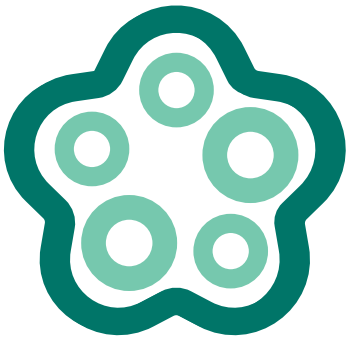
IARD
INTERNATIONAL ALLIANCE FOR RESPONSIBLE DRINKING

HEALTH REVIEW

DRINKING AND 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 129.

Last literature review: July 2019

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DRINKING AND CANCER BACKGROUND

Publication date: July 2021

Introduction

In 2019, cancer was the second-leading cause of death globally after cardiovascular disease among all non-communicable diseases (NCDs) and other causes of death. Cancer accounted for 17.8% of all deaths, according to the Global Burden of Disease Study (GBD) [1].

Cancer incidence (new cases diagnosed within a given year) and mortality rates vary across the globe, with approximately two-times higher incidence rates in high-income countries than in lower-income countries. Although mortality rates have been declining in high-income and middle-income countries, these rates have remained nearly unchanged in low-income countries since the 1990s [1].

Table 1: Top ten cancer sites worldwide in 2020, by number of new cases

Cancer	Number of new cases	Age-standardized incidence rate (per 100,000)
All cancers	**19,292,789**	**201.0**
Breast	2,261,419	47.8
Lung	2,206,771	22.4
Colorectum	1,931,590	19.5
Prostate	1,414,259	30.7
Stomach	1,089,103	11.1
Liver	905,677	9.5
Cervix uteri	604,127	13.3
Oesophagus	604,100	6.3
Thyroid	586,202	6.6
Bladder	573,278	5.6

Source: *Global Cancer Observatory* [2].

The incidence of being diagnosed with cancer varies by cancer site (see Table 1). In 2020, the cancer sites with the highest incidence rates for both men and women combined were: breast, lung, colorectum, and prostate (see Appendix Table 1A for the Global Cancer Observatory's complete list of new cancer cases in 2018). Cancer incidence can further vary by sex [2].

Cancer risk factors

Some established risk factors for cancer include health-related behaviors, existing health conditions, family history, and genetics. These are categorized into modifiable and non-modifiable risk factors (see Table 2).

According to Macmillan Cancer Support, "Everyone has a certain risk of developing cancer. A combination of genes, lifestyle and environment can affect this risk. Doctors do not know the exact causes of cancer. But there are risk factors that can increase your chance of developing it. Having one or more risk factors does not mean you will get cancer. Also, having no risk factors does not mean you will not develop cancer. Around 1 in 3 cases of the most common cancers (about 33%) could be prevented by eating a healthy diet, keeping to a healthy weight and being more active. There are some things you can do to lower your risk of developing cancer. But you cannot reduce your risk completely through your lifestyle." [3]

The following organizations, among others, provide more information on risk factors associated with cancer: American Cancer Society, National Cancer Institute (NCI), Cancer Research UK, Macmillian Cancer Support, Mayo Clinic, and the World Cancer Research Fund (WCRF).

Table 2: Modifiable risk and non-modifiable risk factors for cancer*

Modifiable risk factors	Non-modifiable risk
• Alcohol consumption • Body mass index (BMI) • Dietary fiber intake • Fruit and vegetable intake • Length and frequency of physical activity • Radiation and sun exposure • Smoking • Viruses and infections	• Age • Ethnicity • Family History • Race • Sex (certain cancers, for example, breast, prostate and thyroid cancer)

Sources: *American Cancer Society* [4] and *National Cancer Institute* [5].

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

This Health Review focuses on the role of alcohol consumption as a risk factor for cancer, specifically the cancer sites associated with alcohol consumption as identified by the World Cancer Research Fund (WCRF) and the International Agency for Research on Cancer (IARC).

ALCOHOL AND CANCER RISK

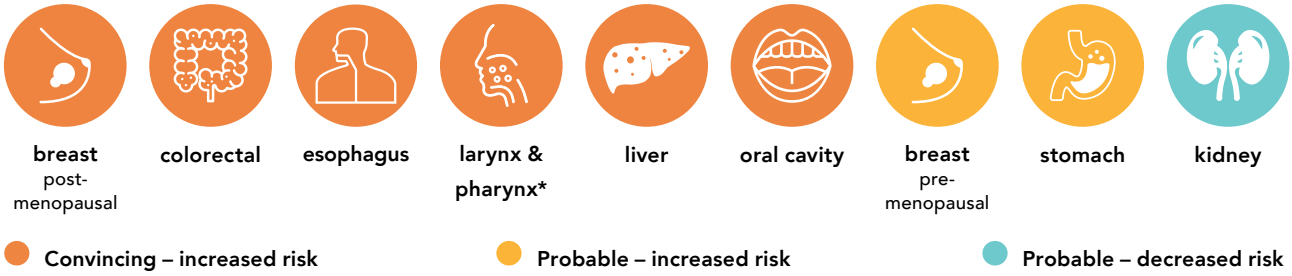
IARC first described alcohol beverages as a Group 1 carcinogen in 1988 [6]. IARC gives this classification to agents or exposures if there is sufficient evidence that they are carcinogenic to humans [6]. Group classifications are based on the strength of the evidence, not the level of risk [6, 7]. (See Glossary on page 129 for a description of IARC's classification of sufficient evidence.)

Both IARC and WCRF report that alcohol consumption is associated with a risk of being diagnosed with certain cancers [8, 9]. According to WCRF:

- "For some cancers, there is an increased risk with any amount of alcohol consumed, whereas for other cancers the risk becomes apparent from a higher level of consumption, of about two or three drinks a day (30 or 45 grams of alcohol per day)" [9].

The 2012 *IARC Monograph* report lists seven cancer sites that are associated with alcohol consumption [8]. WCRF's *Third Expert Report 2018* lists nine cancer sites where there is convincing or probable evidence related to alcohol consumption: eight sites associated with an increased cancer risk and one site with a decreased risk (see Figure 1) [9]. (See Appendix Table 1B for a list of all cancer sites or subtypes reviewed in the *Third Expert Report 2018*.)

Figure 1: WCRF 2018 grading of risk associated with alcohol consumption by cancer site with strong evidence



Source: *The World Cancer Research Fund / American Institute for Cancer Research's Third Expert's Report 2018* [9].
*Pharynx includes nasopharynx, oropharynx, and hypopharynx cancer.

This review focuses on the cancer sites listed by WCRF's 2018 report as having strong evidence of an increase or decrease in risk associated with alcohol consumption as the WCRF's Continuous Update Project (CUP) is more recent and comprehensive than IARC's most recent (2012) review. "Strong evidence", as defined by WCRF, includes sites with "convincing" and "probable" evidence of an increase or decrease in risk associated with alcohol. (See Appendix Figure 1A for descriptions of WCRF classifications and grading of alcohol associated cancers.)

Appendix

Table A1: Estimated number of new cases in 2020, worldwide, both sexes, all ages, regardless of drinking status

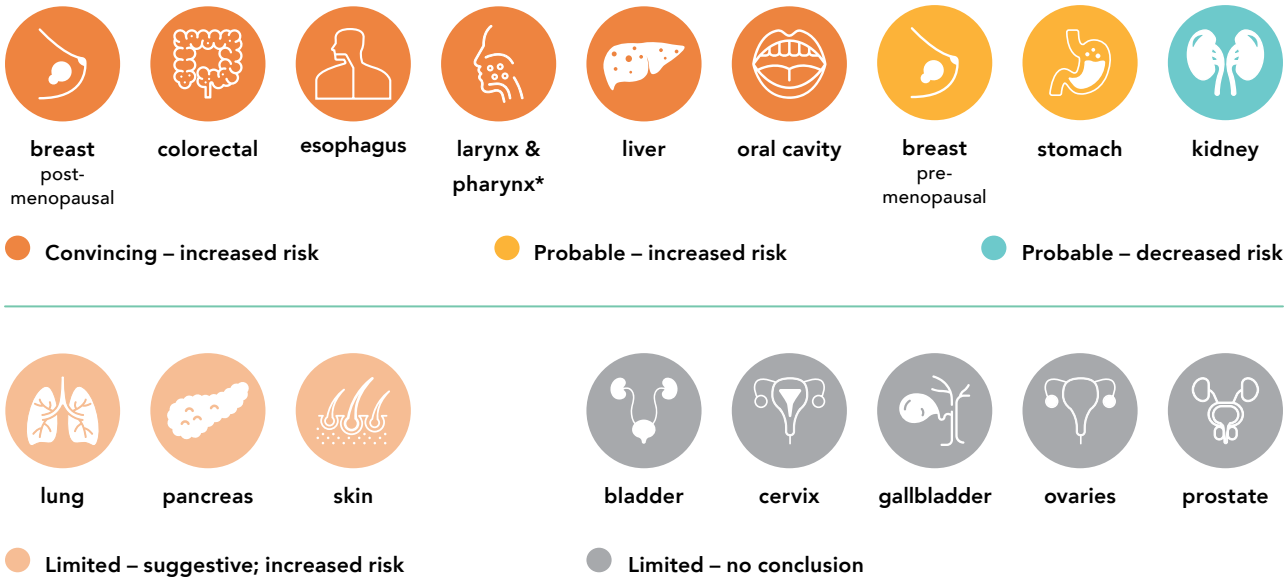
Cancer	Number of new cases	Crude Rate per 100,000	ASR (World) per 100,000
All cancers	**19,292,789**	**247.5**	**201.0**
Breast	2,261,419	58.5	47.8
Lung	2,206,771	28.3	22.4
Colorectum	1,931,590	24.8	19.5
Prostate	1,414,259	36.0	30.7
Stomach	1,089,103	14.0	11.1
Liver	905,677	11.6	9.5
Cervix uteri	604,127	15.6	13.3
Oesophagus	604,100	7.8	6.3
Thyroid	586,202	7.5	6.6
Bladder	573,278	7.4	5.6
Non-Hodgkin lymphoma	544,352	7.0	5.8
Pancreas	495,773	6.4	4.9
Leukaemia	474,519	6.1	5.4
Kidney	431,288	5.5	4.6
Corpus uteri	417,367	10.8	8.7
Lip, oral cavity	377,713	4.8	4.1
Melanoma of skin	324,635	4.2	3.4
Ovary	313,959	8.1	6.6
Brain, central nervous system	308,102	4.0	3.5
Larynx	184,615	2.4	2.0
Multiple myeloma	176,404	2.3	1.8
Nasopharynx	133,354	1.7	1.5
Gallbladder	115,949	1.5	1.2
Oropharynx	98,412	1.3	1.1
Hypopharynx	84,254	1.1	0.91
Hodgkin lymphoma	83,087	1	0.98
Testis	74,458	1.9	1.8
Salivary glands	53,583	0.69	0.57
Vulva	45,240	1.2	0.85

Penis	36,068	0.92	0.88
Kaposi sarcoma	34,270	0.44	0.39
Mesothelioma	30,870	0.4	0.3
Vagina	17,908	0.46	0.36

Source: *Global Cancer Observatory* [2]
ASR = age-standardized rates

Figure 1A: WCRF 2018 classification of evidence and risk associated with alcohol consumption by cancer site

WCRF summarizes the results of its Third Expert Report according to strength of evidence and direction of effect by cancer site and sub-site or sub-type, when relevant, in Section 5, of *Alcohol drinks and the risk of cancer 2018* [10] as follows:



Source: *The World Cancer Research Fund / American Institute for Cancer Research's Third Expert's Report 2018* [9].
*Pharynx includes nasopharynx, oropharynx, and hypopharynx cancer.

The WCRF definitions of their grading criteria as convincing, probable, limited, and unlikely [9] are reproduced here:

Strong evidence: "Evidence is strong enough to support a judgement of a convincing or probable causal (or protective) relationship and generally justifies making public health recommendations."

- **Convincing**: "Evidence is strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce the risk of cancer. The evidence is robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates."

- **Probable**: "Evidence is strong enough to support a judgement of a probable causal (or protective) relationship, which generally justifies making recommendations designed to reduce the risk of cancer."

Limited evidence: "Evidence is inadequate to support a probable or convincing causal (or protective) relationship. The evidence may be limited in amount or by methodological flaws, or there may be too much inconsistency in the direction of effect (or a combination), to justify making specific public health recommendations."

- **Limited – suggestive**: "Evidence is inadequate to permit a judgement of a probable or convincing causal (or protective) relationship, but is suggestive of a direction or effect. The evidence may be limited in amount or by methodological flaws, but shows a generally consistent direction of effect. This judgement generally does not justify making recommendations."

- **Limited – no conclusion**: "There is enough evidence to warrant Panel consideration, but it is so limited that no conclusion can be made. The evidence may be limited in amount, by inconsistency in the direction of effect, by methodological flaws, or any combination of these. Evidence that was judged to be 'limited – no conclusion' is mentioned in Evidence and judgements" [Section 5, Page 24].

Substantial effect on risk unlikely: "Evidence is strong enough to support a judgement that a particular lifestyle factor relating to diet, nutrition, body fatness or physical activity is unlikely to have substantial causal (or protective) relation to a cancer outcome."

References

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6. World Health Organisation (WHO), & International Agency for Research on Cancer (IARC). (1988). Alcohol drinking. IARC Working Group, Lyon, 13-20 October 1987. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, 44, 1-378.

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DRINKING AND BREAST CANCER IN WOMEN

Publication date: June 2022
[Revised to include result tables; updated content in Biological mechanisms section]

Introduction

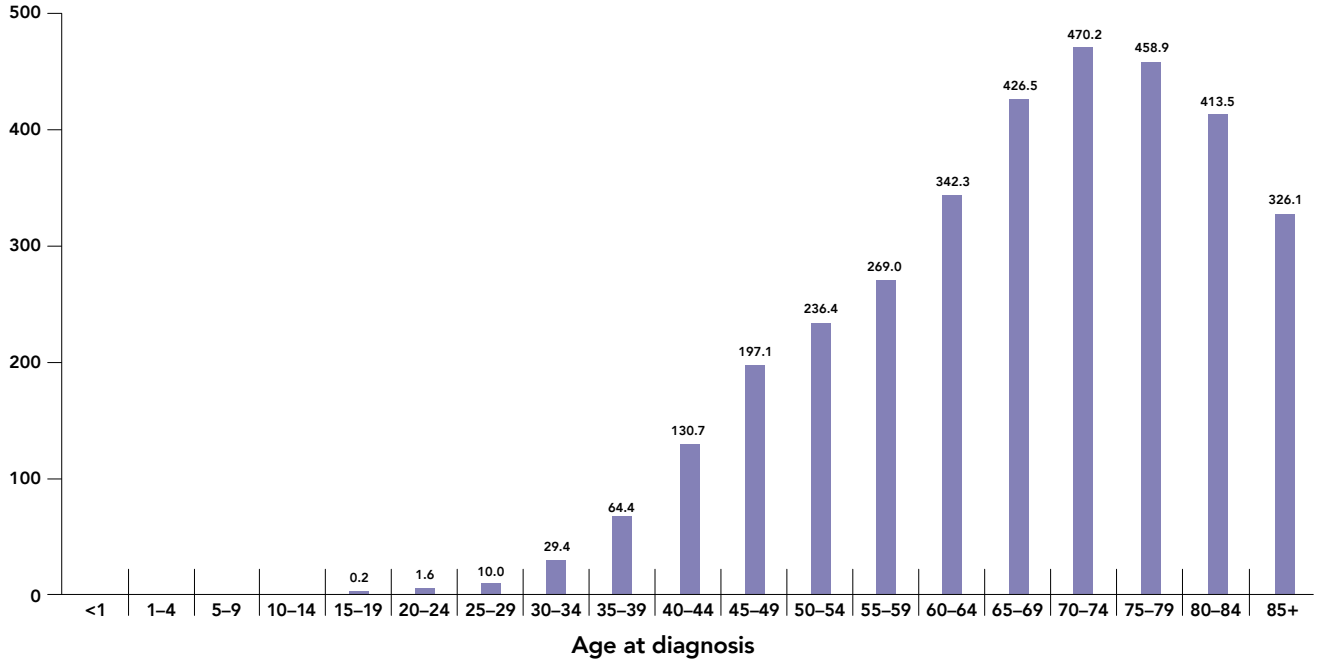
13% Lifetime risk of diagnosis (U.S.)

46 Global incidence per 100,000

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

Breast cancer is the most-diagnosed cancer among women and accounts for 24% of all incident cases of cancer among women globally [3]. Incidence rates vary across countries, from a high of 113 per 100,000 persons in Belgium to a low of 5 per 100,000 persons in Bhutan [3]. Incidence increases with age, and 80% of all female breast cancer cases diagnosed in the U.S. occur in women aged 50 years or older (postmenopausal women) (see Figure 1) [4].

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



Source: *Table 4.11, Age-specific SEER incidence rates 2013-2017* [2]

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

Table 1: Common risk factors for breast cancer*

Modifiable risk factors	Non-modifiable risk factors
Age at first pregnancy/number of pregnancies	Age
Alcohol consumption	Age of first menstrual period
Body mass index (BMI)	Breast tissue density
Breastfeeding	Ethnicity
Breast implants	Family history
Hormonal contraceptives	Height
Hormone replacement therapy (HRT)	Race
Length and frequency of physical activity	Sex
Radiation exposure	

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

**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 differ by population due to environmental, socio-economic, behavioral, or genetic differences.

BIOLOGICAL MECHANISMS OF BREAST CANCER

Researchers are continuing to explore several plausible biological mechanisms that may explain the potential role of alcohol as a risk factor for breast cancer [5, 7, 8], 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 [9, 10]. Evidence from experimental and epidemiological studies indicate that exposure to acetaldehyde in breast tissue may result in *oxidative DNA damage*, thus initiating and promoting cancer growth [7, 8, 11, 12].

Tissue integrity

Alcohol may act as a solvent by changing proteins involved in maintaining tissue integrity and lead to increased invasiveness of toxic substances into cells [5, 11].

- Alcohol consumption may contribute to structural breast tissue changes during the "critical period of increased biologic vulnerability" between first menstrual period and first full-term pregnancy, which may increase risk of future breast cancer development [8]. Additionally, emerging evidence suggests that alcohol may impact gene expression regulation, which is a key factor of *cell proliferation* [8].

Nutritional deficiencies

The role of alcohol in breast cancer risk may also be partly due to the dietary patterns of alcohol consumers. Heavy alcohol consumption has been associated with deficiencies in antioxidants (such as Vitamins A, C, E, folate, and thiamin) and other nutrients that support the process of repairing DNA damage and neutralizing *reactive oxygen species* [7, 8, 11, 12]. The inability to adequately support these processes may, independently and jointly, increase susceptibility for cancer growth. [8, 12].

- For moderate consumers, alcohol may increase insulin-like growth factor (IGF-1), which may increase production of breast tissue cells: both cancerous and non-cancerous [11, 12].

Interaction with estrogen

Alcohol consumption may also increase estrogen levels or sensitivity to estrogen in breast tissue, which may increase the likelihood of hormone receptor expression on cancerous cells [7, 8, 11, 12].

