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Effects of alcohol consumption in general, and wine in particular, on the risk of cancer development: a review

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ABSTRACT

Since 1988, alcohol has been classified as a Group 1 carcinogen, the highest level of risk, by the International Agency for Research on Cancer (IARC). In fact, alcohol consumption is the third leading risk factor for disease and mortality in Europe. It accounts for 4.65 % of the global burden of both injury and disease, making it one of the most preventable causes of injury and death. Tissues in closest contact with alcohol when it is ingested, such as those of the oral cavity, pharynx, esophagus and larynx, have at greater risk of becoming cancerous than other body tissues. The consumption of alcohol is also associated with an increased risk of stomach, colon, rectum, liver, female breast and ovarian cancers. Conversely, recent studies suggest that red wine components inhibit colony formation of human breast cancer and esophageal carcinoma cells, suggesting that wine-derived phenolic compounds may be inhibitory, in contrast to the alcohol component of wine. Because of a lack of systematic studies dealing with the different types of cancer and alcoholic beverages and wine in particular, in this narrative review we summarize the general risk of cancer linked to the consumption of alcoholic beverages, including wine, according to type of cancer, with 140 extracted relevant references from 1966 to 2020. Mostly epidemiological studies concerning large cohorts have been selected. For the cancers of the upper aerodigestive tract, liver, colorectum, breast cancer, pancreatic, prostate, an excessive consumption and/or misuse of alcoholic beverages is correlated with increased risk. Conversely a probable decreased risk has been found for renal/kidney cancers, as well as for Non-Hodgkin lymphomas, such as thyroid lymphomas, associated with the moderate consumption of alcoholic beverages. There is no evidence of ovarian, gastric, head and neck, and lung cancer being linked to the moderate consumption of alcoholic beverages. Cancer is a multifactorial disease, and many factors contribute to effects on health status, usually being both genetic and environmental. Habits (smoking, dietary/lifestyle pattern/ habits, physical activity), should also be taken into account when defining appropriate consumption frequencies for different types of alcoholic drink (wine, beer, spirits). Further research is needed related to wine consumption in the context of a healthy dietary and lifestyle pattern given health-promoting constituents of wine and its effects on cancer incidence.

KEYWORD

alcoholic beverage beverage, wine, cancer risk/risk of cancer, consumption

INTRODUCTION

The importance of alcohol consumption as a contributing factor to the overall cancer burden is often underappreciated. Alcohol consumption has been linked to an increased risk of various types of cancer. It accounts for 4.65 % of the global burden of both injury and disease (Ezzati *et al.*, 2002, Rehm *et al.*, 2009). Twenty years ago, a combined analysis (meta-analysis) of more than 200 studies assessing the link between alcohol and various types of cancer found that alcoholic beverages strongly increased the risks for cancers of the oral cavity, pharynx, œsophagus and larynx (Bagnardi *et al.*, 2001). Statistically significant increases in risk also existed for cancers of the stomach, colon, rectum, liver, female breast and ovaries. Several mechanisms have since been postulated through which alcohol may contribute to an increased risk of cancer. Concurrent tobacco use, which is common among drinkers, enhances alcohol's effects on the risk of cancers of the upper digestive and respiratory tract.

Beyond oncology, both alcohol consumption and abuse pose a significant public health problem. Population surveys have demonstrated that 12 % to 14 % of adults may have an alcohol use disorder (Hasin *et al.,* 2007; Edelman and Fiellin, 2016). More than 40 countries have issued alcohol drinking guidelines (International Alliance for Responsible Drinking guidelines, 2016; OIV, 2019). However, as the amount of alcohol (ethyl alcohol or ethanol) in an alcoholic beverage varies depending on the type of beverage (i.e., beer, wine or spirits) and also the size of the drink consumed, defining risky drinking can be challenging. Moreover, the definition of standard drink differs among countries and ranges from 8 to14 g/day (Dawson, 2011; International Alliance for Responsible Drinking guidelines, 2019). For hepatic tissue, a daily alcohol consumption of 2.6 g has been identified as acceptable (Rehm *et al.,* 2014), although other tissues may be more or less sensitive to the carcinogenic action of alcohol and metabolite, acetaldehyde.

Furthermore, it is important for studies to be adequately adjusted for other confounding factors. These include the impact of smoking in combination with alcohol as a potent synergic risk for head and neck and aero-digestive tract cancers (Hashibe *et al.,* 2009; Taylor and Rehm, 2006), or the dietary intake of vegetables and soybean products, which have shown protective factors for colorectal cancer (Vainio and Weiderpass, 2006; Skjelbred *et al., 2007*), and which also reduce breast cancer risk (Wu *et al.,* 2008). By contrast, barbecued meats or salted food have been reported as factors contributing to the risk of gastric cancer (Kim *et al.,* 2002; Takachi *et al.,* 2010). Additionally, there are many studies in which differences in food consumption patterns have been identified according to age group and sex; for example, differences in food consumption have been found between Brazil and the USA (Bezerra *et al.,* 2014), and the same disparity has been observed in Canadian studies (Riediger *et al.,* 2007; Nasreddine *et al.,* 2006), and in those on Taiwan and Spain (Wu *et al.,* 2007; Ribas-Barba *et al.,* 2007). In terms of dietary habits, a US survey showed that wine consumers with better health were more likely to indicate that they consume wine to benefit their health than those with worse health (Higgins and Llanos, 2015). Judgements of the strength of evidence causally associating alcohol consumption and the risk of certain cancers - reviewed by the World Cancer Research Fund (WCRF) in 2018 (World Cancer Research Fund, 2018) - suggest the following, as detailed in Figure 1:

➔ A convincing increased risk for: mouth, pharynx, larynx and oesophagus, colorectum (men), breast post-menopause (women);

➔ A probable increased risk for: liver, stomach, colorectum (woman), breast pre-menopause (women);

➔ A substantial effect on risk unlikely or a decreased risk: kidney;

➔ No relationship or insufficient evidence for risks are indicated for others cancers including: nasopharynx, lung, pancreas, gallbladder, ovary, endometrium, cervix, prostate, bladder, skin and thyroid.

In this narrative review, we explore the general cancer risk associated with alcoholic beverage consumption, and in particular with wine consumption, for cancers for which there is sufficient evidence, in order to ensure that they are accurately reflected and up-to-date in all recommendations and guidelines. In addition, factors that increase cancer development, as well as any potential protective effects of wine and other alcoholic beverages against cancer development, are described.

