Tobacco use is the largest single recognized cause of human cancer in Western countries. Cigarette smoking alone accounts for about 30% of all cancer deaths in the United States (Doll and Peto, 1981; Centers for Disease Control and Prevention, 2002a) and an estimated 16% of all cancers worldwide (Parkin et al., 1999). In addition to cancer, cigarette smoking causes even more deaths from nonmalignant cardiovascular and respiratory diseases than from cancer (Forey et al., 2002; IARC, 2004). Tobacco smoking causes an estimated 4.9 million deaths annually worldwide (Ezzati and Lopez, 2003b). If current smoking patterns continue, the growing toll is expected to exceed 10 million deaths annually during the twenty-first century (Peto and Lopez, 2001).

The extraordinary burden of cancer and other diseases caused by tobacco products is even more remarkable in that the pandemic is entirely manmade. Tobacco is the only major human carcinogen for which a combination of commercial marketing and physical addiction sustains the epidemic. Tobacco marketing creates the illusion that smoking is desirable and thus encourages nonsmokers to experiment with tobacco usage. Physical addiction to nicotine then obligates continued usage, making it extremely difficult for many smokers to quit. Chronic exposure to the numerous carcinogens and other toxic substances in tobacco is essentially a by-product of the quest to maintain nicotine intake.

Epidemiologic studies have revealed much of what has been learned about the deleterious health effects of tobacco over the last half century (Thun et al., 2002). Humans, unlike other mammals, use tobacco voluntarily. Whereas tobacco smoke is irritating and highly toxic to other species exposed experimentally in laboratory studies, nonsmokers who experiment with tobacco persist though the initial noxious effects until they develop physical and psychological dependence on tobacco (Thun et al., 2002). Epidemiologic (nonrandomized) studies continue to be ethical and feasible, whereas randomized clinical trials of tobacco are not. Epidemiologic studies are better suited than clinical observations to surmount the long delay between the initiation of tobacco use and the onset of cancer and other chronic diseases. The association of tobacco use with various diseases is sufficiently strong that epidemiologic studies have been able to identify unequivocally many diseases caused by smoking despite imprecise quantification of lifetime tobacco exposure (Thun et al., 2002).

This chapter considers the factors that transformed tobacco use from a ceremonial practice in pre-Columbian times to a global epidemic. It also discusses the role of nicotine addiction in sustaining and modifying exposure to the carcinogens in tobacco, the cancers caused by various forms of tobacco use, the global burden of tobacco-attributable disease, the extent to which design changes in cigarettes have altered their pathogenicity, the influence of genetic and other factors on susceptibility to addiction or carcinogenesis, and finally the immense opportunities for prevention.

HISTORY OF TOBACCO USE TO THE MID-TWENTIETH CENTURY

Although tobacco leaves were burned in religious ceremonies and smoked and chewed for pleasure throughout precolonial North and South America (Doll, 1998a), these practices were unknown to Europeans prior to the voyages of Columbus. Tobacco was introduced into Europe by Spanish explorers returning from the New World during the late fifteenth century. The main species of tobacco was named *Nicotiana tabacum* after Jean Nicot, the French ambassador to Portugal who sent tobacco seeds to his queen, Catherine de Medicis. Use of tobacco for medicinal purposes and as a curiosity was promoted first in Spain and later England (Doll, 1998a). Recreational pipe smoking subsequently spread from England to many countries in Europe and Asia. By the late nineteenth century, tobacco was widely used in Europe (Doll, 1998a) and the United States (Fig. 13-1) (U.S. Department of Agriculture, 2002) in the form of cigars, pipes, roll-your-own cigarettes, chewing tobacco, and snuff.

Several new technologies converged at the beginning of the twentieth century to allow manufactured cigarettes to displace traditional tobacco products and to increase total tobacco consumption (Slade, 1989, 1993). Portable paper safety matches, patented in 1889 (Slade, 1989), made it possible to smoke tobacco frequently throughout the day in diverse settings. Cigarette-rolling machines were developed during the 1880s that could mass-produce and package cigarettes that were considerably less expensive than hand-rolled products. New strains of tobacco and new curing processes were developed that produced less irritating smoke that could be inhaled. These innovations were coupled with novel and aggressive advertising campaigns that glamorized smoking of particular brands of cigarettes, beginning with Camel cigarettes in 1913 (Slade, 1993). Free cigarettes were distributed in military rations to allied soldiers during World Wars I and II. Consequently, manufactured cigarettes became the predominant form of tobacco used in the United States (see Fig. 13-1) and most other Western countries by the mid-twentieth century.

In addition to increasing substantially the number of people who used tobacco and the number of cigarettes consumed per person, early changes in cigarette design increased the surface area of respiratory epithelium exposed to the carcinogens in cigarettes. As mentioned, the popularization of manufactured cigarettes required adoption of new strains of tobacco leaf and new curing processes that released a milder, less irritating smoke (Doll, 1998a). The smoke from traditional tobacco products was highly alkaline and released nicotine in an un-ionized form that could be absorbed through the oropharyngeal mucosa (Henningfield et al., 1993; Slade, 1993). In contrast, ionized nicotine from manufactured cigarettes had to be inhaled into the trachea and large bronchi to facilitate rapid absorption. Whereas traditional tobacco products caused intense local contact of the lip and oropharyngeal tissues with tobacco leaf and tobacco carcinogens dissolved in saliva, inhaled smoke caused more extensive exposure of the larynx, trachea, and large bronchi. This compounded the preexisting risk of cancers of the oral cavity and pharynx with a massive increase in the risk of cancers of the trachea, bronchus, and lung (Thun et al., 2002).

PRESENT BURDEN OF TOBACCO-ATTRIBUTABLE MORTALITY

The disease burden attributable to smoking is not static but varies with the number of people smoking and the duration and intensity of regular smoking in the population. In the United States, where manufactured cigarettes were introduced early during the twentieth century, cigarette smoking alone accounts for approximately 440,000 deaths each year.
By the years 2025–2030, if current smoking patterns persist, the burden is expected to be seven million and three million deaths, respectively, in developing and developed countries (Mackay and Eriksen, 2002). This rapid increase reflects the much larger number of current smokers who live in low- and middle-income countries (933 million) than in high-income countries (209 million) (Jha and Chaloupka, 2000). The only other exposures whose impact is known to be increasing with such rapidity are human immunodeficiency virus (HIV) infection and, in Western countries, obesity (Gonzalez et al., 2003). Not all countries follow the exact course of the Lopez et al. model (see Fig. 13–2). In China, for example, the prevalence of smoking among women has remained below 5% despite a high prevalence of cigarette smoking among men for several decades (Corrao et al., 2000). Countries such as Thailand have had markedly reduced per capita cigarette consumption early in the epidemic because of national policies that ban cigarette marketing and discourage smoking. The mix of diseases caused by smoking also varies depending on background risk in various countries. In the United States cardiovascular diseases account for an estimated 32% of deaths caused by active smoking (see Table 13–1) (U.S. Department of Health and Human Services, 2004). In China, where cardiovascular disease risk is generally low, smoking causes more premature deaths due to liver cancer than to heart disease (Liaw and Chen, 1998). In India, smoking appears to cause more deaths from tuberculosis than from any other condition (TATA Institute of Fundamental Research, WHO, and CDC, 2000). Nevertheless, the WHO paradigm illustrates the natural history of the epidemic and its protracted course in the absence of effective national and international tobacco regulation.

**EPIDEMIOLOGY OF TOBACCO USAGE**

The global consumption of manufactured cigarettes increased more than 100-fold during the twentieth century, reaching about 5500 billion cigarettes per year in the year 2000 (Fig. 13–3) (Mackay and Eriksen, 2002). The number of people who smoked tobacco worldwide in 2000 was approximately 1.3 billion (Shafey, 2003). Because no national surveys of smoking prevalence were conducted in the United States prior to 1955, historical information on the rise in cigarette smoking

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**Part III: The Causes of Cancer**

![Figure 13-1. Adult (age ≥18 years) per capita consumption of various forms of tobacco in the United States, 1880–2000. (Source: Adapted from NCI Smoking and Tobacco Control Monograph 8, 1997, p. 13. Data are from the U.S. Department of Agriculture.)](image-url)
Table 13-1. Smoking-Attributable Mortality (percent and number of deaths, US 1995–1999) by Disease

<table>
<thead>
<tr>
<th>Disease (ICD-9 Code)</th>
<th>Year</th>
<th>Year Formally Considered</th>
<th>Relative Risk Estimates</th>
<th>Attributable Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
<td>Classifid</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Current</td>
<td>Former</td>
</tr>
<tr>
<td>HERITABLE DISEASE</td>
<td></td>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Lip, oral cavity, pharynx (140–150)</td>
<td>1964</td>
<td>1964/71*</td>
<td>10.9</td>
<td>3.4</td>
</tr>
<tr>
<td>Esophagus (150)</td>
<td>1964</td>
<td>1982</td>
<td>6.8</td>
<td>4.5</td>
</tr>
<tr>
<td>Stomach (151)</td>
<td>1964</td>
<td>2004</td>
<td>2.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Pancreas (157)</td>
<td>1967</td>
<td>1982</td>
<td>2.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Larynx (161)</td>
<td>1964</td>
<td>1964</td>
<td>14.6</td>
<td>6.3</td>
</tr>
<tr>
<td>Trachea, lung, bronchus (162)</td>
<td>1964</td>
<td>1964/68*</td>
<td>23.3</td>
<td>8.7</td>
</tr>
<tr>
<td>Cervix uteri (180)</td>
<td>1962</td>
<td>2004</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Urinary bladder (188)</td>
<td>1964</td>
<td>1979</td>
<td>3.3</td>
<td>2.1</td>
</tr>
<tr>
<td>Kidney, other urinary tract (189)</td>
<td>1968</td>
<td>1982</td>
<td>2.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Acute myeloid leukemia (205)</td>
<td>1990</td>
<td>2004</td>
<td>1.9</td>
<td>1.3</td>
</tr>
<tr>
<td>CARDIOVASCULAR DISEASE</td>
<td>Coronary heart disease (410–414)</td>
<td>1964</td>
<td>1968</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>Age 35–64</td>
<td></td>
<td>1.5</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Age 65+</td>
<td></td>
<td>1.8</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Other heart disease (390–8, 415–7, 420–9)</td>
<td>1964</td>
<td>1973</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease (430–438)</td>
<td>1964</td>
<td>1989</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Age 35–64</td>
<td></td>
<td>2.4</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Age 65+</td>
<td></td>
<td>6.2</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>Atherosclerosis (440)</td>
<td>1964</td>
<td>1973</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>Aortic aneurysm (441)</td>
<td>1964</td>
<td>1979</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Other arterial disease (442–448)</td>
<td>1964</td>
<td>1979</td>
<td>1.8</td>
</tr>
<tr>
<td>RESPIRATORY DISEASE</td>
<td>Pneumonia and influenza (480–487)</td>
<td>1964</td>
<td>2004</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td>Bronchitis, emphysema (491–492)</td>
<td>1964</td>
<td>1964/1967*</td>
<td>17.1</td>
</tr>
<tr>
<td></td>
<td>Chronic airways obstruction (496)</td>
<td>1964</td>
<td>1967</td>
<td>15.7</td>
</tr>
<tr>
<td>PEDIATRIC DISEASES (765, 769, 770, 798.0)</td>
<td>1964</td>
<td>1969</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>BURN DEATHS (890–899)</td>
<td>1964</td>
<td>1964</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>ENVIRONMENTAL TOBACCO SMOKE</td>
<td>1972</td>
<td>1986</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>


*Lung cancer was classified as causal in 1964 other oropharyngeal cancers in 1971. Long cancer was classified as causal in men in 1964 and in women in 1968. Bronchitis was classified as causal in 1964; other chronic obstructive pulmonary diseases in 1967.

is limited to estimates of per capita consumption based on cigarette sales and census population data. Figure 13–4 illustrates that per capita consumption had already begun to increase in the United Kingdom by 1905 and in the United States by 1910. In contrast, postwar economic conditions delayed the major increase in consumption in Japan until the 1960s and in China until the 1970s (Forey et al., 2002). Per capita cigarette consumption is now decreasing in most Western countries but continuing to increase in many economically developing countries (Corra et al., 2000).