Summary of recent breast 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 breast 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: breast 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".*

BREAST CANCER, UNSPECIFIED

In this section we present results of studies reporting *relative risk* estimates for breast 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 129 for a definition of relative risk (RR) and descriptions of magnitude of risk as weak, modest, moderate, and strong in epidemiologic research.*)

Meta-analyses and pooled prospective cohort studies

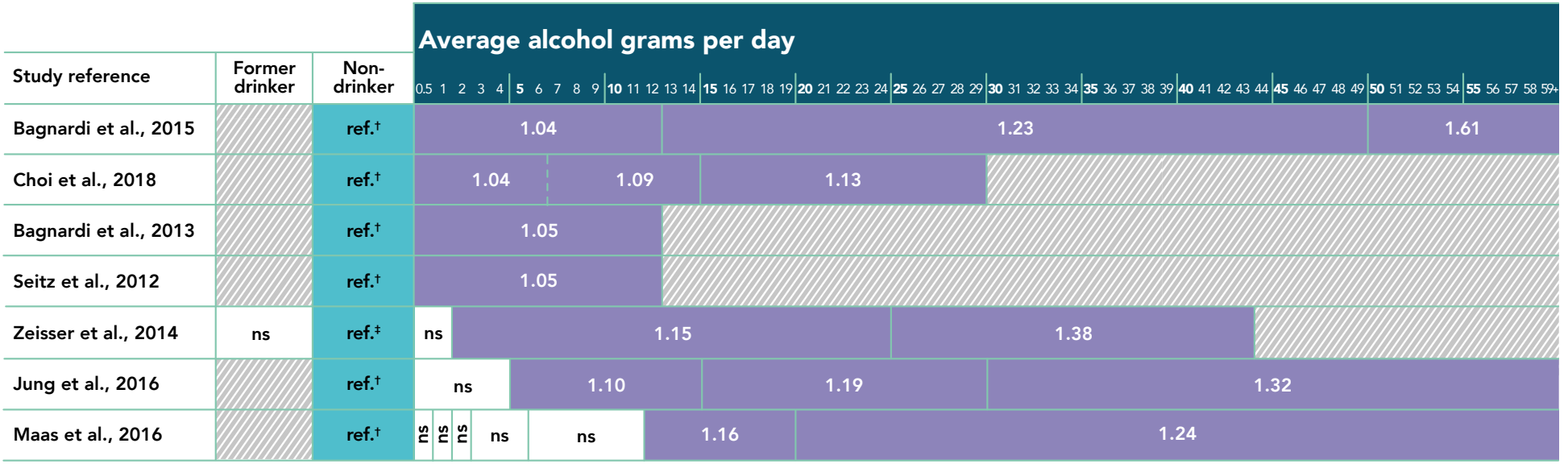
The findings from seven meta-analyses and pooled prospective cohort studies published in the past 12 years suggest an increase in breast cancer risk associated with alcohol consumption. Compared with non-drinkers, risk appears to increase at low drinking levels [13-19] (see Table 2)

- Four studies reported an increased risk starting at more than 0g/day [13-15, 18].
- Three studies reported no increase in risk for their lightest drinking categories compared with not drinking but reported a statistically significant increase starting at 2g/day [19], 5g/day [16], and 12g/day [17].
    - Three meta-analyses compared nondrinkers with drinkers in a light-to-moderate drinking category, up to 12.5g/day [13, 18] and up to 30g/day [15] only. These studies did not include drinking categories above these limits.

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 [20]

Results from these studies indicate that the magnitude of risk grows larger as alcohol consumption increases. Compared to nondrinkers, the lowest levels of average alcohol consumption defined by these studies (up to 13g/day) are associated with a 4% to 5% increase in risk (this is equivalent to a relative risk of 1.04 and 1.05, respectively, which would be described as "weak" [21]), while the highest levels of consumption (more than 50g/day) are associated with a 61% increase in risk (this is equivalent to a relative risk of 1.61 which would be described as "modest" in magnitude [21]). See for example Schoenbach and Rosamond (2000) [21] and the Glossary for descriptions of magnitude of risk as weak, modest, moderate, and strong in epidemiologic research.

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



* All meta-analysis 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)

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.

Individual prospective cohort studies

Twenty prospective cohort studies, many of which are included in the meta-analyses mentioned above, met the review inclusion criteria. These studies indicate that risk for breast cancer increases as alcohol intake increases, potentially starting at low levels of alcohol consumption (see Table 3).

Thirteen studies found an association between some level of alcohol consumption and increased breast cancer risk [22-34], and a minority of the studies (seven) reported no association (null results) [35-41].

- Seven studies reported an increased risk associated with drinking less than 14g/day [22, 23, 25-27, 30, 32].
- Six studies reported an increased risk above, but not below, 14g/day [24, 28, 29, 31, 33, 34].
- As with the findings from meta-analyses, the magnitude of risk for drinkers compared to nondrinkers ranges from a "weak" association to a "moderate" association [21]; see Glossary for definitions of relative risk and magnitude of risk. For example, results from the 13 prospective cohort studies included risk estimates ranging from 1.05 to 1.76.

Differences in risk estimates at given drinking levels across prospective cohort studies are to be expected, given the different characteristics, prevalence of and average level of alcohol consumption, and prevalence of breast cancer, across different populations.

Table 3. Relative risk estimates for alcohol consumption associated with breast cancer for women from individual prospective cohort studies*

Study reference	Occasional drinker	Former drinker	Non-drinker	Average alcohol grams per day
Kabat et al., 2008			ref.†	ns | ns | ns | ns | ns
Kawai et al., 2011			ref.‡	ns | ns | ns
Shin et al., 2015			ref.†	ns | ns | ns
Kim et al., 2017			ref.†	ns | ns | ns
White et al., 2017		ns	ref.†	ns | ns | ns
Betts et al., 2018			ref.†	ns | ns | ns
Zhang et al., 2007			ref.†	ns | ns | ns | ns | ns
Hippisely-Cox et al., 2015			ref.†	1.05 | 1.11 | 1.21 | 1.31 | ns
Klatsky et al., 2014		1.31	ref.‡	1.14 | 1.23 | 1.35
Allen et al., 2009			ns†	ref. | 1.08 | 1.13 | 1.29
Romieu et al., 2015			ns†	ref. | 1.09 | 1.18 | ns
Chen et al., 2011			ref.†	ns | 1.15 | 1.22 | 1.20 | 1.51
Kunzmann et al., 2018			ref.‡	ns | ns | 1.31 | ns | 1.26 | ns | ns
Thygesen et al., 2008				ref. | ns | 1.36 | ns | 4.64
Li et al., 2008		ns	ref.‡	ns | ns | 1.20 | 1.40
Klatsky et al., 2015		1.31	ref.‡	ns | 1.20 | 1.30
Fagherazzi et al., 2015			ref.†	ns | ns | ns | 1.19
Suzuki et al., 2010	ns	1.41	ref.‡	ns | 1.76
Tjonneland et al., 2007			ns†	ref. | ns | ns | ns | ns | ns | 1.36 | ns
Morch et al., 2007			ns	ref. | ns | ns | ns | 2.30 | 1.62

* All individual prospective cohort 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)

CANCER SUBTYPES

Cancers have historically been described and classified according to the site or tissue of origin. More recently, cancers have been further classified by certain features that may be related to type of diagnoses and underlying conditions [5]. Two of these features – diagnosis in relation to menopause (menstruation cessation) status and hormone receptor type – are discussed below.

Menopause

The etiology of breast cancer and the impact of risk factors may differ when diagnosed in women before menopause then when diagnosed after menopause [5]. According to the National Cancer Institute, from 2015 to 2017, the probability of developing postmenopausal breast cancer was over four-times more likely than premenopausal breast cancer [42]. There are many factors that can contribute to this difference: for example, production of sex hormones that stimulate cell growth, such as estrogen and progesterone, increases with age until menopause. Breast tissue is increasingly exposed to hormones over time, thus increasing chances of tumor growth [5, 43]. Furthermore, the difference in risk may be explained by hormone receptor status (discussed below) or modifiable risk factors that change over the life-course such as dietary patterns, level of physical activity, BMI, and use of HRT [24, 44].

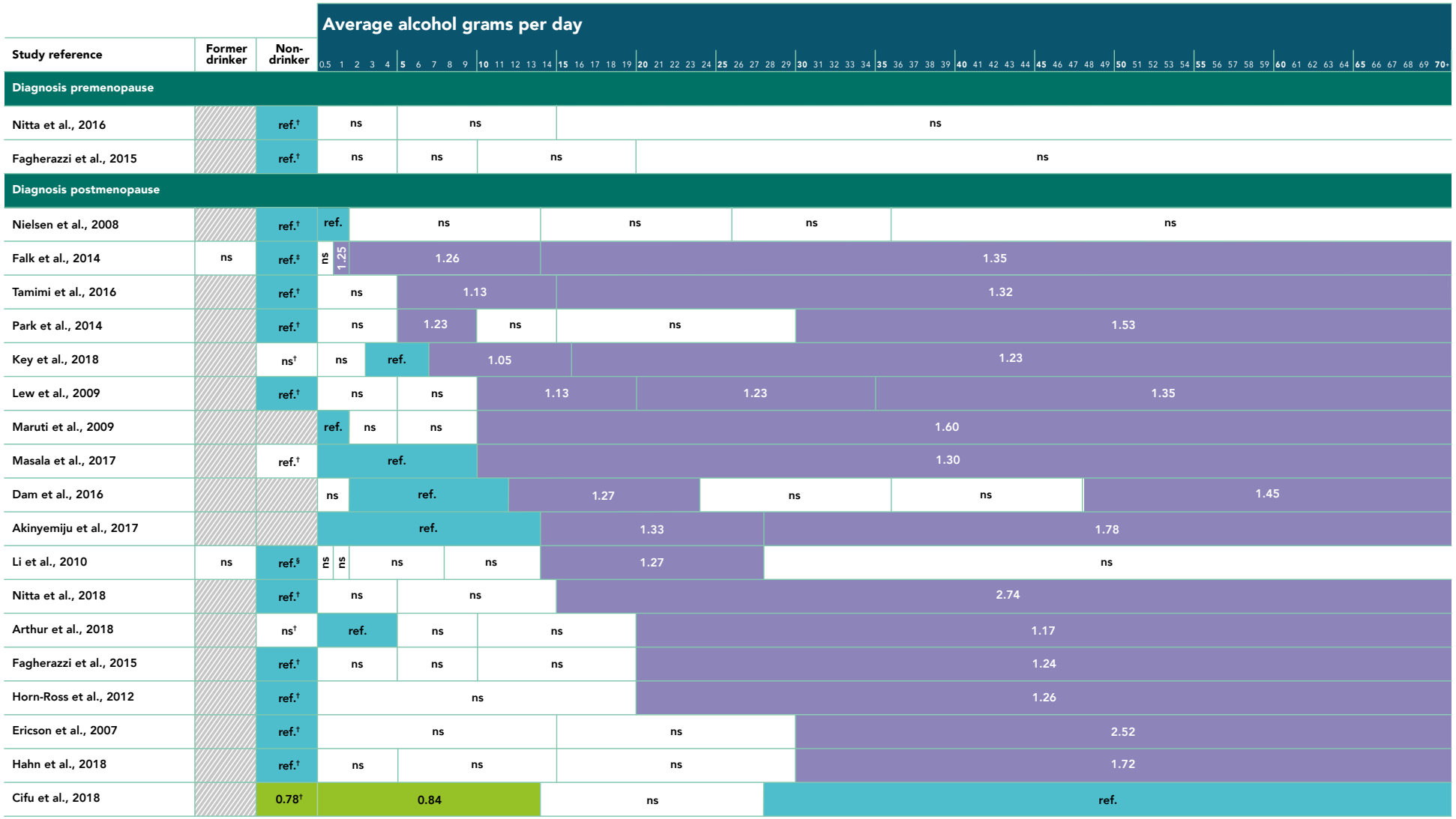
Postmenopausal breast cancer

According to the WCRF, there is "convincing" evidence of an association between alcohol consumption and increased risk of developing postmenopausal breast cancer. The WCRF could not determine a threshold of alcohol intake at which risk appears to increase [5]. (*Please see "Background chapter" for an explanation on the WCRF definitions of strength of evidence.*)

Eighteen prospective cohort studies that examined postmenopausal breast cancer risk associated with multiple drinking categories met the review criteria (see Table 4).

- The majority of studies reported an increased risk associated with drinking, starting at or below 14g/day [44-53], above 14 g/day [24, 54-56] and at 30g/day [57, 58].
- Only one study found no association between alcohol consumption and postmenopausal breast cancer [59].
    - However, this study found that alcohol use among postmenopausal women who used HRT, a potential risk factor, increased the risk of breast cancer, compared to women who did not use HRT [59].
- One study reported a reduced risk for nondrinkers and those consuming less than 14g/day, compared to 28g or more per day [60].

Table 4. Relative risk estimates for alcohol consumption associated with breast cancer based on menopause status for women from individual prospective cohort studies*



Study reference	Former drinker	Non-drinker	Average alcohol grams per day
Diagnosis premenopause			
Nitta et al., 2016		ref.†	ns | ns | ns
Fagherazzi et al., 2015		ref.†	ns | ns | ns | ns
Diagnosis postmenopause			
Nielsen et al., 2008		ref.†	ref. | ns | ns | ns | ns
Falk et al., 2014	ns	ref.‡	ns | 1.25 | 1.26 | 1.35
Tamimi et al., 2016		ref.†	ns | 1.13 | 1.32
Park et al., 2014		ref.†	ns | 1.23 | ns | ns | 1.53
Key et al., 2018		ns†	ns | ref. | 1.05 | 1.23
Lew et al., 2009		ref.†	ns | ns | 1.13 | 1.23 | 1.35
Maruti et al., 2009			ref. | ns | ns | 1.60
Masala et al., 2017		ref.†	ref. | 1.30
Dam et al., 2016			ns | ref. | 1.27 | ns | ns | 1.45
Akinyemiju et al., 2017			ref. | 1.33 | 1.78
Li et al., 2010	ns	ref.§	ns | ns | ns | ns | 1.27 | ns
Nitta et al., 2018		ref.†	ns | ns | 2.74
Arthur et al., 2018		ns†	ref. | ns | ns | 1.17
Fagherazzi et al., 2015		ref.†	ns | ns | ns | 1.24
Horn-Ross et al., 2012		ref.†	ns | 1.26
Ericson et al., 2007		ref.†	ns | ns | 2.52
Hahn et al., 2018		ref.†	ns | ns | ns | 1.72
Cifu et al., 2018		0.78†	0.84 | ns | ref.

* All individual prospective cohort 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)
§ Nondrinker (may include occasional drinkers)

Premenopausal breast cancer

According to the WCRF, there is "probable" evidence that alcohol is associated with an increase in risk of premenopausal breast cancer. The WCRF could not determine a threshold of alcohol intake at which risk appears to increase [5].

Two prospective cohort studies that met the inclusion criteria for this review examined the association between premenopausal breast cancer and multiple drinking level categories (see Table 4).

- Both studies reported no association between any level of alcohol consumption and premenopausal breast cancer, when compared to nondrinkers [24, 56].

The results from these two studies cannot be directly compared with the findings reported by WCRF due to different selection criteria and methods of analysis. WCRF summarized risk for premenopausal breast cancer by comparing undefined highest to lowest alcohol consumption groups and by calculating a *dose-response* trend analysis per 10g increase in alcohol consumption [5]. IARD did not include studies that used unquantified highest and lowest alcohol consumption categories in this review.

Hormone receptor status

There are several breast cancer subtypes that differ in potential causal factors and response to treatment [47, 51, 61]. Hormone receptors are proteins that bind hormones circulating throughout the body; breast cancer subtypes may be defined by the absence or presence of one or more hormone receptor types on the surface and inside breast cells [62]. The most common types of hormone receptors found on breast cells are estrogen receptors and progesterone receptors. When a receptor binds to a hormone, it promotes cell growth, potentially leading to cancerous cells [62].

The following abbreviations in Table 5 will be used in the summary of the research below.

Table 5: Abbreviations of different breast cancer hormone receptor cell types

Hormone receptor cell type	Abbreviation
Estrogen-positive receptor	ER+
Estrogen-negative receptor	ER-
Progesterone-positive receptor	PR+
Progesterone-negative receptor	PR-
Human epidermal growth factor-positive receptor	HER2+
Human epidermal growth factor-negative receptor	HER2-
Estrogen-positive and progesterone-negative receptor	ER+/PR-
Estrogen-negative and progesterone-positive receptor	ER-/PR+
Estrogen-negative and progesterone-negative receptor	ER-/PR-
Estrogen-positive and progesterone-positive receptor	ER+/PR+
Estrogen-negative, progesterone-negative, and human epidermal growth factor-negative receptor	ER-/PR-/HER2-

Several studies have stratified their analysis by hormone receptor status type to determine if hormone receptor status modifies or mediates the relationship between alcohol consumption and breast cancer risk.

Only two meta-analyses or pooled cohort studies met the inclusion criteria for this review and provide summary-level evidence by hormone receptor status, but they offer conflicting results; a 2016 pooled-cohort study found that risk associated with alcohol did not differ by hormone receptor status [16], whereas a 2008 meta-analysis reported increased risk estimates for ER+, ER-, ER+/PR+, and ER+/PR-, and null results for other receptor types when comparing highest to lowest alcohol consumptions [63].

Eleven individual prospective cohort studies grouped breast cancer risk by hormone receptor type [23, 24, 28, 30, 31, 39, 47-49, 53, 64]. Results from these studies, presented below (see Table 6 and Appendix Table A1), suggest that hormone receptor subtype may modify the relationship between alcohol consumption and breast cancer risk. However, the limited number of individual studies and smaller sample sizes for some breast cancer subtypes make it difficult to draw any conclusions.

- Nine of these studies looked at the combination of ER/PR subtypes [23, 24, 28, 30, 31, 39, 47, 49, 53]. Seven studies reported an increased risk among women with ER+/PR+ subtypes [23, 24, 28, 30, 47, 49, 53] associated with alcohol consumption, compared to nondrinkers (or light drinkers [30]), including three studies that examined postmenopausal breast cancers only [47, 49, 53] (see Appendix Table A1). Results for other combinations of ER/PR were less consistent.
    - ER+/PR+ breast cancers are the most common combination of hormone receptor subtypes [65], which may explain why the results for ER+/PR+ mirrored results for all (unspecified) breast cancers within most of the nine studies described above.
- Five studies looked at subtypes for ER or PR cancers separately [28, 31, 47, 48, 64]. Again, the hormone-positive receptor subtype (ER+ or PR+) was linked with an increased risk associated with alcohol, but the negative subtype (ER- or PR-) was not. This was true for four out of five studies examining ER cancers [28, 47, 48, 64] and three out of four studies examining PR cancers [28, 47, 64]. Two of these studies, Key et al. (2019) and Falk et al. (2014), included postmenopausal breast cancers only (see Appendix Table A1).

Table 6. Relative risk estimates for alcohol consumption associated with breast cancer among women from individual prospective cohort studies based on hormone receptor status*

Study reference	Receptor cell type	Occasional drinker	Former drinker	Non-drinker	Average alcohol grams per day
					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+**
Wang et al., 2015	ER+			ref.†	ns | ns | ns | ns | 1.51
	ER-			ref.†	ns | ns | ns | ns | ns
	PR+			ref.†	ns | ns | ns | ns | 1.43
	PR-			ref.†	ns | ns | ns | ns | ns
Suzuki et al., 2010	Overall results	ns	1.41	ref.‡	ns | 1.76
	ER+	ns	ns	ref.‡	ns | ns
	ER-	ns	2.39	ref.‡	ns
	ER+/PR+	ns	ns	ref.‡	ns | ns
	ER+/PR-	ns	ns	ref.‡	ns
	ER-/PR-	ns	2.08	ref.‡	ns
Shin et al., 2015	Overall results			ref.†	ns | ns | ns
	ER+/PR+			ref.†	ns | ns | ns
	ER+/PR-			ref.†	ns | ns | ns
	ER-/PR-			ref.†	ns | ns | ns
Romieu et al., 2015	Overall results			ns†	ref. | 1.09 | 1.18 | 1.08
	ER+/PR+			ns†	ref. | ns | 1.18 | ns
	ER+/PR-			ns†	ref. | ns | ns | ns
	ER-/PR-			ns†	ref. | ns | ns | ns
	ER-/PR+			ns†	ref. | ns | ns | ns
	ER-/PR-/HER-			ns†	ref. | ns | ns | ns

Continued on next page

Table 6. (Continued) Relative risk estimates for alcohol consumption associated with breast cancer among women from individual prospective cohort studies based on hormone receptor status*

Study reference	Receptor cell type	Occasional drinker	Former drinker	Non-drinker	Average alcohol grams per day
					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+**
Fagherazzi et al., 2015	Overall results			ref.†	ns ns ns 1.19
	ER+/PR+			ref.†	ns ns ns 1.32
	ER-/PR-			ref.†	ns ns ns ns
Chen et al., 2011	Overall results			ref.†	ns 1.15 1.22 1.20 1.51
	ER+/PR+			ref.†	ns 1.14 1.27 1.20 1.58
	ER+/PR-			ref.†	ns ns ns 1.39 ns
	ER-/PR-			ref.†	ns 1.25 ns ns ns
	ER-/PR+			ref.†	ns ns ns ns 2.45
Li et al., 2008	Overall results		ns	ref.‡	ns ns 1.20 1.40
	ER+			ref.‡	ns 1.40 1.70
	ER-			ref.‡	ns ns ns
	PR+			ref.‡	ns ns 1.60
	PR-			ref.‡	ns ns ns
	ER+/PR+			ref.‡	ns ns 1.70
	ER+/PR-			ref.‡	ns ns ns
	ER-/PR-			ref.‡	ns ns ns
	ER-/PR+			ref.‡	ns ns

* All individual prospective cohort 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)

FUTURE RESEARCH

Some researchers have focused on examining the joint effect of modifiable risk factors that tend to cluster together by comparing the presence or absence of multiple risk factors combined. While threshold values defining risk may vary from study to study, modifiable risk factors commonly included in joint effect analyses for breast cancer are [45, 54, 60, 61, 66]:

- Alcohol consumption
- Body mass index
- Dietary patterns
- Hormone replacement therapy
- Physical activity
- Smoking

Collectively, these individual modifiable risk factors may have a larger effect than as individual factors [54, 60]. A full 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 five of these modifiable factors (as defined by each study) was associated with a 24% to 35% reduced risk for breast cancer compared to no healthy behaviors [54, 60, 66]. Further research is needed to understand the joint effect of multiple risk factors on breast 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 breast 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.

