Chapter 3
Alcohol and Cancer Epidemiology

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Introduction

In a comprehensive worldwide assessment of cancer risk related to food and nutrition, the American Institute for Cancer Research (AICR 2007) identified alcohol consumption as a "convincing" or "probable" risk factor for esophageal, mouth, and laryngeal cancers, for liver cancer, for breast cancer in women, and for colorectal cancer especially in men. The World Health Organization's *Global Burden of Disease Project* concluded that "A total of 390,000 cases of cancer are attributable to alcohol drinking worldwide, representing 3.6% of all cancers (5.2% in men, 1.7% in women)" each year, with a corresponding annual mortality rate of 233,000, representing 3.5% of all cancer deaths (Boffetta et al. 2006). For the USA, the Alcohol-Related Disease Impact (ARDI) report indicates an annual rate of 2,464 deaths in six different alcohol-related cancer categories for the period 2001–2006 (CDC 2010).

This overview chapter serves as a summary of the impact of alcohol consumption on various cancers while highlighting evidence of the remarkably synergistic interaction between alcohol and other risk factors. The use of Alcohol-Attributable Fraction (AAF) to account for both independent and synergistic effects suggests that the magnitude of alcohol's impact on cancer may be greater than otherwise indicated. Also, the sensitization of alcohol's effect by another risk factor suggests that rates of drinking usually considered safe may in fact be hazardous *if* both factors are concurrent.

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Upper Aerodigestive Tract Cancers

Cancers of the pharynx, larynx, esophagus, and the oral cavity including the tongue account for about 64,500 new cases per year in the USA, or 4.4% of all new cancers and 25,790 or 4.6% of all cancer deaths (American Cancer Society 2009). As a group, these Upper Aerodigestive Tract (UADT) cancers (Fig. 3.1) are characterized by direct exposure to high (i.e., beverage) concentrations of ethanol and clear evidence of alcohol effects as exhibited by significant increases in relative risks (RR) for cancer even at moderate daily doses of 25 g/day (Corrao et al. 2004) and with relative risks in the four- to sixfold range with higher rates of alcohol consumption. But this large analysis of 156 studies covering 15 alcohol-related diseases did not report possible alcohol–tobacco interactions.

Alcohol and tobacco use interaction: Indications of alcohol–tobacco interactions on UADT cancers were noted early on (Wynder et al. 1957) and then supported by Rothman's evaluation of these data using his calculations of a synergy index (*S*, Rothman 1974, 1976). More recent studies use large meta-analyses and scaling to control for spurious associations such as heavier drinkers also being heavier smokers. The data presented in Table 3.1 (Hashibe et al. 2009) are typical of these studies (see also Ansary-Moghaddam et al. 2009) pooling over 11,000 cases and 16,000 controls to evaluate alcohol–tobacco interactive effects on UADT cancers. Note that "alcohol alone" failed to increase the odds ratio (OD) for any of the subsites or for UADT cancers as a whole. By contrast, there is a consistent synergistic effect between smoking and drinking for each of the three cancers included in the study. Using the
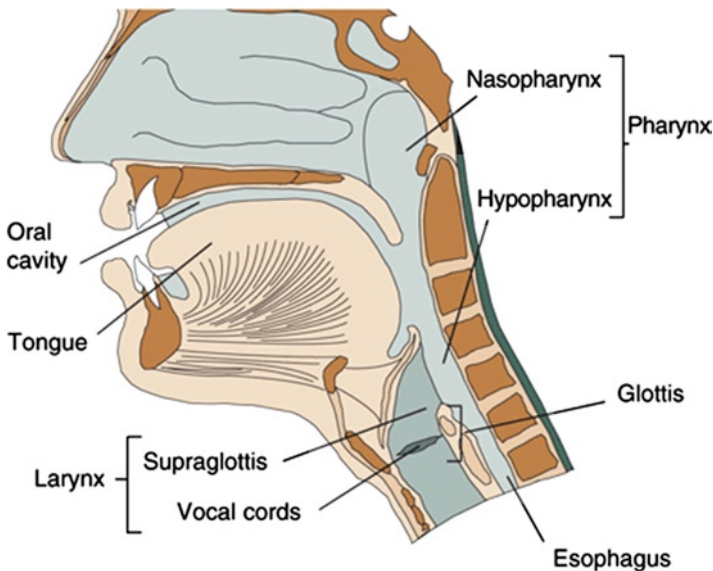

Fig. 3.1 Diagram of upper aerodigestive tract (UADT) cancer sites

Table 3.1 UADT cancers: alcohol and tobacco use on odds ratios (OR), multiplicative interaction parameters (ψ) and population attributable risks (PAR) for head and neck cancer and subsites (from Hashibe et al. 2009)

