Prevention of Tobacco-Related Cancer

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In the United States, approximately 46.3 million people smoke, and nearly 400,000 people die prematurely each year from tobacco-related diseases. This includes 151,000 deaths from cancer, 179,800 from cardiovascular diseases, and 84,500 from respiratory diseases. Cigarette smoking remains the greatest cause of preventable mortality in the United States.1

Americans have dramatically altered their smoking behavior since the first Surgeon General’s report on tobacco was released in 1964. At that time, approximately 40% of the US population smoked; in 1987, it was 29%. The smoking rate is higher among African Americans (34%) than among whites (29%). Smoking is inversely related to level of education; 36% of those without a high school diploma, 33% with a high school diploma, 26% with some college, and 16% of college graduates smoke.1 There also is a similar pattern of higher smoking rates among blue-collar and service workers compared to white-collar workers. Tobacco use is influenced heavily by the tobacco industry’s $2 billion annual advertising and marketing campaigns. Women, minorities, blue-collar workers, adolescents, and even children are bombarded by clever and often insidious marketing and advertising gimmicks.

Richard Peto estimates that worldwide, 3 million deaths were attributed to smoking in 1995, and by 2025, there will be approximately 10 million such deaths, 7 million of which will occur in the developing world.2 For instance, more than 70% of men aged 25 and older in the People’s Republic of China smoke cigarettes. At current smoking rates, there will eventually be approximately 2 million deaths of Chinese men per year directly related to smoking. Worldwide cigarette smoking is the largest single cause of premature death.

In this chapter, we review the pathogenesis and epidemiology of smoking-related cancer. We also discuss addiction, prevention, and cessation of tobacco use.

PHYSIOCHEMICAL COMPOSITION OF TOBACCO SMOKE

In 1992, the US Environmental Protection Agency classified environmental tobacco smoke as one of the most dangerous cancer-causing agents in humans, a Group A carcinogen. Tobacco smoke consists of more than 4000 chemical compounds and approximately 60 known carcinogens. Half of these compounds occur naturally in the green tobacco leaf, where the remainder is generated when the tobacco is burned. The complex mixture of chemicals in tobacco smoke includes carbon monoxide, hydrogen cyanide, benzene, formaldehyde, nicotine, phenol, polycyclic aromatic hydrocarbons (PAHs) and tobacco-specific nitrosamines (TSNAs). It should be noted that only the particulate phase, approximately 5% of the cigarette’s total output, is visible.

For risk assessment, tobacco smoke has been classified as either mainstream or sidestream. Mainstream smoke is that which is inhaled through the column of the cigarette and filter tip. In contrast, sidestream smoke is emitted from a burning cigarette between puffs and inhaled by nonsmokers. Although the chemical composition of mainstream and sidestream smoke is similar, the concentration of many constituents is higher in sidestream, or “passive,” smoke.

Nicotine, the second most abundant constituent of tobacco smoke, is responsible for the addictive properties of tobacco and represents a major source of TSNAs.3 Nicotine is present in both mainstream and sidestream smoke and is rapidly absorbed by the alveoli of the lungs. Nicotine concentrates in the pulmonary veins as a bolus and circulates throughout the body. Subsequent release of dopamine via activation of cholinergic receptors in the brain and modulation of hormones such as epinephrine and cortisol is believed to lead to nicotine dependence. The effect of polymorphisms in the dopamine transporter (SLC6A3) and dopamine D2 receptor (DRD2) genes on smoking initiation and nicotine dependence remains controversial and a subject of intense investigation.

CARCINOGENIC AND GENOTOXIC EFFECTS OF TOBACCO CONSTITUENTS

Both tobacco smoke and smokeless tobacco contain compounds that can initiate tumors, promote the development of previously initiated tumors, or act as cocarcinogens. Tumor initiation has been associated with the neutral subfractions rich in PAHs, whereas promotion has been associated with the weakly acidic subfractions.3 Interestingly, cancer types appear to be compound specific. For example, an association between TSNA exposure and cancers of the lung, larynx, esophagus, and pancreas has been suggested. In contrast, exposure to 4-aminobiphenyl and certain arylamines has been linked to bladder cancer.4 The involvement of benzene (from tobacco smoke) in smoking-induced leukemia has been implicated.5

Efforts to study the carcinogenic effects of cigarette smoke in animal models have been met with limited success. Classic tobacco carcinogenesis studies have been performed by painting cigarette smoke condensates (CSC) onto the skin of rodents. Although it failed to cause tumors under these conditions, CSC significantly increased the incidence of skin tumors in animals previously exposed to β-irradiation.6 One explanation for this exclusive tumor-promoting activity of CSC is that rodent skin is unable to metabolically activate the tumor initiators (PAHs) present in tobacco smoke. In contrast, exposure of xenotransplanted human bronchial epithelial cells to cigarette smoke condensates in vivo has produced invasive neoplasms.7

Subsequent use of animal inhalation models to evaluate the carcinogenic effects of tobacco smoke has been compromised by the inability of most animals to inhale as deeply as humans. Although an increased incidence of respiratory tumors has been observed in smoke-exposed mice, rats, dogs, and hamsters (the last develop laryngeal tumors only) as compared to unexposed controls, the overall tumor incidence has been extremely low, and tumors have been predominantly adenomas and alveologenic adenocarcinomas.3 Results from recent studies in strain A/J mice, which spontaneously develop lung adenomas and adenocarcinomas and additional lung neoplasms upon carcinogen exposure, have confirmed that environmental (sidestream) tobacco smoke is indeed a lung carcinogen.8 Furthermore, the highest lung tumor multiplicity and incidence was observed in animals that were allowed to recover in filtered air for 4 months following a 5-month exposure (6 hr/d, 5 d/wk) to mainstream and sidestream cigarette smoke, a smoking history similar to that of a former smoker.

Of all of the compounds in tobacco smoke, the potent carcinogenicity of PAHs (ie, benzo(a)pyrene) and TSNAs, specifically 4-(methylnitrosamino)-1-(3-pyridyl)-1-butane (NNK), has been most extensively documented. PAHs and NNK induce pulmonary tumors in rodents at doses similar to those experienced during a lifetime of smoking.9 Metabolic activation of PAHs and NNK leads to the irreversible binding of these carcinogens to deoxyribonucleic acid
(DNA) and the formation of bulky DNA adducts. Although chemical carcinogens prefer to bind to guanine, the specific position within this base is dependent upon the chemical properties of the carcinogen. For example, aromatic amines such as 4-amino-biphenyl prefer to bind to the C8 position, whereas PAHs such as benzo(a)pyrene bind preferentially to the N2 position of DNA guanine. When left unrepaired, these adducts can induce gene mutations in oncogenes and tumor suppressor genes, thus converting cells to a preneoplastic phenotype. Mutations in the K-ras oncogene have been detected in more than 50% of non-small-cell lung adenocarcinomas and are believed to be a late event in lung carcinogenesis.10,11 In contrast, p53 mutations, which are present in 50% to 80% of lung tumors, have also been observed in exfoliated cells (sputum, bronchial lavage, or brushings) from chronic smokers and may serve as an early biomarker of lung cancer risk.12 A direct correlation has been established between mutations in the K-ras and p53 genes and extent of tobacco smoke exposure.10,13,14

In addition to gene mutation, alteration of DNA methylation has been identified as a common cause of transcriptional silencing and loss of gene function in tumors.15 Aberrant methylation of the promoter of numerous genes, including p16 and death-associated protein kinase (DAPK), has been found to be common in non-small-cell lung cancers and in the bronchial brushes of former smokers, especially those with a previous history of cancer.16,17 Strong support for p16 promoter methylation as an early predictive marker of lung cancer risk is provided by the detection of hypermethylation in exfoliated cells from chronic smokers without clinical evidence of disease and in the sputum of 100% of squamous cell lung carcinoma patients up to 3 years prior to clinical diagnosis.13,18 Methylation of the adenomatous polyposis coli (APC) gene, the putative gatekeeper of colorectal cancer, was detected in 96% of primary lung cancer tissues and in 47% of the serum and/or plasma samples from the same individuals.19

DNA adducts from tobacco exposure are present in many tissues from smokers, including lung, bronchus, larynx, kidney, bladder, esophagus, liver, aorta, and placenta.20 Adduct levels correlate with the amount smoked and the duration of exposure and decrease in a time-dependent manner following smoking cessation.21 The rate at which adducts are removed from DNA is dictated by the activity of DNA repair enzymes. Deficiencies in the repair enzyme O6-alkylguanine-DNA-alkyltransferase have been observed in fibroblasts from lung cancer patients.22 Recent data indicate that a polymorphism in the x-ray cross-complementing group 1 (XRCC1) gene, a coordinator of base excision repair, may be a predictor of risk for squamous cell carcinoma of the lung in individuals with less than 40 pack-years of smoking.23 Likewise, the adjusted odds ratios for lung cancer risk associated with two polymorphisms in the excision repair complementing group 2 (ERCC2) gene correlate inversely with pack-year history.24

**GENETIC VARIATION IN CANCER SUSCEPTIBILITY**

Detoxication enzymes play a pivotal role in protecting individuals from environmental carcinogens, including the PAHs found in tobacco smoke. These enzymes have been categorized into two groups based on their functional properties. Phase I enzymes, including the cytochrome P450s, metabolically activate xenobiotics as well as endogenous substances (ie, fatty acids, steroid hormones) to highly reactive electrophiles (ie, epoxides and reactive oxygen species). Phase II enzymes inhibit the activity of these oxidative intermediates both by competing with the Phase I carcinogen-activating enzymes and by catalyzing the conversion of reactive electrophiles to inactive, water-soluble conjugates. It is the cellular balance between Phase I and Phase II detoxication enzymes that dictates one’s risk of developing chemically induced cancer.

