Alcohol has been part of the warp and woof of most human societies for thousands of years. People enjoy consuming it: they enjoy its narcotic effects and use it as a social lubricant. Nonetheless, its proscription in many cultures is testimony to the significant costs of alcohol use, the most glaring of which are the consequences of alcohol abuse, including social disruption, addiction, and physical debilitation.

There is little doubt that alcohol is a scourge for those who become addicted. In addition, excessive intake over the long term causes severe damage to the liver, kidney, and circulatory system. It even causes cancer at several sites. Research is making new advances in identifying the causal pathways by which alcohol may have an impact. In addition, more is being learned about the molecular factors that facilitate or hinder the impact of alcohol on cancer risk.

Identifying the linkages of alcohol to cancer risk poses severe epidemiologic challenges. For alcohol intake to affect cancer risk appears to require decades of elevated exposure. Alcohol exposure is generally difficult to measure, and it is correlated with a number of other practices, especially cigarette smoking, that increase cancer risk. Thus, identifying the specific etiologic importance of alcohol is difficult. Because of the social isolation and disruption associated with alcohol abuse, it is doubly difficult to obtain data from those who most abuse alcohol.

This chapter briefly summarizes the present understanding of the mechanisms by which alcohol might affect cancer risk and then proceeds to evaluate the molecular genetic factors that appear relevant to alcohol metabolism and hence the impact of alcohol on cancer risk. Brief reviews of the means by which alcohol’s effects can be studied and their limitations follow. The role of alcohol in cancer at major cancer sites is then used to gauge the likely importance of alcohol to cancer risk and prevention. These sites are either ones for which there is a substantial literature linking alcohol to risk, or they are associated with significant morbidity and mortality.

**ALCOHOL IN CANCER ETIOLOGY: POSSIBLE EXPOSURE MECHANISMS**

Epidemiologic associations have been found between alcohol consumption and risk of cancer at various sites. A number of possible mechanisms may explain this putative relation, including the effects of alcohol on carcinogen metabolism, effects of acetaldehyde, interactions of alcohol with nutritional factors, effects of alcohol on hormone levels, and physical effects of alcohol on tissues. There is evidence that links all kinds of alcoholic beverages to such risks. We focus here on the effects of ethanol consumption on cancer etiology. There may be additional effects related to the compounds found in alcoholic beverages.

Ethanol may affect the activation of carcinogens because of its effects on the induction of several of the p450 cytochromes. There is evidence from an animal model that chronic alcohol exposure can lead to induction of the cytochrome p450s 2E1, 1A1, 2B1, and 3A1 (Roberts et al., 1995). It may also inhibit phase II enzymes, affecting the clearance of carcinogens (Singletary and Gapstur, 2001).

Acetaldehyde has been identified as a carcinogen by the International Agency for Research on Cancer (IARC). There is evidence from animal and cell models that it has mutagenic effects and can affect the cell cycle, apoptosis, and DNA repair (Seitz et al., 1998). Exposure to this alcohol metabolite may explain part of the observed associations between alcohol consumption and cancer risk. Although most alcohol metabolism occurs in the liver, there is alcohol dehydrogenase activity in a number of other tissues (Saleem et al., 1984) with the possibility of exposure to acetaldehyde. Microbial metabolism of alcohol to acetaldehyde may play a role in the carcinogenesis of the upper gastrointestinal tract (Seitz et al., 1998). Acetaldehyde-DNA adducts may form as a result of alcohol exposure. Furthermore, there may be increased levels of malondialdehyde and 4-hydroxyxenal, lipid peroxidation products that may be produced as a result of acetaldehyde metabolism. These substances can bind DNA and affect gene transcription; and they may, with acetaldehyde, bind to proteins to affect cell functioning (Eriksson, 2001).

Some of the observed associations of alcohol and cancer may be caused by alcohol-related effects on the status of nutrients of significance to cancer etiology. For example, alcohol consumption has a negative impact on the absorption, utilization, and excretion of folate (Herbert and Kshitish, 1994). Folate may be related to risk of cancer of the large bowel (Freudenheim et al., 1991; Giovannucci et al., 1993); and in relation to breast cancer risk, women with low folate levels may be particularly vulnerable to the effects of alcohol (Zhang et al., 1999; Sellers et al., 2002). Alcohol consumption may also affect nutritional status for other nutrients that have been suggested to be related to cancer risk. Compared with nondrinkers, drinkers may have lower concentrations of some carotenoids and vitamin C (Lieber, 2000; Singletary and Gapstur, 2001). Alcohol may interfere with vitamin A absorption, increase its degradation (Seitz et al., 1998), and interfere with the synthesis of retinoic acid from retinal (Lieber, 2000; Agarwal, 2001). There may be effects on vitamin D (Lieber, 2000).

The metabolism of alcohol by CYP2E1 leads to increased production of reactive oxygen species, which in turn may exacerbate the effects of lower levels of antioxidant vitamins. Furthermore, acetaldehyde metabolism enzymes, molybdenum hydroxylase (XOR) and aldehyde oxidase (AOR) result in the production of reactive oxygen species (Wright et al., 1999).

Alcohol can have both acute and chronic effects on blood hormone concentrations. Increased concentrations of estrogens and urinary metabolites of estrogen and decreased sex hormone-binding globulin have been found to be associated with alcohol consumption (Dorgan et al., 1994; Muti et al., 1998; Ginsburg, 1999; Onland-Moret et al., 2005). Chronic heavy alcohol consumption also affects aromatization of androgens to estrogens in animal models (Purohit, 2000). These mechanisms may be important for hormone-sensitive tumors such as breast and prostate cancers.

Physical properties of alcohol may also be of significance, particularly for tissues that come in direct contact with alcoholic beverages, such as the upper gastrointestinal tract. It has been hypothesized that the solvent properties of alcohol may enhance the effects of exposure to carcinogens such as those in tobacco. As detailed below, there is evidence of interactive effects of alcohol consumption and smoking on the risk of several cancers. Moreover, local exposure to alcohol may have proliferative effects on tissues (Seitz et al., 1998). Alcohol may affect tissues because of its effects on membrane fluidity (Simonetti et al., 1995).

Alcohol has been shown to have myriad effects on human physiology. Depending on the dose and frequency of use, this exposure...
METABOLISM OF ALCOHOL AND ALCOHOLIC BEVERAGES: ROLE OF GENETIC VARIATION AND OTHER FACTORS

Alcohol is absorbed by the small intestine and delivered to the blood and then the liver. Absorption by the gut is virtually complete. Although approximately 90% of alcohol metabolism occurs in the liver (Agarwal, 2001), there is evidence of metabolism of alcohol by the intestinal tract and of activity of alcohol-metabolizing enzymes in other tissues (Saleem et al., 1984). The increased concentration of alcohol in the blood after ingestion depends on the rate of gastric emptying and of first-pass metabolism of alcohol by the intestinal tract and the liver (Li et al., 2001). Unmetabolized ethanol is distributed to other body organs, with the relative concentrations in each organ depending on the water content of the organ (Ramchandani et al., 2001).