1. Estimation of the general risk induced by the consumption of alcoholic beverage depending on the type of cancer

1.1. Upper aerodigestive tract cancer (UADTC)

Every year, approximately one million new cases of UADTC are diagnosed, ranking it among the top ten of the most common cancers (Ansary-Moghaddam *et al.*, 2009; Guo *et al.*, 2012; International Agency for Research on Cancer, 2012). Cases occur more frequently in men than in women and have their highest incidence in the fifth and sixth decade of life (Parkin, 2006). 60 to 85 % of UADTC have been associated with alcohol and tobacco risk factors (Anantharaman *et al.*, 2011). Alcohol consumption has been identified as a carcinogenic factor for neoplastic conditions of the oral cavity and pharynx (Righini *et al.*, 2008; Shield *et al.*, 2013), although alcohol consumption in the absence of tobacco increases risk specifically for oesophageal cancers (Anantharaman *et al.*, 2011). Even small amounts of alcohol consumed over time (e.g., two drinks/day) have been associated with an increased risk of UADTC (Schütze *et al.*, 2011), alcohol-dependent individuals having a 10 times increased risk of mouth and laryngeal cancer, and laryngeal cancer being the most frequent cancer-causing mortality in alcohol-dependent individuals who reach stable abstinence (Gual *et al.*, 1999). The relationship between alcohol and UADTC mortality is dose-dependent, being disproportionately higher in both moderate and heavy drinkers (Li *et al.*, 2014) compared to light drinkers, especially when alcohol consumption does not decrease after a cancer diagnosis (Druesne-Pecollo *et al.*, 2014; Miller *et al.*, 2006). It has been suggested that alcohol-related cancers of the UADT occur, because the mucosal lining of the UADT comes in direct contact with ethanol and acetaldehyde.

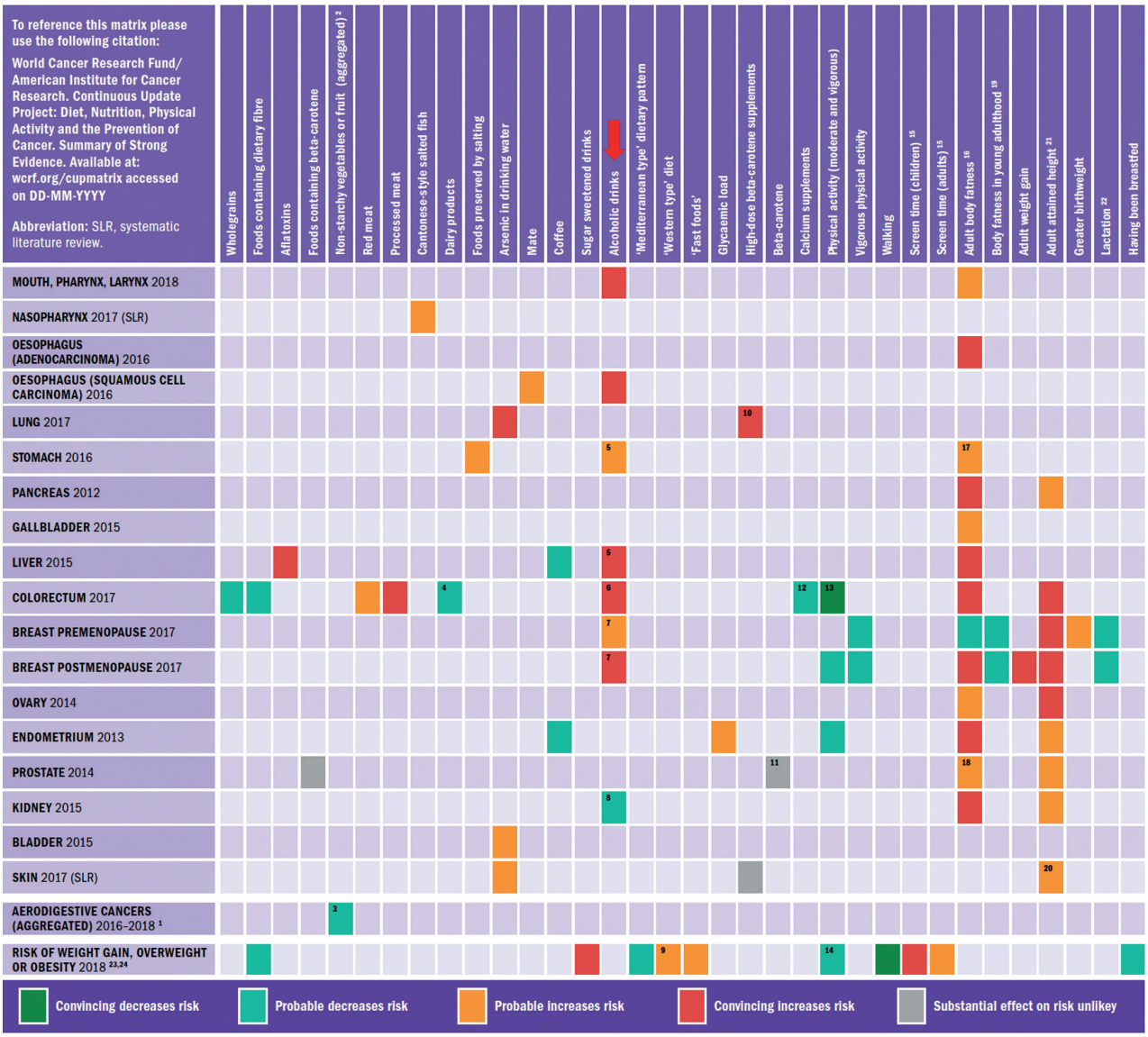
The evidence for the influence of alcohol consumption on the risk of nasopharyngeal cancers is inconsistent. The potential J-shaped dose-response relationship seen by (Chen *et al.*, 2009) suggests a reduced risk of NPC with light alcohol consumption, although heavier alcohol consumption was clearly associated with an increased risk of NPC.

Nevertheless, tobacco, is the dominant carcinogen for UADTC (Anantharaman *et al.*, 2011). The combination of tobacco and alcohol, however, is multiplicative, and it substantially increases the risk of these cancers by 40 to 280 % more when compared to abstainers (Thun *et al.*, 1997; Hashibe *et al.*, 2009). In each study, when the data were adjusted for tobacco smoking, alcohol was found to have a direct effect. When the data were analysed for the source of alcohol, this effect appeared stronger for spirits and beer than for wine (Anderson *et al.*, 1993). In a subsequent prospective cohort study (Grønbaek *et al.*, 1998), those who consumed 7 to 21 drinks of beer and spirits per week had a relative risk three times higher than that of abstainers. Those for whom 30 % of total consumption was wine had a relative risk of 0.5 compared to abstainers. The authors concluded that moderate wine consumption probably does not increase the risk of UADTC, whereas moderate consumption of beer or spirits does. In an early Spanish analysis of oesophageal cancer, it was found that spirits and beer (but not wine) along with tobacco smoking were the greatest risk factors for this cancer (Cayuela *et al.*, 1991). In a subsequent 1997 study, it was noted that the risk of esophageal squamous cell carcinoma was more than doubled with beer and tripled with spirit consumption, whereas drinkers of wine had a 40 % reduced risk of all forms of oesophageal and gastric cancers (Gammon *et al.*, 1997). Certain compounds, such as N-nitrosamines, are found in spirits and to lesser extent in beer, and urethane, a potential carcinogen in experimental studies, may be found in spirits, but not in beer and wine; this should be taken into consideration when explaining the differential effect of alcoholic beverages. In addition, most of the antioxidant compounds found in wine, and to some extent in beer, are almost completely lacking in spirits (Vioque *et al.*, 2008). On another hand, a recent study by Chen *et al.*, 2019 showed that red wines inhibit colony formation of human breast cancer and esophageal carcinoma cells, suggesting that wine-derived phenolic compounds may be inhibitory, in contrast to the alcohol component of wine.

