Alcohol consumption and types of cancer: a review
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Objective The purpose of this review study was to investigate the association between alcohol consumption and common cancers.

Methods This study was conducted in English by February 2019 to include studies reporting alcohol consumption related cancer risks through a search in data bases of the PubMed, Scopus and Web of Science. The search strategy included the keywords: “cancer”, “alcohol consumption or alcohol drinking or underage drinking”. Articles that looked at the relationship between each type of cancer and consumption of alcoholic beverages were entered in to the study and summarized in review.

Results Alcohol consumption is associated with a decreased risk of some types of cancers including: renal cell carcinoma and non-Hodgkin lymphoma. Alcohol could reduce the risk of non-Hodgkin's lymphoma. Also, alcohol is independent risk factor for oral and pharyngeal, laryngeal, esophagus, stomach, colorectal, breast and liver cancer. However, further studies are required to confirm the association between alcohol consumption and pancreas, lung, prostate, endometrium, brain tumor and bladder cancer risks.

Conclusion Given the role of excessive alcohol consumption in the occurrence of various types of cancers, there is a need for a comprehensive plan for alcohol abuse in the community.

Keywords cancer, alcohol consumption, underage drinking, alcohol drinking

Introduction
Alcohol is one of the most preventable causes of injury and mortality in the world and is one of the major risk factors for diseases.1–3 Across the world, adult alcohol consumption has been around 38% over the past 12 months.4 According to a study published in 2011, alcohol accounts for 4% of cancers in the UK.5 Most importantly, alcohol is a major risk factor for cancer. Evidence related to the role of alcohol in cancer related to the early 20th century.6 Epidemiological studies and numerous meta-analysis have supported this relationship.7 So, the International Agency for Research on Cancer (IARC) in 1988 categorized alcohol as a group one of carcinogens (the highest level in terms of risk).8 After the digestion and processing of alcohol in the body, it is changed to a kind of chemical called acetaldehyde, which is the group one carcinogen9 and prevents DNA repair, subsequently increases the risk of cancer.10 Several epidemiological studies have examined the relationship between alcohol drinking and the risk of developing cancer. Based on findings from epidemiological studies, alcohol consumption elevates the risk of various cancers such as breast and intestine11 and is one of the main risk factors for liver malignancies.12 In 2007, the IARC concluded that there is ample evidence that alcohol causes cancer of the mouth, throat, esophagus, larynx, and colorectal.13 In some malignancies, such as prostate cancer, this relationship is dose-dependent.14 In some other tumors, even taking a small amount of alcohol can increase the risk of cancer; as an illustration, it is associated with colon cancer for every two units of alcohol per day (each unit is 10 ml or 8 g) that risk of malignancy is expanded by 9%.15 However, the findings of previous studies suggested that alcohol could reduce the risk of non-Hodgkin’s lymphoma (NHL), thyroid cancer and renal cell carcinoma, but the findings of the studies were inconsistent.16–17

So far, a large prospective study has examined the relationship between alcohol consumption and cancer risk. However, due to the low number of cases and the existence of contradictory results, in most types of cancers no definitive findings have been reported and the epidemiological evidence that systematically addressed is limited. Therefore, this study aimed to investigate the relationship between alcohol consumption and common cancers of various organs of the body, taking into account possible confounding variables for each organ based on existing evidence and review of the literature.

Materials and Methods
This study was conducted in English by February 2019 to include epidemiological evidence from all available randomized control trials, case-control and cohort studies reporting alcohol consumption related cancer risks through a search in data bases of the PubMed, Scopus and Web of Science. The search strategy included the keywords: “cancer”,
“alcohol consumption or alcohol drinking or underage drinking”. In addition, the reference lists of relevant articles were manually searched to find any other potentially eligible articles. Articles about alcohol consumption amount and types of alcohol beverage are also included in the present study. We excluded reviews, commentaries, articles from overlapping samples, conference abstracts, and articles printed in languages other than English. Articles that looked at the relationship between each type of cancer and alcohol consumption were entered into the study and summarized in review.

Results

Study Characteristics

In the initial electronic literature search, 2236 articles were obtained from data bases and 43 articles were obtained using manual search. After removing duplicates using Endnote X7 (n = 1279), the title and abstract of the remaining 1000 articles were reviewed. After this stage, 166 articles were included in the study and 38 of these articles were removed because of scientific reasons and lack of eligible criteria or unrelated to our aim, in all, 128 full papers were reviewed. The most important cancers related to alcohol consumption are summarized in Table 1.

