RESEARCH ARTICLE

Alcohol Consumption and Risk of Cancer: a Systematic Literature Review

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Abstract

This study aimed to discuss the consumption of alcohol as a risk factor for major cancers. We performed a search in the PubMed database, using the following inclusion criteria: meta-analysis published in English in the last 10 years that addressed the relationship between alcohol and the risk of developing cancer. The results indicate that moderate to heavy consumption of alcohol increases the risk of developing cancer of the oral cavity and pharynx, esophagus, stomach, larynx, colorectum, central nervous system, pancreas, breast and prostate. This review did not find any association between alcohol consumption and an increased risk of cancers of the lung, bladder, endometrium and ovary. It was also observed that alcohol consumption may be inversely related to thyroid cancer. Our systematic review has confirmed consumption of alcohol as a risk factor for the development of several types of cancer.

Keywords: Alcoholic beverages - neoplasms - risk and meta-analysis

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Introduction

Cancer is a chronic disease that has become, worldwide, an important public health problem. By the year 2030 20.3 million incident cases and 13.2 million deaths from the disease are expected (Ferlay et al., 2010). Currently in Brazil, cancer ranks high as a cause of death, being second only to diseases of the cardiovascular system (Datasus, 2013).

Most risk factors for developing cancer are considered modifiable, highlighting a sedentary lifestyle, unhealthy diet, smoking and alcoholism. When the individual is exposed to more than one of these factors, the risk of developing the disease increases. Thus, primary prevention measures are needed, focusing mainly on modifiable risk factors (World Cancer Research Foundation and American Institute for Cancer Research, 2007; Bray et al., 2012).

Among the risk factors for cancer that can be modified, tobacco and alcohol use are noteworthy. Alcohol is one of the few psychoactive drugs that are encouraged and accepted by society. Its consumption is increasing worldwide, especially in developing countries. According to Cancer Research UK (2012), there is evidence that, when compared to individuals who do not consume alcohol and do not use tobacco, those who drink and smoke have 50 times more chance of developing some form of cancer. In the UK, alcohol is responsible, every year, for 4% of cancers. Deaths that are related to the consumption of alcoholic beverages amount to 1,804,000 per year or 3.2% of all deaths in the world. In addition, when ingested in excess, alcohol may also be responsible for the development of heart disease, hypertension, stroke, pancreatitis and gastric ulcer (Boffetta and Hashibe, 2006). According to the World Health Organization (WHO, 2002), the number of deaths and limitations caused by alcohol exceeds those caused by tobacco use.

The World Cancer Research Foundation and the American Institute for Cancer Research (2007) report that there is convincing evidence linking the consumption of alcoholic beverages to cancers of the mouth, pharynx, larynx, esophagus, breast and bowel, the latter being only in men. In addition, there is a likely relationship between the consumption of alcoholic beverages and an increased risk of colon cancer and liver cancer in women.

The preparation of this systemic review study is based on these considerations, with the aim of discussing the association between alcohol consumption and the main types of cancer. The expected contribution is the disclosure of consolidated information about this possible risk ratio, contributing to the establishment of strategies to prevent the occurrence of cancer.

Materials and Methods

We performed a systematic literature review of meta-analysis that was conducted to evaluate the association between alcohol consumption and cancer.

The publications were identified in the PubMed bibliographic database, and used the following keywords: cancer, alcohol and meta-analysis. The first two were used as words that appeared on the title and the latter as the type of study chosen. We chose to establish a period of 10 years

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of publication, in order to analyze the most recent studies, which generated a result of 32 papers. The selection of cancer types was based on the most frequent topographies in the country presented by Cancer incidence estimates in Brazil (2013), as follows: oral cavity, esophagus, stomach, colon and rectum, larynx, trachea, bronchus and lung, female breast, cervical, endometrial, ovarian cancers, prostate, bladder, central nervous system (CNS), leukemia, non-Hodgkin lymphoma and skin malignancies. Other cancers with lower incidence such as pharynx, pancreas and thyroid were later included in the selection for the important causal relationship with alcohol.

Publications were selected based on their titles and abstracts. We used the following criteria for inclusion: studies that addressed the relationship between alcohol consumption and the risk of cancer using meta-analysis as a study type, published in English. We chose to exclude publications that dealt exclusively with biochemical, molecular and genetic aspects, as well as duplicate articles.