The first national survey of smoking prevalence among adults in the United States was conducted in 1955, when 57% of men and 28% of women age 18 years and older reported current cigarette smoking (Haenszel et al., 1956). Smoking prevalence was even higher in the United States since the 1964 U.S. Surgeon General Report on Smoking and Health (U.S. Public Health Service, 1964). The crude prevalence of current cigarette smoking in men, age ≥18 years, decreased from 51.9% in 1965 to 25.7% in 2000 (National Center for Health Statistics, 2002). The corresponding decrease in smoking prevalence among women was from 33.9% in 1965 to 21.0% in 2000.

Although the overall prevalence of smoking among adults age ≥18 years decreased in many affluent countries over the last half century, the age at which smokers initiated the habit became progressively younger. Table 13–2 shows the average age of initiation among male and female smokers in birth cohorts from 1870 to 1970 in two American Cancer Society cohorts enrolled in 1959 and 1982 (Thun et al., 1997a, 2002) and in two National Health Interview surveys conducted during 1987–1988 (Burns et al., 1997a) and 1998 (http://www.cdc.gov/nchs/nhis.htm). A similar pattern in which successive generations begin smoking at progressively early ages has occurred in many other countries (U.S. Department of Health and Human Services, 1994). Most smokers in developed countries become addicted to tobacco use during adolescence. Hence the prevention of smoking initiation by adolescents is one of the critical goals of tobacco control (U.S. Department of Health and Human Services, 1994).

**Birth Cohort Patterns in Smoking Prevalence**

The increase in smoking prevalence is not uniform across all age groups of the population but follows clear birth cohort patterns that reflect smoking initiation during the critical periods of adolescence and young adulthood (Giovino et al., 1995; Thun et al., 2002). Within each birth cohort (5- or 10-year interval of birth year), the uptake of smoking reflects social norms, peer behavior, tobacco marketing, and economic conditions that prevail during this period of vulnerability.

In the United States, widespread cigarette smoking was adopted first by white men and then black men (Burns et al., 1997b). Male smoking prevalence increased across successive birth cohorts after 1885–1889, peaking among men born during 1925–1929 and then decreasing in later cohorts because of the growing publicity during the 1950s about the adverse health effects of smoking. Widespread cigarette smoking
among women lagged behind that in men, with peak prevalence occurring in birth cohorts during 1930–1934 and 1935–1939. The increase in smoking initiation among adolescent girls in the United States around 1967 coincides with the introduction of several women’s brands and correlates strongly with increasing expenditures for tobacco advertising and promotion (Pierce et al., 1994; Giovino et al., 1995).

A limitation of birth cohort analyses of smoking prevalence in the United States is that historical data must be reconstructed from surveys beginning in 1965 (Harris, 1983; Burns et al., 1997a) because national surveys were not conducted during the first half of the twentieth century. These reconstructions illustrate the progressive wave-like uptake of cigarette use by successive birth cohorts of Americans, but their quantitative accuracy can be questioned. Contemporary documentation of birth cohort increases in smoking is unfortunately still possible in countries where cigarette smoking is increasing, where birth cohort trends can be monitored as they occur. These trends have important implications for understanding and communicating the epidemiology of tobacco-attributable diseases. Even large increases in age-specific smoking prevalence among young adults initially have little impact on the crude or age-adjusted prevalence for all adults. The full consequences of current smoking practices are not reflected in national lung cancer rates or in analytic studies of smoking until lifetime smoking patterns have been entrenched in a population for approximately 50 years (IARC, 2004). Studies that measure the risks from continued smoking or the benefits from smoking cessation underestimate these parameters in countries where the uptake of smoking has occurred more recently. Birth cohort patterns of cigarette smoking also explain why the downturn in lung cancer death rates seen in older age groups has occurred progressively later over time. In the United States, the age group with the highest lung cancer death rate in white men was age 65–69 in 1950–1959, age 70–74 in 1962–1969, age

**TOBACCO PRODUCTS OTHER THAN CIGARETTES**

Although manufactured cigarettes are the predominant form of tobacco used, 15%–35% of global consumption involves other tobacco products (World Health Organization, 1997). The most common form of smoked tobacco in India involves bidis, traditionally hand-rolled in dried temburni leaf and tied with a string (Mackay and Eriksen, 2002; IARC, 2004). Cigars are defined as shredded tobacco wrapped in tobacco leaf or paper (U.S. Department of the Treasury, 1996). They vary in size from cigarette-sized cigarrillos to cheroots and double coronas (Mackay and Eriksen, 2002). Kretekks are clove- and cocoa-flavored small cigars that originated in Indonesia but are available in the United States (IARC, 2004). Chuttas are coarsely prepared small cigars smoked exclusively in India, sometimes with the burning end held inside the mouth, a practice called “reverse smoking” (IARC, 2004). The previously widespread use of pipes is decreasing throughout Europe and the Americas (World Health Organization, 1997). In Moslem countries, tobacco is frequently smoked in water pipes (IARC, 2004).

The use of spit tobacco products predominates in certain populations. Betel chewing is common throughout much of Southeast Asia and the western Pacific. Betel leaves (*Piper betle*) are mixed with tobacco, areca nut (*Areca catechu*), lime, wood ash, or other substances to form a quid, pan, or nass (Gupta, 1992; IARC, 2004). The mixture is then chewed and/or retained in the mouth. The use of spit tobacco is estimated to cause nearly 100,000 deaths annually from oral cancer in southern Asia (Ezzati and Lopez, 2003a). In the United States alone, several million people use spit tobacco (Glover and Glover, 1992). Moist snuff consists of finely ground tobacco with 20%–55% moisture content, often flavored with mint, wintergreen, or raspberry (Brunnemann and Hoffmann, 1992). A pinch (called a dip or rub) is placed between the gum and the cheek or under the tongue (Glover and Glover, 1992). The use of chewing tobacco remains common among baseball players and some rural populations in the United States. Chewing tobacco products may also be flavored with sugar, molasses, or licorice. In Sweden, a major form of tobacco use involves moist snuff or “snus,” reported to have lower nitrosamine content (Nilsson, 1998).

Products other than manufactured cigarettes are often viewed as anachronistic, yet they cause substantial disease and can undergo rapid increases in usage with aggressive marketing. This was evidenced by the resurgence in the use of moist snuff and chewing tobacco by smoking and Tobacco control Monograph 8, 1997, p. 313 and NHIS 1998 public use tapes (http://www.cdc.gov/nchs/nhis.htm). Thun et al. 2002. Tobacco use and cancer: an epidemiologic perspective for geneticists. Oncogene 21:7307–7325, with permission from Nature Publishing Group. Based on the age of initiation among current cigarette smokers in the analytic cohorts of Cancer Prevention Study I (CPS-I) and CPS-II and published data from the National Health Interview Surveys of 1987 and 1988, whites (Burns, 1994), and unpublished data from the National Health Interview Surveys of 1998, whites.

*Age at initiation is biased towards a younger age because it is based on people aged 19–29 years.
adolescents in the United States during the 1980s (Connolly et al., 1986) and the increase in premium cigar smoking in cigar bars during the 1990s (Gerlach et al., 1998). There is concern that the use of traditional tobacco products can be a pathway to the initiation or resumption of smoking manufactured cigarettes.

### CHEMICAL COMPOSITION OF TOBACCO AND TOBACCO SMOKE

Tobacco smoking generates both mainstream smoke (MS), drawn directly from the burning tobacco into the mouth, and sidestream smoke, released from the smoldering tobacco into the ambient air. The latter mixes with exhaled MS to make up environmental tobacco smoke (ETS). Synonyms for ETS exposure include passive, involuntary, or second-hand smoke exposure (IARC, 2004).

Tobacco smoke is a complex, heterogeneous mixture that contains approximately 4000 identified chemicals (Hoffmann et al., 2001). Of these, at least 3000 are present in the tobacco leaf (Roberts, 1988); other compounds are generated during curing and/or combustion. At least 55 chemicals present in tobacco smoke are considered established carcinogens based on studies of laboratory animals or humans evaluated by the International Agency for Research on Cancer (IARC, 1986; Hoffmann et al., 1997; Hecht, 1999b). Major classes of carcinogens in tobacco leaf and/or smoke are listed in Table 13–3.

The composition of tobacco smoke is affected by many factors, including the tobacco leaf, smoking patterns, chemical additives, pH, type of paper and filter, and ventilation (U.S. Department of Health and Human Services, 2002). Numerous carcinogens are generated by combustion of tobacco, including many polycyclic aromatic hydrocarbons, N-nitrosamines, and aromatic amines as well as formaldehyde, phenolic compounds, and a variety of free radicals (IARC, 1986). Other carcinogens, such as arsenic, cadmium, chromium, nickel, and polonium 210 are incorporated into the tobacco plant from soil, pesticides, and phosphate fertilizers. Other compounds accumulate in tobacco during certain curing processes. For example, fermentation increases the concentration of N-nitrosamines in moist snuff and cigars (Hoffmann and Hoffmann, 1997); exposure of flue-cured tobacco to combustion products from gas heaters is also reported to increase tobacco-specific nitrosamines (TSNAs) (Peele et al., 2001).

Two TSNAs of particular interest have been NNK (4-methylnitrosamo-1-3-pyridyl-1-butanone) and NNN (N-nitrosornornicotine). Their concentrations are greatly increased by the fermentation of tobacco for use in cigars and moist snuff and by the inclusion of ribs and stems in reconstituted tobacco (Hoffmann and Hoffmann, 1997). TSNAs have been proposed as major contributors to the increase in adenocarcinoma of the lung in many countries, as these compounds induce adenocarcinoma of the lung in rodents, independent of the route of administration (Hecht, 1999b).

Nicotine is the principal alkaloid present in tobacco and accounts for 0.05%–4.00% (by weight) of the tobacco leaf (U.S. Department of Health and Human Services, 1988). Absorption of nicotine from tobacco leaf or smoke is the major factor that induces physical addiction. Although nicotine itself is not carcinogenic, addiction to nicotine sustains tobacco use and prolongs exposure to other carcinogens. Furthermore, nicotine is transformed during curing and combustion to TSNAs, which are carcinogenic (Hecht, 2002a). In cultured lung epithelial cells, nicotine inhibits apoptosis, stimulates cell growth, and may function as a tumor promoter (Minn, 2003).

Combustion of tobacco produces an aerosol with a vapor phase (about 90% of the total) and a particulate phase (Hecht, 1999b). The particulate phase is especially rich in carcinogens (Hecht, 1999b). Sidestream smoke contains higher concentrations of nicotine, carbon monoxide, benzene, and several polycyclic aromatic hydrocarbons than does mainstream smoke because combustion is less complete in smoldering than burning tobacco (IARC, 2004). ETS is comprised of a mixture of exhaled mainstream smoke, sidestream smoke, and a small amount of noninhaled smoke released during puffing, diluted in ambient air. ETS exposure is not accurately characterized in terms of “cigarette equivalents” because the ratio of specific components of ETS to nicotine is different in mainstream smoke and ETS. Cotinine concentration in saliva, urine, or serum provides a qualitative indication of recent exposure to ETS but not a quantitative measure of exposure to constituents of smoke other than nicotine (Hecht, 2002a).

### ROLE OF NICOTINE ADDICTION IN SUSTAINING TOBACCO USE

Physical dependence on nicotine is the critical factor that sustains tobacco use among tobacco users. Nicotine from tobacco binds with the nicotinic receptors for acetylcholine in the central and peripheral nervous systems. In the central nervous system (CNS), the receptors regulate the release of neurotransmitters such as dopamine, serotonin, and γ-aminobutyric acid. Exposure to exogenous nicotine stimulates the production of additional nicotine receptors (Benowitz, 1996a). Abstinence from smoking triggers withdrawal symptoms of anxiety, irritability, weariness, constipation/diarrhea, insomnia, intense craving, and difficulty concentrating (Balfour and Fagerstrom, 1996; Arinumi et al., 2000).

Tobacco products vary in their delivery of nicotine in a form that is rapidly absorbed and pharmacologically active. Cigarettes and moist snuff increase plasma nicotine concentration almost immediately (Fig. 13–5), whereas the nicotine replacement products currently available provide much slower nicotine uptake (Benowitz, 1996a). Inhalation of cigarette smoke increases plasma nicotine and produces discernible CNS effects in as little as 7 seconds owing to the large surface area of the lungs. The uptake of nicotine from moist snuff depends on the pH of the product. Commercial brands produce a pH range in saliva from 8.0 (at which 50% of nicotine is free or un-ionized) to 7.0 (where only 10% of nicotine is un-ionized and can be rapidly absorbed) (Federal Register, 1995). Tobacco products that deliver nicotine rapidly reinforce positive associations with the behavioral aspects of smoking and increase the difficulty of cessation (O’Brien, 2001). For most users, tobacco use results in true drug dependence. Withdrawal symptoms among cigarette smokers who attempt to quit may equal the severity of withdrawal from opiates, amphetamines, and cocaine (Consensus Statement, 2000). The strength of the addiction is illustrated by the high failure rate among smokers who attempt to quit (O’Brien, 2001). Approximately 70% of current smokers express a desire to quit, yet fewer than 50% try to stop each year (Centers for Disease Control and Prevention, 2002b). Unassisted, about 2.5% of smokers succeed in quitting permanently on a single quit attempt (Centers for Disease Control and Prevention, 1994). The success rate approximately doubles with appropriate pharmacologic and/or behavioral treatment.

