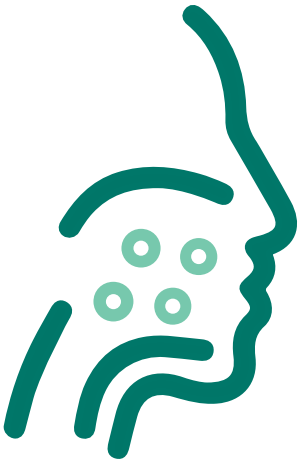
DRINKING AND UPPER AERODIGESTIVE TRACT CANCERS



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 24.

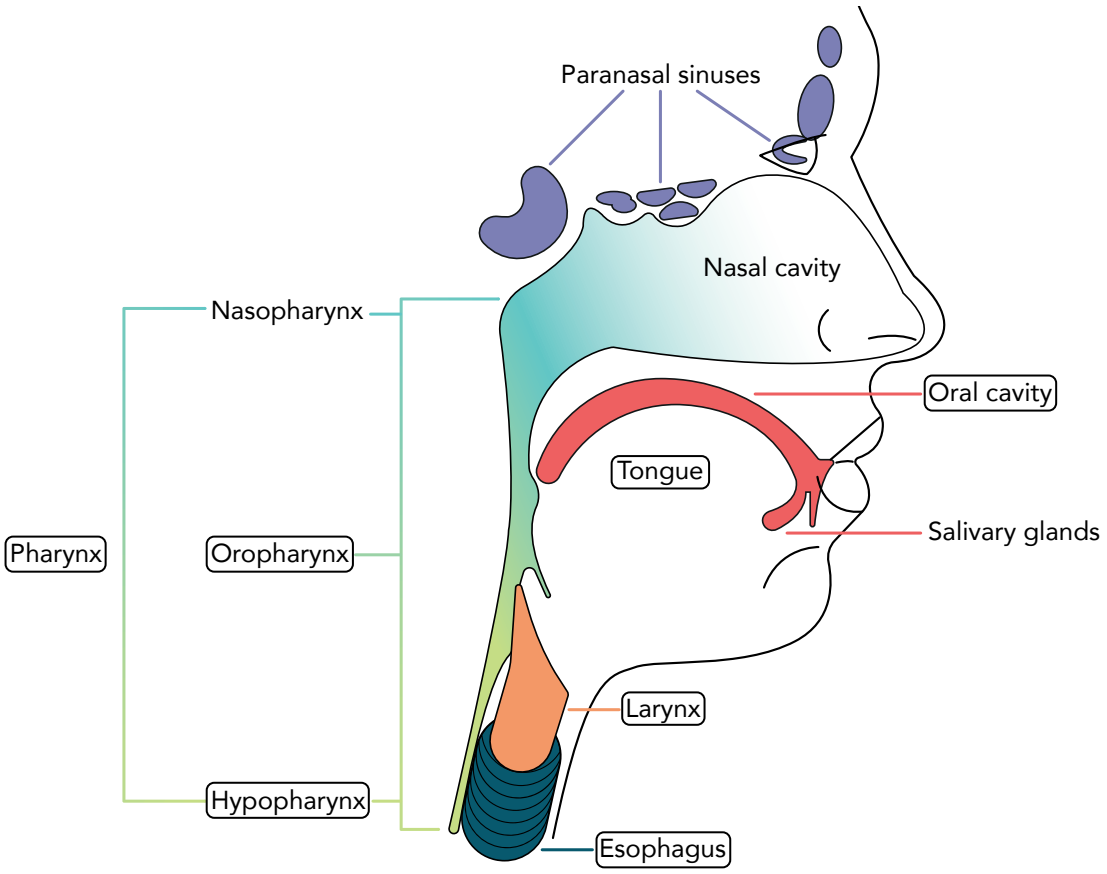
Last literature review: July 2019

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 below 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 24 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	10–15	15–20	20–25	25–30	30–35	35–40	40–45	45–50	50–55	55–60	60–65	65–70	70–75	75–80	80–85	85–90	90–95	95–100	100–105	105–110	110–115	115–120	120–125	125–130	130–135	135–140+
Combined sexes																												
Bagnardi et al., 2013	ref.†	ns																										
Lubin et al., 2010	ref.†	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																		
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: 5	10	15	20	25	30	35	40	45	50	55	60	65	70+
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
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