Initially 14 articles were selected (Hamajima et al., 2002; Key et al., 2006; Moskal et al., 2007; Fillmore et al., 2009; Friberg et al., 2010; Islami et al., 2010; Mao et al., 2010; Tramacere et al., 2010; Turati et al., 2010; Uehara and Kiyohara, 2010; Bagnardi et al., 2011; Ferdiko et al., 2011; Sun et al., 2011; Tramacere et al., 2012). No publications were found regarding thyroid cancer. For this topography, pooled analysis articles were included (Mack et al., 2003; Kitahara et al., 2012). Other references (Tramacere et al., 2010; Turati et al., 2010; Pelucchi et al., 2011; Tramacere et al., 2011; Bagnardi et al., 2012; Galeone et al., 2012; Lubin et al., 2012; Rota et al., 2012; Seitz et al., 2012) were included to give this review a wider scope, yielding a total of 25 articles (Figure 1). Due to the lack of publications, studies on the association between the consumption of alcoholic beverages and leukemia, non-Hodgkin lymphoma, cancer of the cervix and cancer of the skin were not included.

From the reading of the 25 selected articles, we created a table with the following: title, year, author, type of cancer, the inclusion period of the study, number of articles, number of cases, risk measure - including the confidence interval (CI) - and conclusion. For the presentation of the association found in the studies, adjusted analysis was considered, and in its absence, crude analysis. An adaptation of the criteria proposed by Rosenthal (1996), was used to synthesize the magnitude of risk according to the odds ratios (OR) or relative risk (RR); results were presented graphically as: no risk (OR or RR<1): -; low risk (OR or RR=1-1.5): +; moderate risk (OR or RR=1.5-2.5): ++; high risk (OR or RR=2.5-4): +++; and very high risk (OR and RR>4): ++++.

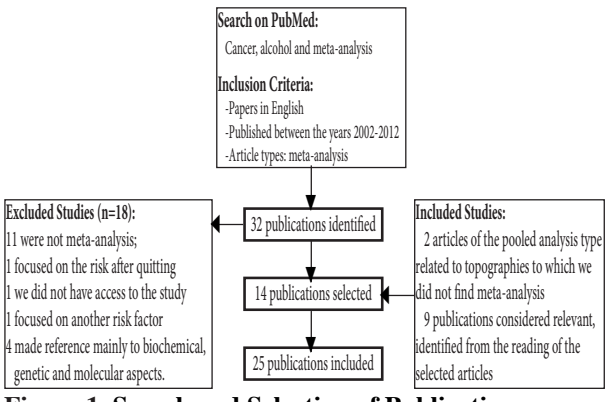

Figure 1. Search and Selection of Publications

Results

Results were presented considering the main aspects of the articles included in this review, in accordance with the location of the cancer, as follows: digestive organs (stomach, esophagus, pancreas, colon and rectum), respiratory (lung, larynx, oral cavity and pharynx), breast and female genital organs (breast, endometrium and ovary), other cancers (bladder, CNS, thyroid and prostate).

Alcohol consumption and the risk of cancer in organs of the digestive system

Three meta-analysis were found (Table 1) that addressed the ingestion of alcoholic beverages and the risk of esophageal cancer (Tramacere et al., 2011; Bagnardi et al., 2012; Lubin et al., 2012). A meta-analysis (Lubin et al., 2012) evaluated the association with esophageal cancer, stratified into the following types: adenocarcinoma of the esophagus, gastroesophageal junction adenocarcinoma and squamous cell carcinoma of the esophagus. After checking the effect of tobacco, increased risk with dose-response for squamous cells carcinoma of the esophagus from the consumption of 3 doses/day (RR 2.15, 95%CI 1.3-3.6) was found. A study including 20 reports of cancer of the esophagus and gastric cardia, after control of confounding by tobacco use, found no significant association (RR 0.94, 95%CI 0.83-1.06) (Tramacere et al., 2011). Assessing the risk of squamous cell cancer of the esophagus due to the light consumption of alcoholic beverages (up to 1dose/day), without adjusting for tobacco, according to the gender and geographical area, an increased risk among men (RR 1.46, 95%CI 1.19-1.80) and in the Asian population (RR 1.49, 95%CI 1.12-1.98) was observed (Bagnardi et al., 2012).

Looking at alcohol consumption and the risk of gastric cancer, a meta-analysis examined the relationship between moderate and excessive intake, anatomical location and dose response from 59 studies (Table 1). In the crude analysis there was an increased risk of cancer among individuals who consumed alcohol in any amount (RR 1.07, 95%CI 1.01-1.13), with this risk becoming higher among those whose consumption was done in excess (>50g/day) (RR 1.14, 95%CI 1.08-1.21) and non-Asians who consumed ≥4 doses/day (RR 1.39, 95%CI 1.14-1.69). When adjusted for smoking, consumption of alcoholic beverages was statistically associated with the risk of gastric cancer (RR 1.12, 95%CI 1.01-1.24) (Tramacere et al., 2012).

