Chapter 3
Cardiovascular Diseases

Introduction

Heart disease and stroke—the main types of cardiovascular disease caused by smoking—are the first and third leading causes of death in the United States, respectively (American Heart Association [AHA] 2002; Anderson 2002). More than 61 million people in the United States suffer from some form of cardiovascular disease (CVD), including high blood pressure, coronary heart disease (CHD), stroke, congestive heart failure (CHF), and other conditions. Nearly 950,000 Americans die each year as a result of CVD, accounting for 39.4 percent of all deaths in 2000 (AHA 2002). This chapter reviews the evidence on the relationship between smoking and CVD. In particular, it examines the associations between smoking and subclinical atherosclerosis, CHD and sudden death, stroke, and abdominal aortic aneurysm (AAA).

Conclusions of Previous Surgeon General's Reports

One of the first topics addressed in the Surgeon General's reports was smoking and CVD, although the 1964 report focused primarily on the relationships between smoking and respiratory diseases, including cancer and chronic lung diseases (U.S. Department of Health, Education, and Welfare [USDHEW] 1964). The report noted that male cigarette smokers had higher death rates from CHD than nonsmoking males. In 1967, the second Surgeon General's report on smoking concluded that the evidence "strongly suggests that cigarette smoking can cause death from coronary artery disease" (USDHEW 1967, p. 27). With a growing number of studies addressing other cardiovascular endpoints, the 1971 and 1974 reports highlighted the associations between smoking and peripheral vascular disease, aortic atherosclerosis, and cerebrovascular disease, including stroke (USDHEW 1971, 1974). The 1979 report concluded that smoking was not only one of the main risk factors for CHD (nonfatal and fatal myocardial infarctions [MIs] and sudden death), but was a causal factor supported by evidence considered to be proved beyond a "reasonable doubt" (USDHEW 1979, p. 4-63). In addition, that report presented evidence of strong associations with morbidity from peripheral vascular disease and aortic aneurysms. In contrast, the association between smoking and stroke was considered "not conclusive" (USDHEW 1979, p. 1-14).

Subsequent Surgeon General's reports reviewed the evidence linking cigarette smoking to CHD. The conclusions in the 1983 Surgeon General's report reaffirmed that cigarette smoking is one of the major independent causes of CHD and, given the prevalence of smoking, "should be considered the most important of the known modifiable risk factors for coronary heart disease" (U.S. Department of Health and Human Services [USDHHS] 1983, p. iv). The evidence considered included a large number of epidemiologic, clinical, and experimental studies carried out with a variety of methods and research designs. Until the 1980s, though, there had been limited evidence related to the reduction of risk after maintained cessation. In an extensive review of updated data on the benefits to cardiovascular health from smoking cessation, the 1990 Surgeon General's report found that "smoking cessation reduces the risk of both ischemic stroke and subarachnoid hemorrhage compared with continued smoking" (USDHHS 1990, p. 11). Other conclusions from that report include the following:

> The excess risk of CHD caused by smoking is reduced by about half after 1 year of smoking abstinence and then declines gradually. After 15 years of abstinence, the risk of CHD is similar to that of persons who have never smoked.
>
> Among persons with diagnosed CHD, smoking cessation markedly reduces the risk of recurrent infarction and cardiovascular death. In many studies, this reduction in risk of recurrence or premature death has been 50 percent or more.

> Smoking cessation substantially reduces the risk of peripheral artery occlusive disease compared with continued smoking.
>
> Among patients with peripheral artery disease, smoking cessation improves exercise tolerance, reduces the risk of amputation after peripheral artery surgery, and increases overall survival (USDHHS 1990, p. 260).

The 1998 Surgeon General's report focused on the impact of smoking in ethnic and racial minority populations in the United States (USDHHS 1998) and concluded that even though more data would be helpful, existing data indicated that the association of tobacco use with CHD did not differ between whites and four major racial and ethnic minority groups. A similar conclusion was reached for women in the 2001 Surgeon General's report on women and smoking (USDHHS 2001).

This chapter is not an exhaustive review of the now vast literature on tobacco smoking and heart and vascular disease, although it does include an update of recent clinical and epidemiologic studies on the subject. The primary focus, however, is a review of the evidence relevant to smoking and subclinical measures of atherosclerosis, including what is understood about the role of smoking in the pathophysiologic processes that cause atherosclerosis and its clinical manifestations (i.e., CVD syndromes including coronary artery disease, AAA, peripheral vascular disease, and stroke). These advances in understanding of pathogenesis deepen the understanding of smoking as a cause of CVD.

Search strategies for this chapter included reviewing previous Surgeon General's reports on smoking, publications originating from the largest observational studies on CVD, and reference lists from important publications; consulting with content experts; and conducting focused literature searches on specific topics including the new literature on subclinical measures.

Biologic Basis

When the association between cigarette smoking and CVD was first identified in epidemiologic studies, the underlying biologic mechanisms were not yet well understood. The injury hypothesis of atherosclerosis, formally proposed in the mid-1970s (Ross and Glomset 1976a,b), provided a framework for considering the atherosclerotic effects of smoking, even though the specific tobacco components and the precise mechanisms for the injury to the endothelium (the inner cellular layer of the arterial wall) were unknown. During the 1990s, research further clarified the pathophysiology of the atherosclerotic effects of cigarette smoking. In addition, in the last three decades a large body of evidence has accumulated, demonstrating that smoking increases the risk for thrombosis (USDHHS 1990; Meade et al. 1993; Miller et al. 1998). This evidence provides an additional framework for understanding the pathophysiologic effects of smoking on the basic underlying processes of CVD. Recent experimental work, including in vitro studies, animal studies, and controlled experiments in humans, has added to the understanding of these mechanisms. This evidence is reviewed in the following section.

Smoking, Atherogenesis, and Thrombosis

The development of atherosclerosis is the main underlying pathophysiologic process of the most clinically significant manifestations of CVD, namely CHD, stroke (cerebrovascular disease), and peripheral arterial disease. Atherosclerosis is a process of hardening of the arteries characterized by deposition of lipid in the inner layers of the arteries, by fibrosis, and by thickening of the arterial wall. Atherosclerotic plaques develop over time, slowly progressing from the early lipid deposition that characterizes fatty streaks, through the more advanced raised fibrous lesions that decrease the space inside the artery (the arterial lumen), to the complicated lesions that are usually associated with clinical events. The process of plaque destabilization and complications is thought to be associated with inflammatory changes and thrombotic complications that obstruct the blood flow and result in clinical manifestations such as MI or stroke. There are underlying complex interactions of the blood (serum and blood cells) with the arterial wall as well as between cellular elements within the arterial wall itself. Table 3.1 offers a basic summary of the stages

Table 3.1 Basic pathogenic mechanisms in atherogenesis

Stage of change	Mechanism
Interactions between blood components and the arterial wall (endothelium)	Hypercholesterolemia (increased low-density lipoprotein [LDL] cholesterol) Endothelial dysfunction Leukocyte and platelet activation and adherence to the endothelium Migration of leukocytes through the endothelium
Changes within the arterial wall	LDL modification (oxidation) LDL accumulation in monocytes, turning them into foam cells Accumulation of LDL and collagen in intercellular space Smooth muscle cell proliferation
Advanced changes, complications	Plaque inflammation Endothelial denudation Platelet activation, micro- and macro-thrombosis Fibrinolysis of thrombi Plaque/thrombi rupture—emboli

and related mechanisms of the complex multistage phenomenon of atherogenesis. Each of these processes is mediated by a variety of chemotactic molecules and cytokines (Ross 1993, 1999).

The following section presents evidence showing that cigarette smoking affects a number of these processes. The evidence demonstrates that this delicate and highly regulated physiologic interface between blood and arterial wall components is adversely and strongly affected by the toxic products added to the bloodstream from cigarette smoke. These toxins then become part of the complex atherothrombotic process underlying CVD (Powell 1998).

Smoking and Endothelial Injury or Endothelial Dysfunction

The critical role of endothelial dysfunction in the early stages of atherosclerosis is now well recognized (Ross 1993, 1999). Endothelial dysfunction is associated with an increased adhesion of circulating monocytes and T lymphocytes to the endothelium as well as with their subsequent migration into the intimal layer of the arterial wall, the layer of cells and tissue innermost to the arterial wall. These cells, in the presence of modified low-density lipoprotein (LDL) cholesterol (e.g., oxidized LDL cholesterol), become foam cells and accumulate in the intima, constituting a key element in the early phases of atherogenesis. Endothelial dysfunction has been experimentally linked to atherosclerosis in animal models (Moore 1973) as well as in humans (Celermajer et al. 1992; Corretti et al. 1995).

Early reports on the possible detrimental effects of cigarette smoking on the endothelium focused mainly on morphologic changes in the endothelium (Pittilo 1990; USDHHS 1990). This research included animals experimentally exposed to nicotine at serum levels similar to those of human smokers, and observational and experimental human studies. The findings included the following:

- Umbilical arteries from cords of infants born to smoking mothers showed endothelial changes absent in cords from nonsmoking mothers (Asmussen and Kjeldsen 1975; Asmussen 1982a,b; Pittilo 1990). These changes included subendothelial edema or swelling, widening of the intercellular junctions between cells, distension of the endoplasmic reticulum, and increased numbers of mitochondria. Similarly, morphologic examinations of uterine arteries in smoking women showed significantly more inter- and intracellular holes in the endothelium than did arteries in nonsmoking women (Bylock et al. 1979).

- Short-term experimental studies in healthy nonsmokers demonstrated that cigarette smoking is associated with an acute increase in the endothelial cell count in circulating blood. Compared with the minimal effects of nontobacco cigarettes, smoking two tobacco cigarettes more than doubled the number of damaged endothelial cells (anuclear carcasses) in the circulating blood of healthy persons (Davis et al. 1985). This effect was not modified by the previous administration of aspirin or rutosides (semisynthetic derivatives of rutin, a naturally occurring flavonoid) (Davis et al. 1986, 1989).

- Other laboratory data support the biologic plausibility of the above effects: cultured rat peritoneal mesothelial cells were exposed to plasma obtained from nonsmoking persons and from persons who had just smoked two cigarettes (Pittilo et al. 1985). Whereas the plasma from nonsmokers had little effect on the cultured cells, the plasma from smokers produced marked morphologic alterations, including blebbing or bubble formation of the luminal membrane. Pittilo and colleagues (1984) reported that exposure of rat endothelium to the blood from a person who had recently smoked two cigarettes resulted in the deposition of large numbers of platelets on the endothelial surface, an effect that was not observed when exposing the endothelium to human blood obtained before smoking. Likewise, in the absence of morphologic changes, cigarette smoke exposure in dogs resulted in an increased endothelial permeability to the coagulable protein fibrinogen (Allen et al. 1988). Pittilo (1990) reviewed animal studies that further supported these observations. A number of experiments with rabbit and rat models conducted during the 1980s consistently found that cigarette smoking was associated with morphologic changes in the endothelium, including cell loss and the formation of blebs and microvillous-like projections into the luminal cell surfaces.

In recent years, more subtle functional changes in the endothelium have been associated with smoking. Even in the absence of morphologic changes, a dysfunctional endothelium can secrete growth factors, chemotactic molecules that draw in inflammatory cells, and cytokines that stimulate the inflammatory process of atherosclerosis. The cytokines and other molecules can stimulate smooth muscle cell proliferation, monocyte/lymphocyte adhesion, and subendothelial migration leading to atherosclerosis and the loss of the endothelium's normal antithrombotic properties (Pittilo 1990; Vogel 1997; Hutchison 1998).

The endothelium regulates the vascular tone by secreting vasodilators (e.g., nitric oxide) and vasoconstrictors (Arnal et al. 1999). The functional status of the endothelium can be studied by examining arterial diameter changes in response to stimuli whose effects depend on the integrity of the endothelium. Quantitative angiography, for example, can measure changes in the coronary artery diameter in response to varying concentrations of acetylcholine, an endothelium-dependent vasodilator. Plethysmography can record changes in the diameter of the brachial artery in response to stimuli from an endothelium-dependent vasodilator (e.g., reactive hyperemia induced by blood flow increase) by measuring the pressure or by ultrasound (Celermajer et al. 1992; Corretti et al. 1995). Using these techniques, young and middle-aged cigarette smokers without disease had a significant reduction in endothelium-dependent vasodilatation compared with nonsmoking controls (Celermajer et al. 1993). This association was dose-dependent (vasodilatation decreased with more pack-years[1] of exposure) and seemed to be potentially reversible (a weaker association was observed in former smokers). Similar effects were seen in young persons who reported exposures to secondhand smoke, also in a dose-dependent fashion (Celermajer et al. 1996). Further studies have confirmed these findings and suggest a synergism between smoking and hypercholesterolemia (Heitzer et al. 1996), raising the possibility that smoking potentiates endothelial dysfunction by enhancing LDL oxidation.

Clinical studies that used measures of endothelial dysfunction in the coronary arteries have also confirmed these results. For example, a 1999 report showed that smokers had no increases in coronary myocardial blood flow (measured with positron emission tomography) in response to a cold pressor test (Campisi et al. 1999). However, after administration of L-arginine (the precursor of nitric oxide), the myocardial blood flow response in smokers normalized, becoming indistinguishable from that of nonsmokers. This observation suggests that the abnormal flow response in smokers is related to endothelial dysfunction (Campisi et al. 1999). Further evidence of the deleterious effects of smoking on endothelial function

[1]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

comes from human experiments showing steady increases in the von Willebrand factor (vWF), a possible marker of endothelial damage, 10 and 30 minutes after smoking two cigarettes (Blann et al. 1998). Compared with nonsmokers, smokers also released smaller amounts of tissue plasminogen activator (TPA) when stimulated by substance P, suggesting another mechanism whereby endothelial cell dysfunction may increase thrombosis (Newby et al. 1999).

Smoking and Thrombosis/Fibrinolysis

In a pathology study of plaque tissue obtained from samples of diseased arteries removed by surgery, plaques from smokers were more frequently complicated by thrombosis along the walls of the arteries than were plaques from nonsmokers (Spagnoli et al. 1994). Proper balance of the tightly regulated coagulation-fibrinolytic systems is critical to plaque stability and blood flow in the later phases of atherosclerosis. This balance between clotting and dissolution of clots depends on extremely complex interactions involving all of the cellular components in the blood-arterial wall interface, especially the endothelial cells and platelets. When this complex system is disturbed, pathologic thrombosis may occur, leading to vascular occlusion by thrombus fragments that could result in clinically manifest infarcts. The association between cigarette smoking and changes in blood vessels that are conducive to thromboses has been previously described (USDHHS 1990; Miller et al. 1998). Evidence suggests that these prothrombotic effects of smoking may be most important to the natural history of atherosclerosis, and probably are the main underlying factors associating smoking with sudden cardiac death (Burke et al. 1997).

The prothrombotic effects associated with cigarette smoking stem partially from the effects of smoking on the endothelium, as discussed in the preceding section. Endothelial denudation exposes circulating plasma coagulation factors to the prothrombotic matrix of arterial and plaque tissue. Moreover, impaired endothelial function results in disturbances of the tightly regulated physiologic interface between blood components and vessel walls, leading, for example, to homeostatic disruptions and increased levels of plasma vWF (Blann et al. 1998). Recent experimental evidence in smoke-exposed animals concurs with parallel comparisons of human carotid artery specimens from smokers and nonsmokers (Matetzky et al. 2000), indicating that smoking increases tissue factor expression (a small molecular-weight glycoprotein that initiates the extrinsic clotting cascade [Toschi et al. 1997]). Together, these animal and human findings suggest yet another mechanism whereby smoking may increase the risk for acute arterial thrombosis (Matetzky et al. 2000).

Furthermore, the direct effects of smoking on the properties of platelets, platelet activation, and platelet adhesion are well proven (Lassila et al. 1988; Lakier 1992), and even nonsmokers exposed to cigarette smoke experience acute increases in platelet aggregability (Davis et al. 1985). As in the endothelial damage discussed above, neither aspirin nor rutosides prevented these acute effects on platelet activity (Davis et al. 1986). Smoking also elevates the plasma concentration of beta-thromboglobulin and the platelet factor, thereby increasing the tendency toward clot formation (Davis et al. 1986).

More recent experiments reinforce and further clarify these earlier results. In controlled experiments using habitual smokers with stable CHD (Hung et al. 1995), blood obtained five minutes after smoking two cigarettes had increases in platelet thrombus formation and whole blood platelet aggregation compared with blood obtained five minutes before smoking. In another experiment, the increased aggregability of platelets in smokers was related to increases in fibrinogen and platelet-fibrinogen binding (Fusegawa et al. 1999).

With regard to fibrinolytic activity, studies have shown that compared with the endothelium of nonsmokers, the endothelium of smokers has a reduced ability to release TPA in response to an infusion of substance P, an endothelium-dependent vasodilator (Newby et al. 1999, 2001). This impaired TPA response may be critical in the acute phase of coronary thrombosis by slowing the conversion of fibrin into soluble products. In combination with the prothrombotic effects of smoking, the imbalance in the coagulation-fibrinolytic systems may precipitate the propagation of microthrombi in the surface of atheromatous plaques, leading to arterial occlusion and clinical manifestations of thrombosis (Newby et al. 1999). Evidence also strongly suggests that smoking has synergistic effects with some pharmacologic substances (e.g., oral contraceptives) in its thrombogenic potential (Lidegaard 1999; Roy 1999).

Fibrinogen is an acute-phase protein that rises quickly in response to a number of stimuli (Gabay and Kushner 1999), and in cross-sectional studies, smoking is strongly associated with increased plasma levels of fibrinogen (Ernst et al. 1987; Folsom et al. 1991, 1992; Miller et al. 1998). In addition, prospective cohort studies show that persons who start or continue to smoke have larger increases in plasma fibrinogen

over time than do nonsmokers (Meade et al. 1987; Folsom et al. 2000), findings supported by a short-term experiment showing decreases in plasma fibrinogen following smoking cessation (Rothwell et al. 1991). Thus, the smoking-associated increase in plasma levels may reflect a chronic inflammatory response associated with the insult to the arterial tissue and other organs (e.g., bronchitis) from long-term smoking. Numerous studies have demonstrated that the fibrinogen level is an independent cardiovascular risk factor (Wilhelmsen et al. 1984; Kannel et al. 1987; Ernst and Resch 1993; Danesh et al. 1998), and the deleterious effects of smoking on CVD risk may be partially mediated by the rise in fibrinogen.

The profound alterations of the fibrinolytic system associated with smoking are also reflected in the strong association between cigarette smoking and plasma levels of certain hemostatic factors. Smoking is associated with increased antithrombin III activity (Folsom et al. 1992) and decreased levels of protein C (Conlan et al. 1993b), factor VIII (Conlan et al. 1993a), factor IX activation peptide, factor X activation peptide, and prothrombin fragment 1+2 (Miller et al. 1998). In contrast to the increases in vWF levels experimentally induced by cigarette smoking (Blann et al. 1998), cross-sectional studies do not show a significant independent association between cigarette smoking status and average vWF plasma levels (Conlan et al. 1993a). The results for factor VIIc are not consistent in the literature, with significant associations in some studies (Miller et al. 1998) but not in others (Folsom et al. 1992).

Smoking and Inflammation

Current concepts of the pathogenesis of atherosclerosis increasingly emphasize the central role of inflammation (Ross 1999). As discussed elsewhere in this report, smoking induces a localized inflammatory response in the lungs and induces a systemic inflammatory response manifested by elevations in inflammatory markers such as the leukocyte count in circulating blood, which is a risk marker (and potentially a risk factor) of CVD (Friedman et al. 1973). Both cross-sectional and longitudinal studies have consistently demonstrated that, compared with persons with lower counts, those with moderately elevated leukocyte counts have an increased risk of CHD, stroke, and sudden death (Friedman et al. 1974, 1975; Prentice et al. 1982; Grimm et al. 1985; Ernst et al. 1987). In a recent meta-analysis, a difference of 2,800 leukocytes/mm^3 within the normal range of the leukocyte count (e.g., comparing persons with 8,400 leukocytes/mm^3 with persons with 5,600 leukocytes/mm^3) was associated with a relative risk (RR) of CHD of 1.4 (Danesh et al. 1998).

The association between cigarette smoking and the leukocyte count is strong and well described in epidemiologic studies (Friedman et al. 1973). There are consistent dose-response relationships with amount smoked, degree of inhalation, duration of smoking, and amount of time since quitting (Petitti and Kipp 1986; Nieto et al. 1992) (see Chapter 2, "Cancer"). Moreover, studies demonstrate that these acute increases in leukocyte counts caused by cigarette smoking are probably due, at least in part, to local inflammatory effects in the bronchial tree (Lehr 1993). However, the effects of cigarette smoking on the activation and adhesion of leukocytes, which initiate the atherosclerotic process when combined with endothelial dysfunction, are perhaps more significant for arterial wall injury. Laboratory studies have demonstrated that both animal and human leukocytes exposed to cigarette smoke express increased chemotactic responses, increased aggregability, and increased expressions of adhesion receptors in response to a variety of stimuli (Anderson 1991; Lehr 1993).

Smoking is also associated with an elevation of the C-reactive protein level, an acute phase protein that provides a measure of inflammatory activity (Das 1985; Tracy et al. 1997; Ridker et al. 2000). Epidemiologic evidence indicates that the C-reactive protein level is positively associated with risks of CHD, stroke, and peripheral arterial disease (Kuller et al. 1996; Ridker et al. 1997; Ridker 2001; Di Napoli et al. 2001).

Smoking, Lipids, and Lipid Metabolism

The evidence supporting an association between smoking and adverse lipid profiles has been reviewed in previous reports (USDHHS 1990), and summarized in a 1989 meta-analysis of 54 studies (Craig et al. 1989). This evidence reveals higher concentrations of total LDL and very low-density lipoprotein (VLDL) cholesterol in smokers compared with nonsmokers, although the most consistent evidence indicates decreased levels of high-density lipoprotein (HDL) cholesterol in smokers compared with nonsmokers (Krupski 1991). The plausibility of a causal association of smoking with decreased HDL is supported by evidence from a population-based, prospective cohort study within the Stanford Five-City Project showing decreasing HDL levels in persons starting to smoke and, conversely, increasing HDL levels in persons who had stopped smoking (Fortmann et al. 1986). These findings have been replicated in other studies (USDHHS 1990).

Smoking may also seriously affect lipid metabolism and LDL modification. Smokers have higher levels of serum malondialdehyde (USDHHS 1990), which may modify LDL cholesterol to promote uptake by macrophages and decrease cholesterol transport from cell membranes to plasma. Malondialdehyde may be a marker of oxidation, and evidence indicates that smoking may promote lipid peroxidation, which is hypothesized to be one key element in the causal pathway of atherogenesis (Steinberg et al. 1989). Furthermore, evidence from an uncontrolled intervention trial demonstrates a significant increase in the HDL/LDL cholesterol ratio in adult smokers without disease following an eight-week period of smoking reduction. The increase was even more pronounced after a further eight-week period of abstinence from smoking (Eliasson et al. 2001). How cigarette smoking could cause changes in serum lipid levels is not entirely understood, but the mechanisms may involve metabolic changes affecting the transport of cholesterol between cells and plasma (de Parscau and Fielding 1986). In laboratory studies, cigarette smoke stimulated the generation of oxidized LDL cholesterol in human plasma (Frei et al. 1991).

Smokers also have elevated levels of plasma and urine F_2-isoprostanes (by-products of lipid peroxidation) compared with nonsmokers (Morrow et al. 1995; Patrono and FitzGerald 1997). Even though no acute effects of smoking were observed, experimental data demonstrated that stopping smoking resulted in a significant reduction in F_2-isoprostane levels within days or just a few weeks. This finding suggests that the in vivo oxidation injury associated with cigarette smoking almost completely disappears within a few weeks of smoking cessation (Morrow et al. 1995; Oguogho et al. 2000).

Smoking and Cardiovascular Function

In addition to the atherogenic effects of smoking, components of cigarette smoke may have adverse effects on the cardiovascular system with regard to oxygen supply and demand, thereby increasing the risk of ischemia. These effects may ultimately precipitate clinical events in persons with compromised coronary circulation that stems from underlying atherosclerosis.

Smoking and Increased Oxygen Demand

Cigarette smoking induces the release of catecholamines (epinephrine and norepinephrine) (Cryer et al. 1976; Hung et al. 1995), which are associated with an increased baseline heart rate and contractility and an increase in vascular tone (Benowitz 1988). In smokers, however, cigarette smoking is associated with a lower than expected heart rate in response to physical exercise (Srivastava et al. 2000), a characteristic that has been associated with increased risks of mortality, arrhythmias, and MI (Lauer et al. 1999).

Even though there is no evidence that smoking is associated with chronic hypertension, there is compelling evidence that smoking acutely increases peripheral vascular resistance and increases blood pressure (Cryer et al. 1976; Koch et al. 1980). These effects seem to be attributable to the pharmacologic properties of nicotine (Benowitz and Gourlay 1997). In carefully controlled experiments in healthy humans, cigarette smoking increased blood pressure and the sympathetic nervous system stimulation to both the blood vessels and the heart (Narkiewicz et al. 1998). Acute and episodic increases in blood pressure, coupled with an increased heart rate, increase the oxygen demands of the myocardium. However, in population studies, cigarette smokers tend to have on average lower blood pressures than do nonsmokers (USDHEW 1979; Friedman et al. 1982).

Smoking, Decreased Oxygen Supply, and Increased Blood Rheology

Studies have long indicated that smoking is associated with a decrease in coronary blood flow (Martin et al. 1984). More recent studies using intracoronary Doppler measurements have demonstrated that smoking causes an immediate constriction of both proximal and distal coronary arteries as well as an increase in coronary vessel tone and hence resistance (Quillen et al. 1993). These effects seem to be mediated by increases in catecholamine levels associated with smoking, suggested by the finding that pharmacologically blocking alpha-adrenergic receptors can reverse the smoking-induced decrease in coronary blood flow in CHD patients (Winniford et al. 1986; Quillen et al. 1993). The decreased vasodilatory response to certain stimuli resulting from the endothelial dysfunction associated with smoking also can limit blood perfusion to the myocardial tissue in certain situations.

The effects of smoking in compromising the oxygen supply to tissues, particularly to the myocardium, are not limited to vasomotor effects but also can be due to smoking-related changes in key physiologic blood components. Carbon monoxide in cigarette smoke diffuses from the pulmonary alveoli to the bloodstream, binds to hemoglobin in the erythrocyte, and forms carboxyhemoglobin, which has a

diminished oxygen-carrying capacity. Compensatory erythrocytosis may result (Rampling 1993). Both hematocrit and hemoconcentration increase with the number of cigarettes smoked. These increases, combined with the hyperfibrinogenemia associated with smoking (see the section on "Smoking and Thrombosis / Fibrinolysis" earlier in this chapter), contribute to the increased blood viscosity associated with smoking, which increases the risk of thrombosis and physically compromises microcirculation (Rampling 1993).

The low-grade inflammatory response associated with smoking not only results in increased plasma fibrinogen levels, but also seems to be responsible for the consistently demonstrated dose-response association between smoking and leukocyte counts (see the section on "Smoking and Inflammation" earlier in this chapter). The level of C-reactive protein, a marker for chronic inflammation and a strong predictor of clinical CHD events (Ridker and Haughie 1998), was associated with pack-years of smoking among persons more than 65 years old in the Cardiovascular Health Study (CHS) cohort (Tracy et al. 1997). This association was present even among persons who had stopped smoking for 30 years or more, suggesting that some of the deleterious effects of smoking on inflammation may persist. These data are consistent with the hypothesis that smoking causes a chronic, increased inflammatory response, especially in the absence of other mitigating factors (Tracy et al. 1997).

The net result of all of these mechanisms (reduced oxygen-carrying capacity of hemoglobin and compromised microcirculation from increased blood viscosity and leukocytosis) is a reduction in the oxygen-delivery capacity of blood both to the heart and to the peripheral tissues. When oxygen demand is increased, the resulting tissue hypoxemia may create a critical imbalance of oxygen need with supply in a person with underlying coronary or peripheral atherosclerosis. Smoking is associated with significant myocardial perfusion abnormalities (Deanfield et al. 1986), thus explaining the increased risk for MI events, unstable angina, and sudden deaths observed in smokers with CHD (Quillen et al. 1993).

Despite abundant laboratory and epidemiologic data linking smoking and a variety of pathophysiologic mechanisms in arterial wall and blood interactions, specific components of smoking responsible for each of these effects are not entirely clear (Pittilo 1990). Both nicotine and carbon monoxide may be involved in inducing endothelial dysfunction and atherosclerosis, although the evidence (animal experiments and laboratory studies of tissue cultures) is not consistent in singling out a specific component as uniquely responsible (Pittilo 1990). Some studies show that nicotine administration to animals results in endothelial abnormalities—increases in the number of endothelial cell carcasses in the blood and decreases in the synthesis of prostacyclin (an inhibitor of platelet aggregation) by endothelial cells (Pittilo 1990). In addition, nicotine seems to be responsible for the platelet activation induced by smoking (Lassila et al. 1988). However, a recent study compared a number of hematologic and coagulation indices in smokers before quitting, after quitting but using nicotine gum or patches, and subsequently when no longer using any nicotine products (Blann et al. 1997). There were significant declines in most outcomes measured after smoking cessation but few changes after stopping the nicotine gum and / or patches. A similar pattern was found in a study of atherogenic and thrombogenic factors in persons attending a smoking cessation program who received either a nicotine nasal spray or a placebo (Ludviksdottir et al. 1999).

Epidemiologic studies have addressed the potential role of nicotine by investigating the risks of heart disease from different forms of tobacco use. Cigar smoking has been associated with an elevated risk for heart disease, but cigar smokers have high intakes of both nicotine and carbon monoxide (Goldman 1977; Pechacek et al. 1985; Iribarren et al. 1999). Of greater interest is the risk for heart disease associated with the use of smokeless oral tobacco, which delivers nicotine rapidly into the bloodstream (Fant et al. 1999). Because of prolonged absorption of nicotine through the buccal mucosa, smokeless tobacco delivers a larger overall exposure to nicotine than cigarette smoking does (Gritz et al. 1981). Smokeless tobacco users are reportedly at an increased risk for high blood pressure (Bolinder et al. 1992) but not for elevated levels of fibrinogen (Eliasson et al. 1995).

One study of Swedish men followed approximately 6,000 smokeless tobacco users for 12 years and compared their cause-specific mortality with that of tobacco smokers and nonsmokers. Although the RR for all CVD was lower than that for tobacco smokers (1.8 [95 percent confidence interval (CI), 1.6–2.0] for smokers of <15 cigarettes per day and 1.9 [95 percent CI, 1.7–2.2] for smokers of ≥15 cigarettes per day), smokeless tobacco users had a statistically increased RR for all CVD of 1.4 (95 percent CI, 1.2–1.6) compared with those who used no tobacco products (Bolinder et al. 1994). The RRs were high for those aged 35 through 54 years at entry into the study. Adjusting for age, body mass index (BMI), blood pressure, diabetes, and a history of heart symptoms or blood pressure medication at the time of entry did not alter the results. In

contrast, two case-control studies from Sweden have not found that smokeless tobacco is a risk factor for MI (Huhtasaari et al. 1992, 1999). However, in one of these studies (Huhtasaari et al. 1999), restricting the analysis to fatal cases of MI (including sudden death) showed a tendency toward an increased risk for snuff dippers.

Carbon monoxide also compromises the oxygen-carrying and oxygen-delivering capacity of the blood, thus promoting the complications of atherosclerosis. Free radicals present in cigarette smoke may also be involved in atherogenesis by promoting oxidative changes in LDL (Church and Pryor 1985). Oxidized LDL is more readily taken up by macrophages to form foam cells in the atherosclerotic plaque and can be directly involved in promoting endothelial and vasomotor dysfunction (Kaufmann et al. 2000). Furthermore, toxic and reactive glycation products found in aqueous extracts of tobacco can modify certain lipoproteins (Apo B), prevent the normal tissue uptake of LDL, and increase levels of circulating LDL (Zieske et al. 1999). These effects explain the epidemiologic findings of higher concentrations of total, LDL, and VLDL cholesterol in smokers than in nonsmokers (Craig et al. 1989).

Summary

A substantial body of laboratory and experimental evidence now demonstrates that cigarette smoking in general and some specific components of cigarette smoke affect a number of basic pathophysiologic processes at the critical interface between circulating blood components and the inner arterial wall. Smoking leads to endothelial injury and cell dysfunction. The effects of cigarette smoking on circulation produce a substantial shift in the hemostatic balance at the endothelium, leading to atherosclerosis and its thrombotic complications. Furthermore, components of cigarette smoke diminish the ability of the blood to carry oxygen and increase the physiologic demands of the myocardium. The overall result of this constellation of toxic effects is to profoundly and adversely affect the homeostatic balance in the cardiovascular system, thus explaining the well-documented relationship between smoking and both subclinical and clinical manifestations of atherosclerosis that are reviewed in the next sections.

Smoking and Subclinical Atherosclerosis

Epidemiologic Evidence

Atherosclerosis is the most common cause of obstruction within the blood vessels supplying the lower extremities. When the obstruction reduces the blood flow sufficiently, a variety of symptoms may occur. The symptoms usually originate in areas distal to the obstruction, but flow from the collateral vessels can alter the pattern. The most common symptom is intermittent claudication, which can cause persons to feel pain in their legs when exercising, but the pain typically resolves within several minutes after the exercise has stopped. The pain is usually localized to the calf, because the most commonly affected vessels are the superficial femoral and popliteal arteries. Epidemiologic studies indicate that about 5 percent of men and 2.5 percent of women over 60 years of age experience intermittent claudication (Jelnes et al. 1986). Noninvasive studies of the peripheral arteries find a prevalence of peripheral arterial disease at least three times higher than the self-reported prevalence of intermittent claudication. One poor outcome of peripheral arterial disease is leg amputation. In 1995, the above- and below-knee amputation rate for legs was 25 per 100,000 adult Americans (Feinglass et al. 1999).

Studies investigating clinical cardiovascular events among adults middle-aged or older are limited in that they only address the factors related to the late phases of the natural history of atherosclerosis. It is widely recognized that this disease has a long natural history, with early pathologic changes (fatty streaks) developing in the teens or early twenties in many persons (Strong and McGill 1969; Strong et al. 1999). Thus, research addressing only associations between risk factors and clinical events that are late outcomes may overlook or underestimate the effects of risk factors in the early stages of atherogenesis and may miss possible opportunities for prevention. Moreover, inferences from studies of clinical events can be limited because of changes in behavior resulting from

symptoms, which in turn could distort the temporal relationship (reverse causality) between suspected risk factors and outcomes. The distortion of this temporal relationship can be particularly problematic in cross-sectional data, as symptoms or disease diagnosis may influence smokers to quit or to reduce the number of cigarettes smoked. Such changes in smoking are documented in a study that compared cross-sectional and longitudinal associations between cigarette smoking and other risk factors with both clinical and subclinical CVD (Nieto et al. 1999).

Studying subclinical markers for atherosclerosis offers an informative complement to disease outcomes for examining the association between risk factors and earlier phases of atherosclerosis (Table 3.2). Subclinical outcomes are less susceptible to temporal biases, and their use makes it possible to study the pathogenesis of the disease at an earlier stage. When researchers study healthy persons in an epidemiologic setting, measures of subclinical disease need to be noninvasive, imposing no risk and minimizing the burden on study participants (Sharrett 1993).

Table 3.3 describes results of studies reported since 1990 that examined the association between cigarette smoking and the presence of atherosclerosis, using carotid intimal-medial thickness (IMT) as the marker for subclinical disease because of its strong association with incident CHD (Chambless et al. 1997) and with stroke events (Chambless et al. 2000). Conducted with adult populations from different countries, these studies showed a remarkably consistent positive association between smoking and carotid IMT. Furthermore, studies that examined trends of IMT with the amount smoked found evidence of a dose-response relationship. Smoking also was associated with changes in carotid IMT in three prospective cohort studies (Salonen and Salonen 1990; Belcaro et al. 1995; Howard et al. 1998a). In a study of participants in the Atherosclerosis Risk in Communities (ARIC) Study who were free of CVD at baseline, cigarette smoking was a strong risk factor for both the presence of greater baseline carotid IMT and the incidence of CHD events during the three-year follow-up period (Sharrett et al. 1999). Results from pooled analyses using ARIC Study and CHS data indicated that smoking seemed to be strongly related to carotid atherosclerosis, regardless of age. These data show a stronger association in older than in middle-aged white adults in the studies (Howard et al. 1997).

The association between clinical manifestations of peripheral arterial disease and smoking is well established (USDHEW 1979; USDHHS 1990; Krupski 1991). Furthermore, recent studies have added new insights into the critical role of smoking in the natural history, severity, and progression of peripheral arterial disease. In a six-year follow-up study of patients with intermittent claudication, current smokers had a higher incidence of severe ischemic leg symptoms ranging from rest pain to gangrene (Smith et al. 1998). More subtle changes also have been documented in prospective studies. Among 415 peripheral arterial disease patients with intermittent claudication (aged 42 through 88 years), smoking was strongly related to a six-minute walk performance (Cahan et al. 1999). Patients with intermittent claudication who were current smokers (but had been asked to refrain from smoking on the day of the experiment) had significantly decreased time to claudication and more severe pain than patients who had quit smoking an average of seven years earlier (Gardner 1996). In this study the effect of smoking remained significant even after controlling for baseline ankle-arm index (AAI), also known as ankle-branchial index, an index of the degree of underlying peripheral arterial disease (Janzon et al. 1981). Experimental data also demonstrate acute effects of smoking on the peripheral circulation among persons with peripheral arterial disease. In a cross-over study of chronic smokers with peripheral arterial disease,

Table 3.2 Markers of subclinical atherosclerosis used in epidemiologic studies

Disease	Marker	Study technique
Generalized atherosclerosis	Ankle-arm index	Blood pressure measured with Doppler
	Carotid intimal-medial thickness	B-mode ultrasound
Coronary atherosclerosis	Coronary calcium	Computerized tomography
Cerebrovascular disease	Lacunar infarcts	Magnetic resonance imaging

smoking two cigarettes significantly decreased the AAI compared with the AAI on comparison days when the participants refrained from smoking (Yataco and Gardner 1999). These recent experiments, including findings from studies using an objective measure of the underlying peripheral arterial disease (the AAI), call into question earlier claims that smoking did not have an effect on exercise performance in this population (Waller et al. 1989).

Table 3.4 summarizes results from studies on smoking and the AAI. The AAI is the systolic blood pressure of the ankle divided by the systolic blood pