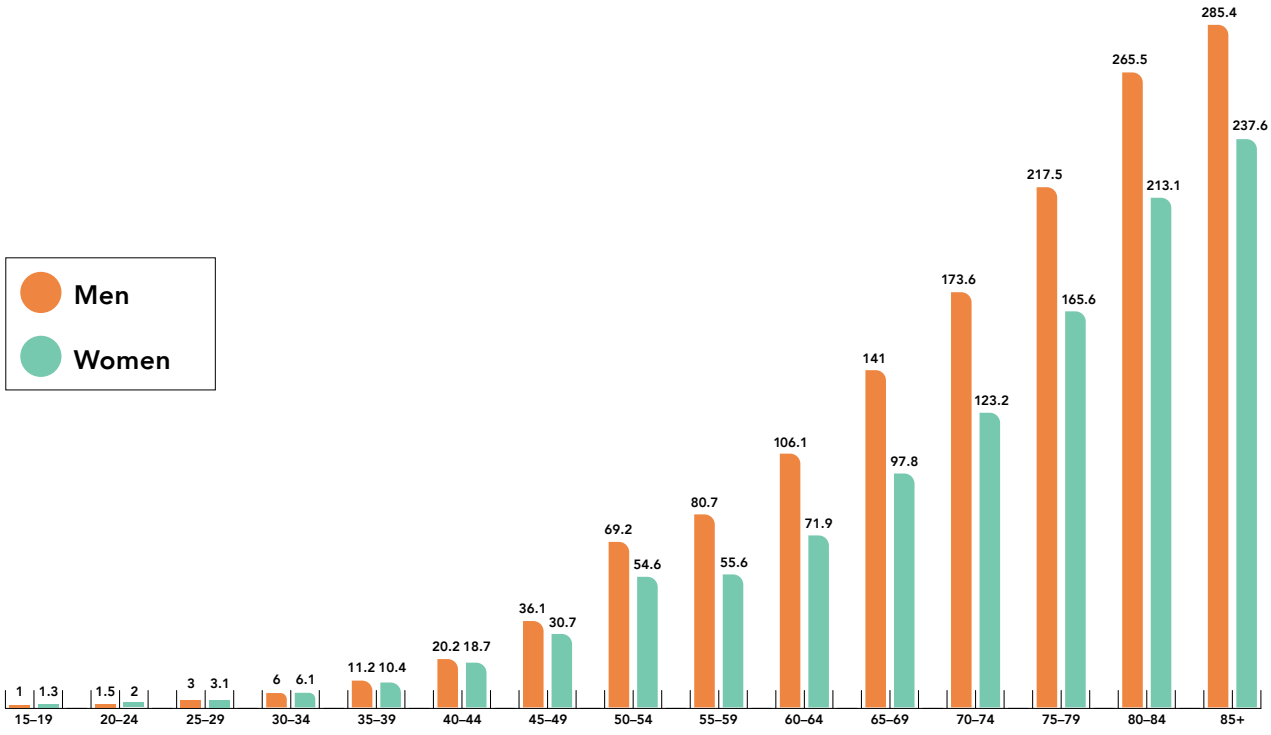
Lifetime risk of diagnosis (U.S.)

Global incidence per 100,000

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

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 the 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]

Several factors may affect colorectal cancer risk, some of which may mediate or modify the relationship between alcohol consumption and colorectal cancer (see Table 1).

Table 1. Risk factors for colorectal cancer*

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

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

** These risk factors are frequently cited by cancer organizations and are listed alphabetically and not according to importance or magnitude of risk.*

The importance (that is, magnitude or 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 may help explain the potential role of alcohol in colorectal cancer risk [6, 7] and some of these are:

- Alcohol is primarily broken down into *acetaldehyde* during metabolism. 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 [8-10] or promoting cell growth [8]. 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 [11-13].

- 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].

    - Heavy alcohol consumption may be associated with deficiencies in vitamins (such as Vitamins A, C, E, folate and thiamin) [11] and other nutrients that support the process of repairing DNA damage and neutralizing *reactive oxygen species* [15, 16].