	Cases, n (%)	Controls, n (%)	OR (95% CI)	PAR (95% CI)
Head and neck cancer overall				
Alcohol alone	831 (7.4%)	1,587 (9.8%)	1.06 (0.88–1.28)	4.0 (1.5–5.3)
Tobacco alone	673 (6.0%)	3,653 (22.6%)	2.37 (1.66–3.39)	33.0 (42.6–25.9)
Tobacco and alcohol	9,146 (81.6%)	8,574 (53.1%)	5.73 (3.62–9.06)	34.9 (17.2–48.0)
Total	11,211	16,152	*ψ = 2.15 (1.53–3.04)*	72.0 (61.2–79.1)
Oral cavity				
Alcohol alone	221 (7.4%)	1,587 (9.8%)	0.79 (0.60–1.04)	−1.1 (−11.4–3.7)
Tobacco alone	191 (6.4%)	3,653 (22.6%)	1.74 (1.10–2.76)	24.8 (19.6–31.1)
Tobacco and alcohol	2,354 (78.7%)	8,574 (53.1%)	4.78 (2.59–8.81)	39.9 (24.9–51.4)
Total	2,992	16,152	*ψ = 3.09 (1.82–5.23)*	63.7 (44.7–74.7)
Pharynx				
Alcohol alone	247 (6.1%)	1,587 (9.8%)	1.28 (0.91–1.80)	5.6 (1.9–7.3)
Tobacco alone	289 (7.2%)	3,653 (22.6%)	1.91 (1.39–2.62)	24.3 (30.7–19.2)
Tobacco and alcohol	3,321 (82.2%)	8,574 (53.1%)	5.42 (3.21–9.16)	41.6 (25.0–53.7)
Total	4,038	16,152	*ψ = 1.90 (1.41–2.56)*	71.5 (57.6–80.2)
Larynx				
Alcohol alone	284 (9.6%)	1,308 (10.0%)	1.21 (0.77–1.92)	2.9 (−0.3–4.4)
Tobacco alone	89 (3.0%)	3,041 (23.2%)	6.76 (4.58–9.96)	52.2 (77.8–36.0)
Tobacco and alcohol	2,541 (85.9%)	6,850 (52.2%)	14.22 (8.26–24.46)	33.4 (4.5–52.1)
Total	2,959	13,130	*ψ = 1.62 (0.85–3.09)*	88.5 (82.1–92.4)

combined data for "Head and neck cancer overall" as an example, in the presence of tobacco use the added effect of alcohol increased the odds ratio (OR) from 2.37 to 5.73, which indicates a tripling the number of *added* cancer cases (from a 137% increase over baseline to a 473% increase over baseline). The statistical significance term ψ > 1 indicates a joint effect greater than expected under a multiplicative model (Hashibe et al. 2009).

Hashibe et al. (2009) go on to calculate the population attributable risk (PAR) for each condition thereby providing estimates of the impact of each risk factor, including interactions, in terms of the fraction (%) of the population affected. Again using overall data, the percentage of cancers attributable to alcohol-alone was 4.0% and to smoking-alone was 33.0%; and the portion attributable to the interaction was 34.9%, which suggests the total PAR for alcohol (also called the alcohol-attributable fraction, AAF) is 38.9%. Or looking at it another way, while the tobacco-attributable fraction is 67.9%, half of that is dependent on alcohol.

Sensitization: A study of women in Great Britain (Allen et al. 2009) designed and sufficiently powered (n = 1.28 million) to assess the effect of moderate drinking on cancer incidence revealed an additional manifestation of the smoking–alcohol interaction on UADT cancers as indicated in Table 3.2. Alcohol consumption, including the category with an intake of ≥7 units/week exhibited no impact on rates for UADT cancers *if* the women were "never smokers". If, however, women were current

Table 3.2 UADT cancers: sensitization of low doses of alcohol associated with tobacco smoking (from Allen et al. 2009)

Alcohol category (units[a]/week)	Never smokers		Current smokers	
	No. of cancers	RR (95% FCI[b])	No. of cancers	RR (95% FCI)
2 or less	165	*1.00* (0.86–1.17)	112	*2.54* (2.10–3.06)
3–6	121	*1.04* (0.87–1.25)	126	*3.57* (2.99–4.26)
7 or more	83	*0.93* (0.75–1.16)	257	*5.22* (4.60–5.92)