Appendix

Appendix 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.

Table A1: Relative risk estimates for alcohol consumption associated with breast cancer among postmenopausal women from individual prospective studies based on hormone receptor status*

Study reference	Receptor cell type	Former drinker	Non-drinker	Average alcohol grams per day (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+)
Key et al., 2018	Overall results		ns	ns (0.5–4) · ref. (5) · 1.05 (6–14) · 1.23 (15+)
	ER+		ns	ns (0.5–4) · ref. (5) · 1.09 (6–14) · 1.28 (15+)
	ER-		ns	ns (0.5–4) · ref. (5) · ns (6–14) · ns (15+)
Li et al., 2010	Overall results	ns	ref.§	ns (0.5–1) · ns (2–4) · ns (5–14) · ns (15–19) · 1.27 (20–34) · ns (35+)
	ER+/PR+	ns	ref.§	ns (0.5–1) · ns (2–4) · ns (5–14) · ns (15–19) · 1.32 (20–34) · ns (35+)
	ER+/PR-	ns	ref.§	ns (0.5–1) · ns (2–4) · ns (5–14) · ns (15–19) · ns (20–34) · ns (35+)
	ER-/PR-	ns	ref.§	ns (0.5–1) · ns (2–4) · ns (5–14) · ns (15–19) · ns (20–34) · ns (35+)
Park et al., 2014	Overall results		ref.†	ns (0.5–4) · 1.23 (5–9) · ns (10–14) · ns (15–34) · 1.53 (35+)
	ER+/PR+		ref.†	ns (0.5–4) · ns (5–9) · 1.35 (10–34) · 1.61 (35+)
	ER+/PR-		ref.†	ns (0.5–4) · 1.89 (5–9) · ns (10–34) · 1.72 (35+)
	ER-/PR-		ref.†	ns (0.5–4) · 1.57 (5–9) · ns (10–34) · 1.58 (35+)
Falk et al., 2014	Overall results	ns	ref.‡	ns (0.5–1) · 1.25 (2–4) · 1.26 (5–14) · 1.35 (15+)
	ER+	ns	ref.‡	ns (0.5–1) · 1.29 (2–4) · 1.29 (5–14) · 1.48 (15+)
	ER-	ns	ref.‡	ns (0.5–1) · ns (2–4) · ns (5–14) · ns (15+)
	PR+	ns	ref.‡	ns (0.5–1) · 1.37 (2–4) · 1.33 (5–14) · 1.64 (15+)
	PR-	ns	ref.‡	ns (0.5–1) · ns (2–4) · ns (5–14) · ns (15+)
	ER+/PR+	ns	ref.‡	ns (0.5–1) · 1.36 (2–4) · 1.30 (5–14) · 1.63 (15+)
	ER+/PR-	ns	ref.‡	ns (0.5–1) · ns (2–4) · ns (5–14) · ns (15+)
	ER-/PR-	ns	ref.‡	ns (0.5–1) · ns (2–4) · ns (5–14) · ns (15+)

* All individual prospective cohort 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)
§ Nondrinker (may include occasional drinkers)

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DRINKING AND COLORECTAL CANCER

Publication date: June 2022
[Revised to include result tables; updated content in Biological mechanisms section]

Introduction

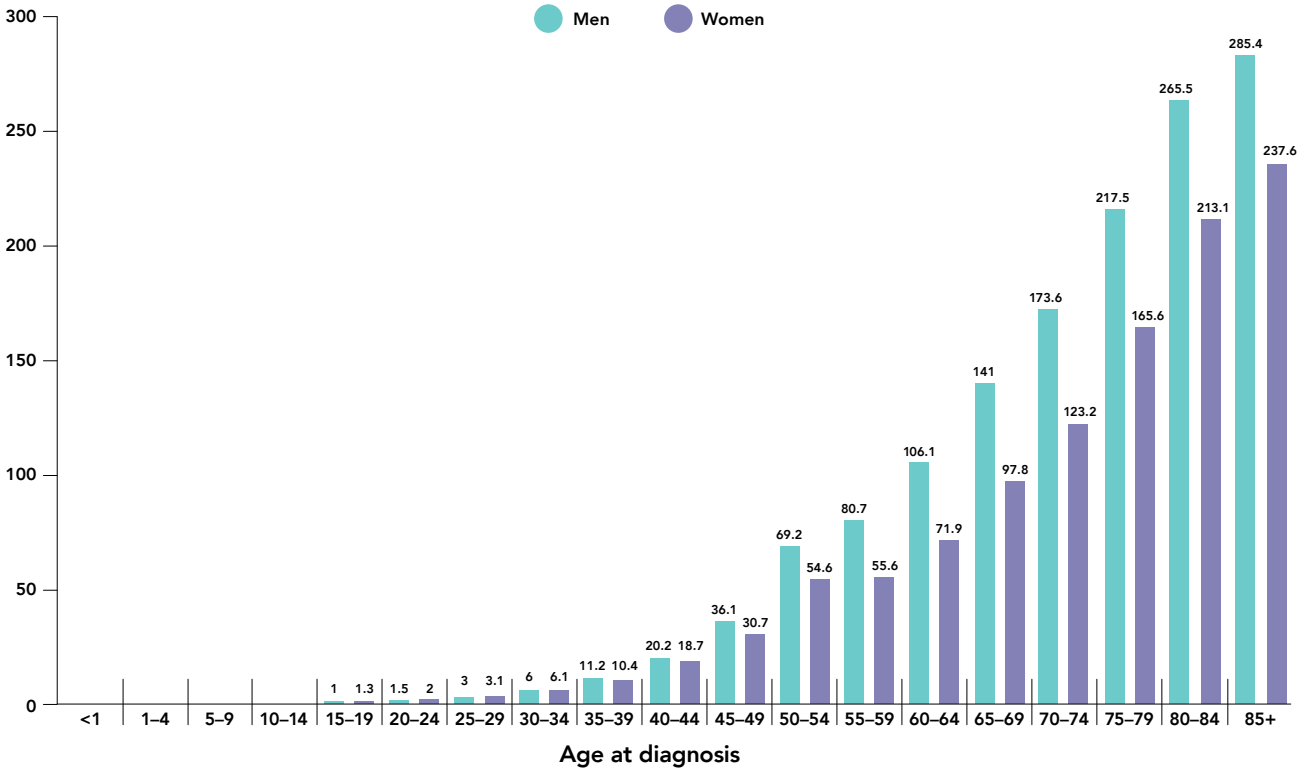
13% **Lifetime risk of diagnosis (U.S.)**

46 **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
	Race
Length and frequency of physical activity	Type 2 diabetes
Smoking	

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 129 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

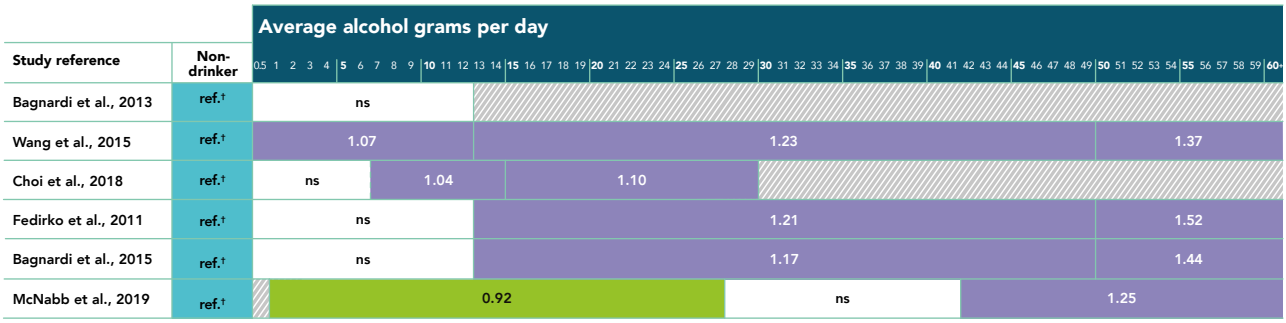
Six meta-analyses met the inclusion criteria for this review and reported on the association between colorectal cancer and alcohol consumption. Five out of six meta-analyses suggest an increased risk for colorectal cancer for men and women combined associated with alcohol consumption [23-28] (see Table 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 (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+**)
Park et al., 2009		ref.†	ns | ns | ns | ns
Kunzmann et al., 2018		ref.‡	ns | ns | ns | ns | ns | ns | ns
Choi et al., 2017		ref.†	1.08 | 1.25 | 1.10 | 1.04
Nishihara et al., 2014		ref.†	ns | 1.28
Bradbury et al., 2020			ref. | ns | ns | 1.21
Nan et al., 2013		ref.†	ns | ns | ns | ns | 1.35
Cho et al., 2012		ref.†	ns | ns | ns | ns | 1.36
Park et al., 2018		ref.†	ns | ns | ns | 1.24
Bongaerts et al., 2008		ref.†	ns | ns | ns | 1.53
Jayasekara et al., 2017		ref.‡	ns | ns | ns | 1.50
Klatsky et al., 2015	ns	ref.‡	ns | ns | 1.40
Ferrari et al., 2007		ns‡	ref. | ns | ns | ns | 1.98

* 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 (5–9) · 1.19 (10–24)
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 (0.5–29) · 1.42 (30–44) · 1.95 (45–59) · 2.15 (60–74) · 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 (0.5–60+)
Choi et al., 2018		ref.†	ns (0.5–4); ns (5–14); ns (15–29); 30–60+
Fedirko et al., 2011		ref.†	ns (0.5–14); 1.08 (15–49); 1.54 (50–60+)
Wang et al., 2015		ref.†	ns (0.5–14); 1.14 (15–49); ns (50–60+)
Mizoue et al., 2008	ns	ref.†	ns (0.5–24); 1.57 (25–60+)
Bagnardi et al., 2013		ref.†	0.93 (0.5–14); 15–60+
McNabb et al., 2019		ref.†	0.88 (0.5–24); ns (25–49); ns (50–60+)

* 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.

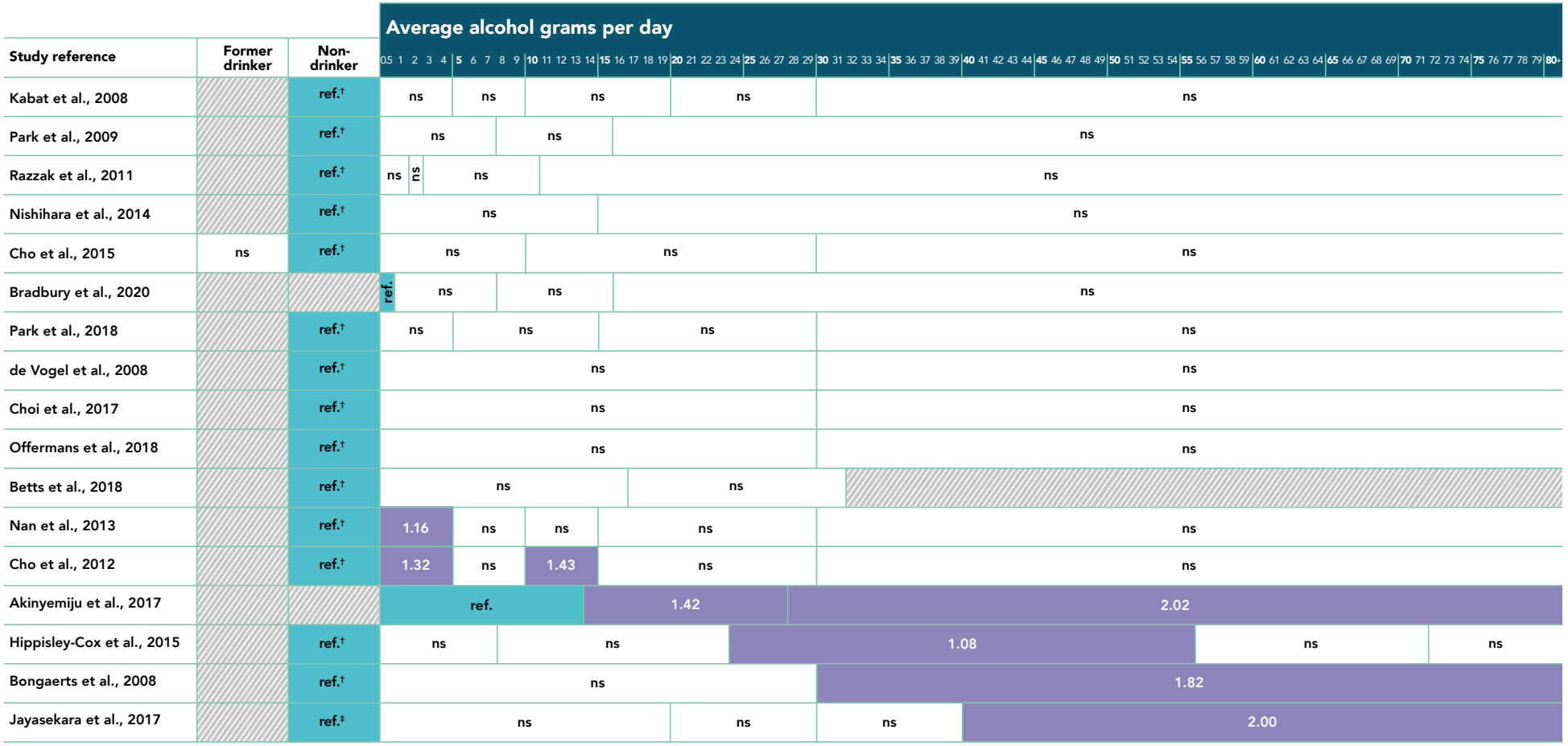
- However, Bagnardi et al. (2013) is a meta-analysis limited to comparing nondrinkers to light-to-moderate drinkers (up to 12.5 g/day) only; there are no risk estimates for categories of drinkers above 12.5g/day.

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.

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DRINKING AND UPPER AERODIGESTIVE TRACT CANCERS

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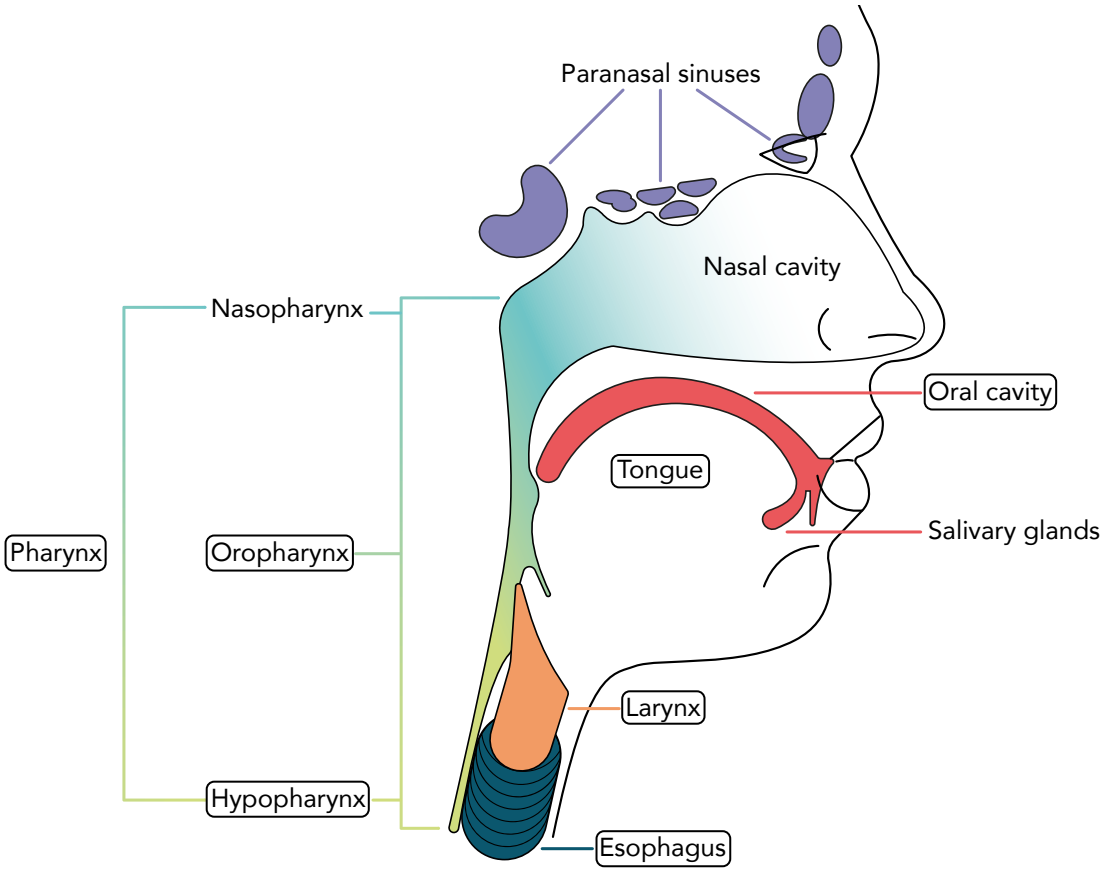
Introduction

The upper aerodigestive tract (UADT) cancers consist of cancers in various sites of the body. According to the National Cancer Institute (NCI), UADT cancers include the esophagus, the organs in the head and neck region, and the upper respiratory region [1]. In the head and neck region, cancer sites may include the oral cavity (lips, mouth, and tongue), pharynx, larynx, paranasal sinuses and cavity, and salivary glands [2]. Note that some of these sites are not included in this review because there is limited or no evidence of an association between cancer at those sites and alcohol consumption.

This review summarizes the results of research from 2007 to June 2019 on alcohol consumption as a risk factor associated with cancers at UADT sites, according to the World Cancer Research Fund's Third Expert Report 2018: esophagus, larynx, oral cavity, and pharynx [3]. These sites are outlined in black in Figure 1.

Figure 1. Anatomy of the upper aerodigestive tract cancers



The table below summarizes key statistics on lifetime risk of diagnosis, median age at diagnosis, and incidence rate for the four main UADT cancer sites summarized in this review.

Table 1. Key statistics of UADT cancer subsites

Cancer site	Lifetime risk of diagnosis (U.S.)	Median age at diagnosis (U.S.)	Global incidence per 100,000
Esophagus	0.5%	68	6.5
Larynx	0.3%	66	2.5
Oral Cavity	1.2%	64	4.5
Pharynx			2.0

Sources: *Global Burden Disease study 2019 (age-standardized data) [4] and the National Cancer Institute SEER Report [5]*

Some cancer data sources and research organizations combine sites for reporting or summary purposes, but these combinations are not always the same. For example, as shown in the table above, the World Cancer Research Fund (WCRF) and NCI combine oral cavity and pharynx, but the Global Burden of Disease study and the Global Cancer Observatory (GCO) do not. The GCO further classifies the nasopharynx, hypopharynx, and oropharynx separately.