### Table 13-3. Classes of Carcinogens in Tobacco Smoke

<table>
<thead>
<tr>
<th>Class</th>
<th>No.</th>
<th>Example(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatic hydrocarbons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monocyclic</td>
<td>1</td>
<td>Benzene</td>
</tr>
<tr>
<td>Polycyclic</td>
<td>10</td>
<td>Benzo[a]pyrene</td>
</tr>
<tr>
<td>Aza-arenes</td>
<td>3</td>
<td>Dibenz[a,h]acridine</td>
</tr>
<tr>
<td>N-Nitrosamines</td>
<td>7</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>Aromatic amines</td>
<td>3</td>
<td>2-Naphthyamine</td>
</tr>
<tr>
<td>Heterocyclic aromatic amines</td>
<td>8</td>
<td>4-Aminobiphenyl</td>
</tr>
<tr>
<td>Aldehydes</td>
<td>2</td>
<td>Formaldehyde</td>
</tr>
<tr>
<td>Organic compounds</td>
<td>14</td>
<td>1-3-Butadiene</td>
</tr>
<tr>
<td>Inorganic compounds</td>
<td>7</td>
<td>Arsenic, cadmium, chromium, hydrazine, nickel, polonium-210</td>
</tr>
</tbody>
</table>

Sources: Adapted from Hoffmann and Hoffmann (1997); IARC (1986), Hecht (1999b).
CIGARETTE YIELD AS MEASURED BY MACHINE SMOKING

A complication when measuring exposure in epidemiologic studies, in addition to the role of nicotine addiction in regulating smoking behavior, is the incompletely documented impact of design changes in cigarettes on both the composition of smoke and smoking behavior. The most noticeable has been a series of changes that reduced the "yield" of tar and nicotine, as measured by machine smoking. A standardized method of testing was developed by the tobacco industry during the 1930s (Bradford et al., 1936) and adopted officially by the Federal Trade Commission (FTC) in 1969 to measure the average nicotine and "tar" yield from the various brands of cigarettes (Institute of Medicine, 2001). The FTC protocol specifies that a smoking machine take one 2-second (35 ml) puff per minute until the cigarette is consumed. Tar and nicotine are extracted from a special filter through which the machine has "smoked" the cigarette. Tar represents the total particulate matter after removing the nicotine and water (Institute of Medicine, 2001). The average sales-weighted FTC tar rating of U.S. cigarettes has decreased from 38 mg in 1954 to 12 mg in 1997 (Fig. 13-6) (U.S. Department of Health and Human Services, 1981, 1989; Kozlowski et al., 2001). During the same interval, the average nicotine rating decreased from 2.3 mg in 1954 to 0.9 mg in 2001. Most of the reduction in machine-measured tar and nicotine yield that occurred before 1970 resulted from the introduction of cellulose acetate filters. Further reductions in the FTC-rated yield, after 1970, were achieved by adding ventilation holes and porous paper to dilute the mainstream smoke, technology to puff the tobacco that decreased the amount of tobacco per cigarette, and modifications that caused cigarettes to burn faster so the testing machine had fewer puffs (Kozlowski et al., 2001).

A major limitation of the FTC protocol is that the cigarette yield ratings, as measured by machine smoking, do not reliably predict the tar and nicotine exposure of individual smokers (Djordjevic et al., 2000; Burns and Benowitz, 2001). Smokers can compensate for design changes in cigarettes to extract greater amounts of nicotine and tar than the FTC rating would indicate. Studies that have measured salivary cotinine as an indicator of nicotine absorption demonstrate a wide range in salivary cotinine in people who smoke cigarettes with the same nicotine rating (Fig. 13-7) (Benowitz, 2001; Jarvis et al., 2001). This is because smokers, unlike smoking machines, seek to maintain their accustomed level of nicotine and can compensate for the change in cigarette design by taking larger and more frequent puffs, obstructing the ventilation holes that dilute the mainstream smoke, and inhaling the smoke more deeply into the lungs to increase the surface area for absorption (Djordjevic et al., 2000; Burns and Benowitz, 2001).

There has been considerable debate about what impact, if any, design changes that have reduced machine-measured tar ratings have had on the carcinogenicity of cigarettes. This is discussed below in the section on variations in the carcinogenicity of cigarettes.

![Figure 13-5](image_url)

Figure 13-5. Plasma nicotine concentration by various tobacco products. Venous blood concentrations (nanograms of nicotine per milliliter of blood) as a function of time for various nicotine delivery systems. Data on cigarettes, oral snuff, and nicotine gum are from Benowitz et al.: Clin Pharmacol Ther 44:23, 1988; data on the nicotine nasal spray are from Schneider et al.: Clin Pharmacokinetic 31:65, 1996; data on transdermal nicotine are from Benowitz: Drugs 45:161, 1993. (Source: Adapted from Henningfield et al.: Econ Neurosci 2:42–46, 2000.)

![Figure 13-6](image_url)

OTHER ASPECTS OF CIGARETTE DESIGN AND COMPOSITION THOUGHT TO INFLUENCE EXPOSURE

Other aspects of cigarette design have also changed substantially over time and vary among countries, although few of these changes have been considered in epidemiologic studies. As mentioned above, the selection of special tobacco strains during the early development of manufactured cigarettes is thought to have altered the pH of smoke and the inhalation patterns of smokers (Doll, 1998a). However, the impact of these changes was either not measured systematically or not reported in the scientific literature. Two aspects of tobacco processing that increase the concentrations of TSNAs were the introduction of reconstituted tobacco during the 1950s (which includes tobacco ribs, stems, and leaves and releases higher concentrations of TSNAs) (IARC, 1986; Hoffmann and Hoffmann, 1997), and the fermentation of tobacco for use in cigars and moist snuff. The concentration of TSNAs in moist snuff far exceeds the limit allowed in other consumer products (Hoffmann et al., 1995). Of further concern is that hemoglobin adducts containing TSNAs have been observed in people who “dip” snuff (Hecht et al., 1994).

Differences in the methods of curing tobacco underlie the distinction between blond tobacco, used by leading American and transnational brands, and black tobacco, which predominated in France, Spain, and several Latin American countries until the 1980s (Maxwell, 2002). Blond tobacco is produced by flue curing during which the tobacco is heated, whereas black tobacco is produced by air-curing with little or no use of artificial heat. Cigarettes made from black tobacco are reportedly more strongly associated with cancer of the bladder (De Stefani et al., 1991; Vineis, 1991; Bartsch et al., 1993) oropharynx (Boffetta, 1993; De Stefani et al., 1998), larynx (Sancho-Garnier and Theobald, 1993), esophagus (De Stefani et al., 1993; Castellsague et al., 1999), and lung (Benhamou and Benhamou, 1993; Armadans-Gil et al., 1999) than are cigarettes made from blond tobacco. Substantial differences have also been observed in the concentration of nitrosamines, nitrates, and nicotine in cigarettes from various countries (Fischer et al., 1991; Gray et al., 1998). Relatively few studies have attempted to integrate information on the differences in chemical composition of cigarettes in various countries with detailed longitudinal information on smoking practices when examining international variations in smoking-attributable risk.

Various novel tobacco products have been developed that reportedly deliver less exposure to certain carcinogens or nicotine than conventional cigarettes. They have been designated “potential reduced-exposure products” (PREPs) by the Institute of Medicine (2001). PREPs include cigarettes and spit tobacco products made from modified tobacco with reduced nitrosamine content, cigarette-like products that deliver nicotine with less combustion of the tobacco, and pharmaceutical products that deliver nicotine, antidepressants, or other medications. Unlike drugs that have been evaluated by the U.S. Food and Drug Administration (FDA) for the treatment of tobacco dependence, most PREPs have not been assessed comprehensively for a sufficient time to determine their hazard compared to conventional tobacco use or their impact on the initiation or cessation of tobacco use.

EXPOSURE MEASUREMENT IN EPIDEMIOLOGIC STUDIES OF TOBACCO

The best and most thoroughly validated external measures of tobacco exposure derive from self-reports (Shields, 2002). Most adults can report whether they have smoked 100 or more cigarettes in their lifetime and whether they now smoke every day or on some days, the definition of current smoking (Kovar and Poe, 1985). Parameters that can be determined from self-reports include smoking status (never, current, former), the number of cigarettes, cigars or pipes smoked daily, the use of spit tobacco, age of initiating tobacco use, and age at cessation.

A meta-analysis of 26 studies that evaluated the validity of self-reported data on tobacco use found that self-reported smoking status predicted biochemical evidence of active smoking with 87% sensitivity and 89% specificity (Patrick et al., 1994; U.S. Department of Health and Human Services, 2001). The sensitivity and specificity of self-reported smoking were higher in studies of adults than in those of children. Smoking history is considered a more sensitive measure of intermittent smoking than are biochemical indices, as the half-life of cotinine is only about 17 hours (Benowitz, 1996b). However, self-reported data on the number of cigarettes consumed per day are thought to underestimate actual consumption by at least 20%. Estimates of per capita consumption based on questionnaire surveys consistently underestimate consumption based on cigarette sales data by 20%–30% (Todd, 1978).
Despite their quantitative limitations, self-reported data on number of cigarettes smoked per day and/or years of smoking are consistently associated with a gradient of risk of developing many cancers. Strong evidence of a dose-response relation exists for all cancers designated causally related to smoking (IARC, 2004). Self-reported information may be less reliable, however, for reflecting more subtle differences in exposures in the intensity of smoking at various ages. Few studies have measured the intensity of adolescent smoking, fluctuations in the number of cigarettes smoked per day at different points in life, the number and duration of unsuccessful cessation attempts, the number of puffs taken per cigarette, average puff volume, depth of inhalation, or retention time in the lung. Most of these factors may not be measurable by questionnaire. However, they may introduce sufficient misclassification of lifetime tobacco exposure to make it difficult to document relatively small differences in the pathogenicity of cigarettes, given the potentially larger variations in smoking behavior.

Another challenge concerns the difficulty of summarizing cumulative exposure to tobacco over a lifetime. The common practice of combining information on intensity and duration of smoking into a single variable of cumulative exposure (pack-years or cigarette-years) is contraindicated. In the British Doctors’ Study, Doll and Peto showed that the duration of smoking is a much stronger predictor of lung cancer risk than is the number of cigarettes smoked per day (Doll and Peto, 1978). Lung cancer risk increases with the fourth or fifth power of years of smoking but only the second power of cigarettes per day. Researchers increasingly recommend that pack-years no longer be used as an exposure variable (Leffondre et al., 2002), just as “ever” smoking is no longer considered an informative summary of the experience of current and former smokers.

**Biomarkers**

Various biomarkers have been used in epidemiologic studies of tobacco and cancers to assess aspects of absorption, metabolism, excretion, and biologic activity of tobacco smoke (Institute of Medicine, 2001; Shields, 2002; IARC, 2004). The most thoroughly studied measures that reflect internal exposure to nicotine and other chemicals in the smoke. Cotinine is the main proximate metabolite of nicotine and is considered the biomarker of choice for indicating exposure to tobacco during the last 2–3 days (Benowitz, 1996a). The concentration of cotinine in plasma, saliva, or urine can reliably differentiate active smoking from ETS exposure (IARC, 2004). Other biomarkers, such as thiocyanate in plasma or saliva, carbon monoxide in exhaled alveolar air, and blood carboxyhemoglobin concentrations, are less sensitive and/or less specific as markers of tobacco exposure than cotinine (Institute of Medicine, 2001). Studies of cotinine have been informative in demonstrating that persons exposed to ETS incur exposures that are less than in active smokers but greater than in nonsmokers.