1.2. Breast cancer

In 2017, breast cancer was the third highest incident cancer, with an estimated 2 million incident cases worldwide and a high prevalence in females; it is, therefore, currently the leading cause of cancer death in females, as well as a non-negligible cause of cancer death in males. It claimed 181,004 lives and resulted in 17.7 million disability-adjusted life years in 2017, making it one of the most burdensome cancers globally (Global Burden of Disease Cancer Collaboration, 2018; Giordano, 2018). A study in which data was collected on gender, age group, and social-demographic status between

SUMMARY OF STRONG EVIDENCE ON DIET, NUTRITION, PHYSICAL ACTIVITY AND THE PREVENTION OF CANCER



1 Includes mouth, pharynx and larynx, nasopharynx, oesophagus (squamous cell carcinoma and adenocarcinoma), lung, stomach and colorectal cancers.
2 Aggregated exposure which contains evidence for non-starchy vegetables, fruit and citrus fruit.
3 The Panel notes that while the evidence for links between individual cancers and non-starchy vegetables or fruits is limited, the pattern of association is consistent and in the same direction, and overall the evidence is more persuasive of a protective effect.
4 Includes evidence on total dairy, milk, cheese and dietary calcium intakes.
5 Stomach and liver: Based on intakes above approximately 45 grams of ethanol per day (about 3 drinks).
6 Based on intakes above approximately 30 grams of ethanol per day (about 2 drinks per day).
7 No threshold level of intake was identified.
8 Based on intakes up to 30 grams of ethanol per day (about 2 drinks per day). There is insufficient evidence for intake greater than 30 grams per day.
9 Such diets are characterised by high intakes of free sugars, meat and dietary fat; the overall conclusion includes all these factors.
10 Evidence is from studies of high-dose supplements in smokers.
11 Includes both foods naturally containing the constituent and foods which have the constituent added and includes studies using supplements.
12 Evidence derived from studies of supplements at dose >200 milligrams per day.
13 Colon cancer only.
14 Aerobic physical activity only.
15 Screen time is a marker of sedentary behaviour.
16 Body fatness is marked by body mass index (BMI) and where possible waist circumference and waist-hip ratio.
17 Stomach cardia cancer only.
18 Advanced prostate cancer only.
19 Young women aged about 18 to 30 years; body fatness is marked by BMI.
20 Malignant melanoma only.
21 Adult attained height is unlikely to directly influence the risk of cancer. It is a marker for genetic, environmental, hormonal and nutritional factors affecting growth during the period from preconception to completion of growth in length.
22 Evidence relates to effects on the mother who is breastfeeding and not to effects on the child who is being breastfed. Relates to overall breast cancer (unspecified).
23 The factors identified as increasing or decreasing risk of weight gain, overweight or obesity do so by promoting positive energy balance (increased risk) or appropriate energy balance (decreased risk), through a complex interplay of physiological, psychological and social influences.
24 Evidence comes mostly from studies of adults but, unless there is evidence to the contrary, also apply to children (aged 5 years and over).

FIGURE 1. Food, nutrition, physical activity, and the prevention of cancer: overview of key judgements by the WRFC report of 2012

1. Includes mouth, pharynx and larynx, nasopharynx, oesophagus (squamous cell carcinoma and adenocarcinoma), lung, stomach and colorectal cancers; **2.** Aggregated exposure which contains evidence for non-starchy vegetables, fruit and citrus fruit; **3.** The Panel notes that while the evidence for links between individual cancers and non-starchy vegetables or fruits is limited, the pattern of association is consistent and in the same direction, and overall the evidence is more persuasive of a protective effect; **4.** Includes evidence on total dairy, milk, cheese and dietary calcium intakes; **5.** Stomach and liver: based on intake above approximately 45 grams of ethanol per day (about 3 drinks); **6.** Based on intake above approximately 30 grams of ethanol per day (about 2 drinks per day); **7.** No threshold level of intake was identified; **8.** Based on intake of up to 30 grams of ethanol per day (about 2 drinks per day). There is insufficient evidence for intake greater than 30 grams per day; **9.** Such diets are characterized by high intake of free sugars, meat and dietary fat; the overall conclusion includes all these factors; **10.** Evidence is from studies of high-dose supplements in smokers; **11.** Includes both foods naturally containing the constituent and foods which have the constituent added and includes studies using supplements; **12.** Evidence derived from studies of supplements at dose > 200 milligrams per day; **13.** Colon cancer only; **14.** Aerobic physical activity only; **15.** Screen time is a marker of sedentary behaviour; **16.** Body fatness is scored according to body mass index (BMI) and, where possible, waist circumference and waist-hip ratio; **17.** Stomach cardia cancer only; **18.** Advanced prostate cancer only; **19.** Young women aged about 18 to 30 years old; body fatness is scored according to BMI; **20.** Malignant melanoma only; **21.** Adult attained height is unlikely to directly influence the risk of cancer. It is a marker for genetic, environmental, hormonal and nutritional factors affecting growth during the period from preconception to completion of growth in length; **22.** Evidence relates to effects on the mother who is breastfeeding and not to effects on the child who is being breastfed. Relates to overall breast cancer (unspecified); **23.** The factors identified as increasing or decreasing risk of weight gain, overweight or obesity do so by promoting positive energy balance (increased risk) or appropriate energy balance (decreased risk), through a complex interplay of physiological, psychological and social influences; **24.** Evidence comes mostly from studies of adults but, unless there is evidence to the contrary, also apply to children (aged 5 years and over).

1990 and 2017 by country has additionally revealed an increasing global breast cancer burden in lower social development index countries (Li *et al.*, 2019).