Globally, combined UADT cancers account for about 7.8% of all new cancer cases for both sexes [6]. Incidence rates for these cancers can vary by geography and sex. For example, the highest incidence rate for combined UADT cancers is 35.8 per 100,000 in Bangladesh and the lowest incidence rate is 1.1 per 100,000 in Belize [6]. Incidence rates increase with age and UADT cancers are more than three-times higher among men than women [4, 6] (see illustrations of sex-specific incidence rates in the U.S. in Appendix Figures A1–A3).

According to the WCRF, alcohol consumption is a risk factor for UADT cancers [3]. Several other risk factors are associated with cancer risk in the UADT region, some of which may mediate or modify the relationship between alcohol consumption and UADT cancer risk (see Table 2). Certain risk factors are only relevant to specific subsites as noted below.

Table 2. Common risk factors for UADT cancers*

Modifiable risk factors	Non-modifiable risk factors
Alcohol consumption Betel quid (gutka) use (factor for oral cavity and lip cancer only) Body mass index Fruit and vegetable intake Human papilloma virus infection Injury to esophagus (factor for esophageal cancer only) Length and frequency of physical activity Smoking UV light (factor for lip cancer only) Workplace exposure to certain chemicals (factor for laryngeal cancer only)	*Achalasia* (a disorder of the esophagus; factor for esophageal cancer only) Age Barret's esophagus (factor for esophageal cancer only) Gastroesophageal reflux disease Genetics Plummer-Vinson syndrome Race Sex Tylosis (factor for esophageal cancer only)

Sources: *American Cancer Society [7-9] and The World Cancer Research Fund / American Institute for Cancer Research's Third Expert's Report 2018 [3]*

**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 differ by population due to environmental, socio-economic, behavioral, or genetic differences.

BIOLOGICAL MECHANISMS OF UADT CANCERS

Researchers continue to explore several plausible biological mechanisms that may help explain the potential role of alcohol consumption in UADT cancer risk [3]. Some of these potential roles 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 [10, 11]. Several studies have shown that acetaldehyde is a *carcinogen* and may increase DNA damage to the liver, UADT, and other tissues by interfering with DNA repair, or promoting cell growth, or both [11, 12]. 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 [13].

- The microsomal ethanol oxidizing system, another metabolic pathway, accounts for a small percentage of ethanol metabolism and is significantly induced at chronic heavy levels of consumption (after a single week of consuming 40g/day or more) [14, 15]. 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, 16].

- Clinical research has demonstrated that individuals with certain gene mutations in ADH, ALDH, and CYP2E1 accumulate higher levels of acetaldehyde in the liver, upper aerodigestive tract, and other tissues during alcohol metabolism than individuals without these mutations [17, 18].

- Epidemiologic research has found that individuals who carry these genetic mutations have an increased risk of alcohol-related cancers [11, 19-23].

Salivary acetaldehyde

Recent research suggests that alcohol is metabolized by bacteria found in the mouth and at heavier drinking levels may result in increased salivary acetaldehyde, which is associated with an increased risk of oral cavity, pharynx, and esophageal cancer [14, 18, 23].

Tissue integrity

Alcohol may act as a solvent by changing proteins involved in maintaining tissue integrity and lead to increased invasiveness of toxic substances into the mucosal lining, especially in the esophagus. This increases the risk of exposure to other carcinogens, such as tobacco [24].

Interaction with tobacco

Epidemiologic research has reported that the combination of alcohol consumption and tobacco use results in a multiplicative (several times greater) effect on the risk of UADT cancers [23, 25-27]. *(Please see the "Joint effect of alcohol and tobacco" section on page 70 for more information.)*
Some studies describe the following mechanisms to explain this effect:

- As described above, alcohol may act as a solvent, facilitating the invasion of tobacco carcinogens into the mucosa of the UADT [24].
- Alcohol consumption, tobacco use, or both, can modify oral bacteria resulting in an imbalanced microbiome and increased acetaldehyde production [18, 25].
- Alcohol-induced expression of CYP2E1 at heavy chronic alcohol consumption levels may activate tobacco carcinogens. This may lead to the inhibition of ALDH and result in higher concentrations of salivary acetaldehyde [11, 18, 24, 25].
- Some studies have shown that tobacco use may modify the interaction between alcohol and the risk of developing UADT cancers among individuals with certain gene mutations [28, 29].

Summary of upper aerodigestive tract 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 cancers in the UADT but excludes esophageal adenocarcinoma, nasopharynx, and salivary gland cancer because of limited or no evidence of an association between cancers at those sites and alcohol consumption.

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, individual prospective cohort studies, and individual case-control studies; systemic reviews were excluded from this review because of the absence of new or pooled risk estimates.
Publication dates: from 2007 through June 2019
Outcomes: esophageal cancer, head and neck cancers, laryngeal cancer, oral cavity cancer, oral cavity and lip cancer, pharyngeal cancer, hypopharyngeal cancer, oropharyngeal cancer, and upper aerodigestive tract 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"*.

In this section we present results of studies reporting *relative risk* estimates for esophageal squamous cell carcinoma, and cancers of the head and neck, oral cavity and lip, pharynx (hypopharynx and oropharynx), and larynx. *(Please see the Glossary on page 129 for a definition of relative risk and descriptions of magnitude of risk as weak, modest, moderate, and strong in epidemiologic research.)* A section on the joint effect of alcohol consumption and tobacco use is included at the end of the chapter to address the combined effect as noted by the American Cancer Society and the WCRF [3, 7-9].

ESOPHAGEAL CANCER

There are two common esophageal cancer subtypes: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) [3, 30]. ESCC mostly occurs in the upper and middle region of the esophagus and EAC occurs in the lower region where the esophagus and the stomach connect [3].

ESCC is identified as the most common form of esophageal cancer globally [3]. According to the WCRF, there is "convincing" evidence of an association between alcohol consumption and increased risk of developing ESCC [3]. The WCRF could not determine a threshold of alcohol intake at which risk appears to increase. *See "Background chapter" for an explanation on the WCRF definitions of strength of evidence.*

This section of the review includes studies that report results for ESCC only; studies reporting results for EAC are not included due to limited or no evidence of an association between EAC and alcohol consumption [3]. Ten studies that reported results for unspecified esophageal cancer (without distinction between ESCC or EAC) are included in the Appendix (see Appendix Table A1) [31-40]. One meta-analysis included in the literature review reported risk estimates for unspecified esophageal cancer comparing highest to lowest consumption categories but was excluded from the summary in the Appendix because it did not quantify those categories in number of drinks or grams of alcohol [41].

Meta-analyses and pooled case-control studies

Six meta-analyses or pooled case-control studies met the inclusion criteria for this review, and their results suggest an increased risk of ESCC associated with some level of alcohol consumption (see Table 3) [42-47].

- Compared to nondrinkers, three meta-analyses reported an increased risk of ESCC associated with alcohol consumption starting above 0g/day [42, 43, 46] and two meta-analyses or pooled case-control studies reported an increased risk above 12.5g/day [44, 45].
    - Two meta-analyses compared nondrinkers with drinkers in a light-to-moderate drinking category, up to 12.5g/day [42] and up to 30g/day [44] only. These studies did not include drinking categories above these limits.
- One pooled case-control study found an increased risk of ESCC associated with alcohol consumption starting at 32g/day, compared to their reference category of 11g/day or less [47].

When stratified by sex, two of three meta-analyses reported an increased risk of ESCC associated with alcohol consumption starting at above 0g/day for men [42, 43]. For women, one of two meta-analyses reported an increased risk associated with drinking 12.5g/day or more [43].

- Bagnardi et al., (2013) compared nondrinkers with drinkers in a light-to-moderate drinking category (up to 12.5g/day) [42] and did not assess risk associated with alcohol consumption greater than 12.5g/day.

Table 3. Relative risk estimates for alcohol consumption associated with esophageal squamous cell cancer from meta-analyses and pooled case-control studies*

Study reference	Nondrinker	Average alcohol grams per day: 5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110+
Combined sexes																							
Bagnardi et al., 2013	ref.†	1.30																					
Islami et al., 2011	ref.†	1.25						2.32									5.38						
Bagnardi et al., 2015	ref.†	1.26						2.23									4.95						
Freedman et al., 2011	ref.†	ns		ns				2.56				4.56			7.17				9.62				
Choi et al., 2018	ref.†	ns		ns			1.98																
Lubin et al., 2012		ref.				ns				2.15					2.74								4.12
Men																							
Choi et al., 2018	ref.†			ns			ns																
Bagnardi et al., 2015	ref.†	1.39						2.25									4.69						
Bagnardi et al., 2013	ref.†	1.46																					
Women																							
Bagnardi et al., 2013	ref.†	ns																					
Bagnardi et al., 2015	ref.†	ns						2.18									8.32						

* All meta-analysis or pooled 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)

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 (Table 3, 5, and 11 only).
- Under the "Study Designs" column, "P" indicates prospective studies and "C-C" indicates case-control studies (Table 4, 6, 8, 10, and 12 only).

Individual prospective cohort and case-control studies

Thirteen individual prospective cohort or case-control studies met the review inclusion criteria. Seven studies reported an increased risk associated with ESCC for men and women combined starting at different levels of alcohol consumption: ≥0g/day [27, 48], ≥13g/day [49, 50], ≥25g/day [34], and ≥30g/day [51, 52] (see Table 4).

When stratified by sex, results were similar to those for men and women combined. Most studies reported an increased risk of ESCC associated with some level of alcohol consumption [53-58].

- One case-control study found an association between alcohol consumption and increased risk of ESCC for men and women combined but reported no association for men or women separately [51].

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

Study reference	Study design	Former drinker	Occasional drinker	Non-drinker	Average alcohol grams per day (5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140+)
Combined sexes					
Menya et al., 2019	C-C			ref.†	2.20 | 4.20 | 5.40 | 6.80
Hashibe et al., 2007	C-C			ref.‡	3.08 | 4.51 | 8.14 | 9.78
Freedman et al., 2007	P			2.06†	ref. | 2.33 | 4.93
Steevens et al., 2010	P			ref.†	ns | ns | 2.44 | 5.34
Vioque et al., 2008	C-C	16.03		ref.§	ns | 8.02 | 23.20
Pandeya et al., 2009	C-C			ref.‡	ns | ns | ns | 1.93 | 4.67
Lee et al., 2007	C-C			ref.‡	ns | ns | 1.70
Men					
Pandeya et al., 2009	C-C			ref.‡	ns | ns | ns | ns | ns
Yang et al., 2017	C-C			ref.†	1.93 | 2.01 | 2.27 | 2.55
Sewram et al., 2016	C-C			ref.†	2.38 | 2.71 | 4.72
Ishiguro et al., 2009	P		ns	ref.#	ns | 2.59 | 4.64
Guo et al., 2008	C-C			ref.†	ns | ns | 3.20
Women					
Pandeya et al., 2009	C-C			ref.‡	ns | ns | ns
Allen et al., 2009	P			1.56†	ref. | ns | 1.56 | 2.99
Sewram et al., 2016	C-C			ref.†	ns | 2.73 | 5.24
Wang et al., 2011	C-C	ns		ref.‡	ns | 3.13 | 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)

‡ Nondrinker (lifetime abstainers)

§ Nondrinker (may include occasional drinkers)

Nondrinker (may include former drinkers)

HEAD AND NECK CANCERS

According to the WRCF there is "convincing" evidence of an association between alcohol consumption and increased risk of cancers of the larynx, mouth, and pharynx: sites located in the head and neck region [3]. Studies that met the criteria and reported only on the subsites in the pharynx, hypopharynx, and oropharynx, are included in the Appendix (see Appendix A2 and A3). Note that this review will not cover nasopharynx cancer due to limited or no evidence of an association with alcohol consumption, according to the WCRF [3]. See *"Background chapter"* for an explanation on the WCRF definitions of strength of evidence.

Eight studies that met the review criteria examined the association between alcohol consumption and head and neck cancers, as a single combined site, and these results can be found in the Appendix (see Table A4 and A5) [27, 35, 44, 59-63].

Laryngeal cancer

Meta-analyses and pooled case-control studies

Seven meta-analyses or pooled case-control studies fit the inclusion criteria for this review and examined the association between laryngeal cancer and alcohol consumption (see Table 5).

An increased risk of laryngeal cancer for men and women combined was associated with alcohol consumption greater than or equal to 12.5g/day, compared to nondrinkers, in three meta-analyses [43, 59, 64]. Two studies reported no association with alcohol consumption, compared to nondrinkers [42, 65].

- One meta-analysis compared nondrinkers with light drinkers (up to 12.5g/day only); consumption greater than 12.5g/day was not assessed [42].

One meta-analysis included in the literature review reported risk estimates for laryngeal cancer 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 [41].

Table 5. Relative risk estimates for alcohol consumption associated with laryngeal cancer from meta-analyses and pooled case-control studies*

Study reference	Nondrinker	Average alcohol grams per day: 5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130	135	140+
Combined sexes																													
Bagnardi et al., 2013	ref.†	ns																											
Lubin et al., 2010	ref.†	ns								ns																		ns	
Bagnardi et al., 2015	ref.†	ns								1.44																		2.65	
Zhang et al., 2015	ref.†	ns								2.06																		3.00	
Islami et al., 2010	ref.†	ns								1.50																		2.46	
Men																													
Bagnardi et al., 2013	ref.†	ns																											
Bagnardi et al., 2015	ref.†	ns								1.50																		2.77	
Lubin et al., 2011	ref.†	ns								ns																		1.89	
Women																													
Lubin et al., 2011	ref.†	ns								ns																		ns	
Bagnardi et al., 2013	ref.†	ns																											
Bagnardi et al., 2015	ref.†	ns								1.59																		ns	
Choi et al., 2018	ref.†			ns						1.74																			

* All meta-analysis or pooled cohort 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)

Four meta-analyses or pooled case-control studies grouped results by sex and reported risk estimates for laryngeal cancer for men [42, 43, 66] and women separately [42-44, 66].

- None of the four studies found an association between laryngeal cancer and their lighter drinking categories for men or women, compared to nondrinkers [42-44, 66].
- For men, two studies reported an increased risk of laryngeal cancer associated with alcohol consumption starting at 12.5g/day [43] and 60g/day [66], and one study found no association [42].
- For women, two studies reported an increased risk of laryngeal cancer starting at 12.5g/day [43] and 15g/day [44] and two studies found no association [42, 66].
    - Two studies compared nondrinkers with drinkers in a light drinking category (up to 12.5g/day and 30g/day) only; consumption levels above 12.5g/day [42] and above 30g/day [44] were not assessed.

Individual prospective cohort and case-control studies

Seven individual prospective cohort or case-control studies met the inclusion criteria for the review of laryngeal cancer. Four included results for men and women combined [60, 61, 63, 67] and three reported sex-specific results [38, 57, 62] (see Table 6).

- Three of four studies found no association between alcohol consumption and risk of laryngeal cancer for men and women combined [60, 61, 67] and one study reported an increased risk associated with an alcohol consumption category of 42g/day or more [63].
- One study reported an association between increased laryngeal cancer risk and alcohol consumption starting at more than 0g/day for men only [38], and one study found an increased risk associated with consumption levels above 10g/day for women only [57].
    - However, Hsu et al. (2014) only examines consumption less than 80g/day and 80g/day or more. This limits the ability to differentiate results for light, moderate, or heavy drinking levels [38].
- One study found no association between alcohol consumption and laryngeal cancer for men or women separately [49].

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

Study reference	Study design	Nondrinker	Average alcohol grams per day: 5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90+
Combined sexes																				
Maasland et al., 2014	P	ref.†	ns		ns		ns				ns									
Applebaum et al., 2007	C-C	ref.‡			ns				ns						ns					
Werbrouck et al., 2008	C-C	ref.†	ns				ns						ns							
Huang et al., 2017	C-C	ref.§			ns				ns						3.44					
Men																				
Freedman et al., 2007	P	1.55†			ref.				ns						ns					
Hsu et al., 2014	P	ref.†							3.88										5.92	
Women																				
Freedman et al., 2007	P	ns†			ref.				ns						ns					
Allen et al., 2009	P	ns†	ref.		ns		1.74				2.02									

* 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)

‡ Nondrinker (may include former drinkers)

§ Nondrinker (lifetime abstainers)

Oral cavity and lip cancer

Meta-analyses and pooled case-control studies

Four studies that met the inclusion criteria for this review examined the association between alcohol consumption and oral cavity and lip cancer (see Table 7). Two out of three studies reporting results for men and women combined found an increased risk associated with alcohol consumption starting at more than 0g/day [59, 68] and the third study reported an increase in risk associated with alcohol consumption starting at 61g/day [65].

- The Turati et al., (2010) study compared nondrinkers with drinkers in a light drinking category (up to 12.5g/day) and a heavy drinking category (50g/day or more) only; consumption levels between 12.5g/day and 50g/day were not assessed [68].

- In a follow-up to their 2010 study [65], Lubin and colleagues reported results for men that were consistent with their previous results for both sexes combined (increased risk starting at 61g/day); results for women showed no association between any level of alcohol consumption and risk of oral cavity and lip cancer [66].

Individual prospective cohort and case control studies

Nine individual prospective cohort or case-control studies met the review inclusion criteria and examined the association between alcohol consumption and risk of oral cavity and lip cancer; six studies reported results for men and women combined and three studies reported results for men or women separately (see Table 8).

- Four of six studies reported an increased risk of oral cavity and lip cancer associated with average alcohol consumption level categories beginning at 15g/day [60, 67] or 45g/day [26, 69] for men and women combined.

- One case-control study reported a reduced risk associated with a category of alcohol consumption of less than 20g/day and an increased risk associated with a category starting at 45g/day, compared to nondrinkers [26].

- The remaining two studies reporting risk estimates for men and women combined found no association [61, 63].

- Three prospective cohort studies reported sex-specific risk estimates for oral cavity and lip cancer.

    - Among men, two studies reported an increased risk associated with consumption levels starting at 21g/day [70] or 40g/day [49], and a third found no association between any level of alcohol consumption and risk of oral cavity and lip cancer [38].

    - Among women, only one study met the review criteria, and it found an increased risk of oral cavity and lip cancer associated with a category of alcohol consumption of 40g/day and over [62].

Table 7. Relative risk estimates for alcohol consumption associated with oral cavity and lip cancer from a meta-analyses and pooled case-control studies*

Study reference	Nondrinker	Average alcohol grams per day: 5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130+
Combined sexes																											
Zhang et al., 2015	ref.†	1.30							2.28																		3.93
Turati et al., 2010	ref.†	1.17																									4.64
Lubin et al., 2010		ref.					ns						ns														1.87
Men																											
Lubin et al., 2011		ref.					ns						ns														1.75
Women																											
Lubin et al., 2011		ref.					ns						ns														ns

* All meta-analysis or pooled cohort 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 8. Relative risk estimates for alcohol consumption associated with oral cavity and lip cancer from individual prospective cohort and case-control studies*

Study reference	Study design	Former drinker	Occasional drinker	Non-drinker	Average alcohol grams per day
Combined sexes					
Werbrouck et al., 2008	C-C			ref.†	ns (5–40); ns (40–90); ns (90–190+)
Huang et al., 2017	C-C			ref.‡	ns (5–40); ns (40–90); ns (90–190+)
Maasland et al., 2014	P			ref.†	ns (5–10); ns (10–20); 3.20 (20–30); 7.50 (30–190+)
Applebaum et al., 2007	C-C			ref.§	ns (5–20); 1.90 (20–30); 4.80 (30–190+)
Radoi et al., 2013	C-C			ref.‡	0.40 (5–10); 0.60 (10–20); ns (20–40); 3.20 (40–190+)
De Stefani et al., 2007	C-C	3.00		ref.#	ns (5–40); 4.30 (40–50); 4.90 (50–185); 7.00 (185–190+)
Men					
Hsu et al., 2014	P			ref.†	ns (5–60); ns (60–190+)
Lu et al., 2018	P		ns	ref.§	ns (5–20); 2.23 (20–30); 3.79 (30–190+)
Freedman et al., 2007	P			1.43†	ref. (5–10); ns (10–40); 1.52 (40–190+)
Women					
Freedman et al., 2007	P			ns†	ref. (5–10); ns (10–40); 2.81 (40–190+)

* 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)

‡ Nondrinker (lifetime abstainers)

§ Nondrinker (may include former drinkers)

Nondrinker (may include occasional drinkers)

Pharyngeal cancer

Meta-analyses and pooled case-control studies

Three meta-analyses or pooled case-control studies examining the association between pharyngeal cancer and alcohol consumption met the review inclusion criteria, and all three reported an increased risk associated with alcohol consumption (see Table 9) [59, 65, 68].