[a]One unit is equivalent to about 10 g alcohol
[b]Floated confidence interval

smokers then even the lowest intake category (≤2 units/week) exhibited increased risk (RR = 2.54) for UADT cancers. And women smokers consuming 3–6 units/week had a 3.57-fold increase in UADT cancers compared to nonsmokers. Since each unit = 10 g of ethanol, this means that intake less that 20 g/week, that is 1½ drinks *per week* (where one drink equals 14 g of ethanol, NIAAA 2007) is sufficient to more than double the risk for cancers of the upper aerodigestive tract. This magnitude of sensitization caused by smoking raises the question whether consumption of alcohol in a range otherwise deemed safe may in fact carry a significant risk if a sensitizing cofactor is also present.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is said to be the fifth most common cancer worldwide and the third most common cause of cancer-related death, with an annual incidence of 564,000 new cases nearly matched by an annual mortality of 549,000 in 2000 (AICR 2007).

Global variation in HCC highlights the impact of multiple risk factors: The concentration of HCC cases in East Asia reflects the impact of infectious hepatitis, particularly HBV in China, Southeast Asia and HCV in Japan, and the combination of HBV and HCV in Mongolia (Globocan 2002; AICR 2007). Hepatitis B also prevails in much of Africa and in Haiti (Andernach et al. 2009), and other risk factors include food-borne aflatoxin exposure in sub-Saharan Africa, Southeast Asia, and China (Liu and Wu 2010), and isolated instances of dietary iron exposure (Kew and Asare 2007).

Alcohol's primary effects and synergistic interactions: Chronic heavy consumption of alcohol is a primary risk factor with significant effects on HCC depending on the quantities consumed. Table 3.3 summarizes the main results of three studies (Donato et al. 2002; Hassan et al. 2002; Yuan et al. 2004). Relatively high alcohol consumption (greater than 4 drinks per day) increased the odds ratios (ORs) to 2.6, 7.0, or 8.0 in the three studies in the absence of viral hepatitis. But a remarkably greater effect occurs when alcohol acts in concert with HBV or HCV, yielding odds ratios for HCC 48, 54, and 109-fold above baseline, respectively. This observation illustrates that the *synergistic* impact of alcohol on HCC can far outweigh its *independent*

Table 3.3 Hepatocellular carcinoma: summary of three studies evaluating the interaction between alcohol consumption and infectious hepatitis, HCV or HBV (representing +/− for HCV RNA and +/− for HBsAg)

	Low alcohol		High alcohol[a]	
	HCV− and HBV−	HCV+ or HBV+	HCV− and HBV−	HCV+ or HBV+
Donato et al. (2002)	1.0 (ref)	55 (30–101), 23 (12–43)[b]	7.0 (4.5–11.1)	109 (51–233), 49 (24–98)
Hassan et al. (2002)	1.0 (ref)	19.1 (4.1–89.1)	2.4 (1.3–4.4)	53.9 (7–415.7)
Yuan et al. (2004)	1.0 (ref)	8.1 (4.6–14)	2.6 (1.3–5.1)	48.3 (11.0–212.1)

[a]Definitions of high alcohol intake differed in each case but all approximated 4 drinks/day
[b]Donato et al. listed HCV and HBV independently

effects (i.e., effects occurring in the absence of other risk factors). Moreover, the combination of alcoholic liver disease and HCV occurs in a significant portion of patients with liver disease (Singal and Anand 2007), which suggests a frequently underestimated contribution to HCC (Mueller et al. 2009).

Alcohol and smoking interaction: While the effects of alcohol and smoking in combination on HCC suggest synergism, results are not always consistent. In a Japanese study, the RR for developing HCC was higher in those who both drank alcohol and smoked than in those who either drank or smoked (Mukaiya et al. 1998). And in another report, heavy smoking had no effect on HCC among light drinkers, but did have a significant effect among heavy drinkers (OR = 5.6; Kuper et al. 2000). Other studies found that while smoking alone increased the ORs for HCC (3.9 for men and 3.1 in women), a significant interaction with alcohol was only observed in women (OR = 2.8 for men and 13.7 for women; Hassan et al. 2008).

Global trends in hepatocellular carcinoma: In countries with the highest incidence rates of HBV such as China, recent trends are toward *decreasing* incidence of HCC largely attributable to widespread HBV vaccination and reduced aflatoxin exposure (Bosch et al. 2004). In Japan, the incidence of HCC is decreasing in younger people, although mortality rates lag behind, reflecting the acquisition of HCV several decades earlier (Tanaka et al. 2008). By contrast, several countries with historically low rates of HCC are experiencing steady increases in the annual incidence of HCC cases. These include Scotland (McDonald et al. 2008), Canada (Cancer Care Ontario 2006), France (Remontet et al. 2003), Australia (Law et al. 2000), and the USA (El-Serag et al. 2003).