There has been intense interest and controversy regarding the link between alcohol consumption and breast cancer. Some initial studies showed a reduced risk or no risk of breast cancer with low to moderate alcohol consumption (Zhang *et al.*, 1999), while some subsequent studies showed an increased risk. Family history of breast cancer and individual alcohol consumption are known individual risk factors for breast cancer (World Cancer Research Fund, 2018). Even low to moderate levels of consumption have subsequently been shown to be a risk factor for breast cancer (Cao *et al.*, 2015; Bagnardi *et al.*, 2015), although this risk may be attenuated by increasing folate intake to more than 400 µg/day (Kim *et al.*, 2017). Breast cancer risk may also be attenuated by other dietary/nutrition factors and lifestyle, and it may differ depending on menopausal status (McKenzie *et al.*, 2015) and type of cancer (Ellingjord-Dale *et al.*, 2017; Zeinomar *et al.*, 2019).

A significantly increased mortality from breast cancer has been shown in heavy drinkers compared to abstainers and light consumers (Longnecker, 1994; Fuchs *et al.*, 1995; Swanson *et al.*, 1997; Chen *et al.*, 2011). In addition, consumption of up to 15 g/day has been shown to decrease the risk of breast cancer (Longnecker, 1994), suggestive of a dose-response relationship between alcohol and breast cancer. The relative risk for one drink per day has been observed to be 1.00, for two drinks per day 1.24, and for three drinks per day 1.38; however, the study in question could not clarify the casual role of alcohol (Longnecker, 1994). Subsequently, the relative risk of breast cancer was shown to increase by 20 % with the consumption of one drink per day and by 50 % with two to three drinks/day (Thun *et al.*, 1997). It has also been suggested that there is a threshold effect of one to two drinks per day (Li *et al.*, 2009).

Regarding menopausal status and its influence on the association between alcohol and breast cancer, Petri *et al.* (2004) suggested that total alcohol consumption of more than 27 drinks per week increases breast cancer risk in pre-menopausal women independently of the type of alcohol, while among post-menopausal women, the consumption of more than six units of spirits per week increase breast cancer risk. A few studies have researched the effects of average consumption alongside the drinking pattern. One such study examined the association between the drinking pattern of alcoholic beverages, particularly wine, and breast cancer (Bessaoud and Daurès, 2008), and showed that women with an average consumption of less than 1.5 drinks per day were at lower risk (OR = 0.58) compared with abstainers. This protective effect was due substantially to wine consumption, since the proportion of regular wine drinkers was predominant in the study population. Furthermore, the study showed that women who consumed between 10 and 12 g per day of wine were at lower risk (OR = 0.51) than non-wine drinkers. Above 12 g per day of wine consumption, the risk

of breast cancer increased, but this association was not significant. Although no association between the pattern of total alcohol consumption and breast cancer was found, the type of alcoholic beverage modified risk. The results supported the hypothesis of the existence of a threshold effect: risk decreased or was not modified when consumption was under a certain threshold; above that threshold, however, the risk increased. The drinking pattern of each type of specific beverage, especially wine, seems important in terms of the association between alcohol and breast cancer. This study also concluded that low regular wine consumption does not increase breast cancer risk.

Estrogen-mediated mechanisms may be the cause of the increased breast cancer risk observed with light alcohol consumption (Li *et al.*, 2009). Some, but not all, studies have shown that increased blood and urine estrogen levels occur with alcohol consumption, and they have speculated that this might be the stimulus for breast cancer risk (Smith-Warner *et al.*, 1998).

Overall, the relative risk of breast cancer appears to increase by 7 % for each additional 10 g of alcohol consumed per day (Hamajima *et al.*, 2002; Allen *et al.*, 2009). A more recent review of data for lighter drinking supported that even in women who drink ≤ 12.5 g/day (≤ 1 standard drink/day) there was a 5 % increase in risk of breast cancer compared to abstainers (Seitz *et al.*, 2012). If there is an increased risk of breast cancer with consumption of alcohol, it should be noted that one in 25 women will eventually die from breast cancer. If this is put into perspective with other diseases, however, one in two women will die from either coronary heart disease or from a stroke. Nevertheless, it has been suggested that the subgroup of women in the 35 to 64 age group with a low risk of coronary heart disease, but with a higher risk of breast cancer, could decrease their risk by reducing their alcohol consumption (Longnecker, 1999). In the case of older women, the protective effect of alcohol consumption by reducing the risk of atherosclerotic and hence coronary heart disease outweighs the weak increase in risk of breast cancer.

1.3. Ovarian cancer

Ovarian cancer is the seventh most common cancer among women worldwide (World Cancer Research Fund International, 2012). The association between alcohol consumption and an increased risk of ovarian cancer was first revealed in the Breast Cancer Detection Demonstration Project (Lacey *et al.,* 2002). However, inconsistent findings have been reported for ovarian cancer in several epidemiological studies. Recently, a case-control study with 1,144 invasive epithelial ovarian cancer cases and 2,513 controls showed that wine consumption of more than one drink a month in at least one year after the age of 20 was associated with a risk reduction (OR = 0.67, 95 % CI: 0.50–0.88) relative to abstainers (Cook *et al.,* 2016). In this study, the reduced risk was stronger for red wine drinkers (OR = 0.44, 95 % CI: 0.19–0.92) than for white wine drinkers (OR = 0.79, 95 % CI: 0.46–1.34). The risk assessed according to level of consumption was lower for women consuming > 2 drinks of wine/month (OR = 0.72, 95 % CI: 0.59–0.89 for all types of wine and OR = 0.59, 95 % CI: 0.44–0.79 for red wine only) than for those consuming only 1 to 2 drinks of wine/month (OR = 0.88, 95 % CI: 0.70–1.13 and OR = 0.64, 95 % CI: 0.45–0.92 for red wine only). Wine consumption initiated prior to the age of 50 was associated with a risk reduction (e.g., at 40 to 49 years old, OR = 0.58, 95 % CI: 0.42–0.78). More recently, the risk of ovarian cancer was found to be 47 % higher in individuals with moderate alcohol consumption (15 to 30 g/day) in a US cohort (Chang *et al.,* 2007). However, in 2015, a meta-analysis of prospective observational studies on 1,996,841 individuals, which included 5,857 cases with ovarian cancer, concluded that alcohol consumption was not associated with the risk of ovarian cancer (Yan-Hong *et al.,* 2015). In this research, low (risk ratio [RR] = 0.96; 95 % CI: 0.93–1.00), moderate (RR = 1.08; 95 % CI: 0.92–1.27), and heavy (RR = 0.99; 95 % CI: 0.88–1.12) alcohol consumption had little to no effect on ovarian cancer incidence, when they compared the risk to abstainers (RR = 1.03; 95 % CI: 0.92–1.27). The same study indicated that light alcohol consumption was associated with a reduced risk of ovarian cancer, whereas heavy alcohol consumption was associated with an increased risk of ovarian cancer. In 2006, a US study investigated the association between a histologic subtype of ovarian cancer and type of alcohol consumed (e.g., wine, beer, or spirits) (Peterson *et al.,* 2006). Women reported their habitual alcohol consumption as young adults (20 to 30 years old) and in the recent past, and no significant association between ovarian cancer and increased alcohol consumption was found in both cases. Regular beer consumption (1 drink/day or more) during the ages of 20 to 30 (OR = 1.55, 95 % CI: 1.07–2.26), but not spirits (OR = 1.35, 95 % CI: 0.86–2.11) or wine (OR = 0.99,

95 % CI: 0.49–2.00), was associated with a statistically significant increase in risk of invasive tumours, whereas no significant relationships were observed for recent drinking, regardless of alcohol type. The elevated risk for early adult regular drinking was confined to serious invasive tumours (OR = 1.52, 95 % CI: 1.01–2.30), but results for other subtypes were based on sparse data and the results were imprecise. In this study, taken together, neither total alcohol consumption as a young adult that in recent past was associated with an increase in the risk of ovarian cancer.