There are three possible pathways for oxidation of alcohol to acetaldehyde: by alcohol dehydrogenases (ADHs) in the cytosol of the cell; by the microsomal ethanol-oxidizing system (MEOS) in the endoplasmic reticulum; and by the catalase in the peroxisomes. The primary pathway is by the ADHs. The MEOS system is induced, leading to alcohol metabolism by cytochrome p450 2E1, at extremely high levels of intake and with chronic alcohol consumption (Lieber, 2000). Catalase, dependent on H2O2, likely does not play a significant role in alcohol metabolism in vivo.

Acetaldehyde is further metabolized by acetaldehyde dehydrogenases (ALDHs) (Lieber, 2000). Nonoxidative condensation of alcohol catalyzed by fatty acid ethyl ester synthases may contribute to alcohol-related tissue damage, particularly in the heart (Agarwal, 2001). Furthermore, acetaldehyde may be metabolized to acetate by enzymes other than ALDH (e.g., XOR and AOR).

Several factors affect the rate of alcohol metabolism and subsequent breakdown of acetaldehyde: genetic variation, nutritional factors, other exogenous factors. Research regarding genetic variation in alcohol metabolism indicates that enzyme variants explain part of the variation in drinking behavior and in susceptibility to diseases associated with alcohol consumption, including cancer.

There are genetic variants of both the ADHs and the ALDHs. In addition to affecting the rate of alcohol metabolism, these genes may affect the amount of alcohol consumed because of their effects on the rate of clearance of acetaldehyde. Acetaldehyde accumulation produces unpleasant sensations such as flushing that can affect drinking behaviors. Genetic variation in other genes, such as those in the dopamine pathway, may affect the experience of reward from alcohol consumption and may have an effect on alcohol consumption itself (Kitson, 1999).

The alcohol dehydrogenases are a family of enzymes; the genes for these proteins map closely to each other on chromosome 4 (Edenberg, 2000). The nomenclature for the genes has recently been changed (Duester et al., 1999). The genes have been grouped into classes; those with the *1 variant compared to those with the *1 (Eriksson, 2001; Hasin et al., 2002), and there is evidence that those carrying the *2 are at lower risk for alcoholism (Chen et al., 1996; Eriksson, 2001). The *2 is found in 70% or more of Asian populations (Eriksson, 2001); the prevalence for Caucasians is generally much lower, less than 5% (Borras et al., 2000; Eriksson, 2001). However, prevalence may be as high as 20% among Ashkenazi Jews (Eriksson, 2001; Carr et al., 2002). One study showed an interaction of this variant with alcohol consumption and breast cancer risk (Stumer et al., 2002). The enzyme coded by the *3 variant can catalyze alcohol metabolism much more efficiently than the other two, leading to a more rapid drop in blood alcohol concentrations. This allele has been identified only among those of African ancestry. There is some evidence that this variant too can affect alcoholism (Ehlers et al., 2001).

There are two alleles in the ADH1C gene. The difference in maximum rate of reaction is much smaller than for the ADH1B alleles, differing by a factor of about two. The *1 codes for the more rapid variant enzyme (Bosron and Li, 1986). A number of studies have found an increased risk of cancer at a number of sites associated with the *1 variant (Coutelle et al., 1997; Harty et al., 1997; Freundheim et al., 1999). In another study, no association with breast cancer was observed, but there was evidence of variation in blood estrogen concentrations associated with the variant (Hines et al., 2000). There may be linkage disequilibrium between this gene and the ADH1B*2 allele in European populations (Borras et al., 2000); observed associations for ADH1C may be confounded by the ADH1B variant. There are two variants in the ADH2 gene; one in the promoter region has been shown to affect function. This ADH is active at higher alcohol concentrations (Edenberg et al., 1999; Stromberg et al., 2002).

ALDH also exists in multiple forms. It is believed that ALDH2, a mitochondrial enzyme, is primarily responsible for acetaldehyde oxidation. One variant of ALDH2 is found in approximately half of the Japanese and Chinese populations. In vitro, this variant, ALDH2*2, has virtually no activity; but individuals who are homozygous for this variant are highly sensitive to alcohol consumption, reacting with flushing of the skin, increased heart rate, and increased skin temperature (Ramchandani et al., 2001). Heterozygotes tend to be sensitive as well, though less so than homozygotes. Because of this reaction, those with the ALDH2*2 gene tend to drink less and are less likely to have alcohol dependence (Chen et al., 1996, 1998). Among those who metabolize acetaldehyde slowly but drink nonetheless, there may be increased organ damage. For example, Matsuo et al. (2001) and Yokoyama (2001) observed that ALDH2*2 was associated with a substantial increase in the risk of esophageal cancer.

Several polymorphisms have been identified in CYP2E1, which as noted, is induced by activation of the MEOS system; it is not clear that the polymorphisms affect function. In a study of Japanese men, one variant in the 5'-flanking region did not affect the amount of alcohol consumed. However, among heavy drinkers, it was associated with alcoholic liver disease (Tanaka et al., 1997). Among African American drinkers, one variant, a 96-bp insertion in the regulatory region that affects gene activity, increases activity in drinkers (McCarver et al., 1998; McCarver, 2001).

Other factors may also affect the rate of alcohol metabolism. Both endogenous and exogenous factors affect the rate of gastric emptying and the subsequent rate of absorption of ethanol from the gastrointestinal tract. The rate at which alcohol is consumed and the foods that are consumed with it affect this process. Independent of the effect of concurrent food consumption on alcohol absorption, consumption of other foodstuffs with alcohol increases the elimination of alcohol. This may result from blood flow in the liver, enzyme activity, or other factors. This effect does not depend on the relative food composition of fat, protein, or carbohydrate. Body height and body weight affect the concentration of alcohol in the blood after ingestion of a fixed amount of alcohol. The difference in metabolism and body weight likely results from differences in lean body
mass (Li et al., 2001). There are also differences in first-pass metabolism between men and women under age 50 (Lieber, 2000). It has been estimated that 50% of the variance in the rate of alcohol elimination is heritable (Li et al., 2001).

EPIDEMIOLOGIC RESEARCH ON ALCOHOL AND CANCER: STRATEGIC OPTIONS

Among the first data used to describe associations between alcohol and cancer risk are those derived from ecologic study designs. These designs evaluate the correlation of population measures of alcohol consumption with the population risk of a given cancer or set of cancers. The unit of analysis is a group or population sector, rather than an individual: it may be a state or province within a nation, or it may be the nation itself. Thus, for example, Macfarlane et al. (1995) studied the correlation of alcohol consumption and mortality due to upper aerodigestive tract cancer among men in 25 industrialized nations and found that alcohol intake and lung cancer were strong co-predictors of subsequent oral cancer. Limitations of this method are, first, that aggregates, rather than individuals, are studied, so the causal dynamics of ecologic correlations are not well identified. In addition, the roster of ecologic unit characteristics that can be studied is large, so identifying which of these characteristics are key and which are not is often not straightforward.