5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80+

* 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

Glossary

- **Acetaldehyde** is a product of the metabolism of ethanol, which begins in the mouth and digestive tract but takes place primarily in the liver. Acetaldehyde is a carcinogen and can damage DNA and increase cell proliferation.
- **Acetaldehyde dehydrogenase (ADH)** is an enzyme that breaks down acetaldehyde into smaller molecules such as acetate, which are further broken down into carbon dioxide and water molecules.
- **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.
- **CYP2E1** is a protein that is induced by ethanol, diabetes, and starvation and metabolizes ethanol and other endogenous and exogenous substances.
- **Reactive oxygen species (ROS)** are a group of highly-reactive molecules containing oxygen that, at low levels, are an important part of metabolism and inflammatory response. An excess of reactive oxygen species can damage cellular proteins, lipids, or DNA, and has been linked with chronic diseases, such as cancer, diabetes, and cardiovascular disease.
- **Relative risk (RR)** is a measure that compares the probability of a given outcome (for example, breast cancer) among a group of people with a given risk factor (for example, alcohol consumption) with the probability of that outcome among a group of people without the risk factor (for example, nondrinkers). A risk estimate above one (RR>1) indicates an increased risk of the outcome associated with the exposure and a risk estimate below one (RR<1) indicates a reduced risk of the outcome associated with the exposure. If the risk estimate is equivalent to one (RR=1) then there is no association between the outcome and the exposure.
    - The magnitude of relative risk describes the strength of the association between the exposure and outcome of interest, or the relative risk estimate. There are several terms used to describe or interpret different relative risk estimates. Some commonly used descriptors are weak, small, moderate, medium, strong, or large [82-86], however, the risk estimates associated with each term may differ or overlap (see Figure 2A-C). For example, according to Schoenbach and Rosamond 2000 [82], 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 [83, 84].

Figure 2A. Descriptions of magnitude of risk

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

Source: *Schoenbach and Rosamond 2000 [82]*

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 [85]*

Figure 2C. Descriptions of magnitude of risk

Effect size: Interpretation suggestions for social science data

Type of effect size estimate	Included indices	RMPE	Moderate effect	Strong effect
Group difference	*d*, Δ, *g*	0.41	1.15	2.70
Strength of association	*r*, *R*, ϕ, *p*, partial *r*, β, r_h, 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

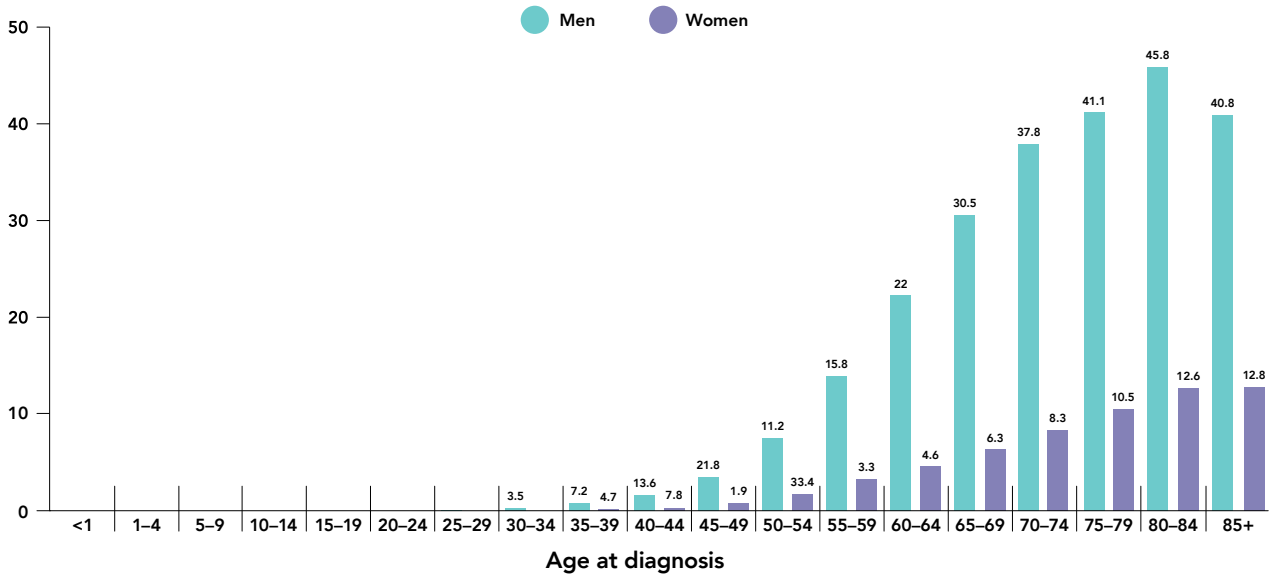
Note. RMPE = recommended minimum effect size representing a "practically" significant effect for social science data. For effects with highly valid dependent measures (e.g., death) and using rigorous controlled outcomes trials, lower values may have practical value. RR = relative risk; OR = odds ratio.