Similar results were observed in a meta-analysis on alcohol and gynaecological cancers per se (Hjartaker *et al.,* 2010), from which the authors concluded that the current body of evidence - which is inadequate for several sites - suggests that no association exists between alcohol consumption and risk of gynaecological cancers.

Furthermore, a Mendelian randomisation study published in 2020 (Zhu *et al.,* 2020), which assessed a potential causal relationship between alcohol use and female hormone-dependent cancers, found no evidence to support a causal association between alcohol consumption and the risk of breast cancer (OR = 1.01, 95 % CI: 0.85–1.21), and even suggested that there is a slightly reduced risk for ovarian cancer (OR = 0.83, 95 % CI: 0.63–1.10), although the results of the applied statistical test did not show significance (p = 0.19).

1.4. Gastric cancer

Gastric or stomach cancer is the fifth most common cancer in the world and the third most common cause of death from cancer, men being twice as likely as women to be affected (World Cancer Research Fund International, 2012). A possible cause of this cancer is *Helicobacter pylori* infection, but alcohol consumption is also cited among risk factors.

In 2018, the WCRF Continuous Update Project found "strong" evidence that consuming three or more alcoholic drinks per day (i.e., ≥ 45 grams of ethanol per day) is a probable cause of stomach cancer (World Cancer Research Fund, 2018). The Stomach Cancer Pooling Project (StoP Project) recently published a pooled analysis assessing the association between alcohol consumption and gastric cancer, based on information from more than 10,000 cases and 26,000 controls evaluated in 20 studies conducted in 10 countries (Pelucchi *et al.,* 2015). In this project, heavy drinkers had a significant excess risk of gastric cancer by approximately 50 %, compared to non-drinkers (Rota *et al.,* 2017). Related to the same StoP Project, an article published in 2017 compared estimates obtained from conventional meta-analyses with individual participant data-pooled analyses. It concluded that meta-analyses of the association between alcohol consumption and gastric cancer tended to overestimate the magnitude of the effects, possibly due to publication bias (Ferro *et al.,* 2018). Some studies, including two meta-analyses published in 2017, have had conflicting results. In the first meta-analysis, 23 cohort studies with a total population of 5,886,792 subjects found that alcohol consumption increased gastric cancer risk (RR = 1.17, 95 % CI: 1.00–1.34) (Han *et al.,* 2017). However, the second meta-analysis of 22,545 cases of gastric cancer and 5,820,431 subjects suggested that light alcohol consumption might play a protective effect on gastric cancer in women, while heavy alcohol consumption was associated with a significantly increased risk of gastric cancer in all subgroups (He *et al.,* 2017). The same effect of moderate alcohol consumption was observed in another meta-analysis (Ma *et al.,* 2017). More recently, in 2019, a case-control study of 316 cases of gastric cancer suggested that excessive alcohol consumption, rather than the current status or frequency of alcohol consumption, contributes to increased gastric cancer risk, especially in Korean women (Kim *et al.,* 2019).

Research results published earlier in 2005, assessed the relationship between quantity and type of alcohol and risk of gastric cancer (Barstad *et al.,* 2005). A pooled database of three population studies conducted from 1964 to 1992, showed that total alcohol consumption itself was not associated with gastric cancer, but that type of alcohol appeared to influence risk. Compared with non-wine drinkers, participants who drank one to six glasses of wine/week had a relative risk ratio of 0.76 (95 % confidence interval (CI: 0.50–1.16), whereas those who drank > 13 glasses of wine/week had a relative risk ratio of 0.16 (95 % CI: 0.02–1.18). A Linear trend test showed a significant association with a relative risk ratio of 0.60 (95 % CI: 0.39–0.93) per glass of wine consumed/day. These relationships persisted after adjustment for age, gender, educational level, body mass index, smoking habits, inhalation and physical activity. There was no association between beer or spirits drinking and gastric cancer, and it was suggested

that daily wine consumption may conversely prevent the development of gastric cancer.

1.5. Colon and rectal cancer

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, and the second leading cause of cancer-related death in the USA (Centers for Disease Control and Prevention, 2016; Ferlay *et al.,* 2015). The latest report by the WCRF concluded that the evidence for alcoholic drinks being a risk factor for colorectal cancer was convincing based on evidence for consumption above approximately 30 g per day (World Cancer Research Fund, 2017). In the described meta-analysis, colorectal cancer risk increased by 7 % overall; 8 % for men and 4 % for women per 10 g increase in ethanol in daily consumption.

The most recently published meta-analysis results (McNabb *et al.,* 2020), however, associated a decreasing risk of CRC for light/moderate drinking (up to 2 drinks/day) (OR = 0.92, 95 % CI: 0.88–0.98, p = 0.005) compared to non-/occasional drinking (≤ 1 g/day). Heavy drinking (2 to 3 drinks/day) was not significantly associated with CRC risk (OR = 1.11, 95 % CI: 0.99–1.24, p = 0.08) and very heavy drinking (> 3 drinks/day) was associated with a significant increased risk (OR = 1.25, 95 % CI: 1.11–1.40, p < 0.001). Moreover, a study published in 2016 suggested that alcohol consumption, particularly more than 28 g/day, is associated with increased CRC risk for DNA mismatch repair (MMR) gene mutation carriers (Dashti *et al.,* 2017).

In 2019, a multi-ethnic cohort study suggested a positive association between alcohol and CRC, with variations according to race/ethnicity, lifestyle factors, alcoholic beverage type, and anatomical subsite of tumors (Park *et al.,* 2018). These results are in contrast to a cohort study from 2008 that described no associations between consumption of beer, wine or spirits, and CRC risk when compared with the abstainers of the specific beverage, and after adjustment for total alcohol consumption. Furthermore, no evidence was found for sex-specific effects of alcohol and alcoholic beverages (Bongaerts *et al.,* 2008).