Several enzyme systems involved in the metabolism and detoxication of xenobiotics exhibit genetic polymorphisms that have been associated with differential susceptibility for cancer. Epidemiological and clinical data continue to suggest that polymorphisms in select Phase I and II detoxication enzymes may serve as biomarkers of increased risk for smoking-related cancers.

**Phase I Enzymes CYP 2D6** Cytochrome P450 2D6 (CYP 2D6) is responsible for converting the tobacco-specific nitrosamine 4-NN to highly reactive metabolites.25 Debrisoquine, an antihypertensive agent, is metabolized solely by CYP 2D6 and serves as a phenotypic marker of enzyme activity. Numerous polymorphisms in this gene have been identified and correlated with variability in the extent of drug metabolism. This has led to the classification of individuals as either recessive poor metabolizers (approximately 9%) or homozygous/heterozygous dominant extensive metabolizers.26 Initial studies demonstrated that individuals who exhibited the extensive metabolizer phenotype (as determined by the ratio of unchanged debrisoquine to 4-hydroxydebrisoquine in the urine) had an increased risk of lung cancer as compared to poor metabolizers.27,28 In contrast, a more recent meta-analysis of data from 18 lung cancer studies indicated that the association between the CYP 2D6 polymorphism and susceptibility for lung cancer is not appreciable.29 Results from DNA-based assays continue to remain equivocal, and lung cancer risk for light and heavy smokers with the poor metabolizer genotype does not differ significantly.30 Two recent studies suggest that nicotine metabolism may be altered in smokers who are CYP 2D6 ultrarapid metabolizers.31,32

An association between the extensive metabolizer phenotype and increased risk for bladder and cervical cancer has been suggested.33–35 Stratification of drug-metabolizing activity by stage of bladder cancer revealed a stronger association with the more aggressive stage III disease.33 In addition, high debrisoquine recovery ratios were found to correlate with bladder tumor recurrence.34 Female smokers who were extensive metabolizers were at increased risk of developing cervical intraepithelial neoplasia.35 In contrast to bladder cancer, progression of cervical intraepithelial neoplasia to squamous cell carcinoma occurs less frequently in extensive metabolizers.35

**CYP 1A1** Cytochrome P450 1A1 (CYP 1A1) is an inducible microsomal enzyme that oxygenates carcinogenic PAHs such as benzo(a)pyrene to facilitate their ultimate detoxication and excretion.36 CYP 1A1 is expressed in normal and malignant lung tissue from smokers, while low expression is detected in nonsmokers.37 Nicotine has been identified recently as a potent and rapid inducer of pulmonary CYP 1A1, suggesting its ability to accelerate the metabolism of carcinogens in cigarette smoke.38 High inducibility of the gene product aryl hydrocarbon hydroxylase in select individuals has been attributed to polymorphisms in the CYP 1A1 gene and correlated with high DNA adduct levels.39,40 Several studies have demonstrated that a point mutation in exon 7 of CYP 1A1 (NcoI polymorphism) occurs more frequently in lung cancer patients than in noncancer controls.41,42 The documented increased risk for lung cancer among female smokers has been attributed in part to gender-based differences in CYP 1A1.43 The frequency of the CYP 1A1 (NcoI) polymorphism was significantly greater among female lung cancer patients than controls.43 Findings from an independent study indicate that CYP 1A1 expression is significantly elevated within the lungs of female smokers as compared to males.40

Initial studies in Japanese patients with an MspI restricted fragment length polymorphism (RFLP) in the 3′ noncoding region of CYP 1A1 reported a relative risk of 3.21 for squamous cell lung cancers.44 Additional investigations in similar Japanese populations have confirmed the association of the MspI polymorphism with increased lung cancer risk.45 Studies to examine this polymorphism in Caucasian lung cancer patients have produced negative results.46–48 The conclusion of a recent meta-analysis of published case-control studies is similar, indicating little support for variation in the CYP 1A1 gene (MspI or Ile-Val polymorphisms) as a determinant of lung cancer risk.49 Evaluation of smoking data from the Nurses’ Health Study suggested that females with the MspI polymorphism who start smoking before age 18 may be at increased risk for breast cancer.50

A third polymorphism in CYP 1A1 that is unique to African Americans has been described.51 Data from Taioli and colleagues indicate that individuals with the variant allele are at increased risk for adenocarcinoma of the lung (odds ratio 2.6; 95% CI, 1.1–6.3).52 A strong interaction with smoking was also apparent. In contrast, no association was observed between
this polymorphism and lung cancer risk in a larger African American population when individuals were stratified for other risk factors, including occupational exposures and micronutrient intake.\textsuperscript{53}  

**CYP2E1** Cytochrome P450 2E1 (CYP 2E1) catalyzes the oxidation and DNA adduct formation of benzene, nitrosamines, and other carcinogens.\textsuperscript{54} A polymorphism in the CYP 2E1 gene has been associated with lung cancer in Japanese populations.\textsuperscript{55} A dose-dependent effect of cigarette smoking was noted in one of these studies.\textsuperscript{55} This association has not been replicated in other populations. However, the CYP 2E1 polymorphism, when combined with polymorphisms in either the CYP 2D6 or GSTM1 gene, has been strongly associated with lung cancer risk, producing odds ratios of 14.0 and 6.0, respectively.\textsuperscript{56}  

**Phase II Enzymes NAT2** Although N-acetyltransferase-2 is classified as a Phase II enzyme, its ability to both inactivate aromatic amines and activate specific arylamine metabolites in cigarette smoke has been suggested.\textsuperscript{57} Corresponding acetylation rates (slow vs rapid) are controlled by a single gene. Slow acetylation is an autosomal recessive trait that occurs in approximately 50\% to 60\% of Western populations, compared to 10\% among Asians. Slow acetylators are less efficient in detoxifying arylamines, which are potent bladder carcinogens.\textsuperscript{58} The prevalence of bladder cancer among male smokers in the United States has been attributed to the carcinogenic arylamines in tobacco smoke.\textsuperscript{59} Slow acetylators possess higher levels of tobacco-related arylamine hemoglobin adducts than rapid acetylators, and adduct levels increase with the number of cigarettes smoked per day.\textsuperscript{60} Data from several studies provide further support for these observations and suggest that slow acetylators are at increased risk for bladder cancer.\textsuperscript{61–63} In contrast, phenotypic and genotypic analyses of lung cancer patients have produced conflicting results, with the majority failing to reveal an association between acetylation status and cancer risk.\textsuperscript{64–66} One explanation for these inconsistencies in estimated lung cancer risk is the recently identified, statistically significant interaction between NAT2 genotype and pack-year history of smoking.\textsuperscript{67} The NAT2 rapid acetylator genotype was found to confer a decreased risk for lung cancer among nonsmokers but increased lung cancer risk in heavy smokers. Likewise, the additive risk of lung cancer faced by those carrying the NAT2 genotype in combination with a polymorphism in microsomal epoxide hydrolase (mEH) is dependent upon cumulative smoke exposure. An association between risk for postmenopausal breast cancer and the slow acetylator genotype has also been established with respect to smoking dose.\textsuperscript{68}  