*These are not anchored to *r* and should be interpreted with caution

Source: *Ferguson 2016 [86]*

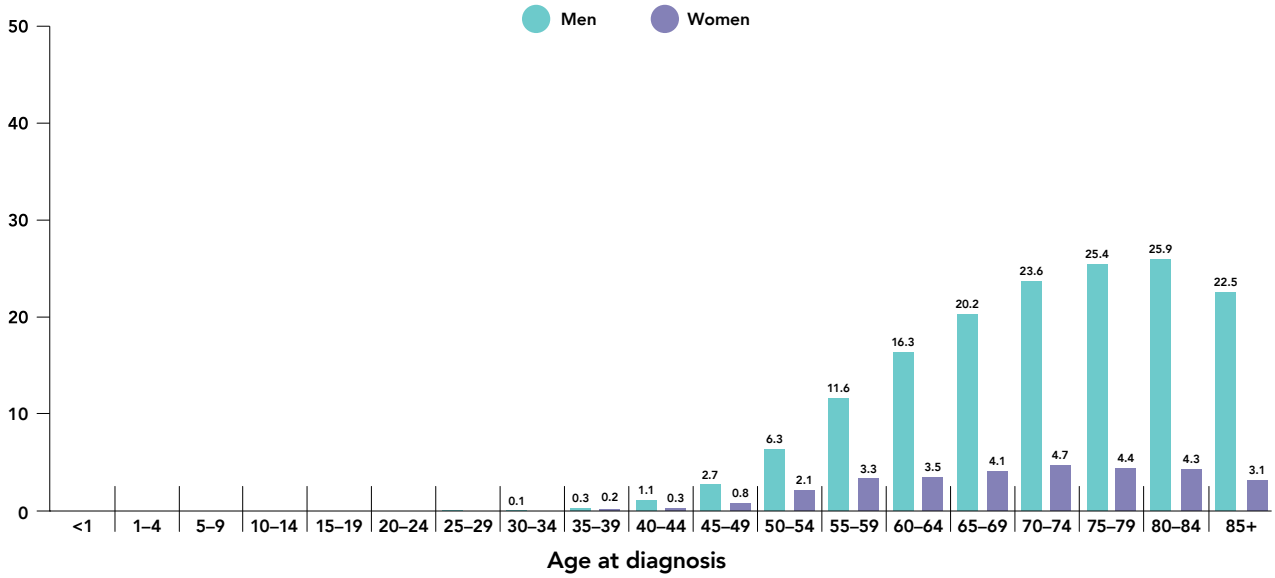
Appendix

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



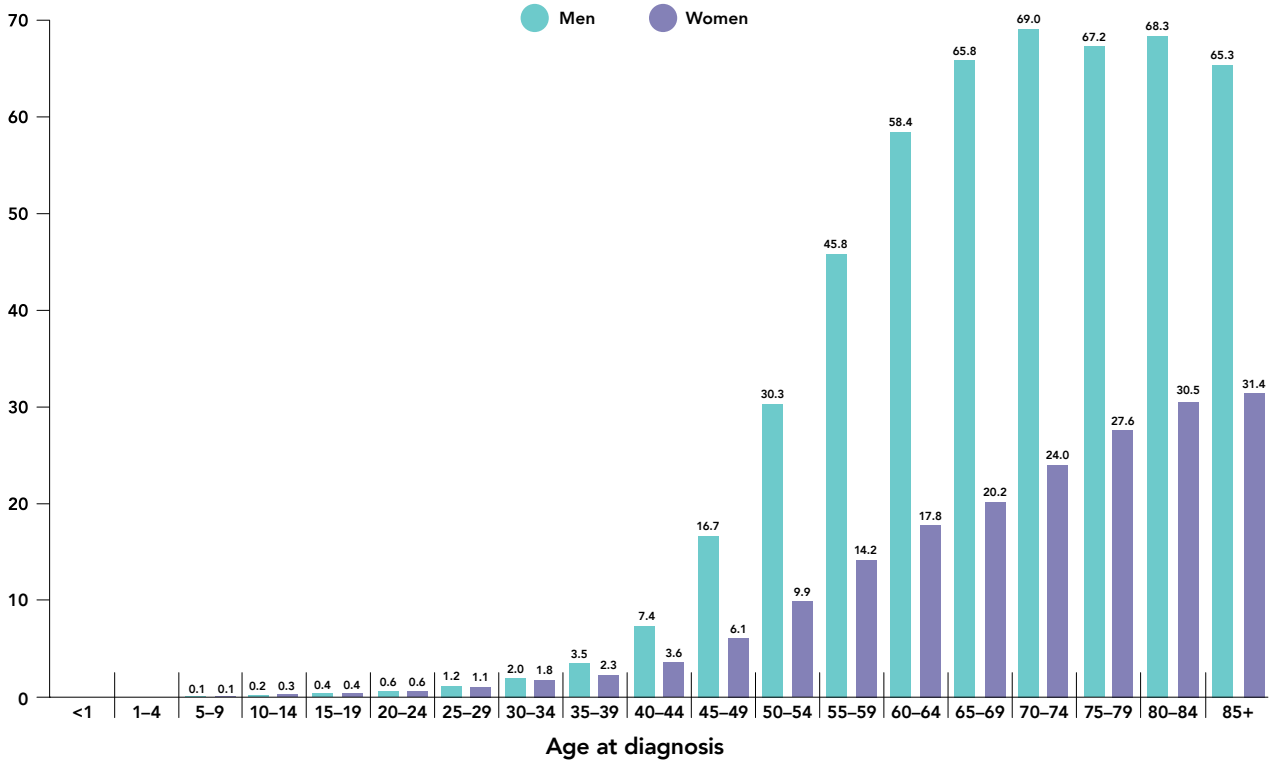
Sources: *SEER 21 Areas, Esophagus SEER Incidence and U.S. Mortality Rates by Age at Diagnosis, 2014-2018 [5]*

