the United States alone, tobacco is responsible for more than 400,000 deaths annually, one third of these attributable to lung cancer. Indeed, tobacco is the leading exogenous cause of human cancers, including 90% of lung cancers.

From 1998 to 2007 in the United States, the incidence of smoking declined modestly, but this trend failed to continue, and approximately 20% of adults remain smokers. More disturbing, the world's most populous country, China, has become the world's largest producer and consumer of cigarettes. China has approximately 350 million smokers who in aggregate consume about 33% of all cigarettes smoked worldwide. It is estimated that more than 1 million people in China die each year of smoking-related diseases; this rate is projected to rise to 8 million deaths each year by 2050. Worldwide, cigarette smoking causes more than 4 million deaths annually, mostly from cardiovascular disease, various types of cancers, and chronic respiratory problems. These figures are expected to rise to 8 million tobacco-related deaths by 2020, the major increase occurring in developing countries. Of people alive today, an estimated 500 million will die of tobacco-related illnesses.

Tobacco reduces overall survival through dose-dependent effects that are often expressed as pack-years, the average number of cigarette packs smoked each day multiplied by the number of years of smoking. The cumulative effects of smoking over time are striking. For instance, while about 75% of nonsmokers are alive at age 70, only about 50% of smokers survive to that age (Fig. 9-8). The only good news is that cessation of smoking greatly reduces, within 5 years, overall mortality and the risk of death from cardiovascular diseases. Lung cancer mortality decreases by 21% within 5 years, but the excess risk persists for 30 years.

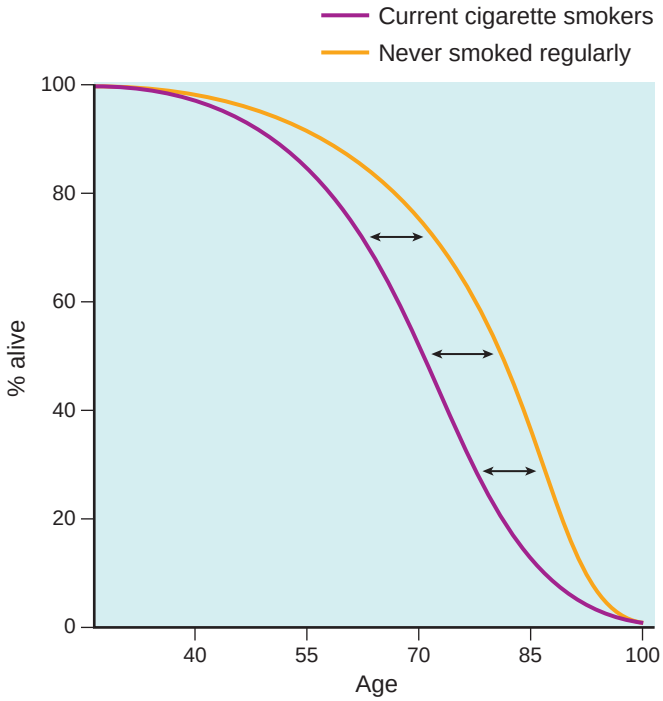

Figure 9-8 The effects of smoking on survival. The study compared age-specific death rates for current cigarette smokers with that of individuals who never smoked regularly (British Doctors Study). Measured at age 75, the difference in survival between smokers and nonsmokers is 7.5 years. (Modified from Stewart BW, Kleihues P (eds): World Cancer Report. Lyon, IARC Press, 2003.)

Table 9-3 Effects of Selected Tobacco Smoke Constituents

Substance	Effect
Tar	Carcinogenesis
Polycyclic aromatic hydrocarbons	Carcinogenesis
Nicotine	Ganglionic stimulation and depression; tumor promotion
Phenol	Tumor promotion; mucosal irritation
Benzo[a]pyrene	Carcinogenesis
Carbon monoxide	Impaired oxygen transport and utilization
Formaldehyde	Toxicity to cilia; mucosal irritation
Nitrogen oxides	Toxicity to cilia; mucosal irritation
Nitrosamine	Carcinogenesis

The number of potentially noxious chemicals in tobacco smoke is extraordinary. Tobacco contains between 2000 and 4000 substances, more than 60 of which have been identified as carcinogens. Table 9-3 provides only a partial list and includes various types of injuries produced by these agents. *Nicotine*, an alkaloid present in tobacco leaves, is not a direct cause of tobacco-related diseases, but is strongly addictive. Without it, it would be easy for smokers to stop the habit. Nicotine binds to nicotinic acetylcholine receptors in the brain, and stimulates the release of catecholamines from sympathetic neurons. This activity is responsible for the acute effects of smoking, such as the increase in heart rate and blood pressure, and the elevation in cardiac contractility and output.

Smoking and Lung Cancer. Agents in smoke have a direct irritant effect on the tracheobronchial mucosa, producing *inflammation* and *increased mucus production (bronchitis).* Cigarette smoke also causes the recruitment of leukocytes to the lung, with increased local elastase production and subsequent injury to lung tissue, leading to *emphysema.* Components of cigarette smoke, particularly *polycyclic hydrocarbons and nitrosamines* (Table 9-4), are potent carcinogens in animals and are directly involved in the development of lung cancer in humans (Chapter 15). CYPs (cytochrome P-450 phase I enzymes) and phase II enzymes increase the water solubility of the carcinogens, facilitating their excretion. However, some intermediates produced by CYPs are electrophilic and form DNA adducts. If such

Table 9-4 Suspected Organ-Specific Carcinogens in Tobacco Smoke

Organ	Carcinogen
Lung, larynx	Polycyclic aromatic hydrocarbons 4-(Methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) Polonium 210
Esophagus	*N'*-Nitrosonornicotine (NNN)
Pancreas	NNK
Bladder	4-Aminobiphenyl, 2-naphthylamine
Oral cavity (smoking)	Polycyclic aromatic hydrocarbons, NNK, NNN
Oral cavity (snuff)	NNK, NNN, polonium 210

Data from Szczesny LB, Holbrook JH: Cigarette smoking. In Rom WH (ed): Environmental and Occupational Medicine, 2nd ed. Boston, Little, Brown, 1992, p 1211.