Types of Alcohol-related Cancers

Oral and Pharyngeal Cancer

The findings of a review study between 1988 and 2009 indicated that alcohol consumption is a risk factor for oral and throat cancers, and if combined with tobacco, this effect is multiplied and synergist. On the other hand, the findings revealed that even after controlling for smoking, alcohol consumption was still a risk factor for oral and thymus cancer. Meta-analysis study findings also showed that the risk of oral

Table 1. Relationship between alcohol consumption and cancer types

<table>
<thead>
<tr>
<th>Cancer types</th>
<th>Risk factor</th>
<th>Protective</th>
<th>Controversial</th>
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<tbody>
<tr>
<td>Oral and pharyngeal cancer</td>
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<tr>
<td>Laryngeal cancer</td>
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<td>Esophagus</td>
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<td>Stomach</td>
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<td>Colorectal</td>
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<td>Liver</td>
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<td>Pancreas</td>
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<td>Endometrium</td>
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<td>Renal cell carcinoma</td>
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<td>Brain tumor</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
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</table>

and throat cancer in alcoholics is dose-dependent. The findings of two meta-analysis studies of more than 30 studies with 14,000 cases showed a significant relationship between alcohol intake and the risk of oral and pharyngeal cancer (OPC), depending on the dose (relative risks, RRs, increasing from 1.29 for 10 g ethanol/day to 13.02 for 125 g ethanol/day). There is a higher RR for cancer of the throat compared with oral cancer, especially in heavy dose. It is estimated that 30% of all OPCs worldwide are attributed to alcohol consumption. Findings from several cohort studies in the United States, Europe and Asia reported increased risk of oral and throat cancer in alcohol users. Adami et al. in a cohort study in Sweden that the risk of oral and throat cancer in alcoholics was four times higher than that of non-alcoholic people (95% CI: 2.9–5.6). Tønnesen et al. also reported that the risk of oral and thoracic cancers in alcoholic men was 3.5 times higher than that of non-alcoholic men (95% CI: 3.0–4.3) and in alcoholic women was 15 times less than non-alcoholic women (95% CI: 10.8–26.0). In oral and thymus cancer the harmful effects of alcohol in both the intracellular and extracellular levels is observed. In this regard, carcinogens can affect the proliferative activity of the stem cells in basal layer. In patients with oral and thoracic cancer, there is a significant increase in salivary acetaldehyde concentration, which can be related to smoking and poor oral health. Acetaldehyde production can also be increased by alcohol intake through bacterial fluoride.

Laryngeal Cancer

The association between receiving alcoholic drinks and the spread of laryngeal cancer was first reported in the early 1900s through clinical reports and mortality statistics, and then confirmed by ecological studies. Several studies have confirmed the role of alcohol in laryngeal cancer. The findings of a meta-analysis study in North America, Europe, Japan, and Korea also showed that the risk of laryngeal cancer is significantly elevated if more than one unit of alcohol per day is received. This risk also increases in non-smokers. Drinking alcohol through direct contact or solvent action affects laryngeal cancer. It is estimated that between 50% and 70% of all esophageal cancer cases are attributed to alcohol in both sexes. Ethanol changes the motility and tone of the lower esophagus, the gastric reflux to the esophagus after esophagitis. This condition increases the risk of Barrett’s esophagus or intestinal metaplasia, dysplasia and adenocarcinoma. Chronic inflammation causes more esophageal mucosal damage to nitrosamines and polycyclic aromatic carbohydrates. These ingredients are present in alcoholic drinks. The relationship between alcohol consumption and the risk of esophageal cancer in various studies (prospective and case-control) has been reported worldwide. In the most recent evaluation by IARC, ethanol in alcoholic drinks has been grouped as one of the carcinogens for humans. In a second report published by the American Cancer Research Association, alcohol was identified as one of the escalating causes of esophageal cancer. Therefore, drinking alcohol is known as one of the risk factors for esophageal cancer.

The risk of esophageal malignancy is dose-dependent. When alcohol is consumed with smoking, the relative risk (RR) of the disease increases significantly. In case of 20 cigarettes per day with one to four units per day, RR increases by 1.5 times. By taking four to eight units per
day, RR increases to 12.3; and if you take more than eight units per day, RR will increase 44.4-fold.\textsuperscript{45} Given that most alcoholics, addicts to tobacco, the synergistic effects of this compound are very important.\textsuperscript{33} The findings of a meta-analysis study showed that alcohol consumption could increase the risk of gastric cancer with odds ratio (OR) of 39/1 (95% CI: 1.20–1.61), even in the case of low alcohol consumption.\textsuperscript{46} Findings from several recent studies have reported that drinking alcohol can increase the risk of gastric cancer, and its main mechanism is probably related to primary metabolites and stalled individuals, which has a topical toxic effect and soars the risk of gastric cancer.