**GSTM1** The glutathione S-transferases (GSTs) are a family of enzymes that catalyze the conjugation of PAHs and other toxic intermediates with glutathione. The resulting conjugate is more water soluble and more readily excreted from the body. The gene encoding the M1 isozyme is absent in approximately 50\% of the general population.\textsuperscript{69} This polymorphic expression can be combined with the ability of M1 to inactivate highly reactive epoxides such as the benzo(a)pyrene-4,5-oxide, and this has prompted Warholm and colleagues to conduct a detailed investigation of the role of the null genotype in determining personal susceptibility to a variety of cancers.\textsuperscript{70} Several studies have suggested an association between the GSTM1 null genotype and increased risk for various smoking-related cancers. A meta-analysis of the relationship between GSTM1 status and lung cancer risk in 12 case-control studies classified the GSTM1 null genotype as a moderate risk factor for all histological subtypes of lung cancer (odds ratio = 1.4).\textsuperscript{71} The unavailability of standardized data on smoking history prohibited the analysis of this variable. It has been concluded from an independent study that smokers with the GSTM1 null genotype are 1.7-fold more likely to develop lung cancer and at a 2.5-fold increased risk for bladder cancer.\textsuperscript{72} Furthermore, results from a recent case-control study suggest that African American smokers with the null genotype are at a very high risk of developing lung cancer (odds ratio = 8.2) as compared to African American nonsmokers with the wild-type genotype.\textsuperscript{73} The trend between increasing risk and greater pack-year history of smoking was highly significant. Several independent investigations have demonstrated that individuals who carry both the GSTM1 null genotype and a second high-risk polymorphism are at significantly increased risk of developing lung cancer. Data continue to emerge that the combined mutant CYP 1A1/1 GSTM1 null genotype confers increased susceptibility for lung cancer.\textsuperscript{39,43,74} Strong support for the ability of individuals with the combined genotype to metabolically activate carcinogens at a fast rate while being less efficient in providing cellular protection from the resulting reactive intermediates is provided by DNA adduct measurements in smokers. For example, high DNA adduct levels are observed in smokers who are slow acetylators for NAT and lack the GSTM1 gene, whereas adduct levels in smokers who are fast acetylators for NAT and GSTM1 positive are low.\textsuperscript{75,76} The potential use of DNA adduct levels as a biomarker of cancer risk remains to be established.  

**Approaches for Smoking Cessation**  
Since our previous review of this area, several important studies have been published, and a range of new priorities has developed in the field of nicotine addiction treatment.\textsuperscript{77} For instance, additional studies concerning the genetic basis of nicotine addiction have been completed, while the issue of “harm reduction” (eg, a “safe cigarette”) represents a new challenge facing scientists and clinicians committed to the prevention of tobacco-related cancers. Despite the growth in the literature on smoking interventions, the prevalence of smoking among adults has not decreased substantially, and it has increased among certain adolescent groups.\textsuperscript{78,79} Nevertheless, since the majority of adult and adolescent smokers want to quit, it is critical that effective smoking cessation treatments be developed and disseminated.\textsuperscript{80,81} Fortunately, the past decade has witnessed a burgeoning of evaluation research on both behavioral and pharmacologic cessation treatments.\textsuperscript{82–85}  

The writing of this chapter fortuitously coincides with an updated Clinical Practice Guideline for smoking cessation treatments from the Agency for Healthcare Research and Quality (AHRQ), which reviewed the accumulated literature on smoking cessation interventions.\textsuperscript{83} To summarize, the key findings from this guideline are as follows: (1) brief tobacco cessation interventions of 3 to 5 minutes can be effective, (2) there is a dose–response relationship between the intensity and duration of behavioral smoking cessation interventions and their effectiveness, (3) there are five “First-line” pharmacotherapies that increase quit rates, (4) clinicians and health care programs must ensure that all smokers are identified and provided with appropriate treatment, and (5) insurance plans should reimburse patients and physicians for the provision of cessation treatment. The guideline also offers a model for the provision of cessation treatment within a healthcare delivery system and stresses the need for treatments to be tailored to the smoker’s readiness to change, unique health risks (ie, cancer patients, pregnant women), ethnic/cultural background, or age (ie, youth vs older smokers).  
Overall, the updated guideline indicates that the most effective smoking treatment involves the combination of tailored behavioral and pharmacologic treatment.\textsuperscript{83} The effects of these treatments are independent and additive, with the combination of the two yielding the highest quit rates.\textsuperscript{83} In the following sections, we review the current literature on smoking interventions. An important issue to consider when appraising these approaches is the need to assess effectiveness in terms of impact value, which is defined as the abstinence rate multiplied by the participation rate.\textsuperscript{86} Traditionally, the relative effect of a smoking treatment is assessed using only the abstinence rate. Thus, a treatment that yields a 30\% abstinence rate is considered twice as effective as a treatment that produces a 15\% abstinence rate with a 50\% participation rate.\textsuperscript{86} As noted, a treatment that yields a 30\% abstinence rate and a 3\% participation rate has an impact value of .009.\textsuperscript{87} A treatment that produces a 15\% abstinence rate with a 60\% participation rate yields an impact value of .09, 10 times the former. The present challenge to the field of nicotine addiction treatment is to devise treatments that yield both a high abstinence and a high participation rate.\textsuperscript{86,87}  

**Self-Help Methods** The most common self-help approach to treating nicotine addiction
involves the use of self-help guides, namely booklets or pamphlets that describe methods for quitting smoking. Self-help guides have been viewed as a promising treatment approach for nicotine addiction since they are very popular with smokers and can be easily and cheaply disseminated. However, empirical support for this approach is lacking. On the one hand, the use of self-help guides compared to no treatment can produce a quit rate of 12%. On the other hand, the AHRQ evaluation indicated that the effect of self-help interventions is weak, inconsistent, and much smaller compared to other intervention modalities, such as behavioral counseling. In addition, a recent meta-analysis involving 45 studies of smoking cessation self-help guides concluded that self-help guides do not increase quit rates when they are added to other forms of smoking cessation treatment. Thus, as a stand-alone therapy, self-help methods should not be regarded as an effective approach to promoting quitting. Indeed, whereas the participation rate for this approach is relatively high, 15%, the quitting rate is relatively low (12%), thus producing an impact value of about .018. 

However, convincing evidence indicates that the quit rate produced by self-help guides can be enhanced when telephone counseling is included as an adjunct. For instance, Boreland and colleagues compared the provision of self-help resources alone to the combination of self-help resources and telephone counseling; at a 3-month follow-up, 13% of participants who received only self-help resources had quit, versus 24% of those who received telephone counseling as an adjunct. In a similar study, Miguez and colleagues found that, at a 12-month follow-up, 14% of smokers who received only self-help materials showed continuous abstinence, versus 27% of those who received adjunctive telephone counseling. In addition, the quit rate produced by self-help guides can be increased by tailoring self-help manuals to the individual’s readiness to quit smoking (ie, stage of change). Prochaska and his colleagues have been at the forefront of this research and have developed a computer-based intervention that provides written cessation instructions tailored to the smoker’s stage of change (ie, an expert system). Velicer and Prochaska compared this expert system to a stage-matched self-help manual alone. Among smokers who received a stage-matched manual, 7-day point prevalent abstinence at an 18-month follow-up was 15.5%, with 6.4% remaining abstinent for at least 6 months. In contrast, among smokers in the expert system arm, 7-day point prevalent abstinence at 18-months was 21.3%, with 9.3% remaining abstinent for at least 6 months. More recently, Prochaska and colleagues compared the expert system to standard self-help manuals using over 4000 smokers. At a 2-year follow-up, the expert system yielded a 25.6% point prevalence quit rate, versus a 19.7% quit rate in the control condition. Thus, self-help treatments that utilize telephone counseling or computer-based tailoring are viable methods for promoting cessation from tobacco use.

**Formal Smoking Cessation Clinics** Most cessation programs available to smokers involve some form of behavioral counseling, either individual or group, and their effectiveness at producing long-term abstinence has been widely demonstrated. In fact, compared to no treatment, the use of behavioral counseling yields cessation rates of 14% to 17%. Of greater interest is research aimed at identifying the specific types of behavioral counseling that yield the greatest quit rates, although such analysis has been hindered by the extreme heterogeneity among studies. Nevertheless, a meta-analysis conducted by the AHRQ concluded that three types of behavioral counseling are particularly effective for promoting quitting. These are (1) the provision of problem-solving or skills training, including techniques to avoid relapse and manage stress; (2) the provision of intratreatment social support, such as encouragement, understanding, and concern; and (3) the provision of extratreatment social support from friends and family. The AHRQ also considers aversive smoking (eg, rapid smoking) to be an effective behavioral approach, although a second meta-analysis concluded that there is insufficient evidence to support this behavioral approach. In particular, effective problem-solving or skills training methods include (1) preparing smokers to recognize events, activities, or internal states that increase the risk for smoking and/or relapse (eg, depression, stress, after meals, alcohol consumption, socializing with friends who smoke); (2) assisting the smoker to develop a repertoire of skills to deal with smoking-related events, activities, or states; and (3) providing information about the quitting process so that smokers can anticipate difficulties and apply newly developed quitting skills. Effective elements of intratreatment social support include (1) assisting smokers to develop confidence in their ability to quit, (2) allowing for the expression of fear and ambivalence about quitting, and (3) encouraging the smoker to identify a reason for quitting. Finally, effective elements of extratreatment social support are (1) training smokers to enlist the help of friends and family, (2) educating smokers about the availability of support groups or quit-lines, and (3) utilizing a “buddy” system.

