are also down substantially. Drug use among youth is on a long-term downward trend. However, cannabis use has not declined among students, and cannabis and driving is now more common than drinking and driving. Also, use of OxyContin has increased as students take their parents' prescription drugs from the medicine chest. Continued vigilance and action will be needed to make sure that cannabis and OxyContin do not become larger problems.

See also **Foreign Policy and Drugs; International Drug Supply Systems.**

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REGINALD G. SMART

CANCER, DRUGS, AND ALCOHOL.

DISEASE BURDEN ATTRIBUTABLE TO ALCOHOL

The World Health Organization's 2000 Comparative Risk Assessment Study (see Ezzati et al. 2004; Lopez et al. 2006; Rehm et al. 2004), found alcohol to be one of the most important risk factors for the global burden of disease, with alcohol ranking fifth, just behind tobacco (the alcohol-attributable burden was 4.0% of the global burden, compared to 4.1% for tobacco). Only underweight resulting from malnutrition and underfeeding, unsafe sex, and high blood pressure (which ranked first, second, and third, respectively) had more impact on the burden of disease than tobacco and alcohol (World Health Organization, 2002).

In 2002, 3.7 percent of all deaths worldwide were attributable to alcohol (6.1% for men; 1.1% for women). In addition, 4.4 percent of all disability-adjusted life years (7.1% for men; 1.4% for women) were attributable to alcohol (Rehm et al., 2006). (These percentages are net numbers that take into account the cardioprotective effect of alcohol.)

CARCINOGENESIS

In studies in which water containing ethanol is administered to laboratory animals, a dose-related increase has been noted in hepatocellular adenomas and carcinomas (U.S. National Toxicology Program, 2004); in head and neck carcinomas, fore-stomach carcinomas, testicular interstitial-cell adenomas, and osteosarcomas of the head and neck (Soffritti et al., 2002); and in mammary adenocarcinomas in female rats (Watabiki et al., 2000). The carcinogenic effect also increased when the ethanol was co-administered with known carcinogens.

The conversion of alcohol (ethanol) to acetaldehyde (the major metabolite of alcohol) in the liver requires the enzyme alcohol dehydrogenase, and acetaldehyde is transformed to acetic acid by the enzyme aldehyde dehydrogenase. Deficiencies in aldehyde dehydrogenase (which is most common among those of Asian descent) result in high levels of accumulated acetaldehyde in the body, which contribute to the development of malignant esophageal tumors (Baan et al., 2007; International Agency for Research on Cancer, 2007).

ALCOHOL AND CANCER

Comparative risk analyses and calculations on the alcohol-attributable burden of disease have revealed that cancer deaths worldwide are the third largest category of deaths caused by alcohol consumption (after unintentional injuries, at 25.9%, and cardiovascular disease, at 23.3%), accounting for 18.7 percent of alcohol-attributable deaths among men in 2002 (Rehm et al., 2006). Among women, the single largest category of alcohol-attributable deaths was cancer deaths, which accounted for 25.0 percent of deaths caused by alcohol consumption.

In February 2007, the Working Group of the International Agency for Research on Cancer (IARC), which comprises 26 scientists from 15 countries, confirmed that research evidence has shown that alcoholic beverages are carcinogenic to humans. Specifically, the group confirmed the causality between alcohol consumption and the occurrence of the following malignant neoplasms: oral cavity, pharynx, larynx, esophagus, liver, colorectum, and female breast cancer (Baan et al., 2007; International