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*

Study reference	Study design	Nondrinker	Average alcohol grams per day		
			5 10 15 20 25 30 35 40 45 50 55 60 65 70+		
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
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

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+

* 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)

References

1. National Cancer Institute. *Aerodigestive tract*. Retrieved 01 November, 2020, from https://www.cancer.gov/publications/dictionaries/cancer-terms/def/aerodigestive-tract

2. National Cancer Institute. (2021). *Head and Neck Cancers*. Retrieved 01 November, 2020, from https://www.cancer.gov/types/head-and-neck/head-neck-fact-sheet-what-are-cancers-of-the-head-and-neck

3. World Cancer Research Fund / American Institute for Cancer Research. (2018). *Diet, nutrition, physical activity and cancer: A global perspective* (Continuous update project expert report 2018). Retrieved from https://www.wcrf.org/diet-and-cancer

4. Institute for Health Metrics and Evaluation (IHME). Global burden of disease study (GBD): Compare visualization hub. Retrieved 01 November 2020, from http://vizhub.healthdata.org/gbd-compare

5. Howlader, N., Noone, A. M., Krapcho, M., Miller, D., Brest, A., Yu, M., et al. (2021). *SEER cancer statistics review, 1975-2018, based on November 2020 SEER data submission, posted to the SEER web site*, April 2021. Retrieved from https://seer.cancer.gov/csr/1975_2018/

6. Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Pineros, M., et al. (2020). *Global cancer observatory: Cancer today*. Retrieved 17 December, 2020, from https://gco.iarc.fr/today/home

7. American Cancer Society. (2020). *Esophageal cancer risk factors*. Retrieved 05 May, 2021, from https://www.cancer.org/cancer/esophagus-cancer/causes-risks-prevention/risk-factors.html

8. American Cancer Society. (2021). *Risk factors for laryngeal and hypopharyngeal cancers*. Retrieved 05 May, 2021, from https://www.cancer.org/cancer/laryngeal-and-hypopharyngeal-cancer/causes-risks-prevention/risk-factors.html

9. American Cancer Society. (2021). *Risk factors for oral cavity and oropharyngeal cancers*. Retrieved 05 May, 2021, from https://www.cancer.org/cancer/oral-cavity-and-oropharyngeal-cancer/causes-risks-prevention/risk-factors.html

10. Ratna, A., & Mandrekar, P. (2017). Alcohol and cancer: Mechanisms and therapies. *Biomolecules, 7*(3).

11. Seitz, H. K., & Becker, P. (2007). Alcohol metabolism and cancer risk. *Alcohol Research and Health, 30*(1), 38-41, 44-37.

12. Vanella, G., Archibugi, L., Stigliano, S., & Capurso, G. (2018). Alcohol and gastrointestinal cancers. *Current Opinion in Gastroenterology, Publish Ahead of Print*(2), 107-113.

13. Seitz, H. K., Matsuzaki, S., Yokoyama, A., Homann, N., Väkeväinen, S., & Wang, X. D. (2001). Alcohol and cancer. *Alcoholism: Clinical and Experimental Research, 25* (5 Suppl ISBRA), 137s-143s.

14. Seitz, H. K., & Becker, P. (2007). Alcohol metabolism and cancer risk. *Alcohol Research & Health, 30*(1), 38-47.

15. Oneta, C. M., Lieber, C. S., Li, J., Ruttimann, S., Schmid, B., Lattmann, J., et al. (2002). Dynamics of cytochrome P4502E1 activity in man: Induction by ethanol and disappearance during withdrawal phase. *Journal of Hepatology, 36*(1), 47-52.

16. Seitz, H. K., & Stickel, F. (2007). Molecular mechanisms of alcohol-mediated carcinogenesis. *Nature Reviews Cancer, 7* (8), 599-612.

17. Pöschl, G., Stickel, F., Wang, X. D., & Seitz, H. K. (2004). Alcohol and cancer: Genetic and nutritional aspects. *Proceedings of the Nutrition Society, 63*(1), 65-71.

18. Toh, Y., Oki, E., Ohgaki, K., Sakamoto, Y., Ito, S., Egashira, A., et al. (2010). Alcohol drinking, cigarette smoking, and the development of squamous cell carcinoma of the esophagus: Molecular mechanisms of carcinogenesis. *International Journal of Clinical Oncology, 15*(2), 135-144.