Moreover, it is now well accepted that there is a dose-response relationship between the intensity of behavioral counseling and its effect on successful abstinence. For instance, when interventions are classified based on the total amount of time that a clinician spends addressing smoking with a smoker in a single contact as minimal counseling (< 3 minutes), low intensity (3–10 minutes), or high intensity (> 10 minutes), there is clear evidence that the probability of successful quitting increases as the contact time increases: Compared to no contact, minimal counseling produces a 13.4% abstinence rate, low intensity counseling yields a 16% abstinence rate, and high intensity counseling generates a 22% quit rate. Convergent results are found when the dosage is classified in terms of total amount of contact time: Compared to no contact time, interventions lasting 1 to 3 minutes yield a 14.4% abstinence rate, interventions lasting 4 to 30 minutes produce an 18.8% quit rate, interventions lasting 31 to 90 minutes yield a 26.5% abstinence rate, and interventions lasting 91 to 300 minutes generate a quit rate of 28.4%. Last, this dose-response relationship is also evident when dosage is classified as number of sessions; when dosage is measured as 0 or 1 session, 2 or 3 sessions, 4 to 8 sessions, or more than 8 sessions, the quit rates produced are 12.4%, 16.3%, 20.9%, and 24.7%, respectively. Despite the substantial evidence supporting the effectiveness of clinic-based interventions, however, a relatively small proportion of smokers partake in this treatment approach (ie, about 6%). If we assume the abstinence rate produced by behavioral counseling to be 17%, the impact value for this treatment approach is .01. Thus, an important challenge for scientists and clinicians dedicated to the prevention of tobacco-related cancers is to better understand effective methods for disseminating high-dose clinic-based treatments to a broader number of today’s smokers.

**Physician-Based Interventions** With upwards of 80% of all smokers visiting a physician at least once each year, physician-delivered smoking cessation interventions represent a cost-effective way to disseminate smoking cessation messages and services to a large number of smokers. This approach to treating nicotine addiction may also be especially effective since smokers perceive their physicians as a valuable, credible, and reliable source of health information and show a high level of adherence to physician health advice. Thus, public-health agencies have tried to urge physicians to implement smoking cessation interventions by providing formal treatment guidelines and training manuals (ie, the 5As). This model, depicted in Table 28-1, involves the following: (1) ask, ensuring that all patients are screened for tobacco use at every visit; (2) advise, providing clear, strong, and personalized cessation messages to patients who smoke; (3) assess, evaluating the smoker’s quit motivation and nicotine dependence to tailor cessation treatment to the smoker’s characteristics; (4) assist, utilization of established strategies for helping patients quit smoking, including behavioral techniques and pharmacologic therapies; and (5) arrange, ensuring that smokers are followed over time in order to evaluate their progress with quitting. Reviews of physician-based treatments of less than 5 minutes indicate that such interventions yield quit rates of about 10% compared to no treatment. Unfortunately, the majority of physicians do not take advantage of this opportunity to provide cessation advice and assistance. In fact, only 20% to 25% of American smokers indicate that they received smoking
cessation counseling from their physician, and this rate actually decreased from 29% in 1993 to 21% in 1995. More recent assessments suggest that the rate of physician adherence to clinical treatment guidelines is improving. For instance, two surveys, one by the California Department of Health Services and one by the National Committee for Quality Assurance, found that 49% to 62% of smokers report receiving quit advice from their physician. Therefore, with an estimated abstinence rate of 21% in 1995. More recent assessments suggest that the rate of physician adherence to clinical treatment guidelines is improving. Further, the gum’s efficacy is dependent on the contribution of adjuvant behavioral therapies. Pinpointing the exact participation rate for pharmacotherapies is complicated, considering the range of therapy types, the transition from prescription to over-the-counter (OTC) status for certain therapies, and the remaining prescription status for several pharmacotherapies. A recent survey conducted after the conversion of the nicotine patch, one of the more popular therapies, from prescription to OTC status indicated that 24% of current and former smokers use the patch. Using this liberal estimate of participation, pharmacotherapies may be expected to have a relatively high impact value of .024 (ie, 10% x 24%). Furthermore, there is fairly reliable data to indicate that the combination of these therapies increases long-term abstinence rates. Yet, two issues remain unresolved in this area: (1) Despite the strength of the evidence concerning the efficacy of pharmacotherapies, few data are available regarding the use of these therapies for light smokers, and for adolescents and pregnant women who smoke; and (2) since few studies have compared these therapies, head-to-head, it is difficult to review the comparative efficacy of these treatments.

Nicotine Gum One of the most used and well-researched nicotine replacement therapies (NRTs) is nicotine gum (ie, Nicorette). In a review of 13 studies that compared the gum to placebo, the AHRQ concluded that this NRT can yield an abstinence rate of about 23%. In addition, the use of the 4 mg dosage of the nicotine gum is more efficacious than the standard 2 mg dosage with smokers who exhibit high nicotine dependence. However, the efficacy of nicotine gum decreases over time and is largely dependent on the contribution of adjuvant behavioral therapies. Moreover, the gum’s efficacy is limited by low compliance due to such factors as inconveniences, side effects (eg, burning, nausea), and bad taste. Consequently, although nicotine gum has been shown to be an effective NRT (ie, versus placebo or a no-gum control), it should be viewed as only one dimension of a comprehensive cessation program.

Transdermal Nicotine Patch “The patch” (ie, Nicotrol and Nicoderm) is perhaps the most popular and well-researched NRT. Meta-analytic assessments of studies comparing the patch to placebo indicate that the patch can yield a quit rate of close to 18%. In addition, since compared to the gum and the inhaler, the patch is associated with fewer compliance problems, pro-

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<th>Table 28-1 A Guide to the Evaluation and Management of Smokers for Physicians</th>
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<td><strong>Step 1 (Ask):</strong> Evaluate the smoking history of every patient</td>
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<tr>
<td>• Institute official policy concerning the mandatory assessment of tobacco-use status (ie, is patient a current smoker, a former smoker, or a nonsmoker)</td>
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<td>• Include assessment of tobacco-use status as part of the collection of vital signs</td>
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<td>• Ensure that the tobacco-use status of each patient is included in the patient’s medical records in a way that is easily detected by the entire healthcare team (eg, smoking status stickers)</td>
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<td><strong>Step 2 (Advise):</strong> Convey concise, forthright, and individualized quitting advice to all smokers</td>
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<td>• Indicate that the patient should quit (not just cut down) immediately and that you will be helping them to achieve this goal</td>
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<td>• Express to the patient that quitting smoking is crucial to ensure their present and future health</td>
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<td>• Associate current smoking with present health problems if applicable and emphasize the economic, health (eg, impact of smoking on fetus), and social (eg, effects of second-hand smoke on family members) impacts of smoking</td>
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<td>• Involve all clinic staff in encouraging patient to quit by reinforcing cessation messages</td>
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<td><strong>Step 3 (Assess):</strong> Evaluate the patient’s readiness to quit</td>
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<tr>
<td>• Assess patient’s readiness to change and willingness to make a quit attempt</td>
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<tr>
<td>• Assess patient’s interest in behavioral and pharmacologic smoking cessation treatments</td>
</tr>
<tr>
<td>• Provide referral to patients interested in formalized cessation programs</td>
</tr>
<tr>
<td>• Consider patients age, ethnicity, age, gender, and particular health-related risks</td>
</tr>
<tr>
<td>• For patients in precontemplation stage, provide motivational messages (eg, identify acute [eg, shortness of breath], long-term [eg, cancer, heart attacks], and environmental [eg, increased risk of cancer and other health problems among family members] adverse health effects of smoking for patient, and review benefits of smoking cessation [eg, improved health, improved self-esteem, cessation of worry about effects of second-hand smoke])</td>
</tr>
<tr>
<td><strong>Step 4 (Assist):</strong> Provide direct smoking cessation assistance to the patient</td>
</tr>
<tr>
<td>• Formulate quit plan: Set quit date within 2 weeks; have patient solicit encouragement and support from family; remove smoking cues from the environment (eg, cigarettes, ashes/straws)</td>
</tr>
<tr>
<td>• Encourage the use of NRT (ie, the patch or the gum) or Zyban</td>
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<tr>
<td>• Provide quit advice: Total abstinence is goal; encourage family members who smoke to quit</td>
</tr>
<tr>
<td>• Provide problem-solving (ie, identify situations which increase the chance of smoking, such as being with other smokers, stress, negative mood, and drinking alcohol) and coping skills (ie, avoid tempting situations, stress management using positive self-talk or exercise) training, and clinician support (ie, confidence in patient’s ability to quit, discuss feelings about quitting, express willingness to help, and listen to patient’s fears about quitting)</td>
</tr>
<tr>
<td>• Provide self-help educational material tailored to individual’s ethnicity, gender, and age</td>
</tr>
<tr>
<td><strong>Step 5 (Arrange):</strong> Schedule follow-up contact to review cessation progress</td>
</tr>
<tr>
<td>• Plan follow-up contacts within 1 week of quit date and within the first month of cessation (eg, telephone or postcard reminders, in-person visits)</td>
</tr>
<tr>
<td>• Reward successes and reinforce cessation advice if relapse occurs; review use of NRT; if relapse occurred, review patient’s thoughts about why it happened and how to avoid relapse in the future, including the need for more intensive behavioral therapies</td>
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</table>