Hepatocellular carcinoma epidemic in the USA: The National Cancer Institute's ongoing "*Surveillance, Epidemiology and End Results*" has documented the steadily increasing incidence rate for HCC from 1975 to 2005, with an annual percent change of +4.5%, and a threefold increase (from 1.5 to 4.9 per 100,000) over the 30-year period (Fig. 3.2; Altekruse et al. 2009).

One factor contributing to this increase in liver cancer is that it is the result of the increasing impact of viral hepatitis (mainly HCV) during the 1990s (El-Serag and Mason 2000; El-Serag et al. 2004). Even so, the majority of hepatocellular cancer
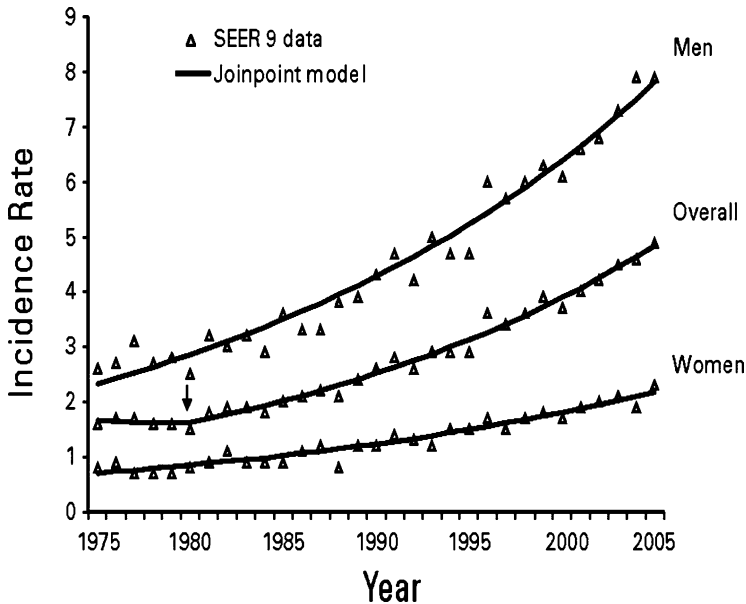
Fig. 3.2 HHC: Annual age-adjusted incidence rates per 100,000 and trends, all hepatocellular carcinoma cases and by sex, 1975–2005 (Surveillance, Epidemiology, and End Results 9, SEER9) (from Altekruse et al. 2009)

patients in the USA (55–78%) remained seronegative for both HCV and HBV (El-Serag et al. 2004; Hassan et al. 2002; Davila et al. 2004) and separate CDC data indicate that there has been a multifold *decrease* in the incidence of HBV and HCV acute hepatitis since the early 1980s (Daniels et al. 2009). Together, this suggests that other factors play a role in the rise in HCC.

The single largest identifiable risk factor among HCC patients, alcoholic liver disease (ALD), is present in about 25% of HCC patients (Davila et al. 2004), but alcohol consumption has been relatively stable (LaVallee and Yi 2010) and thus unlikely to contribute to the rising HCC rate, at least not independently. Instead, some assessments have focused attention on categories of HCC patients who were neither virus positive nor alcoholic (categories designated "non-specific cirrhosis" or "idiopathic", El-Serag et al. 2004) which together account for the majority of patients with HCC. Also referred to as "cryptogenic cirrhosis," these contributing factors of HCC are often assumed to be related to the obesity epidemic in the USA and other Western countries (Marchesini et al. 2008; Qian and Fan 2005), or more specifically to the following: diabetes, nonalcoholic fatty liver disease, dyslipidemia, and other manifestations of the metabolic syndrome (Osterreicher and Brenner 2007; Bugianesi et al. 2007; Siegel and Zhu 2009).