Three publications were identifed (Table 1) that addressed the relation between alcohol intake and the risk of developing colorectal cancer (Moskal et al., 2007; Ferdiko et al., 2011; Bagnardi et al., 2012). One meta-analysis pointed to the increased risk of cancer among alcohol users (RR 1.12, 95%CI 1.06-1.19), with dose-response effect for drinking ≥2 servings/day (RR 1.21, 95%CI 1.13-1.28) for both men (RR 1.24, 95%CI 1.13-

Table 1. Summary of Meta-analysis that Evaluated Alcohol Consumption and the Risk of Developing Cancer in Organs of the Digestive System

Author, Year	Inclusion period	No. of articles	No. of people	Risk analysis (95% CI)		
Esophagus cancer						
Lubin et al., 2011[a]	NR	12	5,427	**Dose - response (dose/day)**		
				Esophagus cancer 1-2: RR=1.09 (0.8-1.4) 3-4: RR=1.27 (0.8-1.9) 5-9: RR=1.56 (0.9-2.7) ≥10: RR= 1.87 (0.9-3.7)	**Gastroesophageal junction** 1-2: RR=0.88 (0.7-1.1) 3-4: RR=1.24 (0.8-1.8) 5-9: RR=1.90 (1.1-3.2) ≥10: RR=1.74 (0.9-3.4)	**Squamous cells carcinoma** 1-2: RR=1.32 (0.9-1.9) 3-4 : RR=2.15 (1.3-3.6) 5-9: RR=2.74 (1.5-5.2) ≥10: RR=4.12 (2.0-8.4)
Tramacere et al., 2012[a]	Up to 2010	24	5,500	**Consumption: yes×no** **Esophagus and gastric cardia** RR=0.94 (0.83-1.06)		
Bagnardi et al., 2012[b]	Up to 2010	27	1,841	**Consumption: ≤1dose/day** **Squamous cells carcinoma** RR=1.30 (1.09-1.56)	**By gender** Male: RR=1.46 (1.19-1.80) Female: RR=1.28 (0.84-1.96)	**By geographical area** NA: RR=1.21 (0.96-1.54) Europe: RR=1.05 (0.79-1.38) Asia: RR=1.49 (1.12-1.98)
Stomach cancer						
Tramacere et al., 2012[a]	Up to 2010	59	34,557	**Consumption: yes×no** RR=1.12 (1.01-1.24)		
Colorectal cancer						
Moskal et al., 2006[b]	1990-2005	16	6,300	**Consumption: high×low** Colorectal: RR=1.34 (0.92-1.96) Colon: RR=1.50 (1.25-1.79) Rectum: RR=1.63 (1.35-1.97)	**By gender (>100g/week)** Colon Male: RR=1.18 (1.13-1.24) Female: RR=1.14 (1.00-1.30)	 Rectum Male: RR=1.19 (1.12-1.26) Female: RR=1.16 (0.94-1.44)
Ferdiko et al., 2011[b]	1986-2010	61	27,226	**Consumption: yes×no** RR=1.12 (1.06-1.19)	**Dose - response** (dose/day) <1: RR=1.00 (0.95-1.05) 2-3: RR=1.21 (1.13-1.28) ≥4: RR=1.52 (1.27-1.81)	**By gender** Women: RR=1.08 (1.03-1.13) Men: RR=1.24 (1.13-1.37)
Bagnardi et al., 2012[b]	Up to 2010	54	12,013	**Consumption:** **up to 1 dose/day** RR=0.99 (0.95-1.14)	**By geographical area** NA: RR=0.97 (0.91-1.04) Europe: RR=1.01 (0.95-1.07) Asia: RR=1.03 (0.90-1.19)	**By gender** Male: RR=1.05 (0.95-1.16) Female: RR=0.93 (0.87-0.99)
Pancreas cancer						
Tramacere et al., 2010[a]	Up to 2009	32	13,457	**Consumption: ≥3 doses/day** RR=1.23 (1.12-1.35)		

*RR=relative risk; CI=confidence interval; NR=not reported; NA= North America; [a]Adjusted for tobacco; [b]Unadjusted

1.37) and women (RR 1.08, 95%CI 1.03-1.13) (Ferdiko et al., 2011). Another publication identified a statistically significant association between alcohol consumption and the risk of colon cancer (RR 1.50, 95%CI 1.25-1.79) and rectum cancer (RR 1.63, 95%CI 1.35-1.97), and when analyzing the dose-response it was observed that, for an increase of 100g of alcohol consumed per week among men, there is an 18% increase in the risk of colon cancer (RR 1.18, 95%CI 1.13-1.24) and a 19% increase in the risk of rectal cancer (RR 1.19, 95%CI 1.12-1.26). This effect was not observed among women (Moskal et al., 2007). A meta-analysis studying colorectal cancer found no statistically significant association between this cancer and a mild intake of alcoholic beverages, regardless of stratification for gender and where the study was conducted (Bagnardi et al., 2012).