Other biomarkers reflect the systemic distribution or biologically effective dose of various components of tobacco smoke (Institute of Medicine, 2001). For example, metabolites of tobacco-specific nitrosamines can be measured in urine (Carmella et al., 1995; Atawodi et al., 1998; Shields, 2002) and other bodily fluids (Hecht, 2002b). Cigarette smoking increases the mutagenicity of urine (Atawodi et al., 1998; Vermeulen et al., 2000), the activation of certain enzymes in body tissue (Whyatt et al., 1995), and the presence of adducts from tobacco-specific nitrosamines or 4-aminohiphenyl attached to DNA, hemoglobin, or lymphocytes (Hecht et al., 1994; Dallinga et al., 1998; Hecht, 1999a). Adducts bound to cellular macromolecules persist longer than nicotine metabolites after abstinence from tobacco use. The number of chromosomal aberrations in cultured lymphocytes and extent of lipid peroxidation have been shown to correlate with the number of cigarettes smoked per day (Shields, 2002).

A limitation of many of these biomarkers is that they reflect recent exposure to tobacco smoke rather than exposures in the remote past. Cotinine and carbon monoxide are affected by smoke exposure within the last few days, thiocyanate (from hydrogen cyanide) within the past few weeks (Jarvis, 1987). Although biomarkers are sensitive measures of current exposure to tobacco smoke, most do not reflect long-term usage.

**Measures of Addiction**

One parameter that has not generally been measured in epidemiologic studies but that may prove informative in future studies is the level of nicotine addiction of individual smokers. The Fagerstrom index is a widely used index of addiction in behavioral studies (Fagerstrom, 1978; Fagerstrom et al., 1996) that measures six correlates of physiological dependence. It includes questions such as: How soon after you wake up do you smoke your first cigarette? Do you find it difficult to refrain from smoking in places where it is forbidden? Do you smoke if you are so ill that you are in bed most of the day? Questions in the Fagerstrom index may correlate with parameters of tobacco exposure that are difficult to measure by questionnaire, such as greater puff volume, depth of inhalation, and retention time in the lung. If this were validated, the Fagerstrom index might provide a useful adjunct to the questions currently used to assess tobacco exposure.

**Epidemiologic Findings Regarding Tobacco and Cancer**

Based predominantly on epidemiologic evidence, active cigarette smoking use is considered causally related to approximately 15 cancer sites. Twelve of these sites are included in the U.S. Surgeon General’s calculation of deaths attributable to cigarette smoking in the United States (see Table 13–1) (U.S. Department of Health and Human Services, 2004). For three other cancer sites (liver, nasal cavity/paranasal sinuses, nasopharynx), the IARC has designated the evidence for a causal relation with smoking as sufficient (IARC, 2004), but the Surgeon General does not currently include them when estimating deaths from smoking (U.S. Department of Health and Human Services, 2004).

Table 13–1 indicates the year in which each cancer site or other condition was formally designated as being smoking-related by the Surgeon General. Only four associations were judged to be causal at the time of the first report on smoking and health in 1964: cancers of the lung and larynx and chronic bronchitis in men who smoked cigarettes and lip cancer in men who smoked pipes (U.S. Public Health Service, 1964). The relative risk estimates associated with each of these conditions exceeded 5.0 among current smokers compared to lifelong nonsmokers in early cohort studies in the United Kingdom (Doll and Hill, 1956, 1964, 1966), the United States (Hammond and Horn, 1958; Dorn, 1959; U.S. Public Health Service, 1964), Canada (Best et al., 1961). Since then, the associations between smoking and many conditions have become considerably stronger as a consequence of earlier age of initiation among smokers. The relations are seen in women as well as men and have been observed in many studies of varying design in different populations.

Many of the cancers associated with smoking are located in the respiratory, gastrointestinal, or genitourinary tracts. We discuss respiratory tract cancers first because the associations between smoking and these sites (especially cancers of the lung and larynx) are stronger than the associations with other cancers. The discussion of specific cancer sites is ordered by the International Classification of Diseases (ICD) code.

**Respiratory Tract Cancers**

**Nasal Cavity and Paranasal Sinuses**

Cancers of the nasal cavity and paranasal sinuses are rare and were not separately designated as causally related to smoking until the IARC review in 2002 (IARC, 2004). Case-control studies in the United States (Brinton et al., 1994; Zheng et al., 1993; Caplan et al., 2000), the Netherlands (Hayes et al., 1999), other European countries (Manne et al., 1999), Hong Kong (Ng, 1986), and Japan (Fukuda and Shibata, 1990) reported relative risk estimates of about 2.0 in current smokers compared to lifelong nonsmokers for squamous cell carcinoma (IARC, 2004). This association is much weaker than the relation of cigarette smoking with cancers of the lung and larynx, but
the nasal cavity and paranasal sinuses are exposed to mainstream tobacco smoke only during exhalation.

Larynx
Cancer of the larynx is second only to lung cancer in the strength of its association with cigarette smoking (see Table 13-1). The risk of death from laryngeal cancer among current smokers compared to lifelong nonsmokers in Cancer Prevention Study II (CPS-II) was similar for men [relative risk (RR) 14.6] and women (RR 13.0) (see Table 13-1). Several population-based case control studies report relative risks of ≥2.5 in men who smoke more than one pack of cigarettes per day (Tuyns et al., 1988; Falk et al., 1989; Zatonski et al., 1991; Zheng et al., 1992a; Hedberg et al., 1994). Because cancer of the larynx is rare among lifelong nonsmokers, some case-control studies combine light or former smokers with never-smokers in the reference category (Choi and Kahyo, 1991; Zatonski et al., 1991; Lopez-Abente et al., 1992; Hedberg et al., 1994), thereby attenuating the association with smoking. Many hospital-based case-control studies (Burch et al., 1981; Graham et al., 1981; Herity et al., 1982; Brownson and Chang, 1987; De Stefani et al., 1987; Franceschi et al., 1989; Sankaranarayanan et al., 1990; Ahrens et al., 1991; Choi and Kahyo, 1991; Freudenstein et al., 1992; Lopez-Abente et al., 1992) also weaken the association with smoking by including persons with other smoking-related diseases in the control group. Risk increases with the duration and intensity of smoking and decreases rapidly after the cessation of smoking (Franceschi et al., 1989). The combination of tobacco smoking with heavy alcohol consumption greatly increases the relative risk for laryngeal cancer (Tuyns et al., 1988; Falk et al., 1989; Franceschi et al., 1990; Choi and Kahyo, 1991; Freudenstein et al., 1992; Lopez-Abente et al., 1992) also weaken the association with smoking by including persons with other smoking-related diseases in the control group. Risk increases with the duration and intensity of smoking and decreases rapidly after the cessation of smoking (Franceschi et al., 1989). The combination of tobacco smoking with heavy alcohol consumption greatly increases the relative risk for laryngeal cancer (Tuyns et al., 1988; Falk et al., 1989; Franceschi et al., 1990; Choi and Kahyo, 1991; Freudenstein et al., 1992; Lopez-Abente et al., 1992; Zheng et al., 1992b; Baron et al., 1993; Dosemeci et al., 1997; Schlecht et al., 1999), although most studies have not been formally evaluated for statistical interaction.

Trachea, Bronchus, Lung
Cigarette smoking is more strongly associated with lung cancer than with any other cancer site (see Table 13–1) (U.S. Department of Health and Human Services, 2004). The relative risk of death from lung cancer among current smokers compared to lifelong nonsmokers was approximately 23 in men and 13 in women in the American Cancer Society (ACS) CPS-II cohort; it increased to about 50 among male long-term (240 years) smokers of 40 cigarettes per day (Thun et al., 1997b). Cigarette smoking is strongly associated with all histologic types of lung cancer. In studies conducted during the 1950s, the association between smoking and lung cancer was largely with Kreyberg type I lung cancers (squamous and small-cell carcinomas) rather than with adenocarcinomas or large-cell carcinomas (Doll et al., 1957; Kreyberg, 1962; Wynder and Hoffmann, 1994). Smoking is still strongly associated with squamous and small-cell carcinomas but has become increasingly associated with adenocarcinoma and large-cell carcinomas located in the periphery of the lung (Thun et al., 1997b). The incidence of adenocarcinoma has also increased in many industrialized countries since the 1970s. This increase more closely follows birth cohort patterns relating to the introduction of filter-tip cigarettes and reconstituted tobacco beginning in the 1950s (Thun et al., 1997b) than period changes that would be expected from improvements in the technology of diagnosing peripheral lung cancer (Thun et al., 1997b). Two changes in cigarettes that may have contributed to the increase in adenocarcinomas were the introduction of filter-tip cigarettes and reconstituted tobacco beginning in the 1950s.

In the United States, cigarette smoking causes an estimated 88% of lung cancer deaths in men and 72% in women (see Table 13–1) (U.S. Department of Health and Human Services, 2004). Lung cancer deaths from smoking comprise about 80% of all cancer deaths attributable to smoking but only 31% of all deaths from smoking (Centers for Disease Control and Prevention, 2002a). Hence, screening efforts to detect and treat lung cancer early cannot effectively prevent the more than two-thirds of smoking-attributable deaths that involve diseases other than lung cancer.

The median delay between the initiation of smoking and death from lung cancer among smokers is approximately 50 years (Thun et al., 2002). The duration of regular smoking has been shown to be a substantially stronger determinant of lung cancer risk than is the number of cigarettes smoked per day (Doll and Peto, 1978; Flanders et al., 2003). Because of the protracted multistage development of solid tumors, the full impact of smoking on national lung cancer rates and on epidemiologic studies manifests only when regular smoking has been entrenched for many decades (IARC, 2004). This phenomenon is frequently misinterpreted, however. During the 1950s and 1960s, prominent scientists (Fisher, 1957, 1958a, 1958b, 1959) and politicians (Macdonald, 1957) interpreted the absence of a large increase in lung cancer mortality among women as evidence that smoking either did not cause lung cancer or that women were resistant to lung cancer, as many women started smoking after World War II (Doll, 1998a). Over time, the relative risk estimates associated with smoking continue to increase in both women and men with the aging of smokers who began at a young age and smoked intensively for many years.

Other issues and current controversies regarding lung cancer from cigarette smoking are reviewed elsewhere. They involve the evidence that women are not more susceptible than men to developing lung cancer from an equivalent amount of smoking (Thun et al., 2002; Bain et al., 2004; IARC, 2004), the complex differences in smoking behaviors and lung cancer risk between African Americans and Caucasians, factors that affect the probability that a smoker will develop lung cancer, and the difficulty of distinguishing historical differences in smoking behavior from other factors influencing lung cancer rates in countries such as Japan.

GASTROINTESTINAL CANCERS
Tobacco smoking is associated with cancer at all sites in the upper aerodigestive tract except the salivary glands (IARC, 2004). The association generally becomes weaker with progression from mouth to rectum. Early cohort analyses grouped many cancer sites into the single category of upper aerodigestive tract cancers. With longer follow-up of large cohort studies and the addition of case-control studies, many individual cancer sites and subsites have been examined separately.

Lip, Oral Cavity, Pharynx
All forms of tobacco use (cigarettes, pipes, cigars, snuff, chewing tobacco, betel, other smoked and smokeless products) cause dysplasia and cancer (predominantly squamous cell carcinoma) of the oral cavity and pharynx. The magnitude of risk from fire and pipe smoking is similar to the risk from cigarettes. On average, the RR of oropharyngeal cancer among persons who currently and exclusively smoke cigarettes is about 10.0 in men and 5.0 in women compared to that of lifelong nonsmokers (see Table 13–1) (Rogot and Murray, 1980; Franceschi et al., 1992; Muscat et al., 1996; U.S. Department of Health and Human Services, 2004). Tobacco use combined with heavy alcohol consumption magnifies the risk of either exposure alone. In one large population-based case-control study, the RR associated with smoking ≥240 cigarettes per day for ≥20 years was 7.4 in men and undefined among women who drank less than one alcoholic drink per week, but it was 37.7 in men and 107.9 in women who drank more than 30 alcoholic drinks per week (Blot et al., 1988). After cessation of smoking, the relative risk of oropharyngeal cancer decreases substantially within the first 10 years after quitting. Premalignant oral lesions such as leukoplakia and erythroplasia have been shown to regress after cessation of tobacco use (van der Waal et al., 1997; Martin et al., 1999).