Malignant neoplasms	ICD-10	Reference to meta-analyses/reviews	Effect	Causality
Lip & oropharyngeal cancer	C00-C14	English et al. (1995); Single et al. (1996, 1999); Sjögren et al. (2000); Gutjahr et al. (2001); Ridolfo & Stevenson (2001) *There is enough data to calculate relative risk for subcategories of disease, e.g. Bagnardi et al. (2001); Corrao et al. (2004)*	Detrimental	Confirmed
Esophageal cancer	C15	English et al. (1995); Single et al. (1996, 1999); Sjögren et al. (2000); Gutjahr et al. (2001); Ridolfo & Stevenson (2001); Rehm et al., 2003, Corrao et al. (2004)	Detrimental	Confirmed
Stomach cancer	C16	Bagnardi et al. (2001) *It was concluded that inconsistencies in research provide inadequate evidence that alcohol causes stomach cancer (English et al., 1995; Baan et al., 2007; IARC Monographs).*	Detrimental	Unclear (inconsistent results)
Cancer of small intestine	C17	Baganardi et al. (2001)	Detrimental	Not confirmed
Colon cancer	C18	Bagnardi et al. (2001); Corrao et al. (2004); Cho et al. (2004); Moskal et al. (2006, 2007); Bofetta & Hashiba (2006). *The IARC has identified colorectal cancer as causally related to alcohol drinking in recent meeting in February 2007 (Baan et al., 2007; IARC Monographs).*	Detrimental	Confirmed
Rectal cancer	C20	Bagnardi et al. (2001); Corrao et al. (2004); Cho et al. (2004); Moskal et al. (2006, 2007); Bofetta & Hashiba (2006). *The IARC has identified colorectal cancer as causally related to alcohol drinking in recent meeting in February 2007 (Baan et al., 2007; IARC Monographs, in press).*	Detrimental	Confirmed
Liver cancer	C22	English et al. (1995); Single et al. (1996, 1999); Sjögren et al. (2000); Bagnardi et al. (2001); Gutjahr et al. (2001); Ridolfo & Stevenson (2001); Rehm et al. (2003); Corrao et al. (2004)	Detrimental	Confirmed
Gallbladder cancer	C23	Baganardi et al. (2001)	Detrimental	Not confirmed
Pancreatic cancer	C25	Baganardi et al. (2001)	Detrimental	Not confirmed
Laryngeal cancer	C32	English et al. (1995); Single et al. (1996, 1999); Sjögren et al. (2000); Gutjahr et al. (2001); Ridolfo & Stevenson (2001); Rehm et al. (2003); Bagnardi et al. (2001), Corrao et al. (2004), Altieri et al. (2005)	Detrimental	Confirmed
Lung cancer	C34	*This was excluded from the list of diseases causally related to alcohol. This decision has not been revised through any further meta-analysis. Recent meta-analyses on alcohol and lung cancer found only a borderline significant result (Bagnardi et al. 2001; Freudenheim et al., 2005) and the last substantive reviews found no sufficient support for a causal relationship (Bandera et al., 2001; Wakai et al., 2007).*	Detrimental	Unclear (inconsistent results)
Female breast cancer	C50	Single et al. (1996, 1999); Sjögren et al. (2000); Bagnardi et al. (2001); Gutjahr et al. (2001); Ridolfo & Stevenson (2001); Rehm et al. (2003); Singletary (2003); Hamajima et al. (2002); Corrao et al. (2004); Key et al. (2006); Singletary & Gapstur (2001); Ellison et al. (2001); Smith-Warner et al. (1998). *English et al. (1995) concluded that there was only limited evidence for causality, although they found a consistent relationship. Subsequent studies using the same criteria have concluded that there is sufficient evidence of a relationship (Baan et al., 2007; IARC Monographs).*	Detrimental	Confirmed
Ovarian cancer	C56	Bagnardi et al. (2001) *English et al. (1995), consistent with IARC (1988), have concluded inadequate evidence that alcohol causes ovarian cancer.*	Detrimental	Not confirmed
Prostate cancer	C61	Bagnardi et al. (2001)	Detrimental	Not confirmed
Kidney cancer	C64	Hu et al. (2003); Hsu et al. (2007)	Beneficial	Lack of carcinogenicity (Inverse trend)
Bladder cancer	C67	Bagnardi et al. (2001b)	Detrimental	Not confirmed
Non-Hodgkin lymphoma	C82-C83	Morton et al. (2005); Besson et al. (2006)	Mainly beneficial or no effect	Lack of carcinogenicity (Inverse association or no association)