The linkage between obesity and the rising incidence of hepatocellular carcinoma is supported by several observations: the timing of the adult obesity epidemic and the rising incidence of HCC are approximately concurrent over the last 25 years
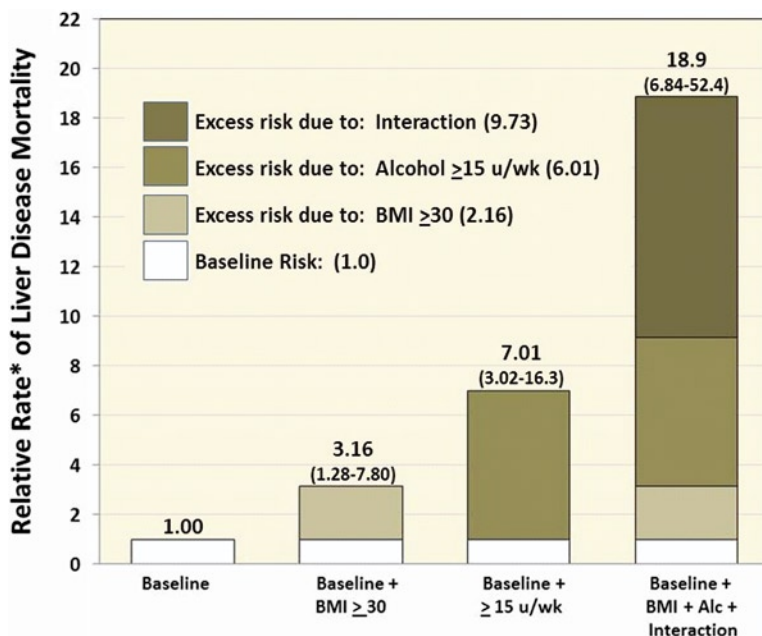
Fig. 3.3 Liver disease mortality as a function of BMI and alcohol consumption in men (data from Hart et al. 2010)
Units = 10 g ethanol.
*Relative Rate (95% CI) adjusted for age, study, social class, smoking, height, bronchitis, FEV1, angina, ischemia on electrocardiogram, and diabetes

(NCHS 2008), and the prevalence of obesity (BMI ≥ 30) in the USA is 32.2% among men and 35.5% among women (Flegal et al. 2010) is sufficient to have a large impact. However, a question arises when taking into account the male to female ratio for hepatocellular carcinoma (about 3.5:1 in Fig. 3.2). If the HCC epidemic were driven by the obesity epidemic, one would expect that men and women would be equally affected and the gender gap evident in Fig. 3.3 should be narrowing.

These observations do not eliminate obesity as an important contributor to the HCC epidemic; rather, they suggest that one or more additional cofactors play a significant role – a role that accounts for the observed gender bias. Likely candidates among risk factors include viral hepatitis B and C, and alcohol consumption. Each is a significant risk factor for HCC on its own, exhibits a greater incidence in men, and has the capacity to interact synergistically with obesity (Davila et al. 2004).

Alcohol and obesity interactions: A hospital-based, case–control study among HCC patients and controls conducted at the M. D. Anderson Cancer Center in Houston provides evidence that alcohol acts as a synergistic agent with diabetes (Hassan et al. 2002). With a background of diabetes, heavy alcohol consumption increased the risk of HCC from OR = 2.4 to 9.9 (Synergy Index, S = 2.9, p < 0.02). Consistent with other reports (Larsson and Wolk 2007), these data show that diabetes is an independent risk

factor for HCC, and support the thesis that alcohol, which is consumed more by men than by women (2.67 to one, Keyes et al. 2008), could enhance the effect of obesity (in this case from RR=2.4 to RR=9.9) on the incidence of HCC.

Another recent study conducted in Scotland serves to illustrate the combined effects of alcohol intake and obesity on all liver disease mortality including cancer. Results indicate that even drinking 14 or fewer units per week significantly increased the relative risk to 5.30 (CI95%: 1.36–20.7, Hart et al. 2010). Since one unit is 10 g of ethanol, this is equivalent to ten drinks per week (or less that 1½ per day) based on NIAAA definition of 14 g per drink (NIAAA 2007). And for intake greater than 14 units (ten drinks) per week, the RRs were 3.16 in normal weight, 7.01 in overweight, and 18.9 in obese men (Fig. 3.3, data from Hart et al. 2010). Thus, these data demonstrate the capacity for obesity to amplify the effects of alcohol on HCC and to sensitize pathophysiologic mechanisms at rates of alcohol consumption usually considered safe.