- The Turati et al., (2010) meta-analysis compared nondrinkers with drinkers in a light drinking category (up to 12.5g/day) and a heavy drinking category (50g/day or more) only; consumption levels between 12.5g/day and 50g/day were not assessed [68]. This study found that risk of pharynx cancer was associated with the heavy drinking category but not the light drinking category.

Individual prospective cohort and case control studies

Four prospective cohort or case-control studies met the inclusion criteria for pharyngeal cancer (see Table 10).

- Three case-control studies reported an increased risk for pharyngeal cancer associated with a drinking category starting at 40g/day [61], 47g/day [69] or 50g/day [67] for men and women combined.

- One study included men only and found an increased risk of pharyngeal cancer associated with its heavier alcohol consumption category (≥80g/day) only [38].

    - However, Hsu et al., (2014) only examines consumption less than 80g/day and 80g/day or more. This limits the ability to differentiate results for light, moderate, or heavy drinking levels [38].

Combination of oral cavity and pharyngeal cancers

Meta-analyses

Five meta-analyses meeting the review criteria examined the association between alcohol consumption and combined oral cavity and pharyngeal cancers (see Table 11). Note that for some studies included in this review the term "oral cavity and pharyngeal cancers may include oral cavity and oropharyngeal cancers only.

- All five studies reported an increased risk associated with alcohol consumption for men and women combined, two at their lowest categories of alcohol consumption [42, 71] and three starting at 12.5g/day or more [43, 44, 72].

    - Some studies looked at the relationship between lighter drinking levels only and cancer risk (heavier levels are not included) [42, 44] or specific drinking levels such as 12.5g/day to 25g/day and above 50g/day [72] and less than 12.5g/day and above 50g/day [71].

One meta-analysis included in the literature review reported risk estimates for oral cavity and pharyngeal cancers 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 [41].

Table 9. Relative risk estimates for alcohol consumption associated with pharyngeal cancer from a meta-analyses and pooled case-control study*

Study reference	Nondrinker	Average alcohol grams per day
Combined sexes		
Zhang et al., 2015	ref.†	1.39 | 2.87 | 5.70
Lubin et al., 2010	ref.	1.52 | 2.30 | 3.67
Turati et al., 2010	ref.†	ns | 6.62

* All meta-analysis or pooled cohort 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 10. Relative risk estimates for alcohol consumption associated with pharyngeal cancer from individual prospective cohort and case-control studies*

Study reference	Study design	Former drinker	Non-drinker	Average alcohol grams per day
Combined sexes				
Werbrouck et al., 2008	C-C		ref.†	ns | ns | 9.35
De Stefani et al., 2007	C-C	3.90	ref.‡	ns | 4.40 | 7.90 | 11.70
Applebaum et al., 2007	C-C		ref.§	ns | ns | 2.90
Men				
Hsu et al., 2014	P		ref.†	ns | 3.27

* 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.

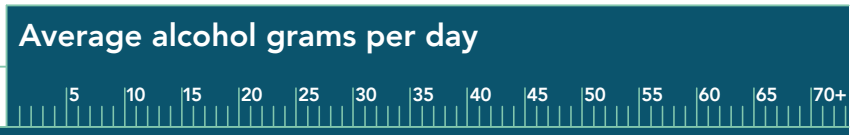
† Nondrinker (may include former or occasional drinkers or both)

‡ Nondrinker (lifetime abstainers)

§ Nondrinker (may include former drinkers)

Table 11. Relative risk estimates for alcohol consumption associated with oral cavity and pharyngeal cancers combined from meta-analyses and pooled case-control studies*

Study reference	Nondrinker	Average alcohol grams per day
Combined sexes		
Bagnardi et al., 2013	ref.†	1.17
Tramacere et al., 2010	ref.†	1.21 — 5.24
Turati et al., 2012	ref.†	1.36 — 5.40
Bagnardi et al., 2015	ref.†	ns — 1.83 — 5.13
Choi et al., 2018	ref.†	ns — 1.12
Men		
Choi et al., 2018	ref.†	ns — ns
Bagnardi et al., 2013	ref.†	1.20
Bagnardi et al., 2015	ref.†	1.20 — 2.01 — 5.33
Turati et al., 2012	ref.†	1.28 — 5.49
Women		
Bagnardi et al., 2013	ref.†	ns
Bagnardi et al., 2015	ref.†	ns — 1.67 — 5.70
Choi et al., 2018	ref.†	ns — 1.18
Turati et al., 2012	ref.†	ns — 5.69



* All meta-analysis or pooled cohort 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)

Results from studies reporting sex-specific risk estimates suggest no association between combined oral and pharyngeal cancers risk and each study's lightest drinking categories for women; however, for men a risk association was reported at lighter drinking levels. For both women and men separately, cancer risk appeared to increase at some level of alcohol consumption [42-44, 72].

Individual prospective cohort and case control studies

Seven prospective cohort or case-control studies analyzed the association between alcohol consumption and combined oral cavity and pharyngeal cancers (see Table 10) [33, 57, 70, 73-76]. Four of these studies reported risk estimates for women [57, 70, 73, 74]; only two studies reported estimates for men [70, 73].

- Three studies reported risk estimates for men and women combined and all three found an association between cancer risk and an alcohol consumption category starting at more than 0g/day [33], 12g/day [75], or 50g/day [76], compared to nondrinkers.
- Two studies reporting risk estimates for men only and four studies reporting estimates for women only found an increased risk of oral cavity and pharyngeal cancers associated with alcohol consumption categories starting at 21g/day or more [57, 70, 73, 74].
  - One study reporting on women only found a reduced risk associated with alcohol consumption less than 15g/day, compared with nondrinkers. This reduced risk was reported among women with higher folate intake but not among women with lower folate intake [74].

Table 12. Relative risk estimates for alcohol consumption associated with oral cavity and pharyngeal cancer combined from individual prospective cohort and case-control studies*

Study reference	Study design	Occasional drinker	Non-drinker	Average alcohol grams per day (5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80+)
Combined sexes				
Szymanska et al., 2011	C-C		ref.†	2.92 | 3.39 | 6.60 | 10.95
Friborg et al., 2007	P		ref.†	ns | 3.80
Matsuo et al., 2012	C-C		ref.†	ns | 2.67
Men				
Lu et al., 2018	P	0.30	ref.‡	ns | 1.86 | 3.20
Hippisley-Cox et al., 2015	P		ref.†	ns | ns | 1.36 | 2.59 | 3.71
Women				
Allen et al., 2009	P		1.18†	ref. | ns | ns | 1.99
Hippisley-Cox et al., 2015	P		ref.†	ns | ns | 1.60 | 2.86 | 4.38
Shanmugham et al., 2010	P		ref.†	0.59 | ns | 1.92
Lu et al., 2018	P	ns	ref.‡	ns | 5.94

* 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)

‡ Nondrinker (may include former drinkers)

UPPER AERODIGESTIVE TRACT CANCERS

Six individual prospective cohort studies meeting the review criteria examined the association between alcohol consumption and risk of UADT cancers as a group; this includes any cancer in the head and neck region, or in the esophagus, or both. The results of these studies are presented in the Appendix (see Appendix Table A6) [38, 77-81]. One meta-analysis included in the literature review reported risk estimates for UADT cancers comparing highest to lowest consumption categories, but was excluded from the summary in the Appendix because it did not quantify those categories in number of drinks or grams of alcohol [41].

MAGNITUDE OF RISK

Results from all the meta-analyses, pooled cohort, and pooled case-control studies included in this review indicate that the magnitude of the risk estimate appears to grow larger as alcohol consumption increases. Compared to nondrinkers, the lowest categories of average alcohol consumption as defined by these studies (up to 13g/day) are associated with a 17% to 39% increase in risk (this is equivalent to a relative risk of 1.17 and 1.39, which would be described as "weak" in magnitude [82]). While the highest levels of consumption (ranges from more than 50g/day to more than 98g/day) are associated with an 146% to 862% increase in risk (this is equivalent to a relative risk of 2.46, which would be described as "moderate" in magnitude and 9.62, which would be described as "strong" in magnitude [82]). See, for example, Schoenbach and Rosamond (2000) [82] and the Glossary for additional resources on magnitude of risk.

JOINT EFFECT OF ALCOHOL AND TOBACCO

Research suggests that ethanol may play the role of a co-carcinogen by acting as a solvent and increasing the permeability of other carcinogens such as tobacco *(please see the Biological Mechanisms section)*. Several studies that investigate the relationship between alcohol consumption and UADT cancers included in this review adjust for tobacco [26, 32, 34, 35, 39, 57, 60, 63, 64, 74, 76, 78]. The joint effect of alcohol and tobacco on UADT cancer risk has been widely studied, and the combination of both risk factors appears to be multiplicative (several times greater) [23, 25, 26]. A complete analysis of studies examining the joint effect of alcohol consumption and tobacco use was outside the scope of this review, but results from recent studies included in this review examined the combined effect of both of these risk factors on the risk of cancers in the UADT or head and neck region are presented in Table 13 [27, 33, 57, 60, 81]. Across all these studies, the risk of being diagnosed with cancer was several times greater for heavy smokers who are also heavy drinkers, compared to both nonsmokers who are heavy drinkers and to heavy smokers who are nondrinkers.

FUTURE RESEARCH

In addition to alcohol and tobacco use, other modifiable risk factors may contribute to the risk of UADT cancers. However, few studies to date have explored the joint effect of multiple risk factors on risk of cancer in the UADT region. Future research could contribute to understanding the interrelationships of co-occurring risk factors by analyzing the effect of clusters of risk factors, based on the frequency of these risk factors found in drinkers.

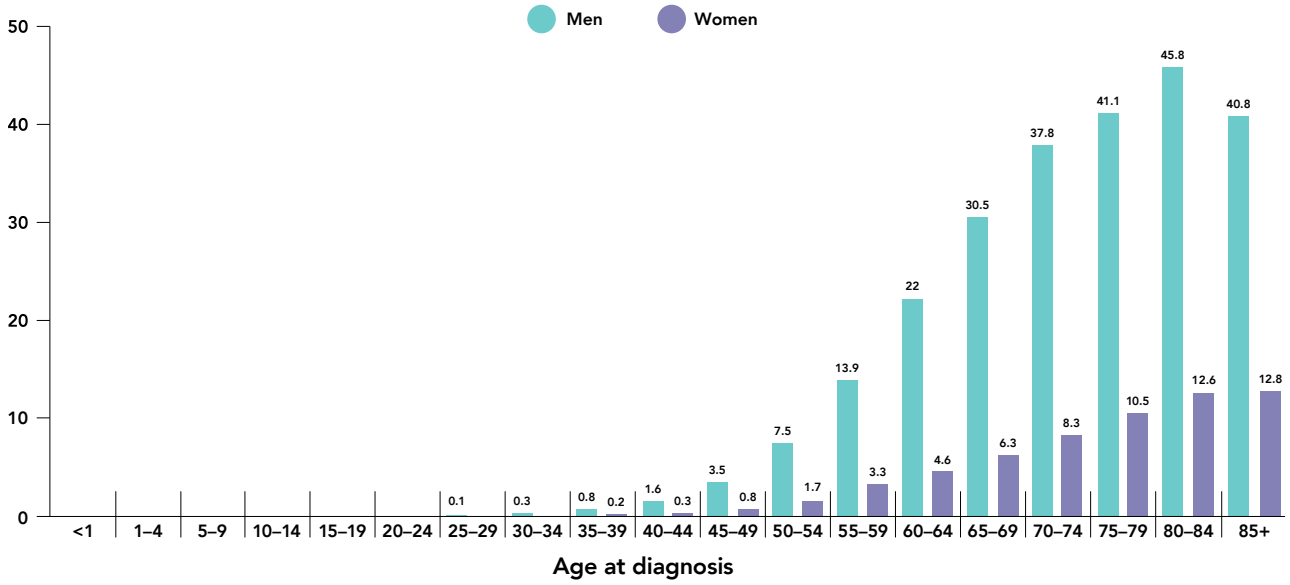
This review did not evaluate risk of bias or overall study quality as this was out of the scope of the review, and instead left interpretation of study quality and findings to the reader. However, the WCRF includes an assessment of study quality in their systematic review [3]. Future systematic reviews could contribute further to a greater understanding of the relationship between alcohol consumption and risk of UADT cancers by assessing study quality. This may also help with understanding the variation in findings among the studies. 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 13. Joint effect analyses of alcohol consumption and tobacco smoking and risk of UADT and head and neck cancers

		Alcohol (g/day)				
UADT cancers	Smoking status (cigarette/day)	**Allen et al., 2009 (women only)**	**≤2.9**	**3–9.9**	**≥10.0**	
		Nonsmoker	ref.	1.04	0.93	
		Former smoker	1.28	1.22	1.46	
		Current smoker	2.54	3.57	5.22	
		Weikert et al., 2008 (men only)	**0.1-30.0**	**30.1–60.0**	**>60.0**	
		Nonsmoker	ref.	0.90	1.71	
		Former smoker	1.50	3.23	4.24	
		<15	2.33	3.55	11.02	
		≥15	5.76	11.75	22.86	
		Weikert et al., 2008 (women only)	**0.1–18.1**	**>18.0**		
		Nonsmoker	ref.	1.94		
		Former smoker	1.71	0.59		
		<15	1.43	7.00		
		≥15	6.04	17.28		
		Szymanska et al., 2011	**Nondrinker**	**0.001–13.5**	**13.6–46.6**	**>46.6**
		Nonsmoker	ref.	1.14	1.59	2.77
		≤15	2.39	5.73	6.85	14.23
		>15–≤30	4.33	7.24	9.69	25.72
		>30	3.52	7.01	10.52	20.60
Head and neck cancer		**Hashibe et al., 2013**	**Nondrinker**	**<28.0**	**≥28.0**	
		Nonsmoker	ref.	1.68	1.37	
		1–19	0.93	1.53	7.89	
		≥20	6.28	3.83	11.07	
		Maasland et al., 2014	**0**	**>0–<5.0**	**5.0–<15.0**	**15.0–<30.0**	**≥30.0**
		Nonsmoker	ref.	1.20	1.23	5.53	2.97
		>0–<20	1.89	1.56	2.04	2.63	3.81
		≥20	2.78	3.88	2.85	3.32	8.28

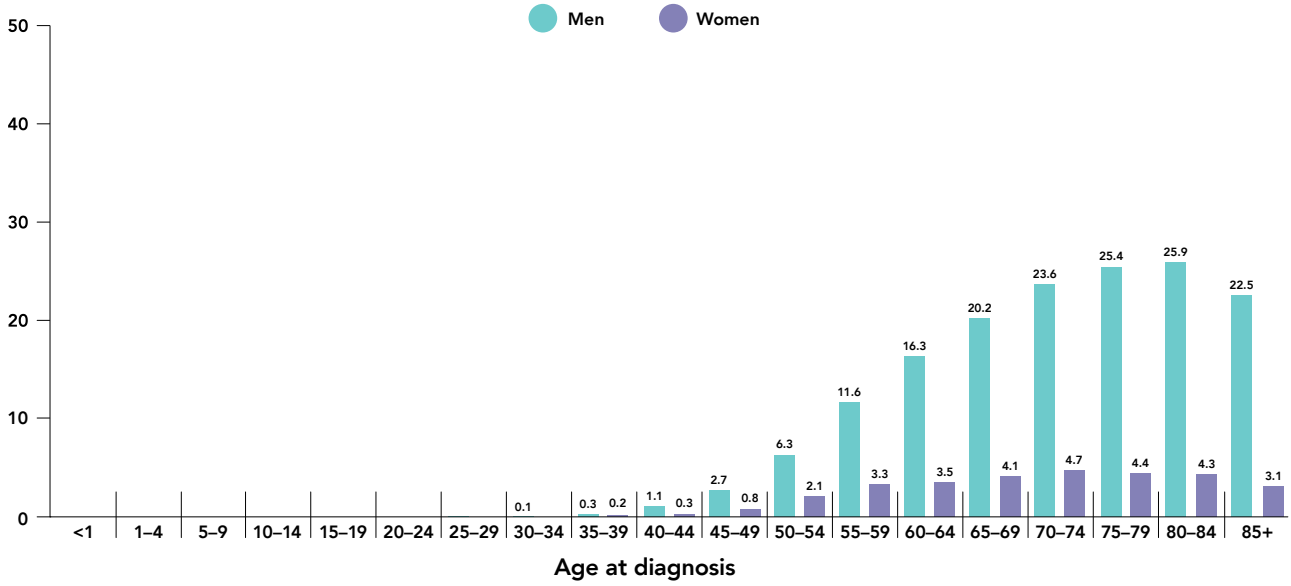
Appendix

Figure A1. Age-specific incidence of esophageal cancer among men and women in the U.S. per 100,000



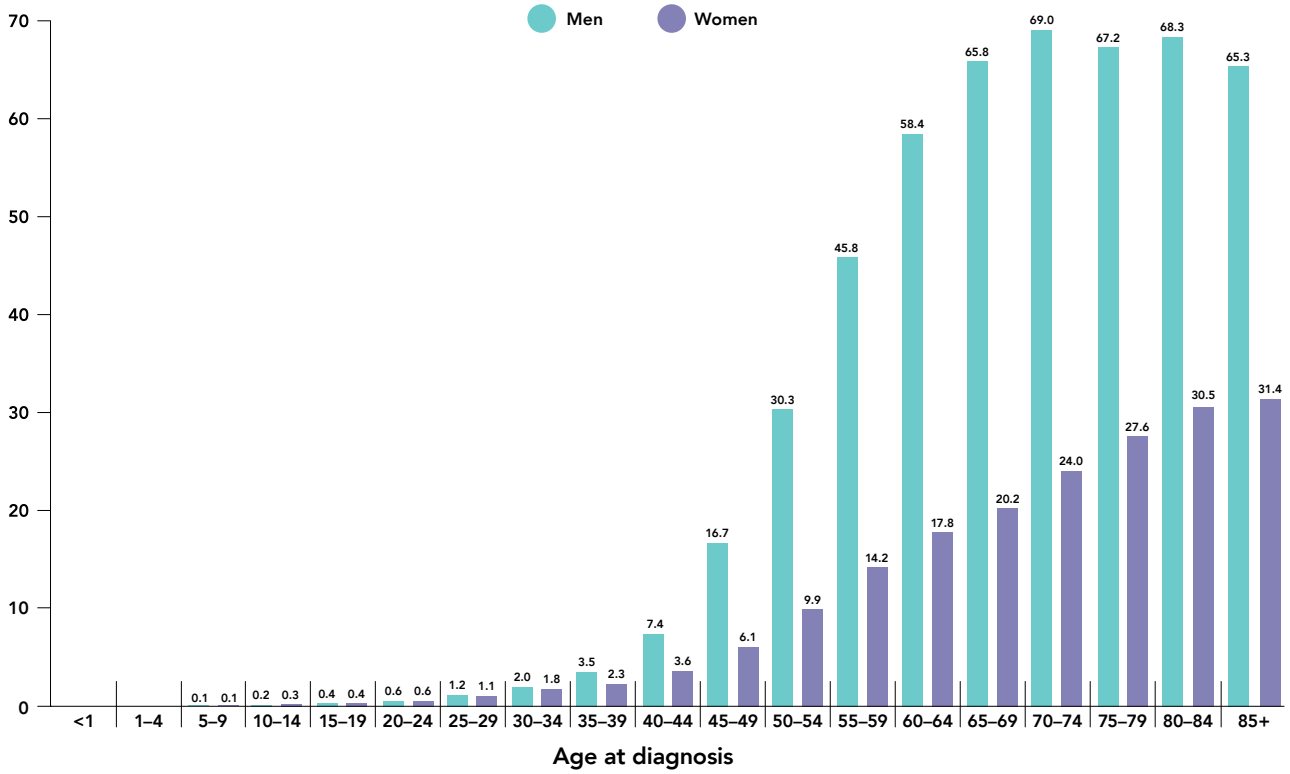
Sources: *SEER 21 Areas, Esophagus SEER Incidence and U.S. Mortality Rates by Age at Diagnosis, 2014-2018 [5]*

Figure A2. Age-specific incidence of laryngeal cancer among men and women in the U.S. per 100,000



Sources: SEER 21 Areas, Larynx SEER Incidence and U.S. Mortality Rates by Age at Diagnosis, 2014-2018 [5]

Figure A3. Age-specific incidence of oral cavity and pharyngeal cancers among men and women in the U.S. per 100,000



Sources: *SEER 21 Areas, Oral Cavity and Pharynx SEER Incidence and U.S. Mortality Rates by Age at Diagnosis, 2014-2018 [5]*

Appendix 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 (Table A4 only).
- Under the "Study Designs" column, "P" indicates prospective studies and "C-C" indicates case-control studies (Table A1, A3, A5, and A6).