The association between alcohol consumption and cancer of the pancreas was studied by a meta-analysis defined as heavy alcohol intake of 3 or more doses per day (Table 1). An increased risk of 23% was found after controlling tobacco effect (RR 1.23, 95%CI 1.12-1.35) (Tramacere et al., 2010).

Alcohol consumption and the risk of cancer of the respiratory organs

Two meta-analyses were identified (Table 2) that evaluated alcohol consumption as being a risk of lung cancer (Uehara and Kiyohara, 2010; Bagnardi et al., 2011). A meta-analysis examining individuals who had never used tobacco found association and dose-response between alcohol consumption and the risk of this cancer (RR 1.21, 95%CI 0.95-1.55) (Bagnardi et al., 2011). In another study, analyzing the risk adjusted for tobacco, the statistical association between alcohol consumption and lung cancer was also not found to be significant (RR 1.00, 95%CI 0.73-1.26) (Uehara and Kiyohara, 2010).

The risk between alcohol consumption and cancer of the larynx was evaluated in two meta-analyses (Islami et al., 2010; Bagnardi et al., 2012) (Table 2). A meta-analysis that adjusted for the effects of smoking, gender and age, reported a 50% higher risk of laryngeal cancer among those who consumed 1-4 doses/day (RR 1.50, 95%CI 1.23-1.83) and 2.46 times higher among those with a consumption of more than 4 doses/day (RR 2.46, 95%CI 1.88-3.22) (Islami et al., 2010). A meta-analysis examining the risk of laryngeal cancer in relation to the consumption of alcohol (up to 1 dose/day) found no statistically significant association (PR 0.90, 95%CI 0.73-1.10), and the same occurred for geographical area and gender (Bagnardi et al., 2012).

Three meta-analyses (Table 2) analyzing the relationship between alcohol consumption and the risk of cancer of the oral cavity and pharynx were identified (Tramacere et al., 2010; Turati et al., 2010; Bagnardi et al., 2012). It was observed that, without adjustment for smoking, alcohol intake, at any intensity, increases the risk

Table 2. Summary of Meta-analyses that Evaluated Alcohol Consumption and the Risk of Developing Cancer of the Respiratory Organs

Author, Year	Inclusion period	No. of articles	No. of people	Risk analysis (95% CI)		
Lung cancer						
Uehara e Kiyohara, 2010[a]	Up to 2010	7	4,733	**Consumption: high×low** RR=1.00 (0.73-1.26)		
Bagnard et al., 2011[c]	1960-2010	10	1,913	**Consumption: yes×no** RR=1.21 (0.95-1.55)	**Response-dose** 10g/day: RR= 1.01 (0.92-1.10)	
Larynx cancer						
Islami et al., 2010[d]	Up to 2010	40	9,351	**Dose/day (**dose/day**)** ≤1: RR=0.88 (0.70-1.12) 1-4: RR=1.50 (1.23-1.83) ≥4: RR=2.46 (1.88-3.22)		
Bagnardi et al., 2012[b]	Up to 2010	13	846	**Consumption:** **up to 1 dose/day** RR=0.90 (0.73-1.10)	**By geographical area** NA: RR=0.89 (0.66-1.20) Europe: RR=0.84 (0.43-1.62) Asia: RR=0.91 (0.60-1.37)	**By gender** Male: RR=0.89 (0.67-1.16) Female: RR=0.93 (0.71-1.22)
Oral cavity and pharynx cancer						
Tramacere et al., 2010[b]	Up to 2009	45	17,085	**Consumption: ≤1dose/day** RR=1.21 (1.10-1.33)	**Response dose** (g/day) 10: RR=1.29 (1.25-1.32) 25: RR=1.85 (1.74-1.96) 50: RR=3.24 (2.89-3.64)	(g/day) 75: RR=5.42 (4.58-6.40) 100: RR=8.61 (6.91-10.73) 125: RR=13.02 (9.87-17.18)
Turati et al., 2010[c]	Up to 2009	45	14,611	**Consumption: ≤1dose/day** Oral cavity RR=1.16 (0.96-1.41) Pharynx RR=1.11 (0.86-1.43)		
Bagnardi et al., 2012[b]	Up to 2010	23	2,036	**Consumption: ≤1dose/day** RR=1.17 (1.06-1.29)	**By geographical area** NA: RR=1.15 (1.01-1.30) Europe: RR=1.44 (0.87-2.37) Asia: RR=1.34 (1.06-1.68)	**By gender** Male: RR=1.20 (1.06-1.36) Female: RR=1.09 (0.89-1.34)