Gender differences: Given that the incidence in HCC is largely driven by risk factors and the risk factors themselves occur more frequently in men than in women, the default assumption of this chapter on epidemiology is that the gender bias for HCC is secondary to the gender bias in risk factors. However, direct biological and endocrinological causes for gender differences in alcohol-induced HCC remain possible and perhaps likely. For example, male mice and ovariectomized female mice are more sensitive to diethylnitrosamine (DEN)-induced HCC than are intact females, and estradiol treatment reinstates resistance to DEN in ovariectomized females (Shimizu et al. 1998; Maeda et al. 2005).
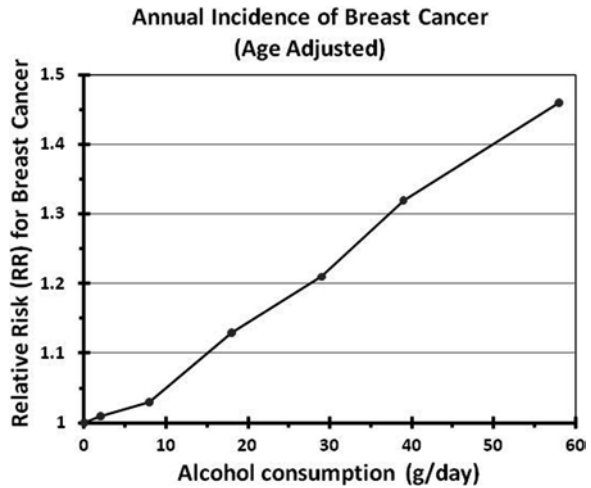
Breast Cancer

Breast cancer was diagnosed in about 192,000 American women in 2009, accounting for 27% of all cancers and 15% of all cancer-related deaths in women (American Cancer Society 2009).

Epidemiological data reveal a near-linear relationship between alcohol intake and breast cancer risk even at very low rates of intake (Fig. 3.4). Reflecting this apparent linearity, investigators express the effect of alcohol on breast cancer as percent increase per unit of alcohol, i.e., 10 g consumed daily. A typical estimate is $7.1 \pm 1.3\%$ for each unit per day (Collaborative Group on Hormonal Factors in Breast Cancer 2002; see also Key et al. 2006). An increased relative risk of 7% per unit (or 10% per 14 g drink) may appear modest compared to values cited above, but breast cancer occurs very frequently and many women drink moderately. It is this combination that results in a large health burden, with breast cancer accounting for estimated 60% of all *alcohol-attributable* cancers in women (Boffetta et al. 2006).

An analysis of *interactions* between alcohol and other risk factors for breast cancer indicates few significant interactions even among risk factors known to exhibit independent effects. Thus, for women whose mother or sister had breast cancer there

Fig. 3.4 Breast cancer: effect of alcohol consumption (g/day) on the annual incidence relative risk (RR) for breast cancer (data from Collaborative Group on Hormonal Factors in Breast Cancer 2002)

was a 12% rate increase per unit consumed. And for nonwhite women or women from developing countries, the effect of alcohol was not significant (Collaborative Group on Hormonal Factors in Breast Cancer 2002). Perhaps surprisingly, risk factors with known independent effects on breast cancer rates, such as parity, excess BMI, use of hormonal contraceptives or hormone replacement therapy did not exhibit *interactions* with alcohol (Collaborative Group on Hormonal Factors in Breast Cancer 2002). While other smaller studies have documented alcohol–HRT interactions for breast cancer; some are based on the absence of an HRT effect among women who do not drink or an alcohol effect only among "never users" of HRT (Colditz et al. 1990; Gapstur et al. 1992; Terry et al. 2006).

Recent advances have indicated that alcohol consumption is strongly related to estrogen receptor positive (ER+) breast cancers. Thus, for women with ER+ cancers, the odds ratio associated with drinking ≥13.8 g/day was 2.16 (1.68–2.76) compared to nondrinkers (Deandrea et al. 2008). Furthermore, the alcohol-associated impact on breast cancer appears to be effective in ER+ invasive lobular carcinoma, but not in ER+ invasive ductal carcinoma (Li et al. 2010).

Pancreatic Ductal Adenocarcinoma

While chronic alcohol consumption is a well-documented cause of chronic pancreatitis, alcohol's effect on pancreatic cancer (PDAC) has been inconsistent (Welsch et al. 2006). Tobacco use is the single most significant risk factor for pancreatic ductal adenocarcinoma (PDAC) (Lowenfels and Maisonneuve 2004), and the co-occurrence of drinking and smoking has made potential connection between drinking and pancreatic cancer difficult to distinguish. However, a recent case–control study found that subjects who were both heavy drinkers and heavy smokers

exhibited a 4.3-fold greater risk for PDAC compared to heavy smokers who drank less than 7 drinks per week (Talamini et al. 2010). And a meta-analysis of 32 publications indicated that high rates of drinking (≥3 drinks/day) were associated with a significantly increased relative risk for pancreatic cancer: RR = 1.22 (1.12–1.34) (Tramacere et al. 2010).