Nasopharynx
Only recently have large cohort studies accrued enough cases over prolonged follow-up to examine cancers of the nasopharynx separately. A 26-year follow-up of men in the U.S. Veterans Study documented an association with current cigarette smoking (odds ratio (OR))
3.9, 95% confidence interval (CI) 1.5–10.3) (Chow et al., 1993) that was stronger in men smoking more than two packs daily (OR 6.4, 95% CI 1.2–33.2). Cigarette smoking is also associated with cancer of the nasopharynx in six population-based case-control studies (Nam et al., 1992; Zhu et al., 1995; Vaughan et al., 1996; Armstrong et al., 2000; Cao et al., 2000; Yuan et al., 2000). None of these studies controlled for Epstein-Barr virus, the principal cause of nasopharyngeal carcinoma worldwide.

**Esophagus**

Tobacco smoking was designated a cause of esophageal cancer by the U.S. Surgeon General in 1982 (U.S. Department of Health and Human Services, 1982) and by the IARC in 1986 (IARC, 1986). The risk of developing any esophageal cancer, irrespective of histologic subtype, is four to seven times higher among current smokers than lifelong non-smokers in most studies (IARC, 2004). The risk increases with the amount and duration of smoking and decreases with earlier age at cessation (U.S. Department of Health and Human Services, 2004). Smoking combined with heavy alcohol consumption greatly increases risk (Inoue et al., 1994; Castellsague et al., 1999), with RR estimates sometimes exceeding 100 (Talamini et al., 2000). Even 1–24 ml of ethanol consumed per day increases the risk associated with each level of smoking (Castellsague et al., 1999). Cigar and/or pipe smokers incur risks of esophageal cancer similar to those of cigarette smokers (Kahn, 1966; Carstensen et al., 1987; Shanks and Burns, 1998).

Smoking was associated with both squamous cell carcinoma and adenocarcinoma of the esophagus in case-control analyses that stratified by histologic subtype (Kabat et al., 1993; Inoue et al., 1994; Vaughan et al., 1995; Ahsan et al., 1997; Castellsague et al., 1999; Lagergren et al., 2000; Talamini et al., 2000). Several studies have suggested that black tobacco may confer a greater risk of esophageal cancer than blond tobacco (De Stefani et al., 1993; Castellsague et al., 1999).

**Stomach**

More than 20 cohort studies and nearly 40 case-control studies have reported an association between tobacco smoking and stomach cancer, with the RR averaging approximately 1.6 in current cigarette smokers compared to that for never-smokers (IARC, 2004). Until recently, stomach cancer was not classified as smoking-related because of uncertainty about potential confounding by Helicobacter pylori infection and diet (IARC, 1986; U.S. Department of Health and Human Services, 1989). However, several case-control studies have stratified the analysis based on *H. pylori* seropositivity and reported substantially stronger associations between smoking and stomach cancer in persons who are seropositive for *H. pylori* than in uninfected individuals (Jedrychowski et al., 1993, 1999; Zardize et al., 2000; Siman et al., 2001; Brenner et al., 2002; Wu et al., 2003). There is some evidence that tobacco smoking adversely affects the progression of intestinal metaplasia to dysplasia in *H. pylori*-affected people (Kneller et al., 1992; You et al., 1999). The most recent IARC review includes stomach cancer among the sites for which the evidence is considered sufficient in humans (IARC, 2004). Smoking appears to be associated with cancers of both the gastric cardia and non-cardia; some case-control studies (Palli et al., 1992; Gammon et al., 1997) but not others (Ye et al., 1999) have reported a stronger association with cancer of the gastric cardia than with other subsites. It has been estimated (Tredaniel et al., 1997) that worldwide the proportion of stomach cancer attributable to smoking is 11% in men and 4% in women in economically developing countries and 17% among men and 11% among women in developed countries.

**Colorectum**

The Surgeon General’s series of reports on the health consequences of smoking first considered smoking in relation to colorectal cancer in 2001 (U.S. Department of Health and Human Services, 2001) and more recently concluded that the evidence is suggestive but not sufficient to infer a causal relation (U.S. Department of Health and Human Services, 2004). Increased risk of colorectal adenomatous polyps is associated with current cigarette smoking in 3 prospective studies (Giovannucci et al., 1994a, 1994b; Nagata et al., 1999) and 13 case-control studies (Kikendall et al., 1989; Cope et al., 1991; Monnet et al., 1991; Zahm et al., 1991; Olsen and Kronborg, 1993; Boutron et al., 1995; Martinez et al., 1995; Longnecker et al., 1996; Nagata et al., 1999; Potter et al., 1999; Almendingen et al., 2000; Breuer-Katschinski et al., 2000; Inoue et al., 2000). With one exception (Kato et al., 1990), the relative risk estimates associated with current smoking range between 1.5 and 3.8 after adjusting for age and other covariates. Prospective cohort studies of colon cancer (Chute et al., 1991; Tverdal et al., 1993; Doll et al., 1994; Heineman et al., 1994; Chyou et al., 1996; Engeland et al., 1996; Nyren et al., 1996; Hsing et al., 1998; Sturmer et al., 2000), and rectal cancer (Chute et al., 1991; Tverdal et al., 1993; Doll et al., 1994; Heineman et al., 1994; Chyou et al., 1996; Engeland et al., 1996; Nyren et al., 1996) have generally reported RR estimates associated with current cigarette smoking of 1.2–1.4 for colon cancer and 1.4–2.0 for rectal cancer. However, there has not yet been a systematic meta-analysis that has evaluated this association across all studies, controlling for other factors known to increase or decrease the risk of colorectal cancer. Cancer of the anus, a malignancy with squamous or transitional cell histology, has repeatedly been found to be positively associated with cigarette smoking (Daling et al., 1992), although confounding by human papillomavirus has not been excluded.

**Liver**

At least 22 cohort and 27 case-control studies have examined the relation between tobacco smoking and hepatocellular carcinoma. Most of the studies reported an association between smoking and liver cancer, with RR estimates of about 1.5–2.5 (Gonzalez et al., 2003). Liver cancer was not classified as smoking-related by the IARC in 1986, however, because of uncertainty about potential confounding by hepatitis virus infection and heavy consumption of alcohol (IARC, 1986; U.S. Department of Health and Human Services, 1989). Hepatitis B virus (HBV) infection causes most liver cancer worldwide, and hepatitis C virus (HCV) infection accounts for a large fraction of the disease in Japan, North Africa, and southern Europe (IARC, 1994). Heavy, but not moderate, consumption of alcohol also contributes to the risk (IARC, 1988).

Recent studies have resolved these concerns about confounding. Several studies have reported a higher risk of liver cancer among non-drinking smokers compared to nondrinking nonsmokers (Chen et al., 1991; Goodman et al., 1995; Kuper et al., 2000). Smoking is also associated with liver cancer among Chinese (Liu et al., 1998) and Japanese (Tanaka et al., 1995) women in whom heavy alcohol consumption is rare (Gonzalez et al., 2003). Several studies have stratified on or adjusted for hepatitis B surface antigen (HbsAg) and anti-HCV and found little attenuation of the association between smoking and liver cancer (Yu et al., 1991; Liaw and Chen, 1998; Kuper et al., 2000). The risk of chronic infection with hepatitits viruses was not higher in smokers than nonsmokers in one study (Evans et al., 2002); however, compared to never-smokers, smokers did experience greater risks. Prospective studies have found an association between liver cirrhosis (Yu et al., 1991) and liver cancer (Yu et al., 1991) and/or liver cancer (Tsukuma et al., 1993).

**Gallbladder, Biliary Tract**

Cigarette smoking was associated with increased mortality from gallbladder and biliary tract cancer among current (RR 1.5, 95% CI 1.1–2.0) smokers in a 26-year follow-up of U.S. veterans (Chow et al., 1995). The association was stronger in persons who began smoking at a younger age or smoked more cigarettes per day. Findings have been inconsistent in case-control studies. Some studies have observed increased risk of biliary tract cancer in smokers (Chow et al., 1994; Moerman et al., 1994; Scott et al., 1999), whereas others have not (Yen et al., 1987; Zatonski et al., 1992; Moerman et al., 1994; Chalasani et al., 2000).
Pancreas

Numerous cohort (n = 17) and case-control (n = 30) studies have reported an association between cigarette smoking and cancer of the exocrine pancreas (IARC, 2004). The risk of pancreatic cancer is also increased among persons who smoked exclusively cigars and/or pipes in most large studies (Shanks and Burns, 1998; Shapiro et al., 2000). The evidence that tobacco smoke is carcinogenic to the human pancreas was classified as sufficient by the IARC in 1986 (IARC, 1986) and by the U.S. Surgeon General in 1982 (U.S. Department of Health and Human Services, 1982). The RR of death from pancreatic cancer among male and female current cigarette smokers compared to neversmokers, is 2.3 for both men and women in the ACS CPS-II (U.S. Department of Health and Human Services, 2004). Risk decreases among persons who stop smoking compared to those who continue in both cohort and case-control studies (IARC, 2004; U.S. Department of Health and Human Services, 2004).

URINARY TRACT CANCERS

Tobacco smoking is an established risk factor for cancer throughout the urinary tract (IARC, 1986, 2004; U.S. Department of Health and Human Services, 2004). Smoking was identified as an important cause of transitional cell carcinomas of the lower urinary tract (renal pelvis, ureter, urinary bladder, urethra) by the IARC in 1986 (IARC, 1986). More recently, the IARC designated the association between smoking and adenocarcinoma of the renal parenchyma as causal, although it was not as strong as that with transitional cell carcinoma (IARC, 2004). Renal adenocarcinoma accounts for most kidney cancers (Doll, 1996). The U.S. Surgeon General did not distinguish between adenocarcinoma and transitional cell carcinoma when estimating that cigarette smoking accounts for 26% of deaths from cancers of the kidney, ureter, and urethra in the United States (40% in men and 5% in women) (U.S. Department of Health and Human Services, 2004).

Renal Pelvis, Ureter

Relatively few studies have specifically examined the association between smoking and cancers of the renal pelvis and ureter (McCredie et al., 1983; Jensen et al., 1988; Ross et al., 1989; McLaughlin et al., 1992b). These studies suggest that smoking is the strongest known risk factor for cancers of the renal pelvis and ureter and is the primary cause of these cancers worldwide (McLaughlin et al., 1992b). The relative risk estimates are at least as high and dose-response relations are steeper for cancers of the renal pelvis and ureter than for bladder cancer in studies in which both types of cancer have been investigated in the same geographic area (Jensen et al., 1987, 1988; McCredie and Stewart, 1992).

Renal Adenocarcinoma

The 1986 IARC monograph on tobacco did not consider the evidence linking smoking to adenocarcinoma of the renal parenchyma with tobacco smoking to be conclusive because most of the available studies were either small or based on death certificates, which the committee did not believe could differentiate reliably between cancers of the renal parenchyma and those arising in the renal pelvis (IARC, 1986). A reevaluation by Doll et al. in 1996 (Doll, 1996) noted that all of the additional studies in Australia (McCredie et al., 1983; McCredie and Stewart, 1992), Canada (Kreiger et al., 1993), China (McLaughlin et al., 1992a), Denmark (Mellemgaard et al., 1994), Italy (Talamin et al., 1990), and the United States (Asal et al., 1988; Maclure and Willett, 1990; Hiatt et al., 1994) with more than 100 affected patients have found an increased risk in cigarette smokers compared to nonsmokers. Furthermore, the RR estimates in these studies were compatible with the estimates from a large collaborative study by McLaughlin et al. (Chow et al., 1995). The latter estimated the RR among current cigarette smokers compared to lifelong nonsmokers to be 1.1 in people smoking 1–10 cigarettes per day, 1.3 in those smoking 11–20 cigarettes per day, and 2.1 in those smoking ≥21 daily (Doll, 1996). The average RR among former smokers was estimated to be 1.2. Studies that adjusted the RR estimates for other potential risk factors such as hypertension, use of diuretics and other medications for hypertension, and obesity did not find a substantial attenuation in the association with smoking (IARC, 2004).