The case-control study design has been an important source of information regarding the importance of alcohol in cancer epidemiology. This study design compares alcohol exposure among cases—individuals who have a given cancer—to exposure among controls—individuals who are comparable but do not have cancer. The reference period for this analysis is a fixed time span prior to the interview; the researcher seeks to ensure that recent illness, which could influence an individual’s alcohol intake, does not distort the true association of alcohol and cancer risk. It has been well documented that this method has great potential to provide unbiased estimates of the association of alcohol and cancer (Cornfield, 1951, 1956; Miettinen, 1976; Miettinen and Cook, 1981). However, a critical limitation of this method in practice is that samples of cases might not represent all cases, and that samples of controls may not represent all those who conceivably could have the cancer under study but do not. Because some patterns of alcohol consumption might alter the probability that individuals are contacted and agree to be interviewed, identifying and obtaining appropriate samples of those with and without cancer may be difficult.

In addition, the study participants usually must attempt to recall their exposure at some point in the past, a period often specified as 1 or 2 years before the interview. People can indeed recall some facets of their prior alcohol exposure (Marshall et al., 1981; Gregorio et al., 1985; Freudenberg and Marshall, 1988). An important dimension of alcohol exposure is the timing and duration of that exposure: it is possible that the impact of alcohol intake varies by cancer. The lag between intake and risk may be a few years for some cancers and several decades for others. The appropriate time span must be identified and reported accurately. The farther in the past, the more likely it is that its role cannot be accurately assessed. Furthermore, average intake is generally queried, whereas the patterns of intake may be important. Aspects of alcohol consumption such as the number of drinks per drinking occasion and whether alcohol is consumed with meals may affect the biologic impact of consumption.

Third, alcohol intake is part of a network of behavioral patterns that might have additional effects on cancer risk. More specifically, alcohol intake is highly associated with several facets of tobacco use, dietary practice, physical activity, occupation, and environmental exposure. It may, in addition, be associated with several physical conditions, such as oral and gastrointestinal health. An accurate description of the importance of alcohol intake to cancer risk requires accurate information on exposure to these other factors (Marshall and Hastrup, 1996) as a first step to the appropriate evaluation of their relevance.

These challenges to alcohol and cancer research are exacerbated by the possibility that much of the deleterious impact of alcohol on risk for some cancers is concentrated among individuals who have exceedingly high intake. Corrao et al. (1999) concluded that the number of high quality studies addressing the shape of the dose-response between alcohol intake and cancer risk was not sufficient to permit conclusions to be drawn. As noted herein, heavy alcohol intake, binge drinking, and alcohol abuse have decided long-term effects on digestion and metabolism. Long-term alcohol abuse negatively affects liver and kidney function, whereas moderate alcohol intake does not; it is likely that these extraordinary abuse effects are transmitted to several organ sites. Alcohol abusers suffer from a number of competing risks of premature debilitation and death. Studying the effects of alcohol in light of the difficulties of identifying, contacting, obtaining data from, and maintaining contact with individuals whose alcohol intake is heavy or excessive remains a serious challenge.

SITE-SPECIFIC FINDINGS

Oral Cavity/Pharynx

One of the more consistent findings in the epidemiology of oral cancer is that alcohol intake is associated with increased risk. This association has been noted in both prospective and case-control studies.
Boffetta et al. (2001) evaluated the standardized incidence ratio as a measure of oral cancer risk among men and women with a history of hospitalization for alcoholic cirrhosis or pancreatitis: among each group of patients, the risk of oral cancer was increased about 12 times that of the general population. Kjaerheim et al. (1998) evaluated a cohort of nearly 11,000 Norwegian men and found the top category of alcohol consumption to be associated with a nearly fourfold elevation of oral cancer risk.

Because oral and pharyngeal cancers are relatively uncommon, case-control studies have played an important role. Wynder et al. (1957), reporting one of the first widely cited case-control studies, found that alcohol intake was associated with a more than fivefold and nearly eightfold elevations, respectively, of oral and pharyngeal cancer risk. Martinez (1969) observed that elevated alcohol intake in excess of four drinks per day was more common in oral and pharyngeal cancer cases than among controls. Bross and Coombs (1976) reported that alcohol intake was associated with an oral cancer relative risk of approximately 3.4. Graham et al. (1977) used the case-control study design, with noncancer hospital controls, to consider alcohol consumption in the context of tobacco consumption and compromised dentition, finding that consumption of two or more drinks per day was associated with a relative risk of almost 3; they observed, however, that the impact of alcohol consumption was diminished among heavy smokers. Tuyns et al. (1988) found elevated alcohol intake to multiply the relative risk of pharyngeal cancer by approximately 10- to 12-fold. Considering the effects of alcohol consumption on the risks of oral and pharyngeal cancer combined, Blot et al. (1988) found that elevated alcohol intake multiplied the relative risk of oral cancer by approximately ninefold. Constructing an index of lifetime consumption of alcohol and representing this consumption by the total estimated kilograms of ethanol intake, Schlecht et al. (2001) found the top category of alcohol intake among nonsmokers to be associated with an approximate doubling of oral cancer risk. Franceschi et al. (1990, 1992) and Zheng et al. (1990) found the oral cancer risk to be about tripled by elevated alcohol intake.

Identifying the specific importance of alcohol versus a key behavioral correlate of alcohol intake—tobacco—is not straightforward. Both alcohol intake and tobacco ingestion are associated with substantially increased risk of oral cancer, and the ingestion of each is highly correlated with that of the other. Both are measured with some error, so it is difficult to identify their separate contributions to risk. Alcohol and tobacco may interact to influence risk, so the impact of alcohol could be altered by the amount of smoking. The nature of the dose-response between alcohol intake and oral cancer risk may well be related to the impact of alcohol in the various populations sampled. For example, Gronbaek et al. (1998) found in a prospective analysis that intake of two or three alcoholic drinks per day was associated with an approximate doubling of oral cancer risk, consumption of six to nine drinks per day was associated with a relative risk of 5, and consumption of 10 or more drinks per day was associated with an even diminished relative risk. Indeed, the only increased risk associated with alcohol consumption was seen among those who consume no wine. The greatest elevation of relative risk was among those for whom 30% or more of consumption was spirits. Similarly, studies in Cuba (Garrote et al., 2001) and Brazil (Schlecht et al., 2001) showed that the greatest elevation of risk was associated with spirits consumption. Consumption of two liquors commonly consumed in Greece—ouzo and tsipouro—was associated with greater elevations of relative risk than was consumption of wine (Zavras et al., 2001).

Larynx

Because laryngeal cancer is also relatively uncommon among cancers, studying the role of alcohol has depended substantially on the case-control method (Wynder et al., 1956, 1976). According to Wynder et al. (1956), the quantity of alcohol consumed increased the risk, which persisted within categories of tobacco consumption. Although this report distinguished the extrinsic from the intrinsic larynx, it did not reveal large differences in the effects of alcohol on risk. A later report (Wynder et al., 1976) indicated that a substantial change had taken place in the male/female ratio, suggesting that this change corresponded to a rapid increase in smoking among women. The report also confirmed that increased relative risk of laryngeal cancer was associated with alcohol consumption (Wynder et al., 1976).