*RR=relative risk; CI=confidence interval; NR=not reported; NA= North America; [a]Adjusted for tobacco; [b]Unadjusted; [c]Study in nonsmokers; [d]Analysis adjusted for smoking, age and sex

Table 3. Summary of Meta-analyses that Evaluated Alcohol Consumption and the Risk of Cancer Development in the Breast and Female Genital Organs

Author, Year	Inclusion period	No. of articles	No. of people	Risk analysis (95% CI)		
Breast cancer						
Hamajima et al., 2002[a]	NR	65	124,941	**Response-dose** < 5g/day: RR=1.01 (p=0.020) 5-14g/day: RR=1.01 (p=0.023) 15-24g/day: RR=1.19 (p=0.048)	25-34g/day: RR=1.22 (p=0.056) 35-44g/day: RR=1.18 (p=0.093) ≥ 45g/day: RR=1.49 (p=0.110)	
Key et al., 2006[c]	1966 to 2003	98	20,000	**Consumption: yes×no** All studies: OR=1.11 (1.06-1.17) Score studies 3: OR=1.22 (1.09-1.37)	**Type of beverage** Beer: RR=1.16 (1.04-1.29) Wine: RR=1.14 (1.05-1.24) Spirits: RR=1.14 (1.06-1.23)	**Response-dose (**ethanol/day**)** 10g : RR=1.10 (1.05-1.15)
Seitz et al., 2011[d]	Up to 2011	113	122,091	**Consumption: ≤1 dose/day** RR=1.03 (1.00-1.07)		
Bagnardi et al., 2012[b]	Up to 2010	85	92,230	**Consumption: ≤1 dose/day** RR=1.05 (1.02-1.08)	**By geographical area** NA: RR=1.06 (1.02-1.09) Europe: RR=1.05 (0.99-1.12) Asia: RR=1.01 (0.89-1.14)	
Endometrial cancer						
Friberg et al., 2010[c]	Up to 2010	7	6,086	**Consumption: yes×no** RR=1.33 (0.92-1.91)		
Turati et al., 2010[b]	Up to 2009	27	13,120	**Response dose (**doses/week**)** ≤7: OR=1.03 (0.76-1.41) 8-14: OR=1.27 (0.86-1.87) ≥15: OR=1.19 (0.80-1.77)		
Sun et al., 2011[a]	Up to 2010	20	7,638	**Consumption: yes×no** RR=0.88 (0.64-1.21)	**Nonsmokers** RR=0.86 (0.62-1.20)	
Ovary cancer						
Rota et al., 2012[b]	Up to 2011	27	16,554	**Consumption: yes×no** RR=1.00 (0.95-1.05)	**Dose-response** ≤1 dose: RR=0.97 (0.92-1.02) 2 doses: RR=1.03 (0.96-1.11) ≥3 doses: RR=1.09 (0.80-1.50)	

*RR=relative risk; CI=confidence interval; NR=not reported; NA=North America; [a]Adjusted for tobacco; [b]Unadjusted; [c]Adjusted for smoking, family history of breast cancer, socioeconomic status, use of oral contraceptives/hormone replacement therapy, age at menarche, age at menopause, age at first birth and parity; [d]Analysis adjusted for age

of developing cancer of the oral cavity and pharynx: 20% higher for a consumption of 10g/day (RR 1.29, 95%CI 1.25-1.32) to up to 13 times higher for a consumption of 125g/day (RR 13.02, 95%CI 9.87-17.18) (Tramacere et al., 2010). In another meta-analysis, when controlling for the effect of smoking, gender and age, authors found no statistically significant association between the consumption of alcoholic beverages (>1dose/day) and

oral cavity cancer (RR 1.16, 95%CI 0.96-1.41) or cancer of the pharynx (RR 1.11, 95%CI 0.86-1.43) (Turati et al., 2010). In unadjusted analyses for tobacco, a meta-analysis reported an increased risk of cancer of the oral cavity and pharynx in individuals who consume up to 1dose/day (RR 1.17, 95%CI 1.06-1.29) in men (RR 1.20, 95%CI 1.06-1.36) and in studies conducted in North America (RR 1.15, 95%CI 1.01-1.30) and Asia (RR=1.34 95% CI 1, 06-1.68) (Bagnardi et al., 2010).