**Stomach**

The findings of a meta-analysis study revealed that alcohol consumption even in the case of low dose could increase the risk of gastric cancer with odds ratio (OR) of 39/1 (95% CI: 1.20–1.61).\textsuperscript{46} Findings from several recent studies have reported that drinking alcohol can raise the risk of gastric cancer, and its main mechanism is probably related to primary metabolites and acetaldehyde, which has a topical toxic effect and increases the risk of gastric cancer.\textsuperscript{47,48} The relationship between drinking alcohol and the risk of gastric cancer is biologically plausible; ethanol is one of the soluble fats and may cause damage to the stomach mucosa. Acetaldehyde metabolite may have a topical toxic effect that may be related to gastric cancer.\textsuperscript{49} Ethanol pathogenesis is associated with gastric mucosal injury with impairment in the balance of gastric mucus defense and external invasion.\textsuperscript{50,51}

**Colorectal**

Several epidemiological studies have shown that increasing alcohol consumption is one of the risk factors for colorectal cancer. The findings of the review and meta-analysis studies\textsuperscript{52–54} and several meta-analysis surveys on case and control cohort studies indicate that alcohol intake is associated with an elevation in colorectal cancer.\textsuperscript{55–56} The findings of several meta-analysis studies showed a positive relationship between alcohol consumption and colorectal cancer, and this relationship is dose-dependent.\textsuperscript{43,53,54} Several studies have also found that with a chronic consumption of about 50 g per day of alcohol, the relative risk of colon cancer was 10–20%.\textsuperscript{43,55} The findings of Dashi et al.\textsuperscript{60} revealed that alcohol consumption, especially more than 20 g per day of ethanol, is associated with colon cancer.

**Liver**

Several studies in various countries have examined the relationship between alcohol consumption and the risk of developing liver cancer (also called HCC) and have confirmed this relationship.\textsuperscript{56–58} Based on systematic and meta-analytic findings, the relative risk of liver cancer for low levels, hazardous and harmful of alcohol consumption, as compared with those who have never consumed alcohol, is respectively 1.45%, 0.33%, and 3.60% (low consumption = 0–19.90 g for females and 039.99 g for males, pure alcohol per day), hazardous consumption = (females 20–39.99 g, males 40–59.99 g), harmful consumption = (females 40+ g, males 60+ g).\textsuperscript{54}

The main role of gastric cancer following alcohol usage is acetaldehyde produced by bacterial flora.\textsuperscript{59} The findings from a meta-analysis study on 19 cohort studies estimated an increase of 16% in liver cancer among those who consumed at least three units of alcohol daily, compared with non-infected individuals.\textsuperscript{66} In fact, in alcoholic people, prolonged and severe alcohol consumption leads to alcoholic cirrhosis, which is a pathogenic stage in liver carcinogenesis.\textsuperscript{66} Along with the carcinogenicity of acetaldehyde, which is the first metabolite of alcohol, other biological mechanisms also explain the effect of alcohol consumption on hepatocarcinogenesis. These include chronic inflammation, the consequences of increased oxidative stress, the induction of cytochrome P-450 and lipid peroxidation and DNA damage, diminished antioxidant defense and DNA repair, reduction of hepatic retinoic acid, excess iron loading, and immune deficiency.\textsuperscript{67}

**Pancreas**

Findings from a prospective study in the United States revealed that alcohol consumption, in particular consumption liquor, at least three units per day increased pancreatic cancer independent of smoking.\textsuperscript{68} Although the findings of some cohort studies\textsuperscript{62,69,70} and three meta-analysis studies\textsuperscript{71–73} showed that there is a positive and significant relationship between alcohol consumption and the risk of pancreatic cancer, other cohort studies\textsuperscript{74,75} did not reveal this relationship. Heavy alcohol consumption causes acute and chronic pancreatitis, but has never been associated with liver cancer.\textsuperscript{69} Findings from a meta-analysis study in 2016 demonstrated that low to moderate alcohol intake did not significantly correlate with the risk of pancreatic cancer, while receiving high amounts of alcohol as well as alcohol drinks increase the risk of pancreatic cancer.\textsuperscript{76} Several biological mechanisms have been proposed to explain the increased risk of pancreatic cancer following heavy alcohol use. Alcohol can cause to inflammatory responses that would lead to overt chronic pancreatitis or diabetes mellitus by inducing mitogenic stimulation.\textsuperscript{77,78} Alcohol consumption also causes asymptomat chronic pancreatitis, which eventually results in pancreatic cancer,\textsuperscript{79–81} although the prevalence of pancreatitis history in the total population of patients with pancreatic cancer is very low.