The first of the studies reported by Wynder et al. (1957) showed increased risk for those who consumed greater proportions of beer and whiskey. Zatonksi et al. (1991) found increased risk in Poland only for consumption of vodka: the risk associated with vodka consumption rose in a dose-response pattern according to years of consumption, so that with more than 30 years of regular vodka consumption the relative risk of laryngeal cancer, adjusted for cigarette consumption, was multiplied by approximately 10 times. Wynder et al. (1976) reported that a more important factor than total alcohol intake was occasional binge drinking. The importance of the drinking pattern is also seen in the finding of Dal Maso et al. (2002) that consumption of alcohol apart from meals, versus consumption only with meals, was associated with near doubling of the risk.

As the effects of both alcohol and tobacco appear relevant to laryngeal cancer risk, distinguishing their separate roles and their interaction poses a challenge. Wynder et al. (1956, 1976), utilizing early statistical techniques to control for limited numbers of other variables, concluded that the approximately twofold elevation of risk they observed with alcohol intake was independent of cigarette and other smoking. Later studies, including those of Williams and Horn (1977), Graham et al. (1981), Tuyns et al. (1988), Falk et al. (1989),
Sankarayyan et al. (1990), Franceschi et al. (1994), and Dosemeci et al. (1997), using newer techniques to control for tobacco, observed similar patterns. Other studies controlling for tobacco intake, including those of Burch et al. (1981), Elwood et al. (1984), Olsen et al. (1985), De Stefani et al. (1987), Zatonski et al. (1991), Choi et al. (1991), Maier et al. (1992), Freudenheim et al. (1992), and Muscat and Wynder (1992), have observed larger (generally at least fourfold) relative risks associated with alcohol intake. Only one large study that adjusted for tobacco intake—that reported by Zheng et al. (1992a, 1992b)—showed no elevation of risk with alcohol intake. In the population Zheng et al. studied, alcohol intake was relatively low: half of the subjects never consumed alcohol; and among those who drank alcohol, the top quartile began at four drinks per day.

Bothari et al. (2002) considered the impact of alcohol among non-smokers and of smoking among non-drinkers. Their findings indicated that among the few alcohol consumers who used no tobacco the relative risk of laryngeal cancer was increased about 2.5 times. For comparison, the relative risk associated with cigarette smoking among nondrinkers is between 13 and 14. Altieri et al. (2002) compared the impact of stopping alcohol consumption to that of stopping smoking. They found that cessation of tobacco consumption had a substantial effect on relative risk, leading to a nearly fourfold decrease in risk within 10 years, but that cessation of alcohol consumption had little impact on risk for nearly 20 years. These findings can either be interpreted as evidence that alcohol alone does not affect risk or that alcohol-induced damage is irreversible.

To date, many studies of laryngeal cancer have treated the larynx as a single organ. In terms of exposure, though, two regions can be identified: the laryngeal-pharyngeal junction, which is exposed directly to alcoholic beverages, and the main body of the larynx—the endolarynx—which has no exposure to liquids. Wynder’s 1956 report distinguished the two (Wynder et al., 1956). It is certainly possible that the part of the larynx exposed to liquids could be more influenced by alcoholic beverage consumption than the sector exposed only to air. Tuyns et al. (1988) distinguished the endolarynx from the hypopharynx, or junctional area, and found substantial effects of alcohol on cancer risk in both regions. Controlling for cigarette consumption, they reported that at each level alcohol intake was associated with increased risk. The importance of extremely high intakes was noteworthy: among light smokers, the relative risks associated with 0-40, 41-80, 81-120, and >120 g of alcohol per day, respectively, were 1.0, 1.6, 2.3, and 3.8. Among those whose smoking was maximal—those who consumed more than 25 cigarettes per day—the corresponding relative risks were 11.5, 18.5, 23.6, and 42.2. For the hypopharynx and epilarynx, however, relative risks among light smokers ranged, respectively, from 1.0 to 3.0, 5.5 to 14.7 among those consuming 0-40, 41-80, 81-120, and 121 or more drinks per day; among heavy smokers, the corresponding relative risks ranged from 4.9 to 18.4 to 37.6 to 135.5. Clearly, then, although intake of alcohol has a greater impact on those regions of the larynx directly exposed to alcohol, relative risk also is modified in regions that are not directly exposed (Tuyns et al., 1988).

As with oral cancer, given the massive impact of tobacco intake on laryngeal cancer and the close connection of tobacco and alcohol intake, it is possible that a substantial proportion of the association of alcohol intake and laryngeal cancer stems from incomplete control for tobacco intake. The association of alcohol and cancer of the endolarynx, not directly exposed to alcohol, tends to be modest: around 2. The latter association can possibly be attributed in large part to resistent confounding by cigarette smoking.

**Esophagus**

Few organs except the oral cavity, hypopharynx, and esophagus are directly exposed to the predigested agents in alcoholic beverages. Thus, observations that esophageal cancer patients were often heavy alcoholic beverage consumers (Wynder and Bross, 1961) led to the development of a substantial epidemiologic literature linking alcoholic beverage intake and esophageal cancer risk. The importance of alcohol vis-à-vis tobacco has been of concern. Although the esophagus is not directly exposed to tobacco smoke, it is bathed in residual condensates of tobacco smoke that accumulate in the mouth and pharynx. Addressing the possible confounding effects of alcohol and tobacco, Wynder and Bross (1961) observed that the then-recent rise in lung cancer associated with cigarette smoking had not been accompanied by a parallel rise in esophageal cancer.

The association of heavy alcohol use with substantially increased risk of esophageal cancer is quite consistent, with a large number of studies indicating relative risks of 8–10 for heavy consumption (Wynder and Bross, 1961; Martinez, 1969; Tuyns et al., 1977, 1979; Potterm et al., 1981; Vassallo et al., 1935; Victoria et al., 1987; Yu et al., 1988; Cheng et al., 1992; Gao et al., 1994; Hu et al., 1994; Castellsague et al., 1999; Gallus et al., 2001; Wu et al., 2001; Boonyaphiphat et al., 2002). Dal Maso et al. (2002) observed a relative risk of more than 13 for consumption of eight or more drinks per day. Among these studies, there appears to be a sharp rise in risk associated with the upper ranges of consumption. A number of small studies, including those of Bradshaw and Schonland (1974), De Jong et al. (1974), Notani (1988), De Stefani et al. (1990), Sankaranarayanan et al. (1991), Sharp et al. (2001), and Yang et al. (2004) have observed smaller or negligible relative risk elevations.

Increases in risk were also observed in prospective studies by Schmidt and Popham (1981) and Hirayama (1990). With the exception of Wynder and Bross (1961), all of these relative risks are derived with some adjustment, either by matching or in analysis, for smoking practices.