Colorectal Cancer

Colorectal cancers (CRC) (i.e., cancer of the proximal colon, distal colon, and rectum) regularly appear on the lists of alcohol-related cancers (e.g., AICR 2007), and various studies have identified gender differences or the differential effects of beer, wine, or spirits (e.g., Bongaerts et al. 2008). However, reviews of this literature include both positive and negative studies (Seitz and Cho 2009). Examples of positive studies include the large NHANES follow-up study (NHEFS) that found the RR for colon cancer was 1.69 (Su and Arab 2004), and a pooled analysis of eight cohort studies indicated a RR = 1.41 for subjects drinking more than 45 g/day (Cho et al. 2004), but with no indication of gender differences or specific beverage effects. Finally, two recent reports came to different conclusions. While a large prospective study in Europe concluded that alcohol consumption was not associated with CRC (Park et al. 2009), a large meta-analysis of 103 cohort studies concluded the pooled RR for alcohol-associated CRC was 1.56 (1.42–1.79), which was about twice that of other significant lifestyle factors including, diabetes, consumption of red meat, obesity, or smoking (Huxley et al. 2009). Finally, it has been suggested that additional confounding effects for CRC may be associated with diet (Larsson et al. 2005) or the microbiome resident in the GI tract (Seitz and Cho 2009; Koivisto and Salaspuro 1998). It is anticipated that an understanding of these additional factors may help resolve apparent discrepancies in the existing literature.

Lung Cancer

Epidemiological studies consistently find strong association between tobacco smoking and the risk for lung cancer, but evidence for an effect of alcohol has been elusive. Some studies found a significant effect of alcohol at doses greater than 50 g/week (Korte et al. 2002). But other studies, each using large pooled-analyses yielded opposing results. One case showed a strong effect of alcohol in male "never smokers" with risk ratios RR = 2.53 for men drinking 5–15 g/day and RR = 6.38 for men drinking ≥15 g/day (Freudenheim et al. 2005), while another focused specifically on lifelong nonsmokers reported "substantial evidence against the hypothesis that alcohol consumption *independently* increases lung cancer risk" (Thun et al. 2009). These results are not easily reconciled into a clear pattern. And an important caveat with all these studies is that the effects of alcohol need not be *independent* to be important, as is the case with the UADT cancers cited above.

Two indirect lines of evidence suggest that the potential interaction between alcohol and tobacco smoking on lung cancer should be reexamined. The first is that contrary to previous expectations there is now clear evidence that chronic alcohol exposure renders the lung susceptible to another stressor, such as sepsis. Characteristics of what has come to be called the "alcoholic lung" include the following: depletion of glutathione, dysfunction of the alveolar epithelium, and the consequent clinical manifestation: acute respiratory distress syndrome (ARDS) (Moss and Burnham 2003; Guidot and Hart 2005; Joshi and Guidot 2007). The second is the emerging evidence indicating a genetic susceptibility to lung cancer associated with the alcohol and acetaldehyde metabolizing enzymes already associated with UADT cancers (Segado Soriano et al. 2005; Minegishi et al. 2007; Park et al. 2010).

Prostate Cancer

The American Institute for Cancer Research report concluded that there were insufficient data to implicate alcohol as a significant contributor of prostate cancer (AICR 2007). The Alcohol-Related Disease Impact (ARDI) report indicated an annual rate of 232 deaths in the USA due to prostate cancer, which is less than one percent of the 27,000 annual total (American Cancer Society 2009). A recent review of the evidence from NCI indicated that while alcohol modestly increases the risk for nonadvanced prostate cancer, there was no association with advanced prostate cancers or mortality (Watters et al. 2010).

Stomach Cancer

The evidence for alcohol-associated stomach cancer is relatively weak. Thus, a population-based case–control study conducted in Montreal found no effect of 7+ drinks per week vs. <7 drinks/week for either all alcoholic beverages or each beverage tested individually (OR = 1.15 for all alcoholic beverages). But then, the same study found there was an effect among subjects drinking 7+ drinks weekly at the highest level of total exposure, i.e., >180 drink-years (Benedetti et al. 2009). Negative results have also been noted in India (Sumathi et al. 2009). On the contrary, ALDH2*2 is associated with increased susceptibility to gastric cancer (Yokoyama et al. 1998).