**Lung**

An elevated risk of lung cancer in the general population has been reported in numerous cohort studies.\textsuperscript{82} The findings of the study, Korte et al.,\textsuperscript{83} revealed that for doses greater than five units per day, the relative risk was between 1.53 and 1.88. There is a positive correlation between alcohol consumption and lung cancer in several reported studies.\textsuperscript{83–85} However, the protective effect of low to moderate alcohol in reducing the incidence of lung cancer has been reported in several studies.\textsuperscript{81–83,86} Rohrmann et al.,\textsuperscript{87} found that the anti-inflammatory, antioxidant, and anti-mutagenic effects of intermediate ethanol produce protective effects. Although this protective effect is only specific for lung cancer and is not observed for other neoplasms.\textsuperscript{88}

**Prostate**

Over the past few decades, a number of overviews and meta-analysis have examined the relationship between prostate cancer and alcohol consumption.\textsuperscript{89–92} According to the findings of Longnecker\textsuperscript{93} and Morton et al.,\textsuperscript{94} there was no association between alcohol consumption and prostate cancer. Breslow and Weed\textsuperscript{95} reviewed 32 studies and reported only six studies that found association between alcohol consumption and prostate cancer.
The findings of Dennis’s meta-analysis on six cohorts and 27 cases-control did not confirm this relationship. Dagene et al. reviewed nine prostate cancer and alcohol studies, and found that in six studies, such a relationship was not confirmed; in two studies, the risk was increased and decreased in one study. The findings of the meta-analysis showed that the small, but significant risk of prostate cancer in men who consumed more than 50 g of alcohol per day was observed at a higher risk for men who consumed more than 100 g per day of alcohol, but there was no significant dose–response relation. This study first considered potential confounders, between the study variables and the moderating effects of tobacco use. Findings from Middleton Fillmore et al. revealed that there was a significant relationship between heavy alcohol consumption after controlling the effects of age, study population, design, and study variables. Rota et al. obtained a significantly higher RR of prostate cancer for each drinking alcohol, low (less than or equal to one drink per day) and moderate (greater than one and less than four drink per day) versus abstaining or occasionally alcohol consumption, but the analysis did not show a meaningful relationship with heavy drinking (greater than or equal to four drinks per day). Overall, the findings of recent meta-analysis and review studies showed a positive relationship, but none of the studies sufficiently controlled the effects of confounding variables, including incorrect categorization of former alcoholics and occasional alcoholics.

Bladder

The role of alcoholic drinks in bladder carcinogenesis has been studied in several epidemiologic studies. According to Framingham Heart Study, there was no significant relationship between alcohol consumption and bladder cancer. However, the findings of a meta-analysis study of urinary cancers showed a slight increase of 1.3% for current alcoholic-drinkers compared with non-alcoholic ones. The findings of specific drinks analyze also revealed uncertain results. Some studies have depicted a higher risk for liquor drinks and showed an inverse relationship to beer drink. The average consumption of alcoholic drinks can prevent from coronary artery disease, diabetes mellitus, renal cell carcinoma, prostate cancer, and NHL. May be due to mechanisms such as improves immune response and increases insulin sensitivity. One of the possible mechanisms of the protective effect of alcohol consumption in bladder cancer is the urogenous contact hypothesis. Meta-analysis study findings showed that drinking beer and wine reduces the risk of bladder cancer. Other mechanisms include anti-inflammatory properties of alcohol and anticholinergic effects of polyphenols in red wine and beer.

Despite the publication of numerous studies in this regard, the role of definitive alcohol on bladder cancer, the effect of various types of alcoholic drinks, patterns of drinking and the role of other factors such as smoking and the frequency of urination for bladder cancer have not yet been proven.

Breast

About 4–5% of all breast cancers are associated with alcohol consumption, and 60% of alcohol-related tumors in women are breast cancer. Several epidemiological studies have shown a positive relationship between alcohol consumption and breast cancer. This risk occurs even with the average consumption of alcohol. For increasing the amount of ethanol consumed daily by 10 g, RR growth by 10%, Kwan et al. found that the risk of recurrence of breast cancer significantly increased in women who had been breast cancer before (especially after menstruation), taking three to four times per week. Systematic study findings showed that alcohol consumption could extend the risk of breast cancer, especially in postmenopausal women. The pathogenic mechanism of the disease was certainly due to oxidative stress induced by acetaldehyde and nutritional changes (folate, Vitamin B6 and B12), but the main cause of it is interaction with estrogen. It is known that estrogen is metabolized by ADH and therefore acts in competition with ethanol. Especially high concentrations of acetaldehyde are associated with high levels of estrogen during the menstrual cycle.