Table A1. Relative risk estimates for alcohol consumption associated with esophageal cancer from individual prospective cohort and case-control studies*

Study reference	Study design	Former drinker	Nondrinker	Average alcohol grams per day: 5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110+
Combined sexes																									
Choi et al., 2017	P		ref.†	1.20			1.93			2.69							3.64								
Szymanska et al., 2011	C-C		ref.†	2.92				2.79					7.03								9.28				
Vioque et al., 2008	C-C	5.40	ref.‡	ns									2.89										7.65		
Kunzmann et al., 2007	P		ref.‡	ns	ns	ns	ns	ns						2.85							3.99				
Zhao et al., 2017	C-C		ref.†	ns																			1.46		
Wu et al., 2011	C-C		ref.†	ns										ns									1.30		1.90
Men																									
Hsu et al., 2014	P		ref.†	4.15																				3.71	
Choi et al., 2017	P		ref.†	1.55													3.17								
Kimm et al., 2010	P		ref.†	2.20					3.10							3.80									4.10
Wu et al., 2011	C-C		ref.†	1.37						1.29					1.37								1.96		
Fan et al., 2008	P		ref.†	ns						ns						2.88								4.65	
Benedetti et al., 2009	C-C		ref.§	ns				ns											3.00						6.50
Women																									
Choi et al., 2017	C-C		ref.†	ns																					ns
Larsson et al., 2007	P		ref.†	ns																					2.45

* 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)

‡ Nondrinker (lifetime abstainers)

§ Nondrinker (may include former drinkers)

Table A2. Relative risk estimates for alcohol consumption associated with hypopharynx and oropharynx cancers from a meta-analysis and pooled case-control study*

Study reference	Nondrinker	Average alcohol grams per day: 5–50	55–70	75–130+
Hypopharynx				
Combined sexes				
Turati et al., 2010	ref.†			9.03
Men				
Lubin et al., 2011		ref. / ns	3.33	7.03
Women				
Lubin et al., 2011		ref. / ns	5.95	19.60
Oropharynx				
Combined sexes				
Turati et al., 2010	ref.†			7.76
Men				
Lubin et al., 2011		ref.	1.46 / 1.91	2.82
Women				
Lubin et al., 2011		ref.	1.60 / 3.21	7.63

* All meta-analysis or pooled 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)

Table A3. Relative risk estimates for alcohol consumption associated with hypopharynx and oropharynx cancer from individual prospective cohort and case-control studies*

			Average alcohol grams per day (5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70+)		
Study reference	Study design	Nondrinker			
Hypopharynx					
Combined sexes					
Huang et al., 2017	C-C	ref.‡	6.63	14.54	20.36
Men					
Lu et al., 2018	P	ref.†	ns	ns	10.11
Oropharynx					
Combined sexes					
Huang et al., 2017	C-C	ref.‡	ns	4.04	7.86
Men					
Lu et al., 2018	P	ref.†	ns	ns	ns

* All meta-analysis or pooled 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)

Table A4. Relative risk estimates for alcohol consumption associated with head and neck cancers from meta-analyses*

Study reference	Nondrinker	Average alcohol grams per day: 5	10	15	20	25	30	35	40	45	50	55	60	65	70+
Combined sexes															
Choi et al., 2018	ref.†	ns		ns		ns									
Zhang et al., 2015	ref.†	1.29				2.67								6.63	
Men															
Zhang et al., 2015	ref.†	1.72				3.00								7.46	
Women															
Zhang et al., 2015	ref.†	1.60				5.37								7.84	

* All meta-analysis or pooled cohort 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 A5: Relative risk estimates for alcohol consumption associated with head and neck cancers from individual prospective cohort and case-control studies*

Study reference	Study design	Nondrinker	Average alcohol grams per day: 5	10	15	20	25	30	35	40	45	50	55	60	65	70+
Combined sexes																
Huang et al., 2017	C-C	ref.‡	ns					1.47						2.21		
Kunzmann et al., 2018	P	ref.‡	ns	ns	ns	ns	ns			2.12				3.12		
Hashibe et al., 2013	P	ref.†	ns				ns				2.37				2.24	
Maasland et al., 2014	P	ref.†	ns		ns			ns				2.90				
Werbrouck et al., 2008	P	ref.†	ns				ns						4.66			
Men																
Freedman et al., 2007	P	1.68†	ref.					ns						1.48		
Women																
Freedman et al., 2007	P	1.46†	ref.					1.99						2.52		

* 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)

‡ Nondrinker (lifetime abstainers)

Table A6. Relative risk estimates for alcohol consumption associated with UADT cancers from individual prospective cohort studies*

Study reference	Study design	Former drinker	Non-drinker	Average alcohol grams per day (5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120+)
Combined sexes				
Klatsky et al., 2015	P	2.90	ref.†	ns | 1.50 | 2.50
Jayasekara et al., 2015	P		ref.†	ns | ns | 2.67
Thygesen et al., 2007	P			ref. | ns | ns | ns | ns | 2.50 | 3.30
Men				
Hsu et al., 2014	P		ref.‡	1.73 | 2.49
Everatt et al., 2013	P		ns‡	ref. | ns | ns | ns | 2.79
Weikert at el., 2009	P	4.14	ns†	ref. | ns | ns | ns | 2.20 | 4.63
Women				
Weikert at el., 2009	P	ns	ns†	ref. | 1.67 | ns | 6.05

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

† Nondrinker (lifetime abstainers)

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

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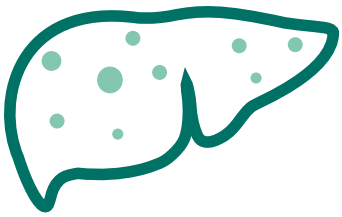
DRINKING AND LIVER CANCER



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Introduction

1% Lifetime risk of diagnosis (U.S.)

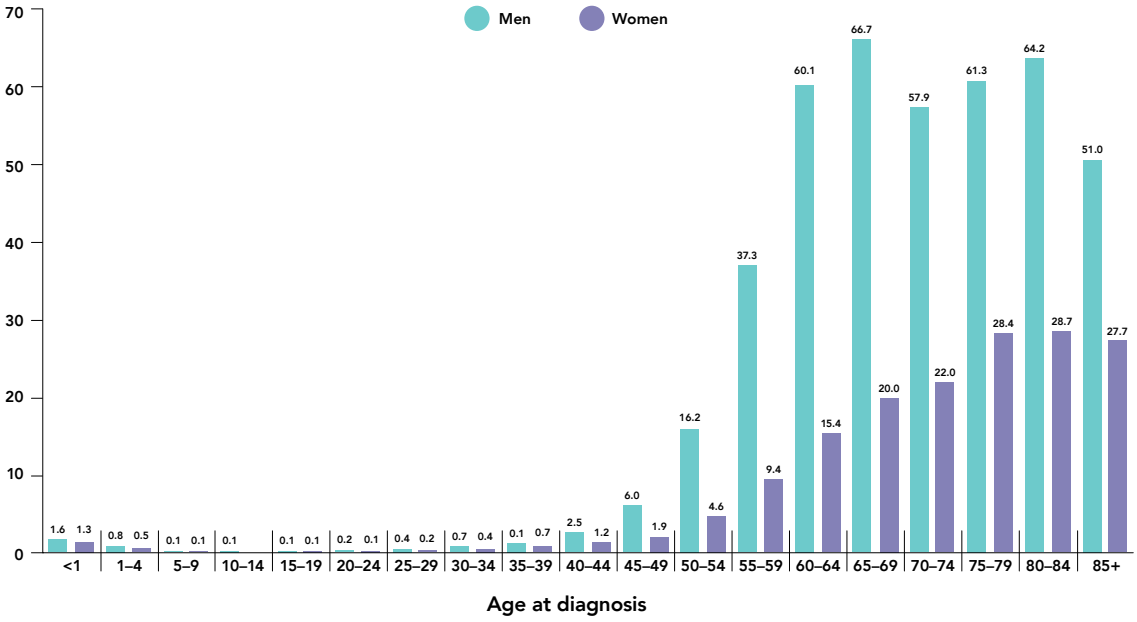
6.5 Global incidence per 100,000

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

Note: Cancers originating in the liver and in the intrahepatic bile ducts (tubes in the liver that carry digestive fluid) are commonly combined when reported in national and international statistics and in some studies. In addition, many studies refer to hepatocellular carcinoma, the most common type of liver cancer, as "liver cancer." Therefore, this review uses the term "liver cancer" to indicate the combination of liver and intrahepatic bile duct cancers, or hepatocellular carcinoma, or both, unless otherwise noted.

Liver cancer is the sixth most common cancer in the world for men and women combined and accounts for 4.7% of all incident cancer cases globally [3]. Incidence rates vary across countries, from a high of 85.6 per 100,000 persons in Mongolia to a low of 1.2 per 100,000 persons in Sri Lanka [3]. Liver cancer incidence increases with age [4]. In the U.S., 88% of new diagnoses occur among those aged 55 years and older; incidence rates are nearly three-times higher among men (13.8 per 100,000) than women (4.9 per 100,000) (see Figure 1) [2].

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



Source: *SEER 21 Areas, Liver and Intrahepatic Bile Duct 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 liver cancer [5]. In addition, several other risk factors are associated with liver cancer risk, some of which may mediate or modify the relationship between alcohol consumption and liver cancer risk (see Table 1).

Table 1. Common risk factors for liver cancers*

Modifiable risk factors	Non-modifiable risk factors
Alcohol consumption Body mass index Caffeine Chronic viral hepatitis B and C Cirrhosis Dietary aflatoxins (toxins produced by fungi) Oral contraceptives Smoking	Age Genetics Inherited metabolic diseases Race Sex
Type 2 Diabetes	

Source: *American Cancer Society [6] 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, 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 LIVER CANCER

Researchers are continuing to explore several plausible biological mechanisms that explain the potential role of alcohol as a risk factor for liver 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), as well as the enzyme CYP2E1 to a lesser extent. Alcohol is converted to *acetaldehyde* by ADH, which is then converted to acetate by ALDH [7, 8]. Several studies have shown that acetaldehyde is a *carcinogen* and may increase DNA damage to the liver by interfering with DNA repair, or promoting cell growth, or both [8, 9]. 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 [10].

- The microsomal ethanol oxidizing system, another metabolic pathway, accounts for a small percentage of ethanol metabolism and is significantly induced at chronic heavy levels of consumption (after a single week of consuming 40g/day or more) [8, 11]. 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 [12, 13].

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

- Epidemiologic research has found that individuals who carry these genetic mutations have an increased risk of certain cancers [9, 12, 13, 15-18].

Nutritional deficiencies

The role of alcohol in liver cancer risk may also be related to the effect of alcohol on dietary intake, or on malabsorption, or utilization of dietary nutrients [19]. The inability to support these processes may independently and jointly increase susceptibility for cancer growth [9, 20].

- Heavy alcohol consumption may be associated with certain nutrient deficiencies (such as vitamins A, B9 (folate), C, and E, glutathione and zinc) [14, 21-23] and other nutrients that support the processes of repairing DNA damage and neutralizing ROS [24].

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 or nitrosamines (compounds formed by nitrates and nitrites) into liver and other tissues [23, 25, 26].

- Heavy consumption may also increase the permeability of molecules, which increases the production of pro-inflammatory substances that interfere with DNA repair [21, 27].

Cirrhosis

Another important mechanism is related to the effect of ROS on increased *oxidative stress* and cirrhosis [13].

- Increased production of ROS due to iron overload and enzymatic activity such as CYP2E1 induction results in alcohol-induced oxidative stress in liver cells and subsequent liver injury [13, 21, 28, 29]. This may increase cell growth and repair [13, 21, 28, 29], potentially leading to fibrosis (excess repair) and the replacement of damaged liver cells with scar tissue resulting in cirrhosis [28, 29], a risk factor for liver cancer [7, 13, 30].

Interaction with hepatitis infection

The process by which liver cancer develops may also be related to the joint effect of heavy alcohol consumption and hepatitis infection [9, 27, 29, 31, 32].

- As described by Dolganiuc in a 2015 review, alcohol-exposed liver cells are prone to several changes that make the cells more susceptible to hepatitis B and C infection [27].

- Prevalence of hepatitis C is three to 30 times higher among patients with alcoholism, compared with the general population, as described by Singal and Anand in their 2007 review [31].

- Chronic heavy drinking may compromise the body's immune response and aggravate damage from hepatitis infection, resulting in a faster progression of disease [29, 32].

- Patients with both hepatitis C infection and alcohol abuse develop more severe fibrosis and higher rates of cirrhosis and liver cancer compared with nondrinkers [31] and experience faster progression from cirrhosis to cancer, as described in a 2002 review by Stickel and colleagues [32].

Summary of recent liver 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 liver 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: liver 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".*

LIVER CANCER

In this section we present results of studies reporting relative risk estimates for liver cancer. *(Please see the Glossary on page 129 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 "convincing" evidence of an increased risk of liver 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 and pooled prospective cohort studies

Six meta-analyses or pooled prospective cohort studies met the inclusion criteria for this review (see Table 2).

- For men and women combined, three meta-analyses reported an increased risk of liver cancer starting at ≥37.5g/day [33], ≥50g/day [34], or ≥98g/day [35], compared to non-drinkers.
- Two meta-analyses found no association between any level of alcohol consumption and liver cancer [36, 37].
- One pooled cohort study, conducted by Petrick and colleagues, reported a reduced risk associated with consumption less than 42g/day, compared to nondrinkers [35].
- None of the six meta-analyses or pooled prospective cohorts reported an increased risk of liver cancer associated with light or moderate drinking level categories, including two studies that exclusively examined drinking levels up to 12.5g/day [36] and up to 30g/day [37].
- The studies that reported results separately for each sex found similar results as those that combined men and women in their analysis [33-38].

Table 2. Relative risk (RR) estimates for alcohol consumption associated with liver cancer from meta-analyses and pooled cohort studies*

Study reference	Nondrinker	Occasional drinker	Average alcohol grams per day
Combined sexes			
Bagnardi et al., 2013	ref.†		ns
Choi et al., 2018	ref.†		ns; ns
Turati et al., 2014	ref.†		ns; 1.16
Bagnardi et al., 2015	ref.†		ns; ns; 2.07
Petrick et al., 2018	ref.†		0.77; 0.57; 0.71; ns; ns; 1.87
Men			
Bagnardi et al., 2013	ref.†		ns
Turati et al., 2014	ref.†		ns; ns
Bagnardi et al., 2015	ref.†		ns; ns; 1.59
Shimazu et al., 2012	1.88‡	ref.	ns; ns; ns; 2.18; ns
Petrick et al., 2018	ref.†		0.74; ns; 1.45
Women			
Bagnardi et al., 2013	ref.†		ns
Turati et al., 2014	ref.†		ns
Choi et al., 2018	ref.†		ns; ns
Shimazu et al., 2012	ns‡	ref.	ns; 3.6
Bagnardi et al., 2015	ref.†		ns; ns; 3.89
Petrick et al., 2018	ref.†		0.7; ns; 2.48

*All meta-analysis or pooled cohort 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 (includes former drinkers)

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 (Table 2 only).
- Under the "Study Designs" column, "P" indicates prospective studies and "C-C" indicates case-control studies (Table 3).

Results from these meta-analyses or pooled prospective cohorts indicate that the magnitude of the risk estimates measuring the association between alcohol consumption and liver cancer appears to grow larger as alcohol consumption increases. Compared to nondrinkers, the lowest categories of average alcohol consumption as defined by these studies (up to 7g/day) are associated with a 23% decrease in risk (this is equivalent to a relative risk of 0.77, which would be described as "weak" [39] in magnitude), while the highest levels of consumption (more than 98g/day) are associated with an 87% increase in risk (this is equivalent to a relative risk of 1.87 which would be described as "moderate" in magnitude [39]). See, for example, Schoenbach and Rosamond (2000) [39] and the Glossary for additional resources on magnitude of risk.

Individual prospective cohort and case-control studies

Eleven individual prospective cohort or case-control studies met the review criteria for examining the association between alcohol consumption and liver cancer, including two studies that reported results for men only [40] or women only [41] (see Table 3).

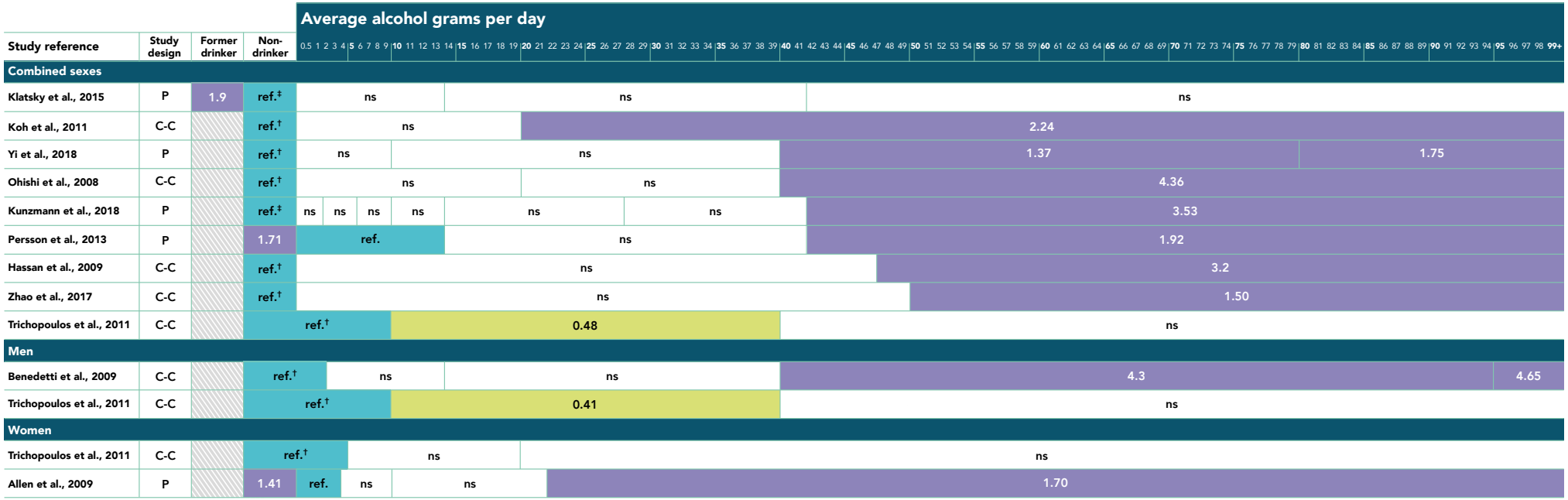
- Most (seven) of the nine studies that reported results for men and women combined found an increased risk of liver cancer associated with drinking categories starting at ≥20g/day [42], at various points between 40 and 50 g/day [43-47], and ≥50g/day [48].

- One study found no association between any alcohol consumption category and liver cancer risk, compared to nondrinkers [49].

- One case-control study reported a reduced risk associated with alcohol consumption less than 40g/day, compared to up to 10g/day, for men and women combined and no increase in risk associated with other drinking categories. The association with reduced risk of liver cancer was found among men, but not women, when results were stratified by sex [50].