Urinary Bladder

Smoking is consistently associated with increased risk of transitional cell carcinoma of the urinary bladder in many epidemiologic studies (Brennan et al., 2000, 2001; IARC, 2004). The association between smoking and bladder cancer was classified as causal by the IARC in 1986 (IARC, 1986) and by the U.S Surgeon General in 1979 (U.S. Department of Health, Education, and Welfare, 1979). An estimated 41% of deaths from cancer of the urinary bladder in the United States are attributable to cigarette smoking (47% in men and 29% in women) (U.S. Department of Health and Human Services, 2004). The risk of bladder cancer among male current cigarettes smokers is approximately two to three times higher than that of never-smokers in prospective studies from the United States, Japan, and Europe (Brennan et al., 2000, 2001). Metabolites of heterocyclic aromatic amines, polycyclic aromatic hydrocarbons, and other carcinogens in tobacco can be detected in urine (IARC, 2004). Smokers have a higher prevalence of preneoplastic changes in the bladder (Auerbach and Garfinkel, 1986), DNA adducts have been detected in exfoliated urothelial cells from cigarette smokers (Talaska et al., 1991). There is limited evidence that the association between smoking and bladder cancer is stronger for smoking black (air-cured) than blond (flue-cured) tobacco (Clavel et al., 1989; D’Avanzo et al., 1990; De Stefani et al., 1991; Lopez-Abente et al., 1991; Monas et al., 1994; Vineis et al., 1984). Meta-analyses of case-control (Marcus et al., 2000a) and case series (Marcus et al., 2000c) studies of smoking in relation to bladder cancer have reported a stronger association among persons with the slow acetylator N-acetyltransferase (NAT2) phenotype.

CANCERS OF THE REPRODUCTIVE TRACT

AND BREAST

Uterine Cervix

Cancer of the uterine cervix, predominantly involving squamous cell carcinoma, is consistently associated with cigarette smoking in many studies. However, the association was not designated as causal by the IARC until 2002 (IARC, 2004) because of uncertainties about confounding by sexually transmitted diseases (Gonzalez et al., 2003). Since the identification of human papillomavirus (HPV) infection as the main cause of cervical cancer (IARC, 1995) studies have examined whether tobacco smoking acts as a cofactor with HPV infection in causing progression from preneoplastic lesions to cancer. Analyses either have been restricted to study participants who are positive for HPV DNA or have tried to adjust for HPV infection in the analysis. In the IARC multicenter, pooled analysis of invasive cervical cancer, restriction did not materially alter the association between smoking and risk (Plummer et al., 2001). Furthermore, in one cross-sectional study, smoking was more strongly associated with high-grade cervical intraepithelial neoplasia than with HPV infection (Deacon et al., 2000).

Smoking is associated with a spectrum of cervical abnormalities, from dysplasia to cervical intraepithelial neoplasia, cervical cancer in situ, and invasive squamous cell carcinoma. Risk increases with increasing intensity and duration of smoking. Whereas smoking is associated with an increased risk of squamous cell carcinoma of the uterine cervix, it was associated with lower risk of adenocarcinoma of the cervix in one multicenter case-control study (Lacey et al., 2001).

Endometrium

Endometrial cancer is the only human cancer reported to be inversely associated with cigarette smoking. More than 25 case-control studies
and 5 cohort studies have examined the association between smoking and endometrial cancer (U.S. Department of Health and Human Services, 2001; IARC, 2004). Most report lower risk among current smokers than nonsmokers, with RR estimates of 0.2–0.9. In only a few studies has the association been statistically significant (Levi et al., 1987; Stockwell and Lyman, 1987; Elliott et al., 1990; Brinton et al., 1993; Weiderpass and Baron, 2001). Adjustment for other factors associated with decreased risk (oral contraceptives) or increased risk (obesity, late onset of menopause, menstrual disorders, infertility, hormone replacement therapy) does not materially alter the inverse association with smoking in these studies. The lower risk of endometrial cancer associated with current smoking was hypothesized by MacMahon et al. (1982) to be caused by a reduction in estrogen production (see discussion of smoking and estrogen, under Breast Cancer).

Vulva and Vagina

Three case-control studies have examined the risk of cancer of the vulva in relation to cigarette smoking (Newcomb et al., 1984; Mabuchi et al., 1985; Brinton et al., 1990). All have found a positive association. None of the studies evaluated the possibility of confounding or biologic interaction with HPV infection (IARC, 1995). A report concluded that, “smoking may be associated with an increased risk for vulvar cancer, but the extent to which this association is independent of human papillomavirus infection is uncertain” (U.S. Department of Health and Human Services, 2001).

Ovary

Eight cohort studies and nine case-control studies have assessed the relation between ovarian cancer and smoking (U.S. Department of Health and Human Services, 2001; IARC, 2004). Most studies found no relation, although few have considered the histologic subtypes of ovarian cancer or examined risk in relation to duration and intensity.

Breast

Numerous case-control and cohort studies have examined the relation between cigarette smoking and breast cancer incidence or death rates (Palmer and Rosenberg, 1993; U.S. Department of Health and Human Services, 2001; IARC, 2004). No consistent association with either increased or decreased risk is seen with overall breast cancer incidence or with subgroups defined by menopausal status, estrogen receptor positivity (Cooper et al., 1989), or initiation of smoking during puberty or before first full-term pregnancy (Terry and Rohan, 2002). Cigarette smoking is also either unrelated or inversely related to benign breast disease. Thus, an extensive literature indicates no substantial overall association between cigarette smoking and breast cancer incidence in women or men (IARC, 2004). However, the possibility of a relation between smoking and breast cancer continues to be studied, in part because carcinogens in tobacco smoke cause mammary cancer in rodents (Ambrosone and Shields, 2001; Hecht, 2002c) and because DNA adducts containing polycyclic aromatic hydrocarbons have been found in exfoliated ductal epithelial cells in human breast milk (Gorlewksa-Roberts et al., 2002; Thompson et al., 2002). One hypothesis that was proposed to explain the absence of an association in epidemiologic studies is that the antiestrogenic effects of smoking may reduce breast cancer risk and thus obscure the deleterious effect of carcinogens from tobacco on breast cancer risk.

Several lines of indirect evidence suggest an antiestrogenic effect from active smoking, although the underlying mechanism for this effect is not known (Baron et al., 1990). Current smokers experience menopause 1–2 years earlier than never-smokers (Lesko et al., 1985; Brinton et al., 1986; Chu et al., 1990). Smokers also have a lower risk of endometrial cancer and endometriosis (both estrogen-responsive conditions), lower mammographic density (Sala et al., 2000; Vachon et al., 2000), and higher risk of osteoporotic fractures (Jensen et al., 1985; Paganini-Hill and Hsu, 1994) than nonsmokers. However, the concentrations of estrogen (estrone and estradiol) measured in plasma or urine are not demonstrably lower in smokers (Freidman et al., 1987; Khaw et al., 1988; Longcope and Johnston 1988; Cauley et al., 1989; Schlemmer et al., 1990; Key et al., 1991; Berta et al., 1992; Cassidten et al., 1992). Some researchers have proposed that the antiestrogenic effect from active smoking may reflect differential metabolism of estrogens through the 2-hydroxylation pathway, producing a metabolite with low estrogenic activity (Michnovicz et al., 1996; Key et al., 1996; Cook et al., 2003).

A related issue is whether the inclusion of women exposed to second-hand smoke in the referent group in epidemiologic studies of breast cancer may obscure an increase in risk associated with active or passive smoking. The reasoning here is that second-hand smoke may contain enough carcinogens to increase a woman's risk of breast cancer but not enough to trigger the antiestrogenic effect of active smoking. According to this theory, the inclusion of women with ETS exposure among the never-smoking comparison group in studies of active smoking may obscure the increase in risk associated with smoking. The practical dilemma is that most women in wealthy countries have been exposed to ETS, given the ubiquity of involuntary exposure over the last half century. Studies that attempt to define a small subset of women who report neither active nor passive smoking and use this as the referent group may introduce bias because such women are likely to be atypical in other respects that relate to breast cancer risk (IARC, 2004).

MALE GENITAL TRACT

Prostate

Studies have consistently shown no association between cigarette smoking and prostate cancer incidence (Hickey et al., 2001; Levi and La Vecchia, 2001; IARC, 2004). However, several cohort studies that have examined death rates from prostate cancer have reported higher mortality in smokers than in lifelong nonsmokers with RR estimates of 1.2–2.0 (Hsing et al., 1991; Tverdal et al., 1993; Adami et al., 1996; Coughlin et al., 1996; Rodriguez et al., 1997; Eichholzer et al., 1999; Giovanniucci et al., 1999). Prostate cancer is a common disease among elderly men, however. The review by the IARC questions whether the association between smoking and increased death rates from prostate cancer represents a true causal effect from smoking, perhaps due to shortened survival, or a bias introduced by accelerated mortality from other smoking-attributable diseases.

Testes

Cancer of the testes has not been extensively investigated but seems unrelated to smoking (Henderson et al., 1979; Brown et al., 1987; Gallagher et al., 1995).

Penis

Studies of smoking in relation to squamous cell carcinoma of the penis have been reviewed elsewhere (Dillner et al., 2000, Moore et al., 2001). Several case-control studies (Hellberg et al., 1987; Maden et al., 1993; Harish and Ravi, 1995; Tsen et al., 2001) but not all (Brinton et al., 1991) that examined this endpoint reported increased risk among smokers. It is still uncertain whether the association is confounded by HPV exposure, however. The IARC has not classified the association as causally related to smoking.

NONMELANOMA SKIN CANCER

Studies of the association of cigarette smoking with nonmelanoma skin cancer have yielded conflicting results. Several studies have reported increased risk of squamous cell but not basal cell carcinoma (Aubry and MacGibbon, 1985; Hunter et al., 1990; Karagas et al., 1992; Grodstein et al., 1995; Sahl et al., 1995; De Hertog et al., 2001).
Despite suggestions that cigarette smoking increases the metastatic potential of melanoma, no consistent smoking-related effect on its incidence or mortality has been observed (Osterlind et al., 1988; Westerdahl et al., 1996; Lear et al., 1998).

LEUKEMIA

Of the hematopoietic malignancies, only acute myeloid leukemia is consistently associated with smoking (Doll 1996; U.S. Department of Health and Human Services, 2001). This association was designated causal by the IARC in 2002 (IARC, 2004) and by the U.S. Surgeon General in 2004 (U.S. Department of Health and Human Services, 2004). The risk of leukemia was first observed to be higher in smokers than nonsmokers by Austin and Cole (1986). The relation was subsequently shown to be stronger for myeloid and monocytic leukemia than for lymphocytic subtypes in the U.S. Veterans cohort (Kinlen and Rogot, 1988). The association has been confirmed in other cohort (Garfinkel and Boffetta, 1990; Doll et al., 1994; Doll, 1996) and case-control studies, as reviewed elsewhere (IARC, 2004). Tobacco smoke contains several leukemogens, such as benzene and radioactive isotopes of polonium and lead. Smokers have much higher levels of benzene in the blood than do nonsmokers. Based on linear extrapolation from the known effects at high doses, Korte et al. (2000) estimated that benzene in cigarettes accounts for 12%–58% of smoking-induced myeloid leukemia.

OTHER CANCERS

Thyroid

Two studies have reported increased risk of thyroid cancer associated with smoking (Sokic et al., 1994; Memon et al., 2002), whereas others have reported lower risk among smokers (Galanti et al., 1996; Kreger and Parkes, 2000; Rossing et al., 2000); still others reported no association (Williams and Horn, 1977; Rogot and Murray, 1980; McTiernan et al., 1984; Anonymous, 1990; Kolonel et al., 1990; Iribarren et al., 2001).

Other Nonepithelial Cancers

Tobacco use is not consistently related to hematologic malignancies, other than leukemia, including lymphoma in aggregate, non-Hodgkin’s lymphoma (Williams and Horn, 1977; Franceschi et al., 1989; Brown et al., 1992; Linet et al., 1992; Zahm et al., 1997; U.S. Department of Health and Human Services, 2001), or multiple myeloma (Boffetta et al., 1989; Mills et al., 1990; Heineman et al., 1992; Linet et al., 1992; Friedman, 1993; Adami et al., 1998). The association with Hodgkin’s disease has not been adequately evaluated (U.S. Department of Health and Human Services, 2001). Primary neoplasms of the CNS are unrelated to active smoking in most studies (Hochberg et al., 1990; Ryan et al., 1992; Hurley et al., 1996; Zheng et al., 2001) but not all of them (Lee et al., 1997). The data regarding soft-tissue sarcoma are limited and mixed (Serraino et al., 1991; Franceschi and Serraino, 1992; Zahm et al., 1992).

BENEFITS OF SMOKING CESSATION

Many of the detrimental effects of smoking can be prevented or reversed by smoking cessation. Strong evidence of the health benefits of smoking cessation first became available for lung cancer but now exists for nearly all the cancers related to smoking and for the major nonneoplastic smoking-attributable diseases (U.S. Department of Health and Human Services, 1990; IARC, 2004). The decrease in relative risk among persons who stop smoking compared to those who continue is an important aspect of the evidence for causation and indicates that continuing exposure influences even the late stages of carcinogenesis, presumably by affecting the transformation of premalignant clones into invasive cancer.