19. Yokoyama, A., Muramatsu, T., Ohmori, T., Yokoyama, T., Okuyama, K., Takahashi, H., et al. (1998). Alcohol-related cancers and aldehyde dehydrogenase-2 in Japanese alcoholics. *Carcinogenesis, 19*(8), 1383-1387.

20. Coutelle, C., Ward, P. J., Fleury, B., Quattrocchi, P., Chambrin, H., Iron, A., et al. (1997). Laryngeal and oropharyngeal cancer, and alcohol dehydrogenase 3 and glutathione S-transferase M1 polymorphisms. *Human Genetics, 99*(3), 319-325.

21. Brennan, P., Lewis, S., Hashibe, M., Bell, D. A., Boffetta, P., Bouchardy, C., et al. (2004). Pooled analysis of alcohol dehydrogenase genotypes and head and neck cancer: A HuGE review. *American Journal of Epidemiology, 159*(1), 1-16.

22. Seitz, H. K., Stickel, F., & Homann, N. (2004). Pathogenetic mechanisms of upper aerodigestive tract cancer in alcoholics. *International Journal of Cancer, 108*(4), 483-487.

23. Stornetta, A., Guidolin, V., & Balbo, S. (2018). Alcohol-Derived Acetaldehyde Exposure in the Oral Cavity. *Cancers (Basel), 10*(1).

24. Poschl, G., & Seitz, H. K. (2004). Alcohol and cancer. *Alcohol and Alcoholism, 39*(3), 155-165.

25. Salaspuro, V., & Salaspuro, M. (2004). Synergistic effect of alcohol drinking and smoking on in vivo acetaldehyde concentration in saliva. *International Journal of Cancer, 111*(4), 480-483.

26. Radoï, L., Paget-Bailly, S., Cyr, D., Papadopoulos, A., Guida, F., Schmaus, A., et al. (2013). Tobacco smoking, alcohol drinking and risk of oral cavity cancer by subsite: results of a French population-based case–control study, the ICARE study. *European Journal of Cancer Prevention, 22*(3), 268-276.

27. Hashibe, M., Boffetta, P., Janout, V., Zaridze, D., Shangina, O., Mates, D., et al. (2007). Esophageal cancer in Central and Eastern Europe: Tobacco and alcohol. *International Journal of Cancer, 120*(7), 1518-1522.

28. Lee, C.-H., Lee, J.-M., Wu, D.-C., Goan, Y.-G., Chou, S.-H., Wu, I.-C., et al. (2008). Carcinogenetic impact of ADH1B and ALDH2 genes on squamous cell carcinoma risk of the esophagus with regard to the consumption of alcohol, tobacco and betel quid. *International Journal of Cancer, 122*(6), 1347-1356.

29. Peters, E. S., McClean, M. D., Liu, M., Eisen, E. A., Mueller, N., & Kelsey, K. T. (2005). The ADH1C polymorphism modifies the risk of squamous cell carcinoma of the head and neck associated with alcohol and tobacco use. *Cancer Epidemiol Biomarkers Prev, 14*(2), 476-482.

30. American Cancer Society. (2021). *Key statistics for esophageal cancer.* Retrieved 05 May, 2021, from https://www.cancer.org/cancer/esophagus-cancer/about/key-statistics.html

31. Fan, Y., Yuan, J. M., Wang, R., Gao, Y. T., & Yu, M. C. (2008). Alcohol, tobacco, and diet in relation to esophageal cancer: The Shanghai Cohort Study. *Nutrition and Cancer, 60*(3), 354-363.

32. Choi, Y. J., Lee, D. H., Han, K. D., Kim, H. S., Yoon, H., Shin, C. M., et al. (2017). The relationship between drinking alcohol and esophageal, gastric or colorectal cancer: A nationwide population-based cohort study of South Korea. *PLOS ONE, 12*(10), e0185778.

33. Szymańska, K., Hung, R. J., Wünsch-Filho, V., Eluf-Neto, J., Curado, M. P., Koifman, S., et al. (2011). Alcohol and tobacco, and the risk of cancers of the upper aerodigestive tract in Latin America: a case–control study. *Cancer Causes & Control, 22*(7), 1037-1046.

34. Vioque, J., Barber, X., Bolumar, F., Porta, M., Santibáñez, M., de la Hera, M. G., et al. (2008). Esophageal cancer risk by type of alcohol drinking and smoking: a case-control study in Spain. *BMC Cancer, 8*, 221.

35. Kunzmann, A. T., Coleman, H. G., Huang, W. Y., & Berndt, S. I. (2018). The association of lifetime alcohol use with mortality and cancer risk in older adults: A cohort study. *PLOS Medicine, 15*(6), e1002585.