Although the evidence tends to indict alcohol as more strongly related than cigarette smoking to esophageal cancer risk, the difference between these associations is not great. In addition, tobacco and alcohol may interact to increase risk. For example, Castellsague et al. (1999) found that among nonsmokers the top category of alcohol consumption was associated with a 14-fold elevation of risk; among heavy smokers, this top category was associated with a 51-fold elevation of risk. Gao et al. (1994) found that alcohol consumption among nonsmokers was associated with a relative risk of 4, whereas consumption among the heaviest smokers was associated with a relative risk of 12. Ke et al. (2002) found a pattern that suggests a three-way interaction involving consumption of alcohol, tobacco, and black Chinese tea. Ke et al. observed that the consumption of this tea at a high temperature was associated with a risk elevation and that it interacted with cigarette smoking to increase risk, much as alcohol does.

There does not appear to be a strong pattern identifying any specific form of alcohol as more likely than others to increase esophageal cancer risk. Several studies have shown that the consumption of distilled spirits is associated with the greatest risk modification (Wynder and Bross, 1961; Tuyns, 1977, 1979; Pottem et al., 1981; Victoria, 1988; Hu et al., 1994; Grunewald et al., 1998); whereas others (Vassallo et al., 1985; Sankaranarayanan et al., 1991; Cheng et al., 1992) observed little evidence of such a pattern. Segal et al. (1987) observed the greatest risk association among native South Africans with the consumption of traditional beer; and Yu et al. (1988) in China and Zambon et al. (2000) in Italy and Switzerland observed wine consumption to be a greater risk factor than either beer or spirit consumption. De Jong et al. (1974) found increased relative risk for those whose major form of alcohol was a distilled product, samsu.

A number of facets of alcohol consumption could be related to its impact. Dal Maso et al. (2002) observed that alcohol consumption outside of meals was associated with little alteration of risk independent of quantity.

Early studies of esophageal cancer focused on squamous cell cancer (Wynder and Bross, 1961; Bradshaw and Schonland, 1974; Vassallo et al., 1985; Victoria et al., 1987; Cheng et al., 1995; Talamini et al., 2000; Bucher et al., 2002; Ke et al., 2002; Wu et al., 2002). More recently, however, there has been a steep increase in the incidence of adenocarcinoma of the esophagus, so that for whites in the United States the rate of adenocarcinoma of the esophagus is now as high as that of squamous cell cancer. Several recent studies have focused on the difference between the risk patterns for adenocarcinoma versus squamous cell cancer of the esophagus (Pera and Pera, 2001). Among whites, the rates for squamous cell cancer and
adenocarcinoma of the esophagus are approximately equal; among African Americans, the incidence of squamous cell carcinoma is 20 times that of adenocarcinoma. The epidemiologic divergence of these cancers with respect to alcohol is becoming clearer (Pera and Pera, 2001; Mayne and Navarro, 2002; Wu et al., 2001), Lagergren et al. (2000), Dhillon et al. (2001), Bollschweiler et al. (2002), and Gao et al. (1994) found alcohol to be weakly or not associated with adenocarcinoma of the esophagus.

In certain regions such as Assam, India, where cigarette smoking is less common than betel nut chewing (Phukan et al., 2001), alcohol appears to impart a risk elevation similar to that seen among smokers in the West; it may interact with betel nut chewing to increase risk, much as it does with cigarette smoking.

Stomach

Stomach cancer in the United States and other Western countries has declined substantially over the past five decades. The reasons for this decline are not entirely clear, but it has made stomach cancer rare enough to be difficult to study in these populations. In addition, changes in exposure to the critical factor or factors responsible for this decline may confound assessments of the importance of alcohol.

One of the key characteristics of this literature is the unanimity with which relatively strong prospective studies have failed to document evidence of etiologic importance for alcohol (Hakulinen et al., 1974; Jensen et al., 1978; Jensen, 1979, 1983; Kono and Ikeda, 1979; Klatsky et al., 1981, 1988; Schmidt and Popham, 1981; Kono et al., 1983, 1985, 1986; Adami et al., 1988, 1992a, 1992b; Hirayama, 1989; Carstensen et al., 1990; Hirayama, 1990; Tonnesen et al., 1994; Galanis et al., 1998). These studies approach stomach cancer in a broad range of populations. The studies reported by Hirayama, Klatsky et al., Adami et al., and Galanis et al. are based on general population samples, whereas those of Kono et al. were reported for physicians. The studies reported by Schmidt and Popham, Hakulinen et al., and Tonnesen et al. are based on samples of alcoholics or problem drinkers, whereas those reported by Carstensen et al., Jensen, and Dean et al. (1979) are based on data from brewery workers. In a cohort of hepatitis B surface antigen (HBsAg)-positive blood donors (Oshima et al., 1984), no association of risk and alcohol consumption was observed. These studies together appear to consider a broad range of use patterns and risk groups, including members of the general population, those who have used alcohol to excess, and those who, by virtue of ready access to alcoholic beverages, are likely to consume large amounts of alcohol. It is possible, of course, that within each of these populations there is too little variance in exposure to allow adequate examination of risk variance.

There is considerable variance among case-control studies regarding the associations observed between alcohol intake and gastric cancer risk. Studies reported by D'Avanzo et al. (1994), Ferraroni et al. (1989), Chen et al. (2000), Chow et al. (1999), Ye et al. (1999), Setiawan et al. (2000), Rao et al. (2002), and Hansson et al. (1994) revealed no association. Chow et al. (1999) observed a curvilinear pattern, with the risk lower among light drinkers than among nondrinkers, the risk then increasing among the heaviest drinkers to a level slightly but insignificantly higher than among nondrinkers. Haenszel et al. (1972) observed a consistent elevation of risk among first generation Japanese migrants living in Hawaii but no elevation among the second generation. Jedrychowsky et al. (1993) observed a strong association of increased risk and vodka drinking. This risk was stronger among those who consumed vodka on an empty stomach, and it was stronger yet among those who reported consuming vodka before breakfast.

On the other hand, several studies revealed increased risk among drinkers: Munoz et al. (2001) observed elevated relative risk among alcohol users and a higher relative risk among ex-users. Ji et al. (1996), Lee et al. (1990), Wu-Williams et al. (1990), Zarridze et al. (2000), De Stefani et al. (1998), Hu et al. (1988), and Boeing et al. (1991) observed increased risk with increased alcoholic beverage consumption. None of these risks was large, most being in the vicinity of 1.5–3.0. It is difficult to discern a pattern in these data: wine and beer were equally likely to increase risk in the study of Haenszel et al. (1972), whereas beer and liquor were linked to increased risk and wine to decreased risk in the study of Boehl et al. (1991). Ye et al. (1999) observed decreased risk among wine drinkers and increased risk among whisky drinkers.

Interactions among alcohol and smoking have been observed. Chen et al. (2000) observed that alcohol was associated with a relative risk of about 1.5. Among smokers, this relative risk was 3.0, whereas among ex-smokers it was 1.7. Hansson et al. (1994) observed a strong, statistically significant interaction of tobacco and alcohol, so that among nonsmokers alcohol use was associated with decreased risk; among smokers, it was associated with a significantly increased risk.