- Some of the studies included in Table 3 defined alcohol consumption categories spanning wide ranges (see for example Koh et al.'s (2011) [42] category of >0 to <50g/day or Hassan et al.'s (2009) [46] ≥20g/day category) and should be interpreted with caution. Such wide ranges make it difficult to precisely determine where a change in risk begins.

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



* All individual prospective cohort or 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)

JOINT EFFECT OF ALCOHOL AND HEPATITIS OR OBESITY

The WCRF and other organizations, such as the American Cancer Society, have identified obesity and hepatitis as risk factors for liver cancer. Several studies that investigate the relationship between alcohol consumption and liver cancer included in this review adjust for obesity [41, 42, 50] or hepatitis B or C infection [29, 33, 47] in their multivariate analyses. Only a few studies have examined the joint effect of alcohol and obesity or hepatitis on the risk of liver cancer (see Table 4). Although a full analysis of studies examining the joint effect and magnitude of risk was outside the scope of this review, some of the results reported include:

- One study reported a "strong" joint effect of hepatitis infection and alcohol use on the risk of liver cancer [RR = 25.4; 95%CI (9.6–41.2)]. As individual risk factors, this study reported relative risks of 2.15 associated with alcohol consumption and 13.7 associated with hepatitis [29]. *(Please see also the Biological mechanisms section for a discussion of the effect of heavy alcohol consumption and hepatitis infection on liver cancer risk.)*

- One of two studies reported a "strong" joint effect of obesity and alcohol use on the risk of liver cancer [RR = 3.82; 95%CI (1.94–7.52)] [51]. As individual risk factors, both studies reported an increased risk of 1.68 and 1.46 associated with alcohol consumption, but no association with obesity [29, 51].

(Please see the Glossary on page 129 for a definition of relative risk and descriptions of magnitude of risk as weak, modest, moderate, and strong in epidemiologic research.)

Table 4. Joint effect analyses of alcohol consumption and hepatitis infection and obesity

Risk factor	Study reference	Alcohol use only	Risk factor only	Joint effect
Hepatitis	Chuang et al., 2015	2.15	13.68	25.4
Obesity (>30kg/m²)	Chuang et al., 2015	1.68	ns	ns
Obesity (>30kg/m²)	Loomba et al., 2013	1.46	ns	3.82

FUTURE RESEARCH

Further research is needed to understand the joint effect of alcohol and obesity, or hepatitis, or both on the risk of liver cancer. In addition, more research is needed to understand how a cluster of modifiable risk factors can impact liver cancer risk. For example, Luu et al. (2021), found that adhering to "healthier" behaviors (having a BMI <23kg/m2, never having smoked, not drinking ≥15 drinks/week for men and ≥8 drinks/week for women, having a Mediterranean diet score within the fourth quartile, and regularly getting six to eight hours of sleep) compared to a few or no healthy behaviors was associated with an 87% reduced risk for liver cancer [52].

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 liver 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.

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DRINKING AND STOMACH CANCER

Publication date: March 2022

Introduction

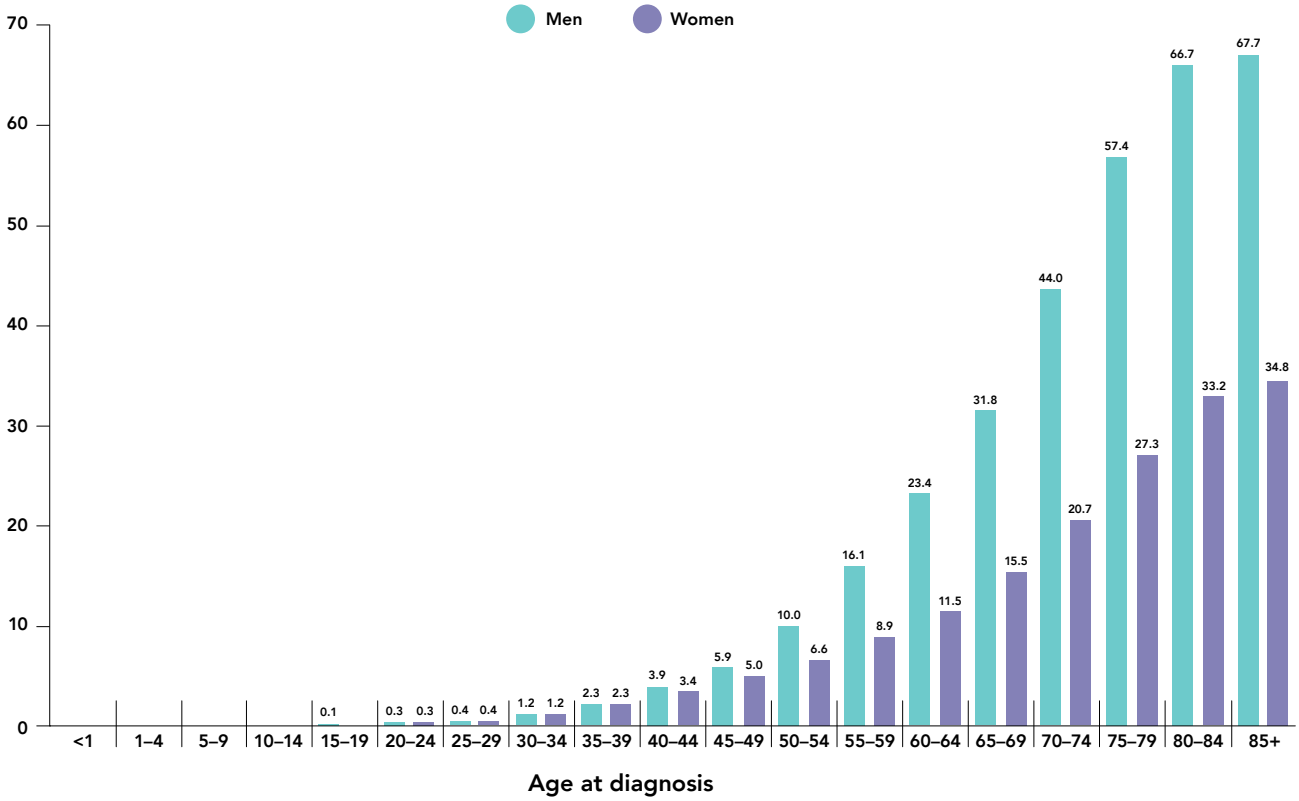
0.8% — **Lifetime risk of diagnosis (U.S.)**

16 — **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 129 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 (0.5–29) / 1.58 (30–70+)
Ferro et al., 2018	ref.†	ns (0.5–4) / 1.13 (5–49) / 1.37 (50–70+)
He et al., 2017	ref.†	ns (0.5–4) / ns (5–24) / 1.13 (25–70+)
Tramacere et al., 2012	ref.†	(no data) (0.5–49) / 1.20 (50–70+)
Men		
He et al., 2017	ref.†	ns (0.5–4) / ns (5–24) / 1.13 (25–70+)
Women		
He et al., 2017	ref.†	0.74 (0.5–4) / ns (5–24) / ns (25–70+)

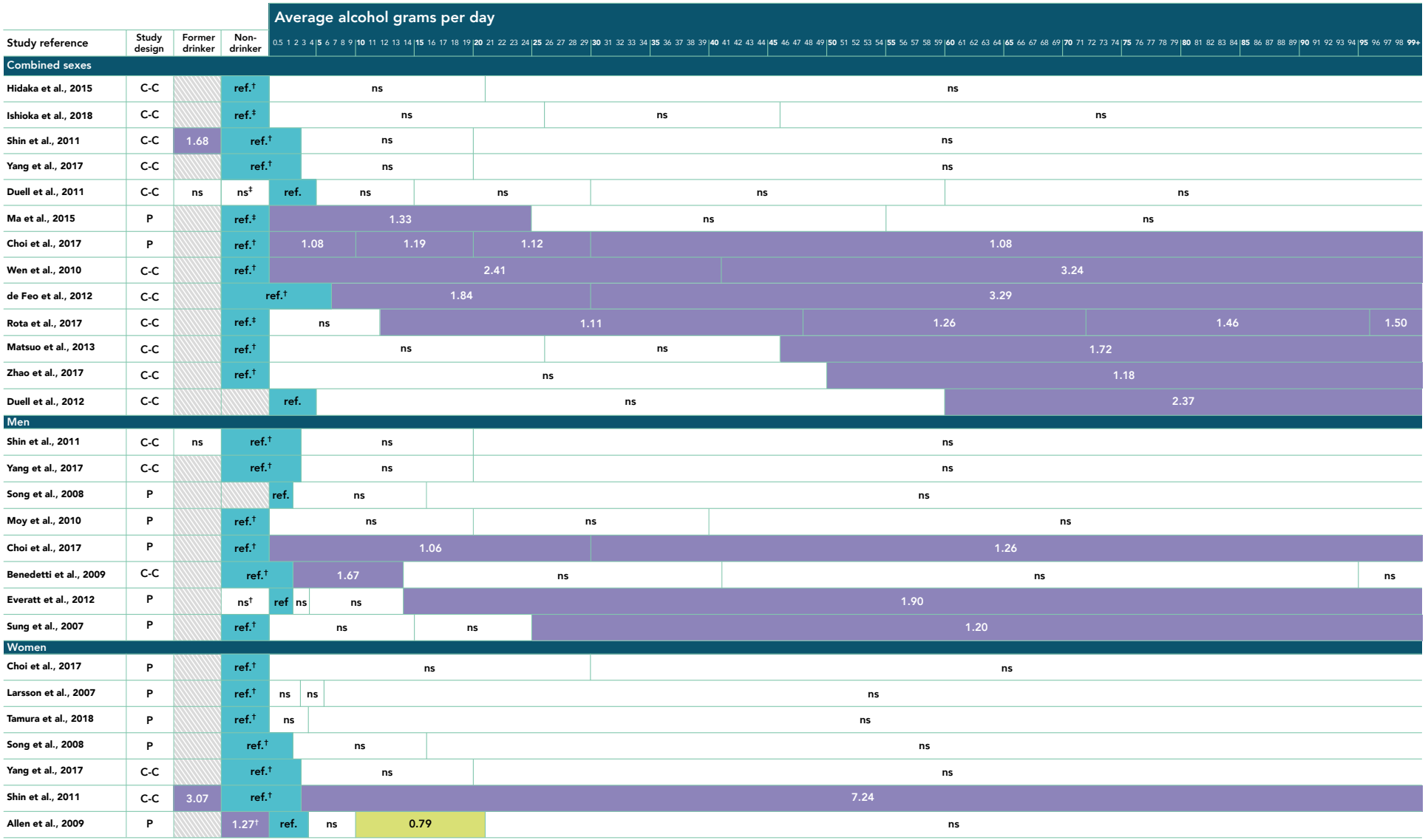
*All meta-analysis study designs published between 2007 and June 2019 and reporting risk estimates for drinking at multiple drinking levels were included in this table.

† 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. 0.5–4 | ns 5–70+
Wang et al., 2018	P	ref.†	ns 0.5–14 | ns 15–39 | 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 35–64 | ns 65–70+
Men			
Sung et al., 2007	P	ref.†	ns 0.5–14 | ns 15–24 | ns 25–70+
Wang et al., 2018	P	ref.†	ns 0.5–14 | ns 15–39 | 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 0.5–14 | ns 15–39 | 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 0.5–4 | ns 5–9 | ns 10–14
Bagnardi et al., 2015†	ref.†	ns 0.5–14 | ns 15–49 | 1.21 50–70+
Men		
Choi et al., 2018†	ref.†	ns 0.5–4 | ns 5–9 | ns 10–14
Bagnardi et al., 2015†	ref.†	ns 0.5–14 | ns 15–49 | ns 50–70+
Women		
Choi et al., 2018†	ref.†	ns 0.5–4
Bagnardi et al., 2015†	ref.†	ns 0.5–14 | ns 15–49 | 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 129 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).

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DRINKING AND KIDNEY CANCER

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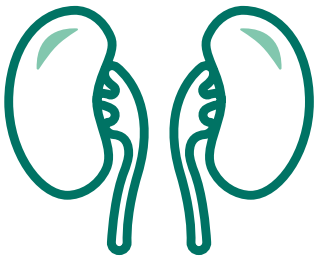


Introduction

1.7% **Lifetime risk of diagnosis (U.S.)**

4.55 **Global incidence per 100,000**

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

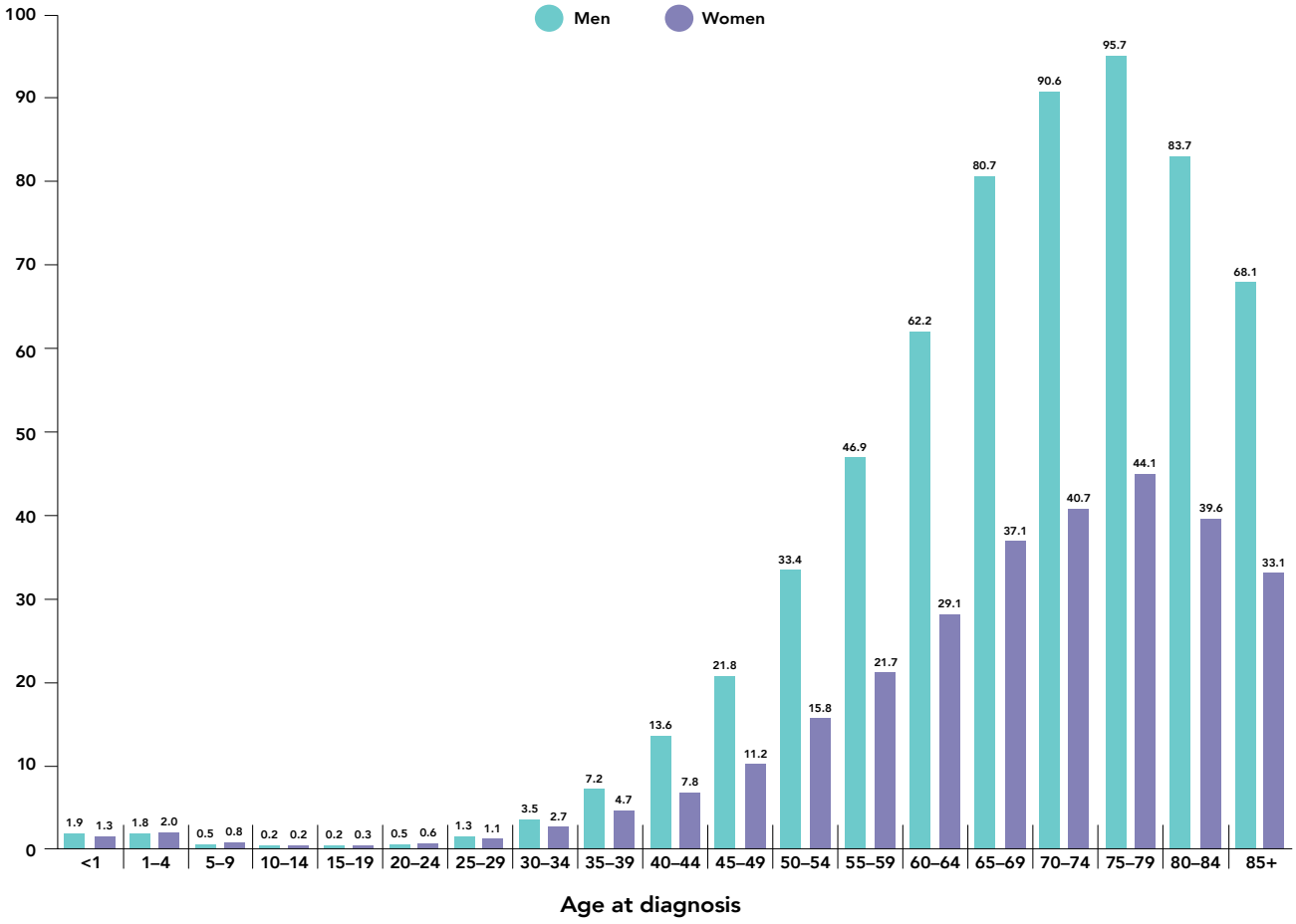
Note: Cancers that start in the kidney and renal pelvis are commonly combined when reported in national and international data. The renal pelvis is located in the center of the kidney and funnels urine to the ureter. Most studies refer to renal cell carcinoma, which is the most common type of kidney and renal pelvis cancer, as "kidney cancer." Therefore, this review uses the term "kidney cancer" to indicate the combination of kidney and renal pelvis cancer, or renal cell carcinoma, or both unless otherwise noted.

Kidney cancer is the 14th most common cancer in the world for men and women combined and accounts for 2.2% of all incident cancer cases globally [3]. Incidence rates vary across countries, from a high of 14.5 per 100,000 persons in Lithuania to a low of zero in the Maldives, the Republic of the Gambia, and Vanuatu [3]. In the U.S., the average age at diagnosis is 64 years, with 77% of new diagnoses occurring among those aged 55 years and older; incidence rates are twice as high among men than women (see Figure 1) [2].

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

The importance (that is, 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.

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



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

Table 1. Common risk factors for kidney cancers*

Modifiable risk factors	Non-modifiable risk factors
Alcohol consumption Body mass index Hypertension Smoking Taking painkillers with phenacetin	Age Personal/family history Genetics Kidney disease Race 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.*

BIOLOGICAL MECHANISMS OF KIDNEY CANCER

Researchers are continuing to explore several plausible biological mechanisms that may explain the potential role of alcohol as a risk or mitigating factor for kidney cancer [4, 6], and some of these are:

- Alcohol consumption may reduce kidney cancer risk by modifying the relationship between insulin and diabetes. Studies have shown that low-to-moderate alcohol consumption increases insulin sensitivity [7-9], especially among women, [10, 11] and is associated with a reduced risk of diabetes [12-14]. Studies have identified an association between diabetes and increased risk of kidney cancer [15, 16].

- Alcohol is a known diuretic [17] and is hypothesized to reduce the risk of kidney cancer by inducing urination and reducing the length of time that epithelial cells are exposed to carcinogens [4, 18, 19].

    - Studies have shown that drinking water suppresses vasopressin, which is a hormone that retains fluid in the kidney; this results in higher urinary output among hydrated individuals, compared to dehydrated individuals [17]. In the presence of alcohol, vasopressin suppression is prolonged despite water volume [19] leading to higher urinary output [17, 19]; however the diuretic effect of alcohol may be reduced in dehydrated individuals [17].

- Some alcohol beverages contain phenolic compounds such as tannins, which can affect their color, taste, and texture. These compounds may exhibit protective properties [20]; however, research in this field of interest is still evolving.

    - Limited research has shown that the antioxidant phenolic compounds resveratrol and xanthohumol may reduce oxidative stress through suppression of cell proliferation, induced cell death, anti-inflammation, and inhibition of *reactive oxygen species* production [21, 22], however their bioavailability (concentration in the blood) is low [22, 23].

Summary of recent kidney 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 kidney 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: kidney 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".*

KIDNEY CANCER

In this section we present results of studies reporting *relative risk* estimates for kidney cancer. (*Please see the Glossary on page 129 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 "probable" evidence of a reduced risk of kidney cancer associated with alcohol consumption up to 30g/day; insufficient evidence is available for intake above 30g/day [4]. (*Please see "Background chapter" for an explanation on the WCRF definitions of strength of evidence.*)

Meta-analyses

Five meta-analyses met the inclusion criteria for this review. Compared to nondrinkers, four meta-analyses found a reduced risk of kidney cancer [6, 18, 24, 25] and one meta-analysis found no association [26] between kidney cancer and alcohol consumption when results are reported for both sexes combined. None of the five meta-analyses found an increased risk associated with any level of alcohol consumption (see Table 2).

When stratified by sex, results for women were found to be generally consistent with those reported for men and women combined [18, 24-26], whereas no association was reported for men at or below 13g/day [18, 24-26] (see Table 2).

- No association was reported by Choi et al., 2018, between kidney cancer and alcohol consumption when both sexes were combined, or for men separately, but a reduced risk was reported for women only [26].
    - Choi et al., 2018 limited the study to comparing nondrinkers to drinkers who consume up to 30g/day; there are no risk estimates for drinkers who consume more than 30g/day [26].