36. Zhao, J. K., Wu, M., Kim, C. H., Jin, Z. Y., Zhou, J. Y., Han, R. Q., et al. (2017). Jiangsu Four Cancers Study: A large case-control study of lung, liver, stomach, and esophageal cancers in Jiangsu Province, China. *European Journal of Cancer Prevention, 26*(4), 357-364.

37. Wu, M., Zhao, J. K., Zhang, Z. F., Han, R. Q., Yang, J., Zhou, J. Y., et al. (2011). Smoking and alcohol drinking increased the risk of esophageal cancer among Chinese men but not women in a high-risk population. *Cancer Causes Control, 22*(4), 649-657.

38. Hsu, W. L., Chien, Y. C., Chiang, C. J., Yang, H. I., Lou, P. J., Wang, C. P., et al. (2014). Lifetime risk of distinct upper aerodigestive tract cancers and consumption of alcohol, betel and cigarette. *International Journal of Cancer, 135*(6), 1480-1486.

39. Benedetti, A., Parent, M.-E., & Siemiatycki, J. (2009). Lifetime consumption of alcoholic beverages and risk of 13 types of cancer in men: Results from a case–control study in Montreal. *Cancer Detection and Prevention, 32*(5), 352-362.

40. Kimm, H., Kim, S., & Jee, S. H. (2010). The independent effects of cigarette smoking, alcohol consumption, and serum aspartate aminotransferase on the alanine aminotransferase ratio in korean men for the risk for esophageal cancer. *Yonsei Med J, 51*(3), 310-317.

41. Jayasekara, H., MacInnis, R. J., Room, R., & English, D. R. (2015). Long-term alcohol consumption and breast, upper aerodigestive tract and colorectal cancer risk: A systematic review and meta-analysis. *Alcohol and Alcoholism, 51*(3), 315-330.

42. Bagnardi, V., Rota, M., Botteri, E., Tramacere, I., Islami, F., Fedirko, V., et al. (2013). Light alcohol drinking and cancer: A meta-analysis. *Annals of Oncology, 24*(2), 301-308.

43. Bagnardi, V., Rota, M., Botteri, E., Tramacere, I., Islami, F., Fedirko, V., et al. (2015). Alcohol consumption and site-specific cancer risk: A comprehensive dose-response meta-analysis. *British Journal of Cancer, 112*(3), 580-593.

44. Choi, Y. J., Myung, S. K., & Lee, J. H. (2018). Light alcohol drinking and risk of cancer: A meta-analysis of cohort studies. *Cancer Research and Treatment, 50*(2), 474-487.

45. Freedman, N. D., Murray, L. J., Kamangar, F., Abnet, C. C., Cook, M. B., Nyren, O., et al. (2011). Alcohol intake and risk of oesophageal adenocarcinoma: a pooled analysis from the BEACON Consortium. *Gut, 60*(8), 1029-1037.

46. Islami, F., Fedirko, V., Tramacere, I., Bagnardi, V., Jenab, M., Scotti, L., et al. (2011). Alcohol drinking and esophageal squamous cell carcinoma with focus on light-drinkers and never-smokers: A systematic review and meta-analysis. *International Journal of Cancer, 129*(10), 2473-2484.

47. Lubin, J. H., Cook, M. B., Pandeya, N., Vaughan, T. L., Abnet, C. C., Giffen, C., et al. (2012). The importance of exposure rate on odds ratios by cigarette smoking and alcohol consumption for esophageal adenocarcinoma and squamous cell carcinoma in the Barrett's Esophagus and Esophageal Adenocarcinoma Consortium. *Cancer Epidemiology, 36*(3), 306-316.

48. Menya, D., Kigen, N., Oduor, M., Maina, S. K., Some, F., Chumba, D., et al. (2019). Traditional and commercial alcohols and esophageal cancer risk in Kenya. *International Journal of Cancer, 144*(3), 459-469.

49. Freedman, N. D., Abnet, C. C., Leitzmann, M. F., Mouw, T., Subar, A. F., Hollenbeck, A. R., et al. (2007). A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. *American Journal of Epidemiology, 165*(12), 1424-1433.

50. Steevens, J., Schouten, L. J., Goldbohm, R. A., & van den Brandt, P. A. (2010). Alcohol consumption, cigarette smoking and risk of subtypes of oesophageal and gastric cancer: A prospective cohort study. *Gut, 59*(1), 39-48.

51. Pandeya, N., Williams, G., Green, A. C., Webb, P. M., & Whiteman, D. C. (2009). Alcohol consumption and the risks of adenocarcinoma and squamous cell carcinoma of the esophagus. *Gastroenterology, 136*(4), 1215-1224, e1211-1212.

52. Lee, C. H., Wu, D. C., Lee, J. M., Wu, I. C., Goan, Y. G., Kao, E. L., et al. (2007). Carcinogenetic impact of alcohol intake on squamous cell carcinoma risk of the oesophagus in relation to tobacco smoking. *European Journal of Cancer, 43*(7), 1188-1199.