As attention has focused on the distinction between adenocarcinoma and squamous cell cancer of the esophagus, a distinction is being drawn between cancer of the gastric cardia and of the distal stomach. It has been suggested that cancer of the gastric cardia and adenocarcinoma of the esophagus might share risk factors. Several epidemiologic inquiries have considered cancer of the gastric cardia apart from that of the distal stomach. Ji et al. (1996) found no risk associated with alcohol consumption. Wu-Williams et al. (1990), Zarridze et al. (2000), and Jedrychowsky et al. (1993), however, did find increased risk associated with alcohol consumption. Jedrychowsky et al. found, as for cancer of the distal stomach, an association of vodka consumption with increased risk.

Large Bowel

Little of the alcohol consumed by an individual directly contacts the large bowel; as already noted, it is absorbed into the bloodstream through the stomach and the small bowel. Some in the blood comes in contact with the large bowel. More likely to come in contact with the lumen of the large bowel are residual nonalcoholic constituents of alcoholic beverages; these, which clearly differ for beer, wine, and distilled liquors, could have a bearing on the colonic and rectal content and environment.

The recent case-control literature tends to show that alcohol increases risk, although a large study by Tavani et al. (1998) observed no increased risk with alcohol intake. A report by Slattery et al. (1999) based on factor analysis indicated that a factor dominated by alcohol intake, but also characterized by low intake of whole grain and fruit intake and elevated intake of fish, was associated with marginally increased colorectal cancer risk. Sharp et al. (2002) found increased risk of cancer of the distal colon and rectum with alcohol intake; no such pattern was apparent for cancer of the proximal colon. On the other hand, the small study of Jedrychowsky et al. (2001) found sizable increases in risk with the consumption of alcohol. A large study conducted in Hawaii among Pacific Rim populations, with careful control for ethnicity, age, and gender, reported by Le Marchand et al. (1997), revealed increased risk with increased alcohol intake. In a later analysis of the same data, Le Marchand et al. (1999) found a strong interaction between alcohol intake and family history; the association of intake and risk was much stronger for those with a family history of colon cancer. A small study reported by Matsuoka et al. (2002) indicated an interaction of the ALDH genotype and alcohol as a factor in colon cancer risk.

The prospective literature is not entirely consistent, with mortality-based studies reported by Doll et al. (1994), Kono et al. (1986), Klatsky et al. (1981), and Camargo et al. (1997) revealing no increase in risk. Gapsjor et al. (1994) observed no increased risk with alcohol intake among the Iowa Women's Study. Hirayama's report (1990) of the experience of 265,000 Japanese indicated no increase in colon cancer risk but a statistically significant increase in rectal cancer risk with alcohol intake. Jensen, comparing cancer morbidity in a cohort of Danish brewery workers—individuals who might be expected to have elevated beer consumption—to that of the Danish population, observed no elevation of risk. Flood et al. (2002), who followed a large cohort of women who were part of a breast cancer screening program, observed only a minimal association of risk and alcohol intake with alcohol consumption, and Camargo et al. (1997) observed no elevation of risk among members of the Physician's Health Study. On the
other hand, Chyou et al. (1996) observed, in a cohort of Japanese, a substantial risk elevation with increased alcohol intake. Ma et al. (1997) studying members of the Physician’s Health Study, observed that the association of alcohol intake and risk was null or negative among those homozygous for the wild-type allele of the methylene tetrahydrofolate reductase gene. For those homozygous for the mutant allele, alcohol was associated with increased risk. Glynn et al. (1996) following members of the α-tocopherol–β-carotene chemoprevention trial, Giovannucci et al. (1995), following members of the Health Professional follow-up study, and Hsing et al. (1998), following a cohort of insurance policy holders have also observed a positive association of alcohol and risk.

Evidence that adenoma is a premalignant lesion that may lead to colon cancer has led researchers to believe that alcohol is associated with increased adenoma prevalence. Ferraroni et al. (1989) and Bourton et al. 1995 were among the few who found alcohol to be associated with increased risk. On the other hand, Giovannucci et al. (1993), Manus et al. (1997), Martinez et al. (1995), Yamada et al. (1997), and Todoroki et al. (1995) observed positive associations between alcohol intake and adenoma prevalence. The analysis by Baron et al. (1998) revealed a positive association between alcohol intake and polyp recurrence. In light of the suspicion that the precursor of adenoma is the hyperplastic polyp, Kearney et al. (1995) found that alcohol was positively associated with the prevalence of hyperplastic polyps, which can be taken as additional evidence of the etiologic significance of alcohol intake.

Thus, evidence that alcohol intake increases the risk of colorectal cancer appears to be accumulating. This evidence is modestly more consistent for cancer of the distal colon and rectum than it is for the proximal colon.

Liver

As already noted, the liver is the primary organ where alcohol is metabolized, and metabolism of alcohol takes precedence over a number of normal liver functions. The liver can apparently handle alcohol in modest quantities, but heavy alcohol intake exacts a severe burden. The first priority for the liver of a heavy alcohol consumer is metabolism of alcohol. Lieber (1990) has described this process. Heavy alcohol consumption may cause the liver to store fat and protein, rather than metabolize it. The presence of stored fat and protein over time swells the liver and impairs its ability to function. Inflammation and necrosis, alcoholic hepatitis, may follow. Continued excessive alcohol intake may eventually cause irreversible replacement of functional liver cells by fibrous scar tissue. Consequences include abnormalities in vitamin and mineral metabolism, reduced ability to counter toxic substance accumulation (Lieber, 1990), and increased risk of liver cancer.

Although our understanding of the specific mechanisms by which alcohol might increase the risk of liver cancer is limited, prospective studies quite consistently point to heavy alcohol consumption as increasing the risk of liver cancer. Prospective studies of alcoholic beverage manufacturing employees (Dean et al., 1979; Jensen, 1979; Carstensen et al., 1990) and of alcohol abusers (Hakulinen et al., 1974; Schmidt and Popham, 1981; Tonnesen, 1994) revealed an increased risk of liver cancer. Prospective studies of more typical populations (Kono et al., 1986; Shibata et al., 1986; Hirayama, 1990) documented increased risk among those with increased alcohol intake. Klatsky et al. (1981) followed a cohort in the San Francisco Bay area and showed no elevation of risk, but the risk in that population was extremely low, and the sample was small.

Oshima et al. (1984) showed, in a cohort of high risk individuals infected with hepatitis B, that risk of liver cancer increased in a dose-response pattern with increasing alcohol intake; the relative risk at the highest intake level indicated an eightfold elevation of risk. Mori et al. (2000) showed, in a small cohort of individuals characterized by hepatitis B and C infections, that alcohol intake increases risk and interacts synergistically with hepatitis infection to increase risk.

Case-control studies have also consistently documented a positive association of risk and alcoholic beverage consumption (Bulatao-Jayme et al., 1982; Stemhagen et al., 1983; Hardell et al., 1984; Inaba et al., 1985; Trichopoulos et al., 1987; La Vecchia et al., 1988; Tsukuma et al., 1990; Braga et al., 2002; Yende et al., 2004). Stemhagen et al. (1983) also observed increased risk among those involved in wine manufacturing. These studies tend to show that risk increases in at least a dose-response pattern, so those with the heaviest intake are clearly at the greatest risk. The study by Lu et al. (1988) is one of few efforts not to observe an association of risk and intake. There is little consistency, however, in the type of alcohol that most increases risk. For example, in Japan, where Shibata et al. (1986) collected data, the most commonly consumed alcoholic beverage, and hence the form of alcohol leading to increased risk, is a distilled rice liquor. In Italy, where La Vecchia et al. (1998) conducted their study, wine is the beverage most commonly consumed and hence is the risk factor.