Adapted from AHRQ.
In the field of nicotine addiction, which contends that motivation to quit smoking can increase rates of abstinence. Overall, the patch is one of the most effective pharmacological therapies available.

**Nicotine Nasal Spray** Nicotrol NS—a nicotine nasal spray—is one of the more recent NRTs available to assist smokers in remaining abstinent. The spray is thought to be effective because it (1) closely mimics the delivery process of smoking and (2) has a faster nicotine uptake rate compared to other NRTs. However, few efficacy studies have evaluated the nasal spray. Nevertheless, meta-analytic assessments of studies that compared the nasal spray to placebo indicate that this NRT can yield a quit rate of close to 30%. In addition, a study that compared the nicotine patch to the nicotine patch plus the nasal spray found that the combination of treatments yielded a cessation rate at 12 months of 27%, versus 11% for the single therapy. However, a head-to-head comparison of the spray to the patch, the gum, and the inhaler reported no significant difference in quit rates across the conditions and also found that the spray produced a significantly higher rate of adverse events, which, in turn, lowered compliance for this form of NRT compared to the others. As such, the spray may not represent the optimal pharmacologic treatment for smokers.

**Nicotine Vapor Inhaler** As with the nasal spray, few studies have assessed the efficacy of the nicotine inhaler. The AHRQ cited three studies in a meta-analysis and concluded that the inhaler yields a quit rate of almost 23% versus placebo. A similar conclusion was reached in a meta-analysis performed by Silagy and colleagues. In addition, a recent study examined the benefits of providing both the nicotine inhaler and the patch to the patch alone. The findings indicated that the addition of the inhaler improved short-term quit rates (42% for combined treatment vs 31% for patch alone at 3 months) but had no effect on 12-month outcomes. Finally, in the only head-to-head comparison, researchers found no significant difference in short-term quit rates when the inhaler was compared to the nasal spray, the gum, and the patch. Nevertheless, the inhaler is thought to represent one of the more efficacious NRTs since it addresses both the physiological dependence on addiction and the behavioral ritual aspects of smoking.

**Nonnicotine Medications (Bupropion)** In the past decade, several lines of research have converged to form the self-medication hypothesis for nicotine addiction, which contends that smokers use nicotine to diminish feelings of sadness, worry, or tension. This theory led researchers to study the use of antidepressants for treating nicotine addiction. The one antidepressant to have received consistent support under scientific scrutiny is bupropion hydrochloride (Zyban). Since our last review, several additional efficacy studies on bupropion have been published. The AHRQ has concluded that bupropion yields an abstinence rate of about 30% versus placebo, a finding that converges with a second meta-analysis of studies in this area. In addition, studies (1) have documented a dose–response effect for bupropion, (2) have found in head-to-head comparisons that bupropion outperforms the patch, and (3) have reported that bupropion, versus placebo, reduces the risk for relapse. Overall, the accumulated data for bupropion indicates that it represents one of the most effective treatment options for those addicted to nicotine. Yet, since bupropion can add a significant expense to a treatment program, produce adverse effects, and be ineffective for some smokers, it has become increasingly important to identify individual differences among smokers that can influence responsiveness to bupropion (eg, the degree to which they exhibit depressive symptoms). Since few studies have explored this issue, such research represents an important priority.

**The Sublingual Tablet, A New NRT** Since our previous review, several studies have examined the effectiveness of a sublingual tablet form of NRT. Overall, the tablet effectively reduces nicotine withdrawal symptoms (eg, irritability, anxiety) and produces quit rates that parallel those yielded from the patch and the gum. For instance, Molander and colleagues reported that the nicotine tablet reduced self-reported nicotine withdrawal symptoms by 50% compared to a placebo tablet, and Wallstrom and colleagues, in a double-blind, placebo-controlled study, found that the nicotine tablet yielded a quit rate at 6 months posttreatment of 33%, compared to 18% for a placebo. Since few adverse events are reported with the nicotine tablet, use of this form of NRT is likely to grow in the coming years.

**Harm Reduction** One of the more polarizing issues in the field of nicotine addiction treatment to have developed in recent years concerns whether reducing—rather than eliminating—tobacco use is a reasonable goal of a nicotine addiction treatment. Harm reduction strategies, which aim to lower exposure to the harmful properties of tobacco, involve reduced smoking rate, use of less hazardous nicotine products (ie, a safe cigarette), or use of less addictive nicotine products. Overall, few studies have been published concerning the relative benefits or drawbacks of harm reduction interventions, and the available data are inconsistent. For instance, on the one hand, certain data indicate that reduced smoking is feasible with pregnant women and yields important health benefits (ie, improved birth weight). Likewise, reduced smoking as a treatment goal can produce significant reductions in exposure to carbon monoxide. On the other hand, studies also show that harm reduction techniques (ie, reducing smoking rates, use of Eclipse, a “safe” cigarette) do not significantly reduce exposure to carcinogenic biomarkers or carbon monoxide. These latter data are likely the result of observations that when smokers reduce their tobacco use rates, they often engage in compensatory smoking, including taking more puffs per cigarette and taking deeper puffs. Thus, based on the current literature, it is unclear whether harm reduction methods are viable options for the control of tobacco-related cancers.

**Tailoring Smoking Cessation Interventions for Special Populations** The field of tobacco control continues to recognize that “one size does not fit all,” meaning that the clinician must consider certain characteristics of the smoker when treatments are provided rather than assuming that generic interventions can be suitable for all smokers. A “treatment matching” or “tailoring” approach improves treatment efficacy and reduces costs. Two approaches to treatment matching, the stepped-care and the trans-theoretical (TT) models, “match” interventions that differ in intensity or content with the smoker’s readiness to quit. In the stepped-care model, smokers with high quit motivation would receive step 1 interventions (eg, self-help), whereas smokers with low quit motivation would receive step 3 interventions (ie, behavioral and pharmacologic treatment). Likewise, in a TT approach, although behavioral processes such as counter-conditioning (ie, choosing healthy behaviors instead of smoking) would be provided to those in later stages of readiness to quit, strategies that enhance awareness of the detrimental effects of continued smoking are critical for individuals in the early stages of change.

In addition to considering the smoker’s readiness to quit, interventions should be tailored to populations that either are at greater risk for the adverse effects of smoking or manifest unique barriers to quitting, such as minority groups, female smokers, adolescents, or cancer patients.

**Stage of Change** Since motivation to quit is a strong predictor of success in a smoking intervention, the stepped-care and the TT models are considered useful approaches to treating nicotine addiction. Despite their intuitive appeal, however, few studies have evaluated whether interventions matched to level of quit motivation (ie, stage-matched) are more effective than unmatched interventions. One study, which attempted to evaluate the stepped-care model, randomized smokers who had relapsed from a previous intervention to either a brief intervention or to one of two “step-up” interventions: a behavioral counseling treatment or a motivational interviewing therapy. Contrary to the model’s prediction, the smokers who received the step-up treatments did not show an increase in abstinence rates at the follow-up assessments compared to the standard brief intervention. In contrast, there has been more study of the TT model, although the results have been inconsistent. On the one hand, a study with college students that compared a TT model-based com-
Although the mortality data concerning trends across ethnic/racial groups indicates that certain minority groups may be at greater risk for tobacco-related cancers. However, several other studies have reported no advantage in terms of quit rates from the use of stage-matched versus nonmatched smoking treatments. Thus, although some research indicates that interventions matched to quit motivation improve abstinence rates, additional research is needed before an unequivocal conclusion can be reached.