Thyroid Cancer (Alcohol Lowers the Risk)

Recent US data indicate that thyroid cancer is diagnosed in about 22,000 individuals each year with a relative low mortality rate of about 1,600 (ACS Table, 2009). Thyroid cancer is unusual in several ways: First, it is one of the few cancers with a significantly higher incidence rate (2.7-fold) in women than in men (i.e., other than

breast and female reproductive system cancers, ACS Table, 2009). Second, very few risk factors have been identified for thyroid cancer, and those that have been identified are uncharacteristic of other cancers (iodine deficiency and childhood exposure to ionizing radiation, Dal Maso et al. 2009). Finally, the risk for thyroid cancer is *decreased* with alcohol consumption especially in women (Nagano et al. 2007; Mack et al. 2003). In the Million Women Study, alcohol reduced the incidence of thyroid cancer by nearly 50% (RR=0.54, $p<0.005$; Allen et al. 2009). The National Cancer Institute's NIH-AARP study confirmed a protective effect due to alcohol (RR=0.57, $p<0.01$) with two or more drinks per day and also indicated that beer was more effective than wine or distilled spirits (Meinhold et al. 2009). Finally, thyroid cancer may not be unique, since several sources including the Million Women Study also found decreased incidence of non-Hodgkin lymphoma (RR=0.77, $p=0.001$) and renal cell carcinoma (RR=0.66, $p=0.03$) associated with alcohol consumption.

Estimating Alcohol's Impact on Cancer Mortality in the USA

As a means for estimating alcohol's total impact on cancer mortality in the USA, Table 3.4 uses two sets of published data: alcohol-attributable fraction (AAF) as determined in Canada (Rehm et al. 2006) and the American Cancer Society (2009) table for 2009. Note that the AAF data approximate those in Table 3.1 (Hashibe et al. 2009), which explicitly takes into account tobacco–alcohol interactions on UADT cancers. The fifth and sixth columns of Table 3.4 are calculated for males and females, which are then summed and compared to the ARDI data cited in the Introduction. The total alcohol-attributable cancer deaths per year are calculated to

Table 3.4 Estimation of alcohol-attributable annual cancer mortality (from Rehm et al. 2006; American Cancer Society 2009; CDC 2010)

Malignant neoplasms listed by Rehm et al. (2006)	Rehm et al. (2006) AAF% deaths		Am Cancer Soc table estimated deaths		AAF% × estimated deaths		Alc. Attr. deaths	ARDI deaths
	Male	Female	Male	Female	Male	Female	Total M+F	Total M+F
Mouth and oropharynx cancers	32.7%	18.5%	5,240	2,360	1,713	437	2,150	376
Esophageal cancer	37.7%	24.2%	11,490	3,040	4,332	736	5,067	478
Laryngeal cancer	42.8%	31.0%	2,900	760	1,241	236	1,477	237
Liver cancer	31.7%	22.0%	12,090	6,070	3,833	1,335	5,168	786
Breast cancer	–	6.4%	440	40,170	–	2,571	2,571	355
Other neoplasms	8.7%	5.1%	–	–	–	–	–	–
Prostate cancer	–	–	27,360	–	–	–	–	232
Totals	30.5%	9.1%	59,520	52,400	11,119	5,314	16,433	2,464

be 16,433, which is much greater than the number (2,464) provided in the ARDI report (CDC 2010) and does not include prostate cancer or "other neoplasms" for which there were missing data cells. This sixfold difference raises the question whether an incomplete accounting of alcohol's synergistic effects may have led to underestimations of alcohol's total impact on cancer deaths in the USA.

Summary

From the overview presented here, it is clear that alcohol consumption is a major risk factor for cancers of the pharynx, larynx, esophagus, and other UADT tissues directly impacted by alcohol during drinking, and for cancer of the liver where alcohol is metabolized. Drinking is also a significant risk factor for breast cancer in women especially in developed countries. Among men, alcohol is a significant risk factor for CRC and for nonadvanced prostate cancer.

Epidemiological evidence emphasizes the observation that while alcohol is an independent risk factor for cancer, it also interacts with other major risk factors including viral hepatitis B and C, smoking and obesity, and that these interactions are typically synergistic.

Synergism can be manifested in several ways, including the following: (1) by a rate of cancer incidence significantly greater than the sum of each of the risk factors alone and (2) by sensitization to low doses of alcohol that would otherwise be considered safe, as in the case of smoking and alcohol on UADT cancers.

There is consistent evidence that alcohol-related cancers occur in about three men for every one woman (other than breast cancer, of course). One of the reasons for this difference probably is the gender bias in the risk factors that contribute to cancer. This is true for alcohol consumption, for HBV and HCV, and for smoking (albeit increasingly less so), but not for obesity. Also, it is likely that biological factor, including the effects of steroid hormones, contributes to the sex differences in cancer rates.

Finally, the epidemiological assessment of recent trends in the incidence of hepatocellular carcinoma indicates decreasing rates in parts of the world where incidence is highest, and increasing rates in developed countries. It is suggested that the increasing trends in HCC could result from the growing impact of obesity interacting with the gender-biased risk factors: alcohol consumption, HCV, and HBV.

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