Table 1. Association between alcohol consumption and cancer identified by various meta-analyses and reviews. ILLUSTRATION BY GGS INFORMATION SERVICES. GALE, CENGAGE LEARNING

Agency for Research on Cancer, 2007). Furthermore, lack of carcinogenicity was confirmed for renal-cell cancer and non-Hodgkin's lymphoma. Evidence on causality between alcohol consumption and risks of other types of cancer was sparse or inconsistent. (These results are summarized in Table 1.) In addition, the working group concluded that there is "sufficient evidence" for the carcinogenicity of ethanol in animals, and it classified the ethanol in alcoholic beverages as carcinogenic to humans

Cancer of the Upper Digestive Tract (Oral Cavity, Pharynx, Larynx, and Esophagus). Causality for these cancers was confirmed during the first IARC Monographs meeting on the evaluation of carcinogenic risks of alcohol to humans (IARC, 1988). Studies showed that daily consumption of approximately 50 grams of ethanol increases the risk for these cancers two to three times, compared with the risk for abstainers. The effects of drinking and smoking were found to be multiplicative.

Liver Cancer. Causality for liver cancer was also confirmed during the first IARC Monographs meeting. The evidence suggests that the consumption of alcohol is an independent risk factor for primary liver cancer.

Breast Cancer in Women. Causality for breast cancer was also confirmed. Based on several epidemiological studies, each additional 10 grams (less than one standard drink) of alcohol per day is associated with an increase of 7.1 percent in the relative risk (RR) of breast cancer (Hamajima et al., 2002), though this risk is possibly higher (Key et al. estimated it at 10% in 2006). Even for regular consumption of about 18 grams of alcohol per day, the increase in RR is statistically significant. Hamajima et al. reported that about 4 percent of the female breast cancer cases in developed countries may be attributable to alcohol consumption. The mechanism of association between alcohol and breast cancer may involve increased levels of estrogen (Boffetta & Hashibe, 2006; Foster & Marriott, 2006) or increased levels of plasma insulin-like growth factor (IGF) produced by the liver due to moderate consumption of alcohol (Yu & Berkel, 1999).

Colorectal Cancer. A causal relation between alcohol and colorectal cancer has been established by the IARC (Baan et al., 2007). Research studies provide evidence for an increased relative risk of about 1.4 percent for colorectal cancer with regular consumption of about 50 grams of alcohol per day, compared with abstainers. This association is similar for both colon cancer and rectal cancer (Cho et al., 2004; Moskal et al., 2007).

Moskal et al. (2007) estimated a 15 percent increase in the risk of colon or rectal cancer for an increase of 100 grams (about 7 standard drinks) of alcohol per week. Low folate intake increases the risk of colorectal cancer, and alcohol could act through folate metabolism or synergistically with low folate intake to increase the risk, however the effects may be moderate (Boffetta & Hashibe, 2006). Moskal et al. also suggested a genotoxic effect of acetaldehyde, a metabolite of alcohol, and genetic polymorphism in subjects as factors for enhancing the risk of colorectal cancer.

Kidney Cancer. Evidence shows no increase in risk for renal-cell cancer with increasing alcohol consumption. Several studies have reported that increased alcohol consumption was associated with a significantly lower risk for renal-cell cancer for both men and women (Hu et al., 2003; Hsu et al., 2007).

Non-Hodgkin's Lymphoma. Several studies have demonstrated an inverse association or no association between alcohol consumption and non-Hodgkin's lymphoma. The majority of the studies show a lower risk in drinkers than in abstainers (Morton et al., 2005; Besson et al., 2006).

Lung Cancer. As evidence for a possible biological mechanism was not conclusive, and residual confounding from smoking could not be excluded, it was decided to exclude lung cancer from the list of diseases influenced by alcohol.