Recent efforts have also focused on the possibility that the associations observed could be confounded. Bulatao-Jayme (1982) controlled statistically for aflatoxin as derived from an index of reported intake of foods contaminated by aflatoxin. The alcohol association persisted. Inaba et al. (1984), Trichopoulos et al. (1987), Tsukuma et al. (1990), and Donato et al. (2002) controlled for hepatitis B infection. Donato et al. (2002) also evaluated possible confounding by hepatitis C. These findings show that alcohol tends to interact with hepatitis, so its impact is greater in the presence of hepatitis B or C than in its absence.

Pancreas

The pathway by which alcohol reaches the pancreas is not generally direct, as most alcohol is absorbed into the blood through the stomach or the intestine and then metabolized in the liver. Nonetheless, there is abundant evidence that long-term, excessive alcohol intake exacts severe costs on the pancreas. Among men in their thirties to early forties in western industrialized countries, most male chronic pancreatitis patients have a history of extended alcohol abuse (Steer et al., 1995); alcohol and tobacco have been identified as distinct risk factors for pancreatitis (Yen et al., 1982; Talalini et al., 1999). Pancreatitis is important to the effects of alcohol inasmuch as 4% of chronic pancreatitis patients develop pancreatic cancer.

The evidence that alcohol contributes substantially to the risk of pancreatic cancer, though, is mixed. Summarizing the evidence up to 1986, Velema et al. (1986) indicated that any increased risk is probably quite modest. Indeed, several strong prospective studies (Hakulinen et al., 1974; Dean et al., 1979; Jensen, 1979; Klatsky et al., 1981; Kono et al., 1986; Hirayama, 1990; Friedman and Van den Eeden, 1993; Michaud et al., 2001; Stolzenberg-Solomon et al., 2001; Isaksson et al., 2002; Lin et al., 2002) observed no association of risk and alcohol consumption practices. Among the prospective studies detecting an association (Schmidt and Popham, 1981; Heuch et al., 1983; Carstensen et al., 1990; Zheng et al., 1993; Tonnesen et al., 1994; Harnack et al., 1997; Ye et al., 2002), only those led by Heuch et al. and Zheng et al. showed more than a weak association of risk with intake. Lagergren et al. (2000) interpreted the association they observed as within a range that could be readily attributed to the resonance of confounding by cigarette smoking.

Case-control studies also provide little evidence of an association of an alcohol–pancreatic cancer association (Mack et al., 1986; Clavel et al., 1989; Bouchard et al., 1990; Farrow and Davis, 1990; Baghurst et al., 1991; Ghadirian et al., 1991; Bueno de Mesquita et al., 1992; Lyon et al., 1992; Mizuno et al., 1992; Zatonsky et al., 1993; Tavani et al., 1997; Villeneuve et al., 2000). The case-control studies revealing an association (Cuzick and Babiker 1989; Partanen et al., 1997; Sober et al., 1998; Silverman, 2001) are in a distinct minority. Among even these studies, only that by Cuzick and Babiker suggested a more than modest increase in risk. The studies showed no tendency for specific types of alcohol to have more impact than others. Several of the case-control studies went to extensive efforts to address the problem of the rapid and severe course of pancreatic cancer, either by organizing rapid case-ascertainment systems or utilizing carefully designed procedures for obtaining interviews from significant others of cases
and from controls. Even with these efforts, the association of alcohol and risk appeared extremely weak or null. The congruence of these findings with those of the substantial number of prospective studies suggests that any effect of alcohol intake on pancreatic cancer risk is slight to negligible.

**Female Breast**

The literature on alcohol consumption and female breast cancer is marked by relatively consistent evidence of a modest impact on risk (World Cancer Research Fund, 1997; Lenz et al., 2000; Singleterry and Gapstur, 2001; Collaborative Group on Hormonal Factors in Breast Cancer, 2002). That is, the relative risk associated with alcohol consumption is not great; it has been estimated that there is approximately 10% increase in risk for an increase in average consumption of one drink per day (Longnecker et al., 1988, 1994, 1995a, 1995b; Smith-Warner et al., 1998). Because of the high prevalence of alcohol consumption, though, the attributable risk associated with alcohol consumption may exceed 10% (Mezzetti et al., 1998). Although there is some evidence that there is a linear increase in risk with alcohol consumption (Smith-Warner et al., 1998), there is also some evidence that risk does not start to increase until intake is above a certain threshold (Howe et al., 1990, 1991). If the latter were true, studies in populations with a low prevalence of alcohol intake might be limited in their power to detect an effect.

Given the importance of menopause to an altered risk of breast cancer, the grouping of pre- and postmenopausal breast cancers in several case-control studies may be a serious limitation. On the other hand, most of these studies controlled statistically for menopausal status, so there is little evidence of strong effect modification by menopausal status and hence little reason to suspect that the analysis in these studies is significantly flawed. Many of the studies, including those reported by Byers and Funch (1982), Le et al. (1984, 1986), Miller et al. (1978, 1992), Chu et al. (1989), Mannisto et al. (1996), Freudenheim et al. (1999), Sneyd et al. (1991), Kato et al. (1992), Rosenberg et al. (1982, 1990), Iscovitch et al. (1989), Morabia et al. (1990), Marcus et al. (2000), Baumgartner et al. (2002), and Kinney et al. (2000), found little evidence of an association. Toniolo et al. (1989), Katsouyanni et al. (1994), and Kinney et al. (2000) observed slight evidence of a positive trend with increased intake, but the association was not statistically significant. Baumgartner et al. (2000) found evidence of increased risk for the highest levels of intake but a significantly decreased risk among those with moderate intake.


Studies focused on postmenopausal breast cancer appear more likely to reveal increased risk with increased alcohol intake. Null or nearly null findings, including those by Chu et al. (1989), Ewertz et al. (1991), Sneyd et al. (1991), Meera et al. (1989), Ferraroni et al. (1989), Hirose et al. (1995), Katsouyanni et al. (1994), Enger et al. (1999), and Cade et al. (1998) have been reported. The point estimates from these studies tend to be positive, but they are within the range that might be expected by chance fluctuations. Rohan and McMichael (1988) observed a significant trend for increased intake to accompany increased risk. Ranstam and Olsson (1995) and Longnecker et al. (1988, 1995a, 1995b) observed statistically significant associations.

What is noteworthy about these case-control reports is the rarity with which they reveal other than positive associations. Although the associations tend to be statistically nonsignificant, they are almost never negative, and it is even less common that they are negative and statistically significant. In the face of this uncertainty, the evidence from cohort studies is particularly pertinent.