Alcohol consumption and risk of breast and female genital organs cancer

Four publications were found (Table 3) evaluating the association between alcohol consumption and the risk of breast cancer (Hamajima et al., 2002; Key et al., 2006; Bagnardi et al., 2012; Seitz et al., 2012). A meta-analysis classified the articles in scores according to the degree of control for confounding. For studies judged high quality, excess risk related to alcohol drinking was 22% (RR 1.22, 95%CI 1.09-1.37). When the dose-response effect was measured an increased risk of 10% for each 10 g of ethanol/day (RR 1.10, 95%CI 1.05-1.15) was observed. The risk remained regardless of the type of beverage consumed (beer, wine or spirits) (Key et al., 2006). Another study, after adjustment for smoking, showed a dose-response effect with a 7% increase in the risk of developing breast cancer for each 10g/day of alcohol consumed ($p<0.001$) (Hamajima et al., 2002). A meta-analysis that adjusted for age, family history, parity, menopause, use of oral contraceptives and hormone replacement therapy, showed an increase of 3% in the risk (RR 1.03, 95%CI 1.00-1.07) (Seitz et al., 2012). Not adjusting for the risk of tobacco consumption, a publication reported a risk increase of 5% for the consumption of 1 dose/day of alcohol (RR 1.05, 95%CI 1.02-1.08) and 6% in studies conducted in North America (RR 1.06, 95%CI 1.02-1.09%) (Bagnardi et al., 2012).

The risk of endometrial cancer among drinkers was analyzed by three authors (Friberg et al., 2010; Turati et al., 2010; Sun et al., 2011). One meta-analysis did not reported statistically significant association between endometrial cancer and alcohol consumption in smokers (RR 0.88, 95%CI 0.64-1.21) and among nonsmokers (RR 0.86, 95%CI 0.62-1.20) (Sun et al., 2011). After adjustment for smoking, oral contraceptive use and body mass index, another meta-analysis did not observe a statistically significant association between the consumption of alcoholic beverages and the risk of endometrial cancer (RR 1.33, 95%CI 0.92-1.91) (Friberg et al., 2010). A similar result was reported by another unadjusted analysis, independent of the intensity of alcohol consumption (Turati et al., 2010).

We identified one meta-analysis assessing alcohol consumption and ovarian cancer, in which no statistically significant association was found (RR 1.00, 95%CI 0.95-1.05), regardless of the intensity of daily consumption (Rota et al., 2012).

Alcohol consumption and the risk of bladder, prostrate, central nervous system and thyroid cancer

There were two publications (Table 4) concerning the association between alcohol consumption and the risk of developing bladder cancer (Mao et al., 2010; Pelucchi et al., 2011). After adjustment for smoking, one meta-analysis found no risk among smokers (RR 1.80, 95%CI 0.54-5.99) or nonsmokers (RR 1.19 95%CI 0.85-1.53)

Table 4. Summary of Meta-analyses that Evaluated Alcohol Consumption and the Risk of Developing Cancer in the Bladder, Prostate, Central Nervous System and Thyroid

Author, Year	Inclusion period	No. of articles	No. of people	Risk analysis (95% CI)		
Breast cancer						
Mao et al., 2010[a]	1980-2009	19	8,299	**Consumption: yes×no** RR=1.80 (0.54-5.99)	**Risk for nonsmokers** RR=1.19 (0.85-1.53)	
Pelucchi et al., 2011[a]	Up to 2010	19	11,219	**Dose-response** <3 doses/day: RR=0.98 (0.89-1.07) ³3 doses/day: RR=0.97 (0.72-1.31)		
Prostate cancer						
Fillmore et al., 2009[b]	Up to 2006	35	NR	**Consumption: yes×no** OR=1.16 (1,06-1.26)	**Type of study** Population control case: OR=1.24 (1.14-1.3) Hospital control case: OR=0.99 (0.87-1.13) Cohort: OR=1.02 (0.85-1.23)	
Central nervous system cancer						
Galeone et al., 2012[b]	Up to 2009	20	4,271	**Consumption: Moderate×Intense** Moderate: RR=1,01 (0.81-1.25) Intense: RR=1.35 (0.85-2.15)	**Types of beverages** Wine: RR=1.01 (0.70-1.48) Beer: RR=0.96 (0.82-1.61) Spirits: RR=1.20 (1.01-1.42)	**By gender** Male: RR=1,65 (1.27-2.13) Female: RR=0,84 (0.63-1.12)
Thyroid cancer						
Mack et al., 2003[b]	1980-1997	10	2.725	**Consumption: yes×no** RR=0.8 (0.7-0.9)	**Wine** (doses/week) ≤2: RR=0.9 (0.7-1.2) >2-11: RR=0.8 (0.7-1.1) >11: RR=0.9 (0.7-1.1)	**Beer** (doses/week) ≤1: RR=0.9 (0.8-1.2) >1-3: RR=0.8 (0.6-1.0) >3: RR=0.8 (0.6-1.0)
Kitahara et al., 2012[c]	1965-2009	5	746.097	**Consumption: yes× no** RR= 0.88 (95%IC 0.82-0.95)	**Smoking historic** Nonsmokers: RR=0.81 (0.67-0.97) Ex-smokers: RR=0.89 (0.82-0.98) Smokers: RR=0.90 (0.76-1.06)	