**Minority Smokers** Data concerning trends in mortality rates for major cancers across ethnic/racial groups indicate that certain minority groups may be at greater risk for tobacco-related cancers. For instance, whereas the death rate due to lung and bronchus cancer has decreased during the past decade for whites, blacks, Asian Americans, and Hispanics, it has significantly increased for American Indians and Alaska Natives. This increased risk for certain minority groups likely reflects greater levels of tobacco use among members of these racial/ethnic groups. Indeed, paralleling the increase in the lung and bronchus death rate for American Indians and Alaska Natives, this minority group exhibits the highest rate of tobacco use at 41.3%, versus 23.6% for whites, 22.8% for blacks, 23% for Hispanics, and 10.7% for Asian Americans. In addition, ethnic minorities are less knowledgeable about the adverse health consequences of smoking, smoke brands higher in nicotine, have poor access to health services, exhibit high rates of life stress, and suffer higher exposure to tobacco advertising. Consequently, there is a critical need for cessation programs that are tailored to be more pertinent and available to these groups and that address the specific factors that contribute to smoking among minorities.

Overall, most of the behavioral and pharmacologic interventions reviewed above have been shown to be efficacious for minority groups. However, it may be necessary to convert the content of interventions into the smoker’s language, to utilize culturally appropriate models and examples, and to respect specific and unique cultural beliefs about smoking and health. A range of smoking cessation materials and programs tailored to the cultural and linguistic characteristics of several ethnic groups have been developed. Few such resources, however, have been systematically compared to generic approaches.

One study, which evaluated an intervention designed for African American smokers, suggests that tailored approaches may be more effective than generic treatments for minority smokers; Orleans and colleagues compared a generic self-help manual to a cessation guide tailored to the unique smoking patterns and quitting needs and barriers of African American smokers. Although there was no short-term reduction in smoking with the tailored intervention, quit rates at the 12-month follow-up were significantly higher for the tailored versus the generic treatment (25% vs 15.4%). Nevertheless, a search for studies that compared smoking cessation treatments tailored to either Asian American, Hispanic, or Native American smokers to generic smoking interventions failed to uncover additional studies. The paucity of research in this area, particularly with regard to Native American smokers, is troubling when considering the continual growth of both the prevalence of tobacco use and the incidence of tobacco-related cancers in this racial/ethnic subgroup. As researchers move forward in this area, behavioral counseling interventions may need to address the particular barriers to quitting that have been identified among various minority groups, including a lack of knowledge concerning the harmful effects of tobacco, a lack of information about how to quit, a tendency to attribute the etiology of cancer to non–tobacco-related causes, social norms that facilitate smoking, lack of social support, high stress and competing life priorities, lack of financial resources, and use of smoking as a coping strategy.

**Women Smokers** Although the mortality rate from lung and bronchus cancer has declined among men, it has actually increased among women and is now the leading cause of cancer deaths among women. Not surprisingly, this trend can be attributed to the substantially lower decrease in tobacco use among women compared to men. Whereas smoking among men decreased by about 20% between 1965 and 1985, this rate dropped by only 6% for women during this time period. Women and especially young girls remain primary targets of marketing campaigns by tobacco companies. With few exceptions, behavioral and pharmacologic smoking interventions are equally as efficacious with women as with men. However, formal evaluations comparing gender-tailored to generic smoking treatments have yet to be conducted and there is a good deal of data indicating that two barriers to quitting—depression and fear of weight gain—may be of particular concern for women compared to men. Thus, currently, it is unclear whether or not smoking cessation treatments that are tailored to women are more effective than generic interventions. Future research that examines the comparative benefits of adding a counseling component to address depression or weight gain between male and female smokers is warranted and may lead to the development of gender-tailored smoking treatments.

Of additional concern regarding nicotine addiction treatment for women is whether or not the intervention is targeted to pregnant women. Smoking during pregnancy is associated with a range of adverse health outcomes, including an increased risk for low infant birth weight, spontaneous abortion, stillbirth, and maternal complications such as placenta previa and abruptio placentae. Despite these negative health effects, about 13% of pregnant women smoke, and this rate is substantially higher among younger pregnant women. Fortunately, a substantial number of intervention studies have been conducted with pregnant women who smoke. The AHRQ guidelines, in their meta-analysis of high-quality studies (eg, randomized studies involving biochemical confirmation of follow-up smoking status), concluded that compared to usual-care interventions (ie, quit advice, self-help materials, and a referral to a stop-smoking program), which yield a 6.6% quit rate, more intensive treatments involving the usual-care components plus longer-term behavioral counseling and tailored quit materials yield a 16.8% abstinence rate. The specific elements of more efficacious treatments include the use of quit materials and quit advice that is tailored to be relevant to pregnant women, the use of social support, and repeated counseling sessions. The use of pharmacotherapies with pregnant women remains an unresolved issue, however. First, the efficacy of NRTs and bupropion with pregnant women has yet to be fully evaluated; a study that evaluated the use of the patch with pregnant women reported that it was not any more effective at promoting abstinence than placebo. However, no additional efficacy study was identified. Second, the safety of using pharmacotherapy with pregnant women remains unknown. However, one study, which evaluated the use of the patch, found no evidence that patch use adversely affected the health of the fetus, while a second study, which evaluated the use of the gum, found significant reductions in serum nicotine with gum use. Thus, as suggested by many, further study of the safety and efficacy of pharmacotherapy for treating nicotine addiction among pregnant women is a priority.

**Adolescents** Tobacco addiction is, as Dr. David Kessler, the former head of the United States Food and Drug Administration stated, a “pediatric disease”: 80 to 90% of adult smokers begin smoking in their teens, and 71% of adult smokers became daily smokers by age 18. Thus, reducing adult smoking rates requires interventions targeted to youth. Two national surveys indicate that the scope of this challenge is daunting. Despite the well-publicized adverse health effects of smoking, and recent data showing an overall decrease in youth tobacco use, smoking among adolescents remains an important public health problem. The Youth Tobacco Surveillance, a national census of tobacco use in 1999 with over 15,000 students from grades 6 to 12, indicated that 9.2% of middle school students and 24.8% of high school students smoke cigarettes. The rate of youth smoking does not vary significantly by gender, but it does vary across ethnic groups: Among high school students, 32.9% of white smoke cigarettes, versus 25.8% of Hispanics and 15.9% of blacks. Alarmingly, data from middle school students suggests that blacks and Hispanics are gaining on their Caucasian peers: 8.8% of middle school whites smoke cigarettes, versus 9% of black and 11% of Hispanic students. Likewise, the Youth Risk Behavior Surveillance reported that 34.8% of high school students were current smokers (vs 27.5% in 1991) and smoking rates were greater among whites and Hispanics, versus blacks (ie, 38.6% and 32.7%, respectively, versus...
encouragement, coping skills training, relapse prevention) yielded a cessation rate at 6 months of 17%, versus 8% for controls. Since most studies that evaluated behavioral counseling treatments for adolescents have been randomized and lacked a control group, additional study of this treatment approach is needed.

To help guide progress in this area, American researchers produced a Blueprint for Action for Youth and Young Adult Tobacco-Use Cessation. This guideline highlights several issues that should be considered as future youth cessation interventions are developed and tested. First, adolescents consider quitting often and attempt to quit frequently. Thus, the dissemination of effective treatments may have a willing audience. Second, youth underestimate the addictive quality of nicotine and minimize how difficult it is to quit. Thus, youth require education about the addictive basis of nicotine and about the low rate of success in quitting among adults. Third, psychological (eg, depression, health values, quit motivation), social (eg, peer support), familial (eg, parental approval or parental smoking status), smoking-related (eg, addiction), and societal (eg, access to cigarettes) factors predict cessation. Thus, comprehensive programs involving behavioral counseling, peer education, NRT, and community restrictions are likely to be most successful. Finally, adolescent smokers are reluctant to partake in formal cessation programs. As such, innovative ways to promote enrollment in cessation programs must be identified. Remaining mindful of these issues when designing cessation treatments for adolescent smokers may lead to the development of more effective treatments and, in turn, a reduction in the prevalence of adult smokers.