The absolute risk of developing cancer or other smoking-related diseases does not decrease after smoking cessation but increases with age at a slower rate in persons who stop smoking than in those who continue. The risk of developing smoking-attributable diseases continues to diverge between the two groups over time. This is reflected by a progressive decrease (below unity) in the RR estimates comparing former to current smokers as time elapses since cessation.

The relation between smoking cessation and the cumulative risk of death from any of the smoking-attributable cancers (as listed in Table 13–1 minus stomach cancer and myeloid leukemia) is depicted in Figure 13–8. This analysis is based on a 9-year follow-up of the CPS-II cohort from 1984–1991, excluding the first 2 years of follow-up (1982–1984) to avoid bias from persons who have stopped smoking because of diseases caused by tobacco. Men and women who continue to smoke cigarettes have the highest cumulative risk of death from these cancers at all ages shown. Cumulative risk increases more slowly with age in persons who have stopped smoking than in those who continue. The cumulative risk is also lower, in absolute terms, with earlier age of quitting. Persons who have never smoked have the lowest cumulative risk.

Figure 13–8 illustrates at least two important points. The first is that smoking cessation at any age avoids much of the future increase in risk seen with continued smoking. The health benefits are greatest when cessation occurs at an early age but are substantial even when cessation occurs by age 50 or 60 (Peto et al., 2000). The absolute risk among persons who quit smoking and their RR compared with those...
who continue are progressively smaller the earlier the age of cessation and the longer the time that has elapsed since cessation. Only in smokers who quit at younger ages does the relative risk of death from these cancers approach unity when compared with that of persons who have never smoked. However, the relevant comparison for a smoker is between the large risk from continued smoking and the much smaller risk from cessation. Most smokers have the option to quit smoking but not the possibility of returning to the status of a never-smoker.

Second, analyses of cessation are more informative if they consider age at cessation rather than time since quitting, as the benefits of cessation are not constant across all ages. Furthermore, measuring the cumulative risk of developing a specified endpoint is more stable than measuring the annual incidence. It is also more meaningful from the perspective of the individual smoker because he or she passes through all of the previous time intervals.

FACTORS THAT MAY MODIFY CANCER RISK

Genetic Influences on Smoking Behavior

Genetic factors can, in principle, modify susceptibility across the entire spectrum of smoking initiation, addiction, carcinogen metabolism, DNA repair, and tumor suppression (Thun et al., 2002). Inherited genetic traits can influence an individual’s tendency to experiment with tobacco, become dependent on its use, stop smoking successfully, and/or relapse. The genetic contribution to smoking behavior is thought to be as least as great as for alcoholism (Arinami et al., 2000). Interestingly, genetic variation becomes an important determinant of smoking behavior only in cultures where tobacco use is prevalent and environmental factors impose fewer constraints on exposure to tobacco and tobacco marketing.

The candidate genes that have received the most attention with respect to smoking behavior include the dopamine D1, D2, and D4 receptors; dopamine transporter and serotonin transporter genes; and the cytochrome P450 subfamily polypeptide 6 (CYP2A6) (Arinami et al., 2000). These genetic and metabolic factors are thought to affect reward pathways of the CNS by influencing the binding and metabolism of nicotine and other neurotransmitters. Research to identify the genetic and biologic determinants of addiction may contribute to developing more effective drugs for the treatment of tobacco dependence and to identifying appropriate pharmacologic and behavioral treatments (personalized genetic counseling) for individual smokers.

Genetic Susceptibility to Tobacco Carcinogenesis

Increasingly, epidemiologists study tobacco-exposed populations to identify genetic traits that confer susceptibility or resistance to problems with carcinogen metabolism, DNA repair, and/or tumor suppression. Valid markers of genetic susceptibility might further our understanding of the mechanisms of carcinogenesis and/or help clarify etiologic relations that are presently confusing or inconsistent (Thun et al., 2002). For instance, available data are conflicting as to whether postmenopausal women with the slow phenotype of N-acetyltransferase are genetically more susceptible to developing breast cancer from tobacco use than other women (Ambrosone et al., 1996) or whether nonsmokers who are homozgyous for the GSTM1 null allele are at particularly high risk of developing lung cancer from ETS exposure (Bennett et al., 1999; Weinberg and Sandler, 1999). It may be clinically valuable to identify subcategories of addicted smokers and individualize smoking cessation treatment or to identify high risk persons for enrollment in chemoprevention trials or special cancer screening programs that are not appropriate for the general population (Bartsch et al., 2000).

So far, many of the published results concerning gene–environment or gene–gene–environment interactions involving smoking have not been reproducible, probably because of the inadequate sample size of these studies, overemphasis on subgroup analyses, and comparatively crude assessment of lifetime smoking behavior. Most published studies have evaluated a small number of single nucleotide polymorphisms (SNPs) rather than all the genetic variants relevant to specific metabolic pathways.

Perhaps the strongest evidence of an interaction between smoking and genetic susceptibility derives from meta-analyses of studies of smoking and a variant of the N-acetyltransferase gene with respect to bladder cancer (Marcus et al., 2000a, 2000c). Persons with the slow acetylator (NAT-2) phenotype are known to be less efficient in detoxifying monoarylamines such as 4-aminobiphenyl. Compared to rapid acetylators, persons with the slow acetylator phenotype have been observed to have higher risk of developing bladder cancer associated with smoking.

Although other genetic polymorphisms are likely to have modest but real effects on the risk of common diseases such as the cancers caused by smoking, much larger studies are needed to define these interactions than have been conducted in the past (Lohmueller et al., 2003). Studies of carcinogen metabolism and/or DNA repair are also needed to quantify lifetime tobacco exposure with more precision than have past studies to distinguish gradations in risk due to exposure from those caused by genetic susceptibility. Several reviews have proposed strategies to improve the design and interpretation of future molecular epidemiologic studies of gene–environment interactions, specifically as they concern tobacco exposure (Houlston, 1999; Bartsch et al., 2000; Brockton et al., 2000; Green et al., 2000; Geisler and Olishan, 2001).

From a public health perspective, identifying genetic susceptibility factors that modify the risks of developing one or another tobacco-related disease is less critical than is the application of measures known to reduce tobacco use. Genetic screening and counseling are unlikely to be effective in deterring smoking initiation among adolescents because teenagers who are most likely to smoke may be the least likely to participate in or accept genetic counseling. Genetic screening is also unlikely to reduce the cost of smoking cessation programs, as approximately 50% of long-term smokers die prematurely because of their tobacco use (Peto et al., 1994), and the expense of genetic screening would outweigh any savings from narrowing the population to be treated (Thun et al., 2002). Nevertheless, personalized genetic counseling may help guide the selection of pharmacologic and behavioral treatments for individual smokers and may motivate some individuals to quit.

Age at Initiation

Beginning smoking at a young age is associated with higher risk of many smoking-related diseases. It is not clear, however, whether early age of initiation is detrimental simply because it leads to longer duration of smoking or whether there is additional risk because the immature lung is more vulnerable to early-stage carcinogenic events. One study has reported that among former smokers, the concentration of DNA adducts in nontumorous lung tissue increased with earlier age of smoking initiation (Wieneke et al., 1999). It is difficult to evaluate whether early age of initiation has an independent effect on lung cancer risk in Western countries because of the relatively narrow range of age of initiation and the strong inverse correlation between age of initiation and duration of smoking among current smokers. Most smokers in the United States become addicted between the ages of 14 and 21 years. The duration of smoking among current smokers is nearly collinear with attained age and moderately correlated with the age of initiation. It is difficult to distinguish the relation between duration of smoking and cancer risk from any additional contribution from early age at initiation or attainment age (Leffondre et al., 2002). Distinguishing these factors is more relevant to mechanistic considerations than to public health, as the initiation of smoking and other forms of tobacco use by children is inherently undesirable.

VARIATIONS IN THE CARCINOGENICITY OF CIGARETTES

Approximately 50 epidemiologic studies have examined the relation between cancer risk and changes that have occurred in cigarette design.
since the 1950s (Burns et al., 2001a; Thun and Burns, 2001; West et al., 2003; IARC, 2004). Most of these studies compared the risks of smoking high-tar (>30mg tar) unfiltered brands that predominated before the 1950s to those associated with smoking filter-tip cigarettes with an FTC tar rating of approximately 20-22mg (West et al., 2003). These studies generally reported a higher risk of lung cancer in persons who smoke unfiltered cigarettes than in those who smoke filter tip brands. A similar pattern, with more limited data has been reported for cancers of the oropharynx, larynx, esophagus, and pancreas. In contrast, only five studies have compared the risks of lung cancer or other diseases among smokers across the range of tar yields that prevail today (Vutuc and Kunze, 1982; Vutuc and Kunze, 1983; Wilcox et al., 1988; Woodward et al., 1999; Harris et al., 2004). Presently, the available data do not support the premise that brands classified as low tar (FTC rating 5-14mg) or very low tar (57mg) confer a lower risk of lung cancer than conventional filter-tip cigarettes (15-21mg) (Vutuc and Kunze, 1982; Vutuc and Kunze, 1983; Wilcox et al., 1988; Woodward et al., 1999; Harris et al., 2004).

Limitations of the epidemiologic studies of low tar cigarettes have been reviewed elsewhere (Burns et al., 2001a; Thun and Burns, 2001). These studies have had limited ability to control for factors associated with self-selection of lower-yield brands. Smokers who are less addicted may be more likely to switch from unfiltered to filter-tip products. Furthermore, studies of “reduced yield” cigarettes have not considered the indirect adverse effects that the marketing of these products may have had on the uptake and/or prolongation of smoking. Brands that deliver lower levels of machine-measured tar are promoted to smokers concerned about the adverse health effects of smoking. Some products are marketed explicitly or implicitly as an alternative to cessation. Addicted smokers may delay genuine efforts to stop smoking because of direct or implied health claims about reduced-yield products.

INTERACTIONS WITH OTHER EXPOSURES

People who use tobacco and who also have substantial exposure to certain other occupational and/or environmental factors are known to incur a greater risk of some types of cancer than would be expected from either exposure alone (IARC, 2004). Only for a few exposures has the interaction with tobacco been evaluated systematically to assess whether statistical interaction exists on either an absolute or a relative scale. Three comprehensive reviews evaluated the epidemiologic studies that assessed the potential interaction between asbestos exposure and cigarette smoking with respect to lung cancer (Errn et al., 1999; Lee, 2001; Liddell, 2001). All of them found a departure from additivity but could not quantify with certainty the degree of statistical interaction on a multiplicative scale. The effect of cigarette smoking when combined with exposure to radon gas or other forms of ionizing radiation in relation to lung cancer has been reviewed comprehensively by the U.S. National Research Council’s Biological Effects of Ionizing Radiation VI (National Research Council Committee on Health Risks of Exposure to Radon, 1998). In general, the statistical interaction between smoking and radon appears submultiplicative but without strong evidence against multiplicative interaction (IARC, 2004).

The combined effect of tobacco use and alcohol consumption has been examined extensively for cancers of the oral cavity, pharynx, larynx, and esophagus and to a lesser extent for cancers of the liver and pancreas (IARC, 2004). In the larger studies cancer risk consistently increased more rapidly with the combination of smoking and heavy drinking than with either exposure alone. Case-control studies that evaluated statistical interaction formally demonstrated a greater than multiplicative relation associated with joint exposure. The evidence is intriguing, albeit limited, that tobacco use combined with certain infectious agents may foster transformation of premalignant abnormalities into invasive cancer of the liver, stomach, uterine cervix, or lung. Several studies have suggested that tobacco smoking, in combination with infection with the hepatitis B virus (Chen et al., 1991; Yang et al., 2002; Sun et al., 2003), human papillomavirus (Ylitalo et al., 1999; Kjellberg et al., 2000), H. pylori (Zaridze et al., 2000; Siman et al., 2001; Brenner et al., 2002), or tuberculosis (TATA Institute of Fundamental Research, WHO, and CDC, 2000; Brenner et al., 2001) may promote malignant progression. The evidence currently available regarding possible interactions between tobacco use and diet is also limited.