    - The inability to support these processes may – independently or jointly, or both – increase susceptibility for cancer growth [9, 17].

    - Alcohol consumption may contribute to folate malabsorption and deficiency, which can modify the association between colorectal cancer and alcohol [18], such that the combination of heavy alcohol consumption and low dietary folate was associated with a 31% (CI 95% 1.00-1.71) increased risk, compared to nondrinkers. However, heavy alcohol consumption and high dietary folate was not associated with colorectal cancer risk [18].

- 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 [9, 17, 19].
  - The gut microbiome may mediate the relationship between alcohol consumption and colorectal cancer risk [17, 20].
  - 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 [17, 18, 21, 22].
  - 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 [19].
- Indirectly, lifestyle and dietary factors (including heavy drinking) may contribute to excess weight gain and influence colorectal risk through metabolic dysfunction, inflammation, *oxidative stress*, and microbiome *dysbiosis* [23].

Summary of recent colorectal cancer research

This chapter of the *IARD Health Review: Drinking and Colorectal 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 individual prospective cohort studies
Publication dates: from 2007 through June 2019
Outcomes: 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 "Methodological issues" chapter.*

Colorectal cancer, unspecified
In this first 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 11 for a definition of relative risk and descriptions of magnitude of risk as weak, modest, moderate, and strong in epidemiologic research.)

META-ANALYSES AND POOLED PROSPECTIVE COHORT STUDIES

The findings from five out of six meta-analyses published from January 2007 to June 2019 suggest an increase in colorectal cancer risk for men and women combined associated with alcohol consumption [24-28]. 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 [28], above 6g/day [26], above 12.5g/day [24, 27], and above 42g/day [25].

- 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) [25].

One meta-analysis, conducted by Bagnardi et al. (2013), reported null results (no association between alcohol consumption and risk of colorectal cancer) [29].

- 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 [29].

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% (this is equivalent to a relative risk of 1.04 and 1.07, respectively) increase in risk, while the highest levels of consumption (more than 50g/day) are associated with a 37% to 52% (this is equivalent to a relative risk of 1.37 and 1.52, respectively) increase in risk, compared to nondrinkers. (Relative risk estimates of 1.07 are considered "weak" and 1.52 are considered "modest"; see, for example, Schoenbach and Rosamond (2000) [30] 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 because these studies reported risk estimates comparing highest to lowest consumption categories, without defining those categories in number of drinks or grams of alcohol and may have combined light drinkers with nondrinkers [31-35].

INDIVIDUAL PROSPECTIVE COHORT STUDIES

The results from 12 individual prospective cohort studies for men and women combined, some of which are included in the meta-analyses described above, mostly indicate an increase in risk starting at more than 30g/day.

Ten studies found an association between some level of alcohol consumption and increased colorectal cancer risk [18, 36-44], and a minority (two) reported no association (null results) [45, 46].

- Seven studies reported an increased risk starting at 30g/day [18, 36, 38, 44], 40g/day [41, 42], and 60 g/day [40].

- One study found an association between any level of alcohol consumption and increased risk of colorectal cancer [39].

- 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 [37, 43].

These results are consistent with the findings of the World Cancer Research Foundation (WCRF) Report on Diet and Cancer, which states that there is "convincing" evidence of an association between drinking 30g or more per day and an increased risk of colorectal cancer [6].

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 [31]. For example, results from the ten prospective cohort studies described above included risk estimates ranging from 1.12 to 1.53.

Cancer subgroup analysis: sex

Recent research has suggested that the association between alcohol consumption and colorectal cancer risk may differ by sex [4, 47, 48]. Some studies and cancer research organizations suggest that, in addition to different drinking patterns, differences in sex hormones (estrogen or progesterone) and levels of alcohol dehydrogenase (ADH: an enzyme that breaks down ethanol into acetaldehyde) 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 [49-51]. When estrogen binds to certain hormone receptors in the colon it may help mitigate cancer growth [50, 52].