The findings of a population-based Danish cohort study of 15,491 men and 13,641 women, aged 23 to 95 years old with a mean follow up of 14.7 years, showed that drinkers of > 14 drinks of beer and spirits/week, but not wine, had a risk of 3.5 (1.8–6.9) of rectal cancer compared with abstainers. Meanwhile, those who drank the same amount of alcohol, but which included more than 30 % of wine, had a risk of 1.8 (1.0–3.2) of rectal cancer. The authors concluded that alcohol consumption is associated with a significantly increased risk of rectal cancer, but the risk seems to be reduced when wine is included in the alcohol consumption (Pedersen *et al.,* 2003). Similarly, the probable attenuating effect of wine in CRC risk was observed in another population-based UK cohort of 24,244 participants after 11 years of follow-up, from which the authors concluded that the daily consumption of ≥ 1 units of wine was inversely associated with CRC risk (HR: 0.61, 95 % CI: 0.40–0.94)(Park *et al.,* 2009).

1.6. Prostate cancer

Prostate cancer is the most common cancer in men, responsible for 20.7 % of Canadian diagnoses and 9.6 % of cancer-related mortality in 2017 (Cancer Statistics. Canadian Cancer Statistics, 2017). Studies of alcohol and prostate cancer report mixed results (Papa *et al.,* 2017; Dickerman *et al.,* 2016; Rota *et al.,* 2012; Bagnardi *et al.,* 2015; Watters *et al.,* 2010). Prospective studies (Dickerman *et al.,* 2016; Platz *et al.,* 2004; Baglietto *et al.,* 2006; Watters *et al.,* 2010) have observed inverse associations between alcohol and the risk of advanced or fatal prostate cancer.

Recently, a prospective cohort study with data from 1986 to 2012 of 5,182 men diagnosed with non-metastatic prostate cancer and alcohol consumers revealed a lower risk of lethal prostate cancer without a dose-response (Downer *et al.,* 2019). Moreover, in 2016, a case-control study observed a weak, non-significant positive association between the high consumption of total alcohol over a lifetime and the risk of high-grade prostate cancer (OR = 1.18, 95 % CI: 0.81–1.73). However, men with a high beer consumption (over 63 drink-years) had an increased risk of high-grade prostate cancer (OR = 1.37, 95 % CI: 1.00–1.89). No association was found for wine consumption (Demoury *et al.,* 2016). In 2013, 2008 and 2002, different studies achieved similar results (McGregor *et al.,* 2013; Rohman *et al.,* 2008; Albertsen and Grønbaek, 2002).

Nevertheless, a 2016 meta-analysis indicated a significantly increased risk of prostate cancer among low (RR = 1.08), medium (RR = 1.07), high (RR = 1.14) and higher (RR = 1.18) volume alcohol consumers compared to abstainers. There

was a significant dose–response relationship for current drinkers (Zhao *et al.,* 2016). In a recent linear and non-linear dose–response meta-analyses of cohort studies on alcohol consumption and prostate cancer risk by types of alcohol and type of prostate cancer (non-aggressive and aggressive), Hong *et al.* (2020) found that total alcohol consumption was not associated with aggressive and non-aggressive prostate cancer, while wine was not significantly associated with non-aggressive prostate cancer.

1.7. Lung Cancer

One in five cancer deaths is due to lung cancer, with 1.59 million estimated deaths in 2012. Lung cancer is the leading cause of cancer death among men worldwide (International Agency for Research on Cancer, 2012). Figure 1 shows that there is no association or insufficient evidence concerning alcohol consumption and the risk of lung cancer, but some researchers have attempted to examine if there is any association between the consumption of alcoholic beverages with the risk of lung cancer.

In 2016, a study of lung cancer in non-smokers gave inconclusive results (García-Lavandeira *et al.,* 2016). Studies published in 2011 and 2002 (Bagnardi *et al.,* 2011; Korte *et al.,* 2002), however, showed a positive association between alcohol and lung cancer, although the first one did not reach statistical significance.

When addressing the effect of spirits, some studies have reported a positive association between the consumption of this type of alcohol and lung cancer risk (Hu *et al.,* 2002; Rachtan, 2002).

Conversely, several studies have demonstrated a beneficial effect of light to moderate wine consumption on pulmonary function. Studies in Scandinavia, Europe and South America have further suggested a possible protective effect of wine ingestion against lung cancer, especially adenocarcinoma (Kamholz, 2006). On a more global scale alcohol misuse has been associated with an increased risk of lung cancer, but the antioxidants in wine may, in theory, provide protection. It seems that low wine consumption acts as a protective factor against lung cancer in people who have never smoked. Low wine consumption showed a protective effect in both women (Hu *et al.,* 2002) and men (Kubik *et al.,* 2008) who drank no more than one drink/week (ORs = 0.7 and 0.96 respectively). By contrast, for those who drank more than one drink/day Cui *et al.* (2008) found a positive association. However, none of the studies reviewed reached statistical significance. The findings of an analysis of three Danish longitudinal population studies conducted on 28,160 men and women showed that a high consumption of beer and spirits was associated with an increased risk of lung cancer in men. Wine consumption, however, even in amounts exceeding recommended levels (> 13 glasses of wine/week) may protect from the development of lung cancer, most probably due to wine's antioxidant content and its regular consumption pattern (Prescott *et al.,* 1999).

1.8. Head and neck cancer

There are 550,000 occurrences of head and neck cancer (HNC) each year, accounting for 4.2 % of all new cancer cases, and being the seventh leading cancer by incidence worldwide (GLOBOCAN 2012 - International Agency for Research on Cancer., 2012; World Health Organization, 2014).

Results of a pooled analysis of 15 case-control studies of head and neck cancer (9,107 cases, 14,219 controls) aiming to investigate the independent associations with consumption of beer, wine and spirits, suggested that the relative risks of head and neck cancer for beer and spirits were comparable, whereas weaker associations with moderate wine consumption were observed. The protective role of wine consumption in HNC risk could be due to the confounding effects of diet and other lifestyle factors, and the presence of heterogeneity in study-specific results (Purdue *et al.,* 2009).

1.9. Renal cell Cancer

The association between alcohol consumption and risk of renal cell cancer has been inconsistent in case-control studies. An inverse association between alcohol consumption and risk of renal cell cancer has been suggested in a few prospective studies, but each of these studies involved a small number of cases. Therefore, a pooled analysis of 12 prospective studies involving 530,469 women and 229,575 men with maximum follow-up times of 7 to 20 years was carried out to establish the relationship between alcohol consumption and renal cell cancer (Lee *et al.,* 2007). Results showed that compared to abstinence, alcohol consumption was inversely associated with the incidence of renal cell cancer among participants who drank 15 g/day or more of alcohol (RR = 0.72, 95 % CI: 0.60–0.86) in both men and women.

This inverse association has been confirmed by more recent articles (Cheng and Xie, 2011; Song *et al.,* 2012; Wozniak *et al.,* 2015).