**Cancer Patients** Continued smoking among cancer patients is associated with poor survival, a greater risk of disease recurrence and a second primary tumor, reduced treatment efficacy, and adverse treatment-related complications such as pulmonary embolism, venous thrombosis, and mucositis. Despite these health issues, about 25% to 35% of cancer patients who smoked prior to their diagnosis continue to do so following their diagnosis, with the prevalence rate increasing as time elapses from the point of diagnosis. Although the time of a diagnosis may increase a patient’s motivation to quit, only four studies have assessed behavioral smoking cessation treatments for cancer patients. A variety of behavioral counseling approaches have been used, along with NRT; however, each study utilized small samples or manifested important threats to internal validity. Consequently, additional intervention research is needed to address nicotine addiction in this population of smokers. This future research should consider recent studies that have yielded data highlighting the need to address the high level of nicotine addiction, depression, and attribution beliefs among these smokers and consider methods for harnessing the access and influence of oncologists to promote cessation in this group of smokers.

**Smokeless Tobacco** Smokeless tobacco contains known cancer-causing agents, such as nitrosamines, polycyclic aromatic hydrocarbons, 30 metals, and a radioactive compound called polonium-210. The most recurrent health problem of smokeless tobacco use is leukoplakia, a preneoplastic oral lesion of the soft tissue; upwards of 79% of smokeless tobacco users can show evidence of leukoplakia, 85% of which may be in the most advanced stage. Between 3 and 6% of leukoplakia lesions can be expected to progress to oral squamous cell carcinoma. Although use of smokeless tobacco increases risk for cancers of the mouth, esophagus, pharynx, larynx, stomach, and pancreas, early-stage leukoplakia can regress upon cessation of smokeless tobacco use. Although use of smokeless tobacco products among Aboriginal women and female athletes has been documented, smokeless tobacco is consumed almost exclusively by men. Moreover, most users are white, aged 18 to 25 and either athletes or in the military. The current rate of smokeless tobacco use is 14.2% among male high school students, 22.5% among athletes, and 7 to 9.3% among military personnel. Thus, the relatively few intervention studies in this area have been directed to these demographic subgroups. Two recent studies examined self-help treatments. Severson and colleagues randomly selected smokeless tobacco users to receive either a self-help manual or a manual plus a cessation video and telephone counseling. At 6 months, 18.4% of those receiving the manual reported abstinence, versus 23.4% of those in the enhanced treatment arm. In a second study by this group, smokeless tobacco users were randomly selected to receive either a cessation manual and video or the LifeSign, a credit card–sized computer that assists the user to quit via gradual reduction. At a 6-month follow-up, 18.4% of participants in the manual/video condition were abstinent, versus 24.5% of those who received LifeSign. The use of NRT for treating smokeless tobacco use, while supported by research documenting the addictive nature of smokeless tobacco, remains largely unexplored. A recent study found that patch use reduced smokeless tobacco use in the short-term. However, additional research is needed to understand the utility of pharmacotherapy for smokeless tobacco users. Finally, a dental visit has been gaining recognition as an optimal time to introduce smokeless tobacco cessation treatment, since more than one-half of the population routinely visits a dentist, and the early consequences of smokeless tobacco use can be detected during an oral exam. Recent studies suggest that dentist-delivered smokeless tobacco cessation treatments are feasible and can be effective, indicating the need to develop and evaluate this treatment approach more fully, especially for male athletes and military personnel.

**Environmental Tobacco Smoke (ETS)** The Environmental Protection Agency described the causal link between environmental tobacco
smoke (ETS) exposure and a range of serious illnesses, including asthma, acute lower and upper respiratory illnesses (ie, bronchitis, pneumonia), middle ear disease, reduced lung function, and impaired lung development. ETS exposure can also cause genetic changes that subsequently cause cancer. The risk for ETS-related illnesses and mortality is linked in a dose–response fashion to the number of cigarettes you are exposed, the most common form of ETS. Children and adolescents are especially vulnerable to the effects of ETS because (1) children show proportionately higher levels of ventilation than adults, leading to greater intake of ETS; (2) the chemical constituents of tobacco can be passed on to infants via breast-feeding; (3) children are limited in their ability to avoid ETS exposure and may be reprimanded for complaining about it; and (4) children spend a great deal of time at home, thus increasing the duration of exposure. Nevertheless, about 50% of all children in the United States may be exposed to ETS, with parental smoking, particularly among mothers, being the most prevalent source. Thus, a growing priority in the field of tobacco control is the development and evaluation of methods to reduce and eliminate child exposure to ETS.

Few studies have explored methods for reducing parental smoking to reduce ETS-related morbidity. Mandated household smoking bans are unlikely, since an individual’s privacy rights currently outweigh society’s duty to protect children’s health. Media campaigns to educate smokers about the importance of reducing child ETS exposure have yielded minimal results. Studies of formal clinical interventions with parents who smoke, involving educational pamphlets, risk feedback via child cotinine levels, and brief counseling, have shown only modest results. Likewise, studies of physician interventions, in which physicians provide quit advice and self-help material, showed modest reductions in ETS exposure. However, two recent studies suggest that training physicians in providing cessation counseling can enhance the effects of physician-based interventions. Indeed, there is growing recognition for the role that physicians can play in reducing child ETS exposure: Tyc and colleagues and Stein and colleagues extended the AHRO model to the pediatric setting. Since pediatricians are the physicians with the greatest level of access to children and their parents, their adoption of this model may represent an effective approach for reducing parental smoking and limiting child ETS exposure. Yet, only about 50% of pediatricians ask parents about smoking behavior, and only 8 to 19% of pediatricians provide parents who smoke with cessation counseling or quit advice. Such data likely reflect the limited time that pediatricians have with their patients, a lack of reimbursement for smoking treatments, and a lack of training among physicians to provide cessation counseling. Thus, if the potential for pediatricians to have an impact on child ETS exposure is to be harnessed, societal changes are needed along with novel methods for training pediatricians in providing appropriate nicotine addiction treatment.

The Genetics of Tobacco Addiction
Despite the potent addictive nature of tobacco, there is a large degree of variability in people’s reaction to tobacco initiation and cessation. Many can be occasional users or never progress to addiction after experimentation, whereas others quickly progress to regular use after initial exposure; likewise, some can easily quit and maintain abstinence, whereas others battle their addiction forever. Although psychological and social factors can account for some of this variability, genetic polymorphisms—in individually or in combination—may account for some of this variability as well. Recent analyses suggest that genetic factors explain about 50% of the variability in smoking initiation and about 70% of the variability in the ability to quit smoking. Several genetic pathways have been proposed to explain the genetic influence on smoking and cessation behavior, including genes responsible for metabolizing nicotine (eg, CYP2A6) and genes responsible for regulating physiological reward, namely dopaminergic and serotonergic genes.

Polymorphisms in CYP2A6, a P450 enzyme responsible for metabolizing nicotine, have been the focus of much research. Some research has reported a relationship between the *2 and *3 alleles of this gene and a lower likelihood of being a smoker and a link between an inactive CYP2A6 allele and lower levels of smoking. However, the methods involved in this research have been criticized and replication has been elusive. A second line of research has focused on genes in the dopamine pathway, since these play a central role in regulating biochemical processes that provide reward and pleasure. Indeed, nicotine stimulates the release of dopamine, which, in turn, triggers a cascade of biological events that humans experience as rewarding and pleasurable. Thus, certain people may start smoking and have a harder time quitting because they have a genetic profile that yields low rates of dopamine, a condition referred to as the reward deficiency syndrome.

Polymorphisms in genes in the dopamine pathway, since these play a central role in regulating biochemical processes that provide reward and pleasure. Indeed, nicotine stimulates the release of dopamine, which, in turn, triggers a cascade of biological events that humans experience as rewarding and pleasurable. Thus, certain people may start smoking and have a harder time quitting because they have a genetic profile that yields low rates of dopamine, a condition referred to as the reward deficiency syndrome. Most research in this area has assessed the effect of polymorphisms on dopamine receptor genes, including DRD1, DRD2, DRD4, and DRD5 receptors. Although certain studies have linked dopaminergic polymorphisms that reduce the availability of dopamine (eg, DRD2-AI) to smoking initiation and quitting behavior, other studies have failed to show a linkage. Other research has examined variation in the dopamine transporter gene (SLC6A3) as a correlate of tobacco use. These studies assessed the relationship between the presence versus the absence of the 9-allele of this gene and smoking behavior. Since the presence of the 9-allele may decrease levels of dopamine transporter, thereby increasing levels of dopamine, individuals with the 9-allele may be less likely to smoke and may have an easier time quitting versus those without this allele. Two studies found support for this hypothesis, although a third study did not. A third line of research focuses on the effect of genes that regulate serotonin on smoking behavior, since this neurotransmitter plays a role in depression and anxiety, psychological conditions linked with smoking behavior. One study failed to show that polymorphisms in tryptophan hydroxylase (TPH), which modulates serotonin production, directly affect smoking status. However, the A allele for TPH has recently been associated with age of onset of regular tobacco use and with the likelihood of tobacco use initiation.