**Lung**

Consumption of alcoholic beverages does result in exposure of the lung to alcohol. As already noted, most alcohol is absorbed into the blood from the stomach and small intestine. Transformed via the circulatory system to the liver, it is metabolized to acetaldehyde prior to additional breakdown. It is clearly possible for alcohol or acetaldehyde to come into contact with pulmonary tissue. Either of these could function as carcinogens or as solvents to potentiate other carcinogens, such as those in tobacco smoke. It is important, however, that alcohol comes into contact with pulmonary tissue in much smaller amounts and concentrations than with oral, pharyngeal, or esophageal tissue.

Nonetheless, there is evidence linking alcohol consumption and lung cancer risk. Positive case-control study results, including those reported by Bandera et al. (1997), De Stefani et al. (1993, 1996), Rachtian and Sokoloski (1997), Carpenter et al. (1998), and Stockwell and Matanoski (1984, 1985) are balanced by negative studies, including those by Koo (1988), Mayne et al. (1994), Holst et al. (1988), and Kabat and Wynder (1984). The results reported by Koo are especially important in that the study was conducted among nonsmoking women; it is possible that among these subjects confounding by cigarette smoking is minimized. Among prospective studies, positive associations have been reported by Potter et al. (1992), Hirayama et al. (1990), Klatsky et al. (1981), Pollack et al. (1984), Carstensen et al. (1990), Dean et al. (1979), Doll et al. (1994), Prescott et al. (1999), and Chyou et al. (1995). The efforts by Klatsky et al., Dean et al., and Doll et al. focused on mortality rather than on morbidity; given the lethality of lung cancer, the distortions induced by this focus are probably slight. More importantly, several prospective studies, including those by Gordon and Kannell (1984), Kono et al. (1986), Steen et al. (1990), and Yuan et al. (1997) are negative. Especially important null results are those based on the Finnish α-tocopherol and β-carotene intervention trial among heavy smokers (Woodson et al., 1999) and those based on the β-carotene and retinal intervention among those with heavy exposure to tobacco and asbestos (Omenn et al., 1996).

That cigarette smoking is an overwhelming risk factor for lung cancer and is strongly correlated with alcohol consumption cannot be overlooked. The likelihood of confounding of the alcohol–lung cancer association by the combination of the cigarette smoking–lung cancer association and the cigarette smoking–alcohol consumption association is extremely high; modest imprecision in the measurement of smoke exposure can readily induce resonant confounding into measures of the impact of alcohol consumption. Even minuscule 5%–10% misclassification of cigarette smoke exposure can resonate, so a null but correlated variable can appear to alter risk by 20%–50% (Marshall and Hastrup, 1996; Marshall et al., 1999). It is not necessary that the variables used to operationalize exposure be misclassified. For example, cigarettes per day and the duration of smoking can be assessed perfectly; however, to the degree that other factors (e.g., brand, filter, depth of inhalation) add further variance to smoke
exposure, the investigator’s measures are less than perfect, and the opportunity for resonant confounding is excellent. Conventional methods of covariate adjustment would not eliminate this possibility of resonant confounding. Thus, in light of the overwhelming importance of cigarette smoking and the likelihood that confounding by cigarette smoking has not been completely removed, reviews by Korte et al. (2002) and White et al. (2002) that alcohol is not likely to be a significant risk factor for lung cancer appear justified.

Prostate

Some ingested alcohol reaches the prostate, and the by-products of alcohol metabolism can be expected to reach and affect this organ as well. The totality of the epidemiologic evidence, however, is that alcohol is not a significant risk factor for prostate cancer.

It is pertinent that the advent of the prostate-specific antigen (PSA) screening test has radically altered the identification and treatment of prostate cancer, sizably increasing its incidence (Gann, 1997). Prostate cancer is diagnosed frequently but is infrequently a cause of death (Marshall and Wood, 2002). As a result of widespread application of the PSA test, the identification of asymptomatic and possibly non-life-threatening cases has increased substantially. Clearly, these changes have had an impact on the epidemiology of alcohol in regard to prostate cancer.

The extant epidemiologic literature on alcohol and prostate cancer, comprehensively reviewed by Dennis (2000) and Dennis and Hayes (2001), is dominated by results suggesting that alcohol is not associated with prostate cancer risk. Exceptions include two case-control studies (Hayes et al., 1996; Sharpe and Siemiatycki, 2001). The report by Hayes et al. is noteworthy for its inclusion of large numbers of both European Americans and African Americans. The elevation of risk Hayes et al. observed resulted from extremely heavy alcohol consumption: the intermediate intake category was 22–56 drinks per week; and the heavy drinking category was 57 or more drinks per week. On the other hand, three other case-control studies reported no association (Jain et al., 1998; Lumey et al., 1998; Crispo et al., 2004). The report of Jain et al., as large as that of Hayes et al., observed no alteration of risk. Two prospective studies—those of Adami et al. (1992a, 1992b) and Tonneson et al. (1994)—observed an increased risk among those with elevated alcohol intake. On the other hand, prospective studies reported by Hakulinen et al. (1974), Jensen (1979), Carstensen et al. (1990), Hiatt et al. (1994), Sorensen et al. (1998), Breslow et al. (1999), and Schulman et al. (1999) reported no evidence of an association of alcohol intake and prostate cancer risk. There is limited evidence that prostate cancer and alcohol are linked and considerable evidence that they are not.

CONCLUSIONS

Clearly, alcohol consumption, a behavior, can be modified. Given evidence that alcohol consumption increases the risks of some cancers, modification of alcohol consumption represents a ready means of decreasing cancer risk. The degree to which this cancer risk might be altered depends on the significance of the cancers for which alcohol has a role and the importance of alcohol for each of those cancers.

Table 14-1 presents estimates of the total numbers of cancer cases in 2002 and the total numbers of deaths for the cancer sites reviewed in this chapter. These estimates amount to some 800,000 cases and 360,000 deaths. The right-hand column presents our judgment as to whether the totality of the evidence supports a causal role for alcohol consumption.

This chapter has noted that our understanding of the importance of alcohol in cancer is limited. Although large quantities of data have been collected, the complexities by which alcohol exacts its effects, as well as the difficulty of studying those effects, are significant barriers to understanding. It is not particularly satisfying to weigh the epidemiologic evidence and then merely posit that the evidence does or does not support a causative role for alcohol. Given the limitations of our methods and understanding, one could perform a meta-analysis or otherwise squeeze the data to extrude some single number that summarizes the etiologic importance of alcohol for each cancer site. Whether this number would have significant meaning, though, could be heartily debated.

Thus, our judgment is that the evidence implicates alcohol in oropharyngeal, esophageal, liver, large bowel, laryngeal, and breast cancer. Alcohol appears to be much more important to some sites than to others. It has a large impact on the risks of oral and esophageal cancer and has a much more modest impact on the risks of large bowel and breast cancer. For some sites, the evidence is difficult to dispute, whereas for others disputes will continue. In the United States in 2002, the incidence of the cancer that appeared to be alcohol-related added up to slightly fewer than 300,000 cases and 135,000 deaths. The evidence suggests that alcohol has some component causal role and that control of alcohol intake would result in reduced incidence of and mortality attributable to these cancer sites.

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