Results from these meta-analyses indicate that the magnitude of the risk estimate is considered "weak" across the alcohol consumption spectrum (see, for example, Schoenbach and Rosamond (2000) [27] and the Glossary for additional resources). Compared to nondrinkers, the lowest levels of average alcohol consumption defined by these studies (up to 12.5g/day) are associated with an 8% to 10% decrease in risk (this is equivalent to a relative risk of 0.92 to 0.90), whereas the highest levels of consumption (more than 15g/day) are associated with a 28% decrease in risk (this is equivalent to a relative risk of 0.72).

Individual prospective cohort and case-control studies

Eleven individual prospective cohort or case-control studies met the review criteria for examining the association between alcohol consumption and kidney cancer among men and women combined [20, 28-37] (see Table 3).

- Three of six cohort studies found a reduced risk of kidney cancer associated with alcohol consumption for men and women combined starting at less than 15g/day [20, 29, 32] but two of these reported no association with consumption greater than 15g/day [29, 32].
- Four out of five case-control studies reported a reduced risk starting at alcohol consumption above 0g/day [33, 34], 21g/day [35], and 48g/day [36].
- Four of 11 studies reported no association between alcohol consumption and kidney cancer for men and women combined [28, 30, 31, 37].

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

Study reference	Nondrinker	Average alcohol grams per day
Combined sexes		
Choi et al., 2018	ref.†	ns (0.5–4.9) | ns (5–14.9) | ns (15–29.9)
Bellocco et al., 2012	ref.†	0.90 (0.5–9.9) | 0.79 (10–49.9) | ns (50+)
Bagnardi et al., 2015	ref.†	0.92 (0.5–9.9) | 0.79 (10–49.9) | ns (50+)
Lee et al., 2007	ref.†	ns (0.5–4.9) | 0.82 (5–14.9) | 0.72 (15–70+)
Xu et al., 2015	ref.†	ns (0.5–9.9) | 0.75 (10–39.9) | ns (40+)
Men		
Choi et al., 2018	ref.†	ns (5–14.9) | ns (15–29.9)
Bagnardi et al., 2015	ref.†	ns (0.5–9.9) | 0.83 (10–49.9) | ns (50+)
Xu et al., 2015	ref.†	ns (0.5–9.9) | 0.76 (10–49.9)
Lee et al., 2007	ref.†	ns (0.5–4.9) | ns (5–14.9) | 0.71 (15–70+)
Women		
Xu et al., 2015	ref.†	0.87 (0.5–9.9) | 0.72 (10–39.9)
Bagnardi et al., 2015	ref.†	0.85 (0.5–9.9) | 0.65 (10–49.9)
Lee et al., 2007	ref.†	ns (0.5–4.9) | ns (5–14.9) | 0.73 (15–70+)
Choi et al., 2018	ref.†	ns (0.5–4.9) | ns (5–14.9) | 0.93 (15–29.9)

*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.
- 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.

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

Study reference	Former drinker	Nondrinker	Average alcohol grams per day
Prospective studies			
Schouten et al., 2016		ref.†	ns | ns | ns | ns
Klatsky et al., 2015	ns	ref.‡	ns | ns | ns
Macleod et al., 2013		ref.†	ns | ns | ns
Schouten et al., 2008		ref.†	ns | 0.66 | ns | ns
Wozniak et al., 2015	ns	ns‡	ref. | 0.73 | ns | ns | ns
Karami et al., 2015		ref.†	ns | ns | 0.67
Case-control studies			
Hsu et al., 2007		ref.‡	ns | ns | ns
Antwi et al., 2018		ref.†	0.54 | 0.43 | 0.41
Hu et al., 2009		ref.†	0.8 | 0.78 | 0.65
Greving et al., 2007		ref.†	ns | ns | ns | ns | 0.60
Pelucchi et al., 2008		ref.†	ns | 0.76 | 0.70

*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)
‡Nondrinker (lifetime abstainer)

Nine individual prospective cohort or case-control studies met the review criteria and reported risk estimates for men and women separately: eight for men [20, 32, 33, 36, 38-41] and eight for women [20, 32, 33, 36, 38, 39, 41, 42] (see Tables 4 and 5).

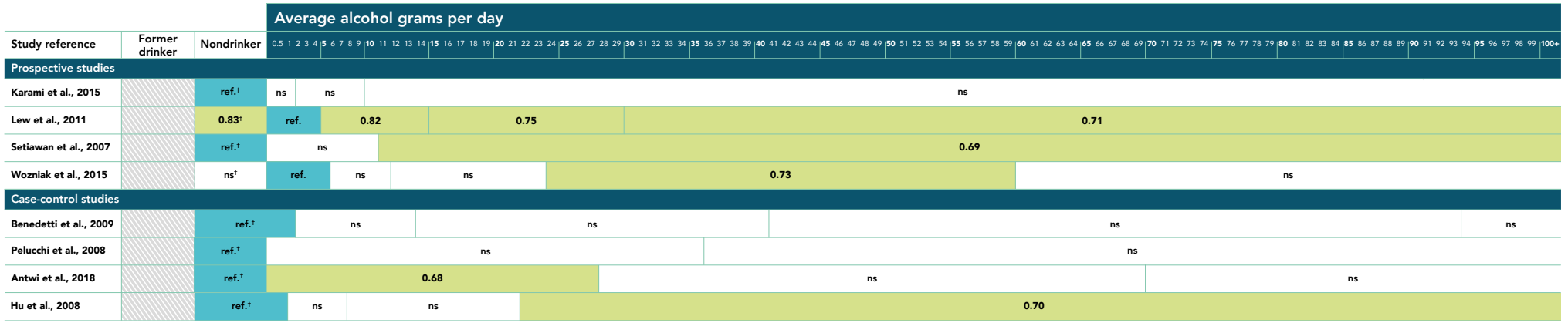
- Among men, five studies reported a reduced risk associated with alcohol consumption starting at more than 0g/day [33], 5g/day [38], 11g/day [39], 22g/day [41] and 24g/day [32], and three reported no association [20, 36, 40].
    - Wozniak et al., 2015 reported a reduced risk associated with alcohol consumption between 24g/day and 60g/day, but otherwise found no association with kidney cancer at any other level of consumption [32].
- Among women, five studies reported a reduced risk associated with alcohol consumption starting at more than 0g/day [33], 2g/day [20], 8g/day [41], 16g/day [42], and 30g/day [38], and three reported no association [32, 36, 39].
    - Karami et al., 2015 reported a reduced risk associated with alcohol consumption between 1.75g/day and 9.75g/day, but otherwise found no association with kidney cancer at any other level of alcohol consumption [20].

FUTURE RESEARCH

The plausible biological mechanisms that may explain the potential role of alcohol as a risk or mitigating factor for kidney cancer remain unclear. To obtain a better understanding, more research is needed. Additionally, to obtain a precise estimate of a potential threshold of alcohol consumption associated with kidney cancer risk, more refined drinking categories would need to be included.

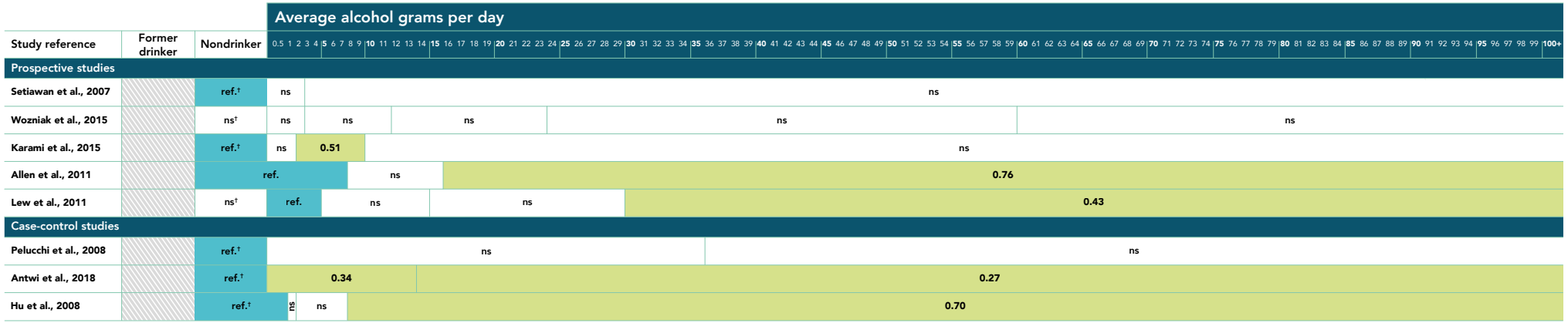
This review did not evaluate risk of bias or overall study quality as this was out of the scope of the review, and instead left interpretation of study quality and findings to the reader. However, future systematic reviews could contribute to a greater understanding of the relationship between alcohol consumption and kidney 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 4. Relative risk estimates for alcohol consumption associated with kidney cancer for men only from individual prospective cohort and case-control studies*



*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 associated with kidney cancer for women only from individual prospective cohort and case-control studies*



*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)

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DISCUSSION OF CONCEPTUAL AND METHODOLOGICAL ISSUES

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CLASSIFICATION ISSUES AND POTENTIAL ERRORS

The way in which drinkers and nondrinkers are classified in studies may affect observed outcomes for cancer. Some of the issues and examples of different types of potential classification errors include the following:

Drinking patterns

There is little consistency in defining drinking-level categories across research studies on alcohol consumption and health outcomes or describing those levels as light, moderate, or heavy. For example, studies can define categories:

- in 5g increments
- by combining all drinkers consuming up to one full drink and then combining all drinkers consuming more than one drink per day in another category, or
- by combining and describing all drinkers consuming more than one but less than five drinks per day as moderate drinkers, or
- by describing drinkers consuming alcohol occasionally and up to 8g/day as light drinkers, drinkers consuming between 8g/day and 24g/day as moderate, and over 24g/day as heavy.

A wider range of consumption within a single drinking level category can make it difficult to determine more precisely where risk increases. For example, studies that combine occasional, light, and moderate drinkers in a single category fail to provide data on risk associated for each of these different drinking patterns [1, 2].

Discussion of study limitations in meta-analyses and individual studies often includes the inability to assess the role of different drinking patterns on cancer risk, including binge drinking [2-4]. For example, although research has shown an increased risk of breast cancer beginning at light or moderate drinking levels, few studies have investigated the relationship between binge drinking and breast cancer risk [5, 6]. Additional research on refined categories of average alcohol consumption and binge drinking frequency would provide more robust evidence on the relationships among patterns of drinking and cancer risk.

Former drinkers and lifetime abstainers

The "sick-quitter" hypothesis postulates that many former drinkers have stopped drinking for health reasons and was first described in 1988 [7]. If these individuals are classified as nondrinkers in the same group as lifetime abstainers, their existing health conditions may make it appear that nondrinkers are at a higher risk than light or moderate drinkers for a given health outcome or, conversely, that the risk associated with drinking compared with abstaining is lower than it actually is. This effect is sometimes referred to as "abstainer bias". A group of researchers have claimed that this bias (the potential to influence the overall results) applies to all studies that combine lifetime abstainers and occasional and former drinkers in the field of alcohol and cardiovascular disease and all-cause mortality [8, 9], but may not apply to breast cancer studies [10].

Over the past decade, studies have accounted for this potential source of bias by separating former drinkers from lifetime abstainers or testing whether risk estimates differ when former drinkers are included or excluded in the nondrinker category. This bias has often been accounted for in research on alcohol and cardiovascular disease or all-cause mortality [11-16] and in research on alcohol and cancer, including in many studies in the *IARD Health Review: Drinking and Cancer* [1, 5, 17-23].

Another method of addressing this potential bias is to examine results when study participants with a history of a given health condition are first included and then excluded from the analysis, as in Dam et al. 2016 [24].

- **Reporting errors**

Self-reported alcohol consumption data are likely to be subject to inaccuracies due to recall errors (difficulty with accurately remembering past behavior) and social desirability bias (the desire to provide a response viewed favorably by others). The latter may be especially relevant in some cultures for surveys asking questions about potentially sensitive information, such as alcohol consumption. If respondents have underreported their consumption and are misclassified into a lighter drinking category, this would result in an error in the risk estimate [25].

There are methods for minimizing potential underestimation errors:

- Some studies collect multiple measures of alcohol consumption over time [26, 27].
- Other studies collect health data (biomarkers or clinical diagnoses of alcohol-related conditions), which are then used to identify and separate respondents who misreport their consumption from other respondents [23, 28]. This approach has demonstrated that alcohol-related cancer risk associated with "light-moderate" drinking or <1 drink/day appears to be restricted to underreporting; there was no observed association between alcohol consumption at this same level of drinking and cancer risk among unlikely underreporters, as identified by the researchers through previously reported heavier intake or an alcohol-related diagnosis [23, 28].

- **Relevant time period of alcohol consumption**

Another issue that is relevant to cancer epidemiology is the assessment of the timing of exposure to a risk factor of interest.

It is currently unclear whether cancer risk is affected by recent drinking patterns, drinking patterns during a critical period of development (for example, puberty), or the accumulation of drinking patterns over a lifetime.

It is also difficult to discern for any given cancer diagnosis whether carcinogenesis is associated with first exposure to a risk factor, prolonged exposure, only in the presence of an additional risk factor or factors, or whether exposure to a risk factor accelerates cancer development [29].

At present, alcohol assessment varies across research studies, making it difficult to determine whether risk estimates reflect recent or historic drinking patterns.

Few studies have attempted to test whether alcohol consumption in early adulthood, in the recent time period, or over a lifetime is more strongly associated with risk. Additionally, these results have been somewhat inconsistent. More research could help demonstrate whether consumption during one time period is a more accurate predictor of risk than another and whether that reference period differs for various cancer sites. For example:

- One study of cancers of the upper airway and digestive tract found a weak, non-statistically significant association for drinking during early adulthood (aged from 20 to 29 years) and a modest association with both recent and lifetime consumption measures [22].

- A similar finding for male participants was reported in a study of pancreatic cancer [30].

- A 2004 study of Danish women found that recent alcohol consumption was more accurately associated with breast cancer risk than either lifetime consumption or early adulthood consumption [31], a finding confirmed in a larger 2007 multi-cohort study in Europe [32]. A 2011 study in the U.S., however, concluded that a cumulative lifetime alcohol intake measure was more accurate than a baseline or current alcohol measure, and that drinking in early adulthood and later adulthood were both linearly associated with breast cancer risk (although the trend for alcohol intake during early adulthood did not reach statistical significance) [33].

- McNabb and colleagues, in their 2018 meta-analysis, suggest that results indicating that former drinkers have an increased risk of colorectal cancer compared to lifetime abstainers may be due to the impact of a longer-term drinking history on colorectal cancer risk. Their study found a reduced risk of colorectal cancer among light to moderate drinkers, compared with nondrinkers, but the authors acknowledge that the inclusion of former drinkers with lifetime abstainers in the reference group may have influenced their observed protective effect [34].

CONFOUNDING BIAS

Various factors that are related to drinking, or to not drinking, may explain observed associations between alcohol consumption and cancer risk. This potential source of error is referred to as confounding bias.

Many factors may be associated with both drinking behavior and cancer incidence or mortality and should be accounted for in a study's design or in the data analysis as much as possible to minimize confounding bias.

- These include individual factors, such as sex, race, and ethnicity; genetic and physiological factors; behavioral factors, such as smoking, diet, and physical activity; social and economic factors; and existing mental and health conditions.

- Because epidemiological studies are unable to control for all potential confounders, the possibility that the results could be explained by residual confounding cannot be excluded, and the results of observational studies should be interpreted with reasonable caution.

    - When risk estimates exceed 2.0, or are less than 0.5, it is increasingly less likely that the risk association can be explained by unmeasured confounding and more likely that the observed association reflects a true association [35].

Smoking is a strong risk factor for most cancers [36, 37], and there is a high correlation between alcohol consumption and smoking in general and heavier drinking and heavier smoking in particular [38]. Even though smoking can be adjusted for in a study of the relationship between alcohol and cancer, residual confounding may still influence the risk relationship. This means that, in studies that include smokers and nonsmokers, the relationship between alcohol and cancer may be driven by the effect of alcohol in smokers. Studies that separate results for smokers and nonsmokers more effectively examine independent effects of alcohol consumption [37].

SELECTION BIAS

Selection bias may occur when individuals participating in a research study are not representative of the population being studied and can therefore distort (underestimate or overestimate) the relationship between alcohol consumption and cancer risk.

▶ Healthy cohorts

Healthier individuals may be more likely to participate in a research study and continue participating throughout the course of the study than individuals with health issues. This is likely to result in a lower incidence of cancer in the study population over the course of the study, which may make the observed cancer risk lower than it actually is in the general population.

In addition, risky or heavy drinkers can be less likely to be included in a study sample population or to participate in a study due to other factors including social isolation, homelessness, or mental illness. This makes it more likely that a lower incidence of alcohol-related health outcomes will be observed in the study population, making the observed cancer risk lower than it actually is in the general population.

▶ Survival bias

Another type of selection bias relates to survival: drinkers who have died prematurely from an alcohol-related cause cannot be included in a research study, therefore people who are still alive and available to be selected into a research study may not accurately reflect the full population of drinkers. This bias assumes that individuals dying at younger ages are more likely to be drinkers than non-drinkers because alcohol is a leading risk factor for the causes of death that are more prevalent among younger individuals (unintentional injuries and violence) [39].

Selection bias complicates the interpretation of research about other risk factors that are associated with more than one health outcome. This bias cannot be easily adjusted or controlled for by researchers, nor are its potential effects on research outcomes easily quantifiable.

However, "selection" of the study population from a source population does not necessarily produce biases that distorts the risk estimate. Participants in an epidemiological study do not have to be representative of the general population for an association to be *internally valid*. Thus, investigators can study "select" groups and maintain the expectation that results will be meaningful (for example, nurses participating in the Nurses' Health Study). This is why results from large, long-term follow-up studies produce important pieces of evidence; these types of studies focus on the relationship of alcohol to cancer risk by minimizing differences in other factors (socioeconomic or lifestyle) among participants that could affect cancer risk.

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GLOSSARY

- **Acetaldehyde** is a product of ethanol metabolism, which takes place in the liver and other tissues and leads 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.
- **Achalasia** develops because of damage to the nerves in the esophagus making it difficult to pass food and liquid to the stomach.
- **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.
- **Cell proliferation** is the multiplication of cells due to cell division.
- **CYP2E1** is a protein that is induced by ethanol, diabetes, and starvation and metabolizes ethanol and other endogenous and exogenous substances.
- **Dose-response** describes the relationship between the amount of exposure and the amount of risk of the outcome.
- **Dysbiosis** is an imbalance in the gut's population of microbes.
- **Enzymatic activity** consists of proteins reacting together to speed up the rate of a chemical reaction.
- **Epidemiological studies** examine the distribution of disease and other health outcomes among human populations and the determinants of those health outcomes. A key feature of an epidemiological study is the measurement of a health outcome (for example, colorectal cancer) among a population at risk, where the measurement of a risk factor (for example, alcohol consumption) and the health outcome are assessed at the same time, longitudinally, or retrospectively, depending on the study design.
- **Hormone replacement therapy (HRT)** – also known as menopausal hormone therapy (MHT) – is treatment with estrogen and progesterone to relieve menopause symptoms.
- **Human epidermal growth factors** are proteins that control breast cell growth and repair. If mutated, they can reverse their activity and contribute to increased cell growth instead.
- **IARC's classification of sufficient evidence** is described as "a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between exposure to the agent and cancer in studies in which chance, bias, and confounding could be ruled out with reasonable confidence" [1].

- **Insulin-like growth factor (IGF)** are proteins that have a similar sequence to insulin and mediate hormone growth activity.

- **Internal validity** is the extent to which the results define the true relationship in the study population between a risk factor and a health outcome, and other factors or methodological issues related to study design or implementation are unlikely to have altered the observed relationship. In contrast, a study is said to have external validity if its results can be applied from the study population to the general population.

- **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 [2-6], however, the risk estimates associated with each term may differ or overlap (see Figure 2A-C). For example, according to Schoenbach and Rosamond 2000 [2], 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 [3, 4].

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

Source: Schoenbach and Rosamond 2000 [2]

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 [6]

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 [5]

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