53. Guo, Y. M., Wang, Q., Liu, Y. Z., Chen, H. M., Qi, Z., & Guo, Q. H. (2008). Genetic polymorphisms in cytochrome P4502E1, alcohol and aldehyde dehydrogenases and the risk of esophageal squamous cell carcinoma in Gansu Chinese males. *World J Gastroenterol, 14*(9), 1444-1449.

54. Sewram, V., Sitas, F., O'Connell, D., & Myers, J. (2016). Tobacco and alcohol as risk factors for oesophageal cancer in a high incidence area in South Africa. *Cancer Epidemiol, 41*, 113-121.

55. Yang, X., Chen, X., Zhuang, M., Yuan, Z., Nie, S., Lu, M., et al. (2017). Smoking and alcohol drinking in relation to the risk of esophageal squamous cell carcinoma: A population-based case-control study in China. *Scientific Reports, 7*(1), 17249.

56. Ishiguro, S., Sasazuki, S., Inoue, M., Kurahashi, N., Iwasaki, M., Tsugane, S., et al. (2009). Effect of alcohol consumption, cigarette smoking and flushing response on esophageal cancer risk: A population-based cohort study (JPHC study). *Cancer Letters, 275*(2), 240-246.

57. Allen, N. E., Beral, V., Casabonne, D., Kan, S. W., Reeves, G. K., Brown, A., et al. (2009). Moderate alcohol intake and cancer incidence in women. *Journal of the National Cancer Institute, 101*(5), 296-305.

58. Wang, Y., Ji, R., Wei, X., Gu, L., Chen, L., Rong, Y., et al. (2011). Esophageal squamous cell carcinoma and ALDH2 and ADH1B polymorphisms in Chinese females. *Asian Pacific Journal of Cancer Prevention, 12*(8), 2065-2068.

59. Zhang, Y., Wang, R., Miao, L., Zhu, L., Jiang, H., & Yuan, H. (2015). Different levels in alcohol and tobacco consumption in head and neck cancer patients from 1957 to 2013. *PLOS ONE,* 10(4), e0124045.

60. Maasland, D. H., van den Brandt, P. A., Kremer, B., Goldbohm, R. A., & Schouten, L. J. (2014). Alcohol consumption, cigarette smoking and the risk of subtypes of head-neck cancer: results from the Netherlands Cohort Study. *BMC Cancer, 14*, 187.

61. Werbrouck, J., De Ruyck, K., Duprez, F., Van Eijkeren, M., Rietzschel, E., Bekaert, S., et al. (2008). Single-nucleotide polymorphisms in DNA double-strand break repair genes: Association with head and neck cancer and interaction with tobacco use and alcohol consumption. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 656*(1), 74-81.

62. Freedman, N. D., Schatzkin, A., Leitzmann, M. F., Hollenbeck, A. R., & Abnet, C. C. (2007). Alcohol and head and neck cancer risk in a prospective study. *British Journal of Cancer, 96*(9), 1469-1474.

63. Huang, C.-C., Hsiao, J.-R., Lee, W.-T., Lee, Y.-C., Ou, C.-Y., Chang, C.-C., et al. (2017). Investigating the association between alcohol and risk of head and neck cancer in Taiwan. *Scientific Reports, 7*(1), 9701.

64. Islami, F., Tramacere, I., Rota, M., Bagnardi, V., Fedirko, V., Scotti, L., et al. (2010). Alcohol drinking and laryngeal cancer: overall and dose-risk relation--A systematic review and meta-analysis. *Oral Oncology, 46*(11), 802-810.

65. Lubin, J. H., Gaudet, M. M., Olshan, A. F., Kelsey, K., Boffetta, P., Brennan, P., et al. (2010). Body mass index, cigarette smoking, and alcohol consumption and cancers of the oral cavity, pharynx, and larynx: modeling odds ratios in pooled case-control data. *American Journal of Epidemiology, 171*(12), 1250-1261.

66. Lubin, J. H., Muscat, J., Gaudet, M. M., Olshan, A. F., Curado, M. P., Dal Maso, L., et al. (2011). An examination of male and female odds ratios by BMI, cigarette smoking, and alcohol consumption for cancers of the oral cavity, pharynx, and larynx in pooled data from 15 case-control studies. *Cancer Causes Control, 22*(9), 1217-1231.

67. Applebaum, K. M., Furniss, C. S., Zeka, A., Posner, M. R., Smith, J. F., Bryan, J., et al. (2007). Lack of association of alcohol and tobacco with HPV16-associated head and neck cancer. *J Natl Cancer Inst, 99*(23), 1801-1810.

68. Turati, F., Garavello, W., Tramacere, I., Bagnardi, V., Rota, M., Scotti, L., et al. (2010). A meta-analysis of alcohol drinking and oral and pharyngeal cancers. Part 2: Results by subsites. *Oral Oncology, 46*(10), 720-726.