Stomach Cancer. The association of stomach cancer with the consumption of alcoholic beverages is not confirmed. Epidemiological studies show inconsistent results and the interpretation of the findings is not clear.

TOBACCO AND CANCER

The role of tobacco as a carcinogen is well established and described elsewhere.

Malignant neoplasms	ICD-10	Reference to meta-analyses/reviews	Effect	Causality
Oropharyngeal cancer	C00-C14, D00.0	English et al. (1995)	Detrimental	Confirmed
Esophageal cancer	C15, D00.1	English et al. (1995)	Detrimental	Confirmed
Stomach cancer	C16, D00.2	Tredaniel et al. (1997)	Detrimental	Confirmed
Pancreas cancer	C25, D01.9	English et al. (1995)	Detrimental	Confirmed
Laryngeal cancer	C32, D02.0	English et al. (1995)	Detrimental	Confirmed
Trachea, bronchus and lung cancers	C33-C34	Simonato et al. (2001)	Detrimental	Confirmed
Cervical cancer	C53, D06	Plummer et al. (2003)	Detrimental	Confirmed
Urinary tract cancer	C64-C68	Zeegers et al. (2000)	Detrimental	Confirmed
Renal cell carcinoma	C64	Hunt (2005)	Detrimental	Confirmed
Bladder cancer	C67, D09.0	Brennan et al. (2000; 2001)	Detrimental	Confirmed
Acute myeloid leukemia	C92.0	Brownson et al. (1993)	Detrimental	Confirmed

Table 2. Association between tobacco and cancer identified by various meta-analyses and reviews. ILLUSTRATION BY GGS INFORMATION SERVICES. GALE, CENGAGE LEARNING

In 2004, the U.S. Surgeon General added the following diseases to the list of those for which evidence is sufficient to conclude a causal relationship between smoking and disease: stomach cancer, renal cell carcinoma, uterine cervical cancer, and pancreatic cancer. (For the full list of the malignant neoplasms casually associated with tobacco, see Table 2.)

ILLEGAL DRUGS (MARIJUANA) AND CANCER

In many countries, marijuana is the second most commonly smoked substance (after tobacco), and it is considered to be the least risky among the various illegal drugs. However, there is a concern that smoking marijuana may be a risk factor for tobacco-related cancers, because the smoke of marijuana, like that of tobacco, contains a number of the same carcinogens. However, smoking marijuana may actually be more harmful than smoking tobacco, since more tar is inhaled and retained when smoking marijuana.

Several studies support the biological plausibility of an association of marijuana smoking with lung cancer on the basis of molecular, cellular, and histopathologic findings. However, the role of marijuana as a risk factor for lung cancer is difficult to assess because most marijuana smokers are also tobacco smokers. The epidemiologic evidence that marijuana smoking may lead to lung cancer is limited and inconsistent (Mehra et al., 2006; Hashibe et al., 2005, 2006).

An IARC study reviewed several epidemiological studies that assessed the association of marijuana use and cancer risk including lung, head and neck, colorectal, non-Hodgkin's lymphoma, prostate, cervical cancers, and glioma (Hashibe et al., 2005). Due to methodological limitations in the existing studies—including selection bias, possible underreporting where marijuana use is illegal, small sample sizes, limited generalizability, and too few heavy marijuana users in the study samples—the authors concluded that the reviewed studies are not adequate to evaluate the impact of marijuana use on cancer risk. In view of the growing interest in medicinal marijuana, further epidemiologic studies are needed to clarify the true risks of regular marijuana smoking on cancer and other health conditions.

See also **Alcohol: Chemistry and Pharmacology; Cannabis Sativa; Complications: Liver (Clinical); Complications: Immunologic; Epidemiology of Alcohol Use Disorders; Epidemiology of Drug Abuse; Tobacco: Medical Complications.**

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