In 2015, a dose-response meta-analysis showed that each 5 g/day increment of alcohol consumption corresponded to a 5 % decrease in risk of renal cell carcinoma for males and 9 % for females (Xu *et al.,* 2015). Alcohol consumption from wine, beer, and spirits was each associated with a reduction of risk. When these associations were examined separately by gender, statistically significant inverse associations were restricted to alcohol from wine among females (RR = 0.82, 95 % CI: 0.73–0.91) and to alcohol from beer and spirits among males (RR = 0.87, 95 % CI: 0.83–0.91 and RR = 0.95, 95 % CI: 0.92–0.99, respectively). It was concluded that gender-specific and beverage-specific differences exist in the association between alcohol consumption and renal cell carcinoma risk.

1.10. Non-Hodgkin lymphoma (NHL)

There were an estimated 356,000 new cases of NHL and 192,000 deaths from NHL worldwide in 2008, and NHL is the 8th most commonly diagnosed cancer in men and the 11th in women (Ferlay *et al.*, 2010). Alcohol consumption has also been associated with reduced risk of NHL. In 2010, a study examined the role of alcohol consumption on NHL survival by type of alcohol consumed and NHL subtype (Han *et al.*, 2010). Compared to never drinkers, better overall five-year survival rates (75 % vs 69 %), and better five-year disease-free survival rates (70 % vs. 67 %) were observed in wine drinkers.

In particular, wine consumption was inversely associated with the overall survival and the disease-free survival in wine drinkers for more than 25 years, diagnosed with diffuse large B-cell lymphoma (DLBCL): (HR=0.36, 95% CI: 0.14–0.94 for HR = 0.38, 95% CI 0.16–0.94) respectively. On the other hand, a positive association between liquor consumption and the disease-free survival was shown among DLBCL patients (HR = 2.49, 95% CI 1.26–4.93).

This association was also shown in studies subsequently published in 2011 and 2012 (Gapstur *et al.*, 2011; Tramacere *et al.*, 2012). Findings from a large prospective study support the hypothesis that current alcohol consumption of > 2 drinks/day might be associated with a 22 % lower risk of NHL among men and women compared to abstainers (Gapstur *et al.*, 2011). The evidence from a meta-analysis also indicated a favourable effect of alcohol on NHL risk. The risk of NHL among alcohol drinkers compared with abstainers was reduced by 15 % (Tramacere *et al.*, 2012).

1.11. Thyroid cancer

In 2012, about 230,000 new cases of thyroid cancer were estimated among women and 70,000 among men, with an age-standardised (world population) rate of 6.10/100,000 women and 1.90/100,000 men. International comparisons are complex due to differences in diagnosis and ascertainment of the disease (La Vecchia *et al.*, 2015).

Certain studies have suggested that alcohol may reduce the risk of thyroid cancer in women, but the effect in men remains unclear. The association between alcohol and thyroid cancer was analysed in the large prospective NIH-AARP Diet and Health Study with self-reported beer, wine, and spirits consumption (Meinhold *et al.,* 2009). This study involved 200,556 women and 295,992 men; aged 50 to 71 years old. During an average of 10 years of follow-up, 585 thyroid cancer cases were identified. A history of self-reported diabetes was associated with a 25 % increase in thyroid cancer risk. This appeared to be primarily due to a 46 % significantly increased risk of thyroid cancer among women, with only a slight change in risk observed among men. The finding of an elevated risk was observed for both papillary and follicular histologic types of thyroid cancer (Aschebrook-Kilfoy *et al.*, 2011). Overall, however, the thyroid cancer risk decreased with greater alcohol consumption (two drinks/day vs none, RR: 0.57, 95 % CI: 0.36–0.89, P-trend = 0.01). These results suggest a potential protective role for alcohol consumption in thyroid cancer. This reduction of thyroid risk cancer has also been observed in subsequent studies. A case-control study observed that younger age at initiation and increasing duration of alcohol consumption were also associated with a reduced risk of thyroid cancer in a dose-dependent manner (Huang *et al.,* 2018). Compared to people who never drank alcohol, people who drank alcohol > 31 years were 50 % less likely to develop thyroid cancer (OR = 0.50, 95 % CI: 0.32–0.80). Analyses stratified by specific subtypes of alcohol demonstrated an inverse association for beer (OR = 0.69, 95 % CI: 0.49–0.96) and wine consumption (OR = 0.71, 95 % CI: 0.53–0.96)

compared to participants who never consumed alcohol, but no significant association was found for spirits consumption (OR = 0.75, 95 % CI: 0.53–1.04) (Huang *et al.,* 2018).

1.12. Liver cancer

Liver cancer is the sixth most common cancer worldwide, with 782,000 new cases having been diagnosed in 2012. It is the second most common cause of death from cancer and is more common in men than women. The risk increases with age, with most cases diagnosed involving people over 75 years of age (World Cancer Research Fund, 2020). There is convincing evidence that heavy alcohol consumption increases the risk of primary liver cancer in a dose dependent relationship, with the consumption of ≥ 3 drinks/day having a moderate detrimental role in liver cancer risk and a lack of association with moderate drinking (Shimazu *et al.,* 2012; Turati *et al.,* 2014). The most probable mechanism of alcohol associated liver cancer is through the development of liver cirrhosis, although other pathways may also play a role. Heavy alcohol consumption such as eight drinks/day increases the risk of liver cancer by 86 %. There is some evidence that risks are markedly higher in women; the risk of liver cancer in women with heavy alcohol consumption is approximately nine times that of non-drinkers, whereas the risk in men is 1.6 times that in abstainers. However, data are limited and further studies are needed to confirm this apparent difference between the genders (Lewis *et al.*, 2008). In 2015, a meta-analysis associated current drinkers with an increased liver cancer risk in case-control studies (RR = 1.55, 95 % CI: 0.38–2.73). The dose–response relationship between alcohol and liver cancer was apparent with increasing alcohol intake: RR = 1.08 for 12 g/day (~1 drink), 1.54 for 50 g/day, 2.14 for 75 g/day, 3.21 for 100 g/day, and 5.20 for 125 g/day of alcohol. The study concluded that approximately 12 g alcohol/day may be associated with a 1.1 times higher liver cancer risk (Chuang *et al., 2015).*

Risk of liver cancer is thought to be affected by synergistic interactions between alcohol and tobacco, and between alcohol and Hepatitis. The most probable mechanism of alcohol-related liver carcinogenicity is through development of liver cirrhosis, although other events such as changes in hepatic metabolism of carcinogens may also play a role (Boffetta and Hashibe, 2006).