CIGARS, PIPES, AND SMOKED PRODUCTS

besides cigarettes

Cigar and/or pipe smoking is strongly related to cancers of the oropharynx in many studies (Hammond and Horn, 1958; Kahn, 1966; Doll and Petro, 1976; Carstensen et al., 1987; Shanks and Burns, 1998; Iribarren et al., 1999; Shapiro et al., 2000). Persons who exclusively smoke pipes or cigars also have increased risk of cancer of the larynx (Kahn, 1966; Franceschi et al., 1990; Shanks and Burns, 1998; Shapiro et al., 2000), esophagus (Kahn, 1966; Doll and Petro, 1976; Carstensen et al., 1987; Shanks and Burns, 1998; Shapiro et al., 2000), lung (Hammond and Horn, 1958; Kahn, 1966; Doll and Petro, 1976; Lubin and Blot, 1984; Benhamou et al., 1986; Damber and Larsson, 1986; Carstensen et al., 1987; Steineck et al., 1988; Qiao et al., 1989; Chow, et al., 1992; Lange et al., 1992; Lubin et al., 1992; Tverdal et al., 1993; Ben Shlomo et al., 1994; Wald and Watt, 1997; Shanks and Burns, 1998; Boffetta et al., 1999; Iribarren et al., 1999, 2001), stomach (Kahn, 1966; Kneller et al., 1991; Tverdal et al., 1993), colon and/or rectum (Doll and Petro, 1976; Tverdal et al., 1993; Heineman et al., 1994; Hsing et al., 1998; Knekt et al., 1999; Chao et al., 2002), liver (Carstensen et al., 1987), pancreas (Kahn, 1966; Carstensen et al., 1987, 1988; Tverdal et al., 1993; Muscat et al., 1997; Partanen et al., 1997; Shanks and Burns, 1998; Shapiro et al., 2000; Iribarren et al., 2001), biliary tract (Chow et al., 1994), urinary bladder (Carstensen et al., 1987; Jensen et al., 1987; Shanks and Burns, 1998; Shapiro et al., 2000; Pitard et al., 2001), and renal pelvis (Jensen et al., 1988). The magnitude of risk for upper aerodigestive cancers is similar to that from cigarette smoking and is amplified by the combination of cigar and/or pipe smoking and alcohol consumption. Smoking of other tobacco products such as bidis is associated with cancers of the upper aerodigestive tract and to some extent lung cancer (IARC, 2004).

SECONDHAND SMOKE

Many scientific consensus committees have concluded that exposure to environmental tobacco smoke (ETS) causes lung cancer in humans (National Research Council, 1986; U.S. Department of Health and Human Services, 1986; Australian National Health and Medical Research Council, 1987; U.S. Environmental Protection Agency, 1992; California Environmental Protection Agency, 1997; U.S. Department of Health and Human Services, 2002; IARC, 2004). ETS exposure (also called secondhand smoke, passive smoking, and involuntary exposure to tobacco smoke) was associated with increased lung cancer risk among nonsmokers married to smokers in more than 50 studies (IARC, 2004). A meta-analysis of these studies (Hacksaw et al., 1997) reported a pooled relative risk estimate of 1.24 (95% CI 1.13-1.36). Further evidence for causation is that persons with involuntary exposure to ETS breathe the same multitude of carcinogenic and toxic substances to which active smokers are exposed and that they absorb, metabolize, and excrete higher concentrations of tobacco-specific carcinogens than persons unexposed to ETS (Scherer and Richter, 1997; IARC, 2004).

In contrast, studies have shown no consistent association between ETS exposure and breast cancer. The two largest prospective studies that control adequately for other risk factors for breast cancer found no association with ETS exposure (Wartenberg et al., 2000; Egan et al., 2002). Several other cohort studies (Hirayama, 1984; Lee et al., 1999) and case-control studies (Sandler et al., 1985a, 1985b; Smith et al., 1994; Morabia et al., 1996; Lash and Aschengrau, 1999; Johnson et al., 2000; Chang-Claude et al., 2002; Kropp and Chang-Claude, 2002) have reported an association between breast cancer risk and...
biopsy tissues, and hemoglobin from smokers (Vineis et al., 1996; Airoldi et al., 2002; Gonzalez et al., 2003). Given the ubiquitous presence of ETS exposure in many Western countries during the last half-century, there is concern that women who report no exposure to ETS are atypical in other respects that introduce bias (IARC, 2004).

**SPIT TOBACCO**

The use of spit tobacco products (moist snuff, chewing tobacco, tobacco combined with betel leaf) is associated with increased risk of cancers of the oral cavity, pharynx, larynx, and esophagus (IARC, 2004). Relative risk estimates for cancer of the oral cavity range from 3 to 20 or more, with the risk increasing with the duration of use. Premalignant changes (leukoplakia) and cancers occur frequently on the anterior tongue, buccal mucosa, or gingiva, areas in direct contact with tobacco. Risk is higher for persons who use oral snuff than chewing tobacco, possibly because of the close mucosal contact generated by snuff dipping. In many cases, the premalignant changes may regress after cessation of exposure to tobacco products.

**BIOLOGY OF TOBACCO USE AND CANCER**

Much of the evidence of the carcinogenicity of tobacco and tobacco smoke to humans derives from epidemiologic studies and is supported by extensive mechanistic evidence (Hecht, 2002a). As noted, many chemicals in the tobacco leaf and/or smoke cause cancer in humans or in experimental studies of animals. Certain carcinogens in tobacco smoke are known to cause specific types of cancer in occupationally exposed populations.

Benzene, for instance, is an established cause of myeloid leukemia (Jarvis, 1987). It has been estimated that the concentration of benzene in tobacco smoke accounts for 12%–58% of the increased risk of acute myeloid leukemia attributable to smoking (Korte et al., 2000). The aromatic amines 4-aminobiphenyl and 2-naphthylamine are known to cause bladder cancer in occupationally exposed populations (IARC, 1987) and are thought to contribute to the increased risk of bladder cancer in smokers (Doll, 1999b). N-Nitrosodimethylamine, known to cause renal and other cancers in rats and rat offspring (U.S. Department of Health and Human Services, 2002), is also found in tobacco smoke (Doll, 1996).

Carcinogens and procarcinogens from tobacco smoke reach most tissues through the body by either direct exposure to tobacco leaf and/or smoke or indirect exposure to substances dissolved in saliva and swallowed, absorbed, circulated systemically in the bloodstream, or accumulated and excreted in urine or stool. The fact that smoking was associated with so many types of cancer was initially counted as evidence against these relations being causal (Berkson, 1955, 1958). However, tobacco is now recognized irrefutably as the cause of multiple types of human cancer (IARC, 2004). Mutagens and carcinogens are detectable as adducts bound to DNA and proteins throughout the body. A tobacco-specific n-nitrosamine (Prokopczyk et al., 1997) and metabolites of benzo(a)pyrene (Melikian et al., 1999) have been found in the cervical mucus of smokers, and DNA adducts have been identified in cervical tissue (Melikian et al., 1999). Metabolites of the N-nitroso compound 4-(methyltrinitosamino)-1-(3-pyridyl)-1-butanone (NNK) have also been identified in the urine of smokers (Hecht, 2002b). Adducts of 4-aminobiphenyl have been demonstrated on the DNA of exfoliated bladder cells (Talaska et al., 1991), bladder biopsy tissues, and hemoglobin from smokers (Vineis et al., 1996; Airola et al., 2002; Gonzalez et al., 2003). Advances in biochemistry and molecular biology also provide considerable evidence about the biologic mechanisms by which tobacco use may cause cancer. In the case of lung and other aerodigestive tract cancers, polycyclic aromatic hydrocarbons (PAHs) present in tobacco smoke have been shown to induce more frequent guanine to thymine transversions in circumscribed parts of the p53 and ras genes (Hainaut and Pfeifer, 2001; Gonzalez et al., 2003). These transversions have been proposed to be a molecular signature of the mutational effects of PAHs in tobacco smoke (Hainaut and Pfeifer, 2001).

Tobacco use causes progressive genotypic and phenotypic changes in many organs that correspond to the stages of neoplastic development (Thun et al., 2002). Systematic autopsy studies of tissues affected by tobacco demonstrate an increase in the prevalence and/or severity of precancerous lesions and “field changes” from tobacco use in the larynx (Auerbach et al., 1970), bronchi (Auerbach et al., 1961, 1962), esophagus (Auerbach et al., 1965), and pancreas (Auerbach and Garfinkel, 1986). Both smoked and spit tobacco products cause leukoplakia in the oropharynx, a premalignant lesion that generally regresses after discontinuation of tobacco use. Biopsy studies of head and neck cancers demonstrate a “field effect,” in which clones of genetically damaged cells extend beyond the microscopically visible abnormalities (Westra and Sidransky, 1998). An autopsy study of pancreatic tissue noted an increased prevalence of atypical nuclei in ductal and parenchymal cells among smokers (Auerbach and Garfinkel, 1986).

**ANIMAL STUDIES OF CARCINOGENICITY**

Experimental studies have established that tobacco smoke and its condensate are carcinogenic in various animal species (IARC, 2004). topical application of tobacco smoke condensate to the skin of mice or rabbits induces benign and malignant epithelial tumors. Prolonged inhalation of tobacco smoke induces carcinoma of the larynx in Syrian hamsters. Topical application of benzo(a)pyrene to the cheek pouch of hamsters induces cancers of the oral cavity (Cheng et al., 1994). Injection of tobacco smoke condensates into gingival tissues of rabbits induces leukoplakia (Roffo, 1930). Tobacco smoke condensate and specific chemicals in tobacco smoke cause cancers of the rodent esophagus and forestomach when administered orally by gavage (U.S. Department of Health and Human Services, 2002). N-Nitrosodimethylamine induces esophageal cancer in the offspring of pregnant mice after intruterine exposure by diet or gavage.

It is difficult to identify animal models that exactly replicate the pulmonary exposure from smoking in humans because tobacco smoke is irritating and highly toxic to other species. Only humans inhale tobacco smoke voluntarily. Involuntary exposure causes other species to modify their breathing patterns toward shallow inhalation. Consequently, although inhalation exposure does cause lung tumors occasionally in some species, the principal evidence that tobacco causes lung cancer in humans derives from epidemiologic studies of humans.

**OPPORTUNITIES FOR PREVENTION**

Two complementary approaches are needed to reduce the devastating effects of tobacco on health (U.S. Department of Health and Human Services, 2000). In the long term, progress depends on the systematic application of primary prevention measures that can reduce the initiation of tobacco use by young people and end the pandemic during the second half of the twenty-first century. In the near term, substantial reductions in smoking-attributable cancers and other diseases can be achieved by providing counseling and treatment to facilitate cessation among the 46 million Americans who currently smoke.

A variety of community-based interventions have proven effective in reducing tobacco consumption and decreasing smoking initiation when these measures are applied as part of comprehensive tobacco control (Centers for Disease Control and Prevention, 1999). They include regulatory approaches (restrictions on tobacco marketing, laws ensuring clean indoor air, enforcement of laws restricting minors’ access to tobacco), economic approaches (increasing the price of cigarettes through excise taxes, thereby decreasing demand), and...
countermarketing campaigns to redefine social norms regarding tobacco use. States such as California, Massachusetts, and Florida have implemented comprehensive tobacco control programs that have been particularly effective in reducing youths' tobacco use (Bauer and Johnson, 2001). Nationally, the prevalence of cigarette smoking among U.S. high school students decreased sharply between 1997 and 2001 for males and females of the three largest racial and ethnic subgroups despite large increases in marketing expenditures by the tobacco industry (Burns et al., 2001b; Everett and Warren, 2001; Johnston, 2001; Kopstein, 2001; Centers for Disease Control and Prevention, 2002c). These temporal trends demonstrate that it is possible to prevent the uptake of tobacco use by young people if measures that have been proven to be effective are applied.

About 70% of current smokers in the United States report that they want to quit smoking (Centers for Disease Control and Prevention, 2002b); 41% succeed in quitting for at least 1 day, but only about 5% remain abstinent at 3–12 months (Centers for Disease Control and Prevention, 2002b). Several pharmacologic and behavioral treatments have been shown to increase success rates (Centers for Disease Control and Prevention, 2002b), although they are widely underused (Fiore et al., 2000). Approved therapies include nicotine replacement (gum, patch, inhaler, nasal spray), sustained-release bupropion hydrochloride (Centers for Disease Control and Prevention, 2000; Anderson et al., 2001), and behavioral treatment. The latter methods are most effective when they include practical counseling (problem solving/skills training), social support as part of treatment, and help with securing social support outside of treatment (Anderson et al., 2001). A combination of pharmacologic and behavioral treatment enables 20%–25% of persons attempting to quit to remain abstinent 1 year after treatment (U.S. Department of Health and Human Services, 2000). Tobacco dependence frequently involves relapse, however, and is best characterized as a chronic disease that may require periodic treatment (U.S. Department of Health and Human Services, 2000).

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