*RR=relative risk; CI=confidence interval; NR=not reported; [a]Adjusted for tobacco; [b]Unadjusted; [c]Adjusted for age, sex, race, education, histology of cancer (papillary and follicular), tobacco and cohort

Table 5. Summary of Meta-analysis that Evaluated Alcohol Consumption and the Risk of Developing Cancer

Cancer site	Men	Women	Both genders
Oral cavity and pharynx	+	*	*/++++
Esophagus[a]	+	*	+/++++
Larynx[a]	*	*	*/++
Colorectal	*/+	*/+	*/++
Central nervous system	++	*	*/+
Pancreas[a]			+
Breast[a]		*/+	
Prostate	*/+		
Lung			*
Bladder			*
Stomach[a]			+
Endometrium		*	
Ovary		*	
Thyroid[a]			*/-

*No statistical significance; [a]Blank for no info. Analysis adjusted by tobacco; Legend: -: OR or RR<1; +: OR or RR from 1-1.5; ++: OR or RR from 1.5-2.5; +++: OR or RR from 2.5-4; ++++: OR or RR>4

(Mao et al., 2010). Another meta-analysis, after adjustment for smoking, did not observe an increased risk of cancer when consumption was <3 doses/day (RR 0.98, 95%CI 0.89-1.07) and >3 doses/day (RR 0.97, 95%CI 0.72-1.31) (Pelucchi et al., 2011).

Prostate cancer was the subject of one meta-analysis (Table 4), which examined the risk according to different designs used in the studies. Considering all the designs, authors found a 16% increase in the risk of developing prostate cancer per dose/day consumed (RR 1.16, 95%CI 1.06-1.26). When analyzing by type of study, case-control studies remained statistically significant, with an increased risk of 24% per dose/day (95%CI 1.14-1.34). These results were not adjusted for tobacco consumption (Filmore et al., 2009). CNS tumors were evaluated by one meta-analysis (Table 4) without control for tobacco. Authors observed a statistically significant association in the use of distillates (RR 1.20, 95%CI 1.01-1.42) and in male consumers (RR 1.65, 95%CI 1.27-2.13) (Galeone et al., 2012).

Two papers (Table 4) addressing the relationship between alcohol intake and the risk of developing thyroid cancer were included in this review (Mack et al., 2003; Kitahara et al., 2012). In the pooled analysis, no association was found in the crude analysis (RR 0.80, 95%CI 0.70-0.90), regardless of the type of alcoholic beverage or the amount consumed (Mack et al., 2003). A pooled analysis adjusting for age, sex, race, education, histology of cancer (papillary or follicular), tobacco use and cohort, found a negative association between alcohol consumption and the risk of developing thyroid cancer (RR 0.88, 95%CI 0.82-0.95). A reduction in risk for those who had never smoked (RR 0.81, 95%CI 0.67-0.97) and for former smokers was also observed (RR 0.89, 95%CI 0.82-0.98) (Kitahara et al., 2012).

The synthesis of the magnitude of the risk of cancer caused by alcohol consumption is shown in Table 5.

Discussion

To the best of our knowledge, this is the first systematic review of meta-analysis on the effect of alcohol consumption and the risk of developing cancer. Although several methodological limitations can be attributed to the primary studies included in the meta-analysis, this review enables the current scientific evidence about the real risks posed by the consumption of alcohol in cancer development to be summarized.