Other studies have shown that activity levels of ADH in the stomach and liver are higher in men than women [53-55]. Higher ADH activity could indicate that men may be exposed to higher levels of acetaldehyde (see "Biological mechanisms of colorectal cancer" section for an explanation of the role of acetaldehyde), which may increase cancer risk [53].

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

The findings from six out of seven meta-analyses suggest an increase in colorectal cancer risk for men associated with alcohol consumption [24-29, 56]. 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 [26], 12.5g/day [24,27,28], 23g/day [56], and 42g/day [25].

- One study reported no association between drinking and colorectal cancer risk for men [29]. However, it only compared nondrinkers to drinkers who consumed up to 12.5g/day and did not include higher consumption categories [29].

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 [32].

Individual prospective cohort studies

Nineteen prospective cohort studies that provided separate risk estimates for men, many of which are included in the meta-analyses mentioned above, found similar results to those of the meta-analyses described above [18, 36-39, 41, 43-45, 48, 57-65]. A minority of these studies (three) found no association between alcohol and colorectal cancer risk among men [41, 45, 61].

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 [37, 39, 43, 44, 59, 62, 63, 65] and half reporting risk increasing at levels at or above 28g/day [18, 36, 38, 48, 57, 58, 60, 64].

- 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 [58].

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 [24-29, 56]. The results of these meta-analyses and the 17 individual prospective cohort studies for women were mixed.

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 [27, 28] and above 22g/day [56], and two studies reported no association [24, 26].

- 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 [26].

Two studies found a reduced risk associated with alcohol consumption at or below 12.5g/day [29] and 28g/day [25] 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 may have combined light drinkers with nondrinkers [32].

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.

Ten studies reported no association between alcohol and colorectal cancer at any level of consumption [37, 39, 43-45, 59-61, 66, 67] and a minority (seven) reported an increased risk [18, 36, 38, 41, 48, 58, 63], most often associated with drinking 24g/day or more [36, 41, 48, 63].

- 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 [18, 38].

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) [30]. For example, results from the meta-analyses show a range of 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. Although threshold values defining risk may vary from study to study (for example, 14 or fewer U.K units per week [68] or up to 24g/day for men and 12g/day for women [69]), the modifiable risk factors commonly included in joint effect analyses for colorectal cancer are [58, 68-72]:

- Alcohol consumption
- Body mass index (BMI)
- Dietary patterns
- Physical activity levels
- Sleep duration
- Smoking patterns
- Waist circumference

Collectively, these modifiable risk factors may have a larger effect than individually [69, 71]. A complete analysis of studies that examined 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 factors (as defined by each study) was associated with a reduced risk for colorectal cancer of between 25% and 77% (inclusive), compared to adherence to only one or no healthy levels [68-71].

Similarly, other studies have found an increased risk of 106% [58] and 191% [72] associated with adopting only one or no healthy behaviors, compared to adherence to four or five healthy behaviors (this is the same concept as in the previous paragraph but with opposite reference categories).

Further research is needed to understand the joint effect of multiple risk factors on colorectal cancer risk.

Glossary

- **Acetaldehyde** is a product of ethanol metabolism, which takes place in the liver and breast tissue and can lead to DNA damage.
- **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, colorectal 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; 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 [30, 73-76], however, the risk estimates associated with each term may differ or overlap (see Figure 2A-C). For example, according to Schoenbach and Rosamond 2000 [30], a moderate risk is equivalent to a relative risk of 1.8 to 3.0, while Craun and Calderon n.d., states that moderate to strong risk is equivalent to a relative risk greater than 1.5 [73, 76].

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

Note. Adapted from *Schoenbach and Rosamond 2000* [30]

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. Adapted from *Hopkins 2002* [74]

Figure 2C. Descriptions of magnitude of risk

Table 1
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	.41	1.15	2.70
Strength of association	r, R, φ, ρ, partial r, β, r_b, tau	.2	.5	.8
Squared association indices	r^2, R^2, η^2, adjusted R^2, ω^2, ϵ^2	.04	.25	.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 outcome 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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