Understanding the genetic basis of nicotine addiction is a complex process that poses a unique set of conceptual and methodological issues. Indeed, nicotine addiction is likely a product of an interaction between genetic and psychological factors, as has been suggested in certain studies. In addition, in this evolving field, new genes are drawing attention, such as the recently identified neuropeptide, cholecystokinin. Yet, as studies in this area move forward, there is a growing promise that understanding the genetic basis of nicotine addiction can lead to novel personalized treatments for nicotine addiction and innovative ways to prevent the development of nicotine addiction. Thus, the future of nicotine addiction treatment and prevention will be best served by testing new theoretical models, such as the reward deficiency syndrome.

Prevention of Tobacco Use
The most effective way to reduce the rate of mortality attributable to tobacco-related cancers is to prevent smoking initiation. Since nearly all smokers begin to use tobacco when they are under the age of 18, tobacco prevention efforts must be directed towards children and adolescents. The past several decades have seen the implementation of numerous tobacco use prevention programs, however few of these programs have been subjected to rigorous scrutiny. Successful tobacco prevention initiatives depend on an understanding of the specific factors that determine smoking initiation and, fortunately, there has been a good deal of study of this issue. Sussman provided a framework for conceptualizing the process of smoking initiation. First, personality (eg, depression, low self-esteem), family (eg, having parents who smoke), and peer (eg, having friends who smoke) factors increase susceptibility to smoking. Next, experimentation is likely if the child or adolescent is exposed to peer encouragement, has poor parental monitoring or parental disapproval, is exposed to commercial advertising for tobacco use, and exhibits a curiosity about the consequences of tobacco use. Third, during the experimental phase, expectations about the consequences of tobacco use (eg, the relief of anxiety or depression, peer acceptance) develop and shape attitudes about continued use. During this...
phase, genetic susceptibility factors may influence sustained tobacco use. Finally, physiological and addictive factors develop and serve to mold casual smoking into regular, sustained use.

Tobacco prevention initiatives have been either (1) school-based education and counseling programs or (2) community-based programs. At first, school-based programs were designed to promote awareness of the harmful effects of tobacco use, based on the assumption that if children were made aware of the adverse health effects of smoking, they would abstain. Although few of these programs were rigorously evaluated, relying only on addressing "an information deficit" is insufficient to prevent tobacco use. Since most majority of the school-based prevention programs implemented and tested over the past decade have utilized the social-influence model, which emphasizes the need for "inoculation" against the social pressures that increase the risk for initial tobacco use. However, a recent large scale study comparing 20 schools that received a social-influence intervention to 20 schools that served as controls reported no significant impact of the intervention, casting serious doubt on the veracity of the social-influence model for youth tobacco prevention. Thus, an important priority remains the development and evaluation of more effective school-based tobacco prevention interventions. One novel approach is the application of the expert system to adolescent tobacco use prevention. A recent evaluation of this approach did not find it to be effective, however. Additionally, many have suggested the need to evaluate programs that combine school-based interventions with community-wide initiatives, and initial evaluation of this approach has been positive.

Community-wide prevention programs involve mass-media education (eg, antismoking billboards and television commercials) and legislative policy (ie, restricting advertising and access, raising taxes, and instituting bans) to influence individual behavior and societal norms concerning adolescent smoking. Recent reviews and meta-analytic studies suggest that community-based prevention programs reduce adolescent smoking rates. In particular, comprehensive tobacco control programs instituted in California, Massachusetts, Oregon, Arizona, and Florida involving mass-media counter-advertising, school-based education programs, tobacco taxation, and regulating policies have lowered adolescent smoking rates. Since most community-based programs have used a variety of measures to prevent adolescent tobacco use, however, it is difficult to identify the relative impact of specific elements of community-wide interventions. Some data suggest that mass-media education can have an independent effect on youth tobacco use; counter-advertising approaches like the "truth" campaign have been linked to a 19% reduction in smoking among high school students, and qualitative analyses show that counter-advertising messages that emphasize tobacco industry manipulation, rather than the immediate and long-term health consequences of smoking, are most effective with youth. Furthermore, although many states and cities have banned tobacco advertising, few studies have evaluated the impact of this approach on youth tobacco use rates. Inconsistent findings regarding advertising restrictions have been attributed to the use of partial versus complete bans; however, some have suggested that complete bans on tobacco advertising can yield a 6% reduction in rates of tobacco use among youth. Restricting youth access to tobacco products through enforcement of laws preventing tobacco sales to those under age 18 (eg, the "It's the Law" campaign) lowers illegal sales of cigarettes to minors; however, the effectiveness of this approach is dependent on implementation of penalties to nonadherent vendors, and it is still unclear whether reducing the sale of tobacco products to minors translates into lower overall rates of youth tobacco use. Moreover, although the introduction of tobacco taxes has led to inconsistent effects on the rate of youth tobacco use, this approach is considered to be an important method for preventing smoking among adolescents. Since youth have limited funds, increasing the price of tobacco products may be a particularly effective deterrent. Small increases in the price—has been the case—are less effective than more substantial increases. Finally, the use of formal restrictions on smoking has become more prevalent in the past decade, with most workplaces and public places (eg, restaurants, hotels) prohibiting smoking. One study reported that smoking bans at home, in public places, and at school yield significant reductions in youth tobacco use. Whereas the effectiveness of smoking bans is influenced by the degree of enforcement, bans may be converting a cultural norm such that smoking is no longer socially acceptable. Therefore, there is good reason to believe that counter-advertising, restricting tobacco advertising and youth access to tobacco, tobacco taxation, and smoking bans are all necessary and essential elements of community-based tobacco prevention programs. Nevertheless, future research is needed to distill the comparative impact of each of these program elements.

SUMMARY
Our goal here was to describe the state-of-the-science on the prevention of tobacco-related cancers. Fortunately, the scientific and social movement to eradicate tobacco use has gained momentum over the past few years, especially with the distribution of funds from the Master Settlement Agreement. There has been a significant growth in our understanding of effective cessation strategies and for the recognition of the need to consider the impact value of these strategies. An important priority for future research is to identify effective methods for training physicians to implement established smoking cessation treatment guidelines (see Table 28-1). In addition to more training opportunities, legislative change is needed to ensure that physicians are reimbursed for providing cessation treatment. Furthermore, research is needed to better elucidate methods for personalizing treatments, including the tailoring of interventions to the smoker's readiness to quit, cultural identity, gender, age, and health status, and the use of the stepped-care model. Research into the genetic basis of nicotine addiction may also lead to the development of interventions tailored to the specific biological needs of the smoker. To this point, however, the use of reducing—rather than eliminating—tobacco use does not appear to be a viable goal of cessation programs, nor does the development of a "safe cigarette" seem to be a reasonable alternative to tobacco use. Moreover, the use of smokeless tobacco products remains an important public health concern; thus, novel treatment and prevention approaches are needed, especially ones targeted to young male athletes and to those in the military. Finally, the burgeoning literature on tobacco prevention indicates that school-based programs require refinement, since programs that rely on the social-influence model may not be effective. In addition, the implementation of school-based programs may need to be accompanied by community-based prevention initiatives. Prevention programs should also consider targeting treatment elements to children who are at higher risk for initiating smoking, and the current genetic research may reveal certain biological susceptibility factors that can help guide these targeted prevention campaigns.

Preventing tobacco-related cancers clearly requires the development of effective tobacco prevention and cessation programs. Progress concerning methods for treating nicotine addiction and approaches to preventing tobacco use has been significant; however a considerable amount of additional research is needed before the eradication of the human burden of addiction to tobacco products is realized. Fortunately, a significant increase in funding for tobacco research has occurred in recent, years and a greater commitment to tobacco control has developed in all strata of government. Thus, in the coming years, we anticipate additional important discoveries and progress concerning methods of treatment and prevention of tobacco use, which should translate into significant reductions in the rate of tobacco-related cancers.

REFERENCES
3. International Association for Research in Cancer. Tobacco


205. Witschi H, Joaop J, Pinkerton KE. The toxicology of envi-