Alcohol, alone, can not be considered a causative agent of cancer. However, studies with animals show alcohol as a factor that influences the risk of developing the disease in users who consume it excessively. In addition, alcohol can act as a co-carcinogen agent, i.e. the alcoholic beverage associated with other risk factors may cause promotion or acceleration of the disease (Doll et al., 1999). For the American Cancer Society (2012) ethanol, a chemical found in alcoholic beverages, is responsible for the onset of cancer. The amount of drinking by the individual is more important than the type of beverage consumed. Acetaldehyde is the most toxic metabolite of ethanol because it has mutagenic and carcinogenic properties (Seitz and Stickel, 2007). Experiments showed an increase in the appearance of tumors when ethanol was injected on the oral or esophageal mucosa of animals (Seitz et al., 1998). Alcohol acts on the mucosa as a solvent, causing the penetration of carcinogens. Thus the molecular composition of cells is modified, which explains the increased risk of cancer in individuals who combine alcohol and tobacco. The increased risk of cancers associated with overweight and obesity may be indirectly related to alcohol, since it contributes to weight gain. Chronic alcoholism associated with nutritional deficiency increases the risk of cancer (Poschl and Seitz, 2004; Winstanley et al., 2011).

According to Bagnardi et al. (2011) the consumption of alcohol increases the risk of cancer of the oral cavity, pharynx, larynx, esophagus, stomach, colon, rectum, liver, breast and ovaries. It also highlights the existence of a minimal risk related to lung cancer and prostate cancers. The authors emphasize the need for further studies regarding these and other types of cancer, due to the large differences observed in the analyzed publications. A significant difference in risk on females compared to males is also noted. Other authors (Inoue et al., 2007) found no relationship between alcohol consumption and increased risk for the development of cancer in women. These studies also report that the risk becomes greater in individuals who consume alcohol and tobacco simultaneously (Inoue et al., 2007; Bagnardi et al., 2011). However, even though alcohol and tobacco are factors that act synergistically, ensuring the increased risk, alcohol is considered an independent risk factor for many types of cancer (Pelucchi et al., 2006).

There is a definite relationship between alcohol consumption and cancers of the mouth, pharynx, esophagus, liver, colon, rectum and breast. In relation to other types of cancer, there is a suspicion of an association, with the exception of bladder, endometrial and prostate cancer, of which there is no evidence (Boffetta and Hashibe, 2006).

In the meta-analysis that did not control the effect of tobacco on the study of the association between

alcohol consumption and the risk of developing cancer, an increased risk for developing colorectal cancer and prostate cancer, among men, and in both sexes for cancers of the oral cavity and pharynx was evidenced. For these cancers, it is necessary to perform further studies to monitor the effect of tobacco as a possible confounding variable in the observed association. As tobacco is considered an important risk factor for cancer and having as an assumption that smoking is associated with alcohol consumption, because most individuals who smoke also consume alcoholic beverages, adjustment for tobacco as a confounding factor is needed thus avoiding incorrect conclusions about the actual effects of alcohol.

The meta-analysis identified in this literature review suggests that moderate to heavy alcohol consumption after controlling for tobacco increases the risk of cancer of the esophagus, stomach, pancreas, larynx and breast. An inversely related risk in the development of thyroid cancer among ex-smokers and nonsmokers was also observed. However, it would be incorrect to state the protective effect of alcohol, and studies to verify the biological plausibility of this effect are needed.

This study found no association between alcohol consumption as a risk factor for lung, bladder, central nervous system, endometrium and ovary cancers.

This systematic review has limitations inherent to the articles included in the meta-analysis identified for this study. The inclusion of publications with significant associations and exclusion of studies with negative results may be a limitation. Furthermore, since the selection of the types of cancer to be included in this study was based on the most frequent topographies in Brazil (INCA, 2011), cancers of the liver, nasal cavity and paranasal sinuses, to which alcohol was defined as a carcinogen by the IARC (2013), were not included in this review, which may be a limitation. Another limitation is the region where the studies were conducted, which included mainly populations originating from North America, Europe and Asia. In addition, the associations may reflect cultural aspects, customs and lifestyles of each geographic region. Furthermore, no study included data from Latin America, pointing to the need to explore this topic in comprehensive regional studies.

In conclusion, after controlling for the effect of tobacco, this systematic review suggests that moderate to heavy consumption of alcohol increases the risk of developing cancers of the esophagus, stomach, larynx, pancreas and breast. In the meta-analysis that did not control the effect of smoking as a confounding variable in the association between alcohol consumption and the risk of developing cancer, there was evidenced an increased risk of prostate cancer among men, and for both sexes an increased risk of cancers of the oral cavity and pharynx, colorectal and central nervous system. It was observed that alcohol may be an inversely related risk for the development of thyroid cancer among ex-smokers and nonsmokers. Additionally, this meta-analysis review found no association between alcohol consumption and the development of lung, bladder, endometrium and ovary cancers.

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