1.13. Pancreatic cancer

Globally, 458,918 new cases of pancreatic cancer have been reported in 2018, and it has been estimated that there will be 355,317 new cases by 2040. (Rawla *et al.*, 2019). In the large prospective European Prospective Investigation into Cancer and Nutrition (EPIC) study with 478,000 participants, there was no indication of a statistically significant association of alcohol consumption at baseline, nor of average lifetime alcohol consumption with pancreatic cancer risk. A high lifetime alcohol consumption from spirits tended to be associated with a higher risk (RR = 1.40), but no association was observed for wine and beer consumption (Rohman *et al.*, 2009), suggesting no association of alcohol consumption with the risk of pancreatic cancer.

In a relatively recent case control study, the results showed no association between alcohol consumption and pancreatic cancer; however, a non-significant increased risk was observed with heavy drinking. Furthermore, smoking modified the association between alcohol and pancreatic cancer risk: among current smokers, consuming alcohol (light, moderate, and heavy) was associated with a more than two-fold increased pancreatic cancer risk, which was statistically significant among heavy drinkers (Rahman *et al.*, 2015). Heavy alcohol consumption contributes to pancreatitis, which may be a prelude for increased pancreatic ductal adenocarcinoma risk. However, data from consortia involving multiple case-control and cohort studies suggest that moderate or light alcohol consumption does not increase pancreatic cancer risk (Zakhari, 2015). A 2016 meta-analysis of cohort studies observed, however, that heavy alcohol consumption was associated with an increased risk of pancreatic cancer (risk ratio [RR], 1.15; 95 % CI: 1.06–1.25). A pooled analysis also showed that heavy spirits consumption was associated with an increased risk of pancreatic cancer (RR, 1.43; 95 % CI: 1.17–1.74) (Wang *et al.,* 2016). Similar results for heavier alcohol consumption have been subsequently observed (Luncenteforte *et al.,* 2012).

DISCUSSION

Alcohol has had a long and complicated role in human society and health. Excessive consumption of alcoholic beverages causes enormous morbidity and mortality worldwide, but the health effects of alcohol consumption within recommended guidelines are diverse and complex. Established effects include increased high-density lipoprotein

cholesterol and antithrombotic activity, providing plausible mechanisms for the observed association of moderate drinking with lower risk of coronary heart disease and ischemic stroke, but with higher risk of haemorrhagic stroke. However, moderate consumption increases sex steroid hormone levels and may interfere with folate metabolism, both of which are potential mechanisms for the observed associations of moderate drinking with several forms of cancer, particularly breast and colorectal. Genetic susceptibility to the effects of alcohol on cancer and coronary heart disease also differs across the population. Recommendations regarding drinking in moderation must be individualised to reflect the potentially competing effects of alcohol on several chronic diseases. Wine contains components that enhance possible health benefits.

According to the different studies taken into account in this review, alcoholic drinks are, or may be, a cause of various cancers, irrespective of the type of alcoholic beverage. The causal factor is evidently alcohol (ethyl alcohol or ethanol) itself. There is no significant evidence that alcohol protects from any cancer. The extent to which alcoholic drinks are a cause of various cancers depends on the amount of alcohol consumed and how it is consumed; some epidemiological studies have also identified the type of alcoholic beverage consumed. The evidence reviewed in the present paper suggests that certain alcoholic beverages seem to have different effects. For example, for cancers of the mouth, pharynx, and larynx, the evidence appears stronger for consumption of beer and spirits than for wine. There is, however, the possibility of residual confounding; wine drinkers in many countries tend to have healthier diets and lifestyles than beer or spirit drinkers. Apparent discrepancies in the strength of evidence may also partly be due to variation in the amounts of different types of alcoholic beverages consumed. In general, the evidence suggests similar effects for different types of alcoholic beverages.

More specifically, for breast cancer, most of the analyses on potential risk modification associated with alcohol consumption did not seem to adjust for confounding factors such as low folate intake, concomitant hormone therapy, or binge drinking. While results are not completely consistent, several studies have suggested that an increase in breast cancer risk from alcohol may be attenuated, or even prevented, by avoiding such behaviour; that is, by ensuring adequate folate intake, not binge drinking, and avoiding post-menopausal hormone replacement therapy.

For colorectal cancer, (unlike the interpretation of a J-shaped association between alcohol and coronary heart disease) if a J-shaped association between alcohol and colon cancer (i.e., moderate drinkers have a lower risk than abstainers) were to be found, it could be argued that some people who developed gastro-intestinal symptoms before cancer was diagnosed may have reduced their alcohol consumption or stopped drinking completely (protopathic bias). Therefore, the J-shaped association would not be a reflection of a causal relationship between alcohol and colon cancer, but rather of a reverse causation; in other words, the association with alcohol consumption - especially from none to moderate - may reflect the consequences of pre-disease status. The group identified as ‘abstainers’ could include a number of ex-heavy drinkers who may be at increased risk of cancer; their presence in this group may make the risk of cancer seem higher among abstainers than it might be among true, long-term abstainers.

Regarding wine specifically and cancers per se, it should also be emphasised that some synergistic habits, both good and bad, can be essential for tumour initiation and development. The effect of alcohol on cancer risk will depend therefore on the context, such as alcohol with or without a meal, the nature of the foods consumed (e.g., processed and red meats, addition of aflatoxins and salt) as well as concomitant tobacco smoking. The average consumption of omega-6/omega-3 acids in habitual diets should also be considered. It is suggested that more than one third of the cancers could be prevented by a healthy diet, regular physical activity, and no weight gain according to the WCRF 2018 report. Since cancer is a multifactorial disease, a person with a healthy diet, who exercises regularly, maintains a healthy body mass index (BMI) and regularly and moderately consumes wine during a meal may be less likely to develop cancer than a person who does not drink alcohol, but does not have an healthy diet, has a sedentary lifestyle and is overweight.

How to live prudently and enjoy wine at the same time? The risk seems to be more important for tobacco smokers, alcohol addictions and women. It is clear that for tobacco smokers, alcohol consumption multiplies the risk for cancers of the mouth, oesophagus, larynx, and pharynx. For those not able to limit their consumption it is best not to drink at all. For women, the increased breast cancer risk should be taken seriously, as

this has become a common cancer for women for which risk increases with the numbers of drinks consumed. Awareness needs to be raised about this fact, as a recent study showed that only about 25 % women aged 15 to 44 years are aware that, aside family history, alcohol can be a risk factor for breast cancer (Khushalani *et al.,* 2020).

There is insufficient data, however, to affirm that a moderate red wine consumption during meals in the frame of a healthy lifestyle is associated with an increased risk of cancer. Conversely, we know that this practice is beneficial for cardiovascular diseases, diabetes mellitus and other chronic and degenerative diseases, and possibly for some cancers. For this reason, therefore, the relationship between alcohol consumption and cancer should continue to be explored.

We should remember that it is easy to draw the wrong conclusions when a particular factor related to eating and drinking habits, such as wine consumption, is analysed out of context without taking cultural and culinary habits into account.

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