69. De Stefani, E., Boffetta, P., Deneo-Pellegrini, H., Ronco, A. L., Acosta, G., Ferro, G., et al. (2007). The effect of smoking and drinking in oral and pharyngeal cancers: A case-control study in Uruguay. *Cancer Letters, 246*(1), 282-289.

70. Lu, Y., Sobue, T., Kitamura, T., Matsuse, R., Kitamura, Y., Matsuo, K., et al. (2018). Cigarette smoking, alcohol drinking, and oral cavity and pharyngeal cancer in the Japanese: a population-based cohort study in Japan. *Eur J Cancer Prev, 27*(2), 171-179.

71. Tramacere, I., Negri, E., Bagnardi, V., Garavello, W., Rota, M., Scotti, L., et al. (2010). A meta-analysis of alcohol drinking and oral and pharyngeal cancers. Part 1: overall results and dose-risk relation. *Oral Oncol, 46*(7), 497-503.

72. Turati, F., Garavello, W., Tramacere, I., Pelucchi, C., Galeone, C., Bagnardi, V., et al. (2012). A meta-analysis of alcohol drinking and oral and pharyngeal cancers: Results from subgroup analyses. *Alcohol and Alcoholism, 48*(1), 107-118.

73. Hippisley-Cox, J., & Coupland, C. (2015). Development and validation of risk prediction algorithms to estimate future risk of common cancers in men and women: Prospective cohort study. *BMJ Open, 5*(3), e007825.

74. Shanmugham, J. R., Zavras, A. I., Rosner, B. A., & Giovannucci, E. L. (2010). Alcohol-folate interactions in the risk of oral cancer in women: A prospective cohort study. *Cancer Epidemiology Biomarkers and Prevention, 19*(10), 2516-2524.

75. Friborg, J. T., Yuan, J. M., Wang, R., Koh, W. P., Lee, H. P., & Yu, M. C. (2007). A prospective study of tobacco and alcohol use as risk factors for pharyngeal carcinomas in Singapore Chinese. *Cancer, 109*(6), 1183-1191.

76. Matsuo, K., Rossi, M., Negri, E., Oze, I., Hosono, S., Ito, H., et al. (2012). Folate, alcohol, and aldehyde dehydrogenase 2 polymorphism and the risk of oral and pharyngeal cancer in Japanese. *European Journal of Cancer Prevention, 21*(2), 193 198.

77. Jayasekara, H., MacInnis, R. J., Hodge, A. M., Hopper, J. L., Giles, G. G., Room, R., et al. (2015). Lifetime alcohol consumption and upper aero-digestive tract cancer risk in the Melbourne Collaborative Cohort Study. *Cancer Causes Control, 26*(2), 297-301.

78. Thygesen, L. C., Keiding, N., Johansen, C., & Gronbaek, M. (2007). Changes in alcohol intake and risk of upper digestive tract cancer. *Acta Oncol, 46*(8), 1085-1089.

79. Klatsky, A. L., Li, Y., Nicole Tran, H., Baer, D., Udaltsova, N., Armstrong, M. A., et al. (2015). Alcohol intake, beverage choice, and cancer: A cohort study in a large kaiser permanente population. *The Permanente Journal, 19*(2), 28-34.

80. Everatt, R., Tamosiunas, A., Virviciute, D., Kuzmickiene, I., & Reklaitiene, R. (2013). Consumption of alcohol and risk of cancer among men: A 30 year cohort study in Lithuania. *European Journal of Epidemiology, 28*(5), 383-392.

81. Weikert, C., Dietrich, T., Boeing, H., Bergmann, M. M., Boutron-Ruault, M. C., Clavel-Chapelon, F., et al. (2009). Lifetime and baseline alcohol intake and risk of cancer of the upper aerodigestive tract in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *International Journal of Cancer, 125*(2), 406-412.

82. Schoenbach, V. J., & Rosamond, W. D. (2000). *Relating risk factors to health outcomes. In Understanding the Fundamentals of Epidemiology* Department of Epidemiology, School of Public Health, University of North Carolina at Chapel Hill: Chapel Hill, North Carolina. pp. 161-207.

83. Monson, R. (1990). *Occupational epidemiology, 2nd Edition.* Boca Raton, Florida: CRC Press Inc.

84. Craun, G. F., & Calderon, R. L. (2006). *How to intrepret epidemiological associations.* Retrieved from http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.481.3696&rep=rep1&type=pdf

85. Hopkins, G. W. (2002). *A scale of magnitudes for effect statistics.* Retrieved 28 May, 2021, from https://www.sportsci.org/resource/stats/effectmag.html

86. Ferguson, C. J. (2016). *An effect size primer: A guide for clinicians and researchers* (doi:10.1037/14805-020). Washington, DC, US: American Psychological Association