Endometrium

A cohort study found that alcohol consumption of two units or more could increase the risk of endometrial cancer in women after menstruation. However, there was no such relationship in people who consume less than one drink or one to two drinks per day. The role of unopposed estrogens in endometrial cancer etiology has been confirmed. Daily use of alcohol is associated with high levels of circulating estrogen in postmenopausal women. Alcohol consumption also raise the estrogen levels in postmenopausal women with estrogen replacement therapy. Therefore, it is likely that women drinking alcoholic drinks are at enhanced risk for endometrial cancer. However, the findings of a prospective study between the 1980s and 2010 on 6807 women who participated in the study found that drinking <5 g daily (about half a day) would reduce the risk of endometrial cancer by 22% (multivariable RR = 0.78; 95% CI: 0.66–0.94). Getting more alcohol does not; however, produce a protective effect against endometrial cancer [multivariable RR for 5–14.9 g (one drink), 15–29.9 g (two drinks), or ≥30 g (two drinks)] versus 0 g per day were 0.88, 0.83, and 0.78 (95% CI: 0.49–1.25), respectively.

Renal Colon Carcinoma

The implications of a meta-analysis study on 15 case-control studies revealed an inverse relationship between alcohol consumption and renal cell carcinoma (OR 0.67, 95% CI: 0.62–0.73). The dose–response meta-analysis manifested that an increase in alcohol consumption of 12 g of ethanol per day was associated with a significant reduction of 5% risk of renal cell carcinoma.

Other study findings from 12 prospective studies also indicated an inverse relationship between alcohol consumption and renal cell carcinoma.

The findings of another meta-analysis study in 2012 showed an inverse relationship between alcohol consumption and renal cell carcinoma in both genders. It was also observed that drinking one drink per day has protective effects, but drinking too much does not have protective effects.

Brain tumor

Alcohol is able to cross the cerebrospinal fluid and is therefore a risk factor for brain cancer. Ethanol is oxidized to acetaldehyde which is a genotoxic metabolite in the brain. Alcohol consumption is in relation to the risk of brain cancer.
in adults has been studied in a number of studies from the early 1970s and usually inconsistent findings revealed in both general use and for various types of alcoholic drinks. For instance, the findings of a cohort study on glioblastoma, which is a type of brain cancer with a low survival rate, showed that there is a dose risk with increasing alcohol consumption for this cancer. This finding was similar for beer and wine. On the other hand, according to a study of 908 cases of brain cancer, there was no correlation between alcohol consumption and brain cancer, and a relative risk of 1.17 reported for taking more than 15 drinks per week compared with drinking occasionally (for example less than two drinks per week). Systematic and meta-analytical findings from 19 studies involving 4200 cases of brain cancer suggest that there is no significant relationship between alcohol consumption and adult brain cancer, although further studies are needed to investigate the potential effects of high doses of alcohol.

Findings of another meta-analysis study on 19 observational studies showed that there is no significant relationship between alcohol consumption and the risk of glioma.

**Non-Hodgkin’s Lymphoma**

According to The Monograph 96 of the IARC, published in 2007, the risk of NHL in alcohol users was lower than those who did not consume alcohol. Similar results were obtained by the next IARC. In addition, the World Cancer Research Fund (WCRF) reported that there was an inverse relationship between drinking alcohol and NHL. The results of a meta-analysis study manifested that the risk of NHL among alcohol users is 15% less than those who do not consumed alcohol.

**Conclusion**

The purpose of this review study was to investigate the association between alcohol consumption and the incidence of common cancers. Based on the results of studies, alcohol is associated with a reduction in the risk of renal cell carcinoma and NHL. Conversely, alcohol is a risk factor for oral and thoracic cancers, larynx, esophagus, stomach, colorectal, liver and breast. However, further studies are needed to confirm definitively the association between alcohol and the development of pancreatic, lung, prostate, bladder, endometrial and brain tumors. Given the role of excessive alcohol consumption in the occurrence of various types of cancers, there is a necessity for planning a comprehensive project for alcohol abuse in the community.

**Conflicts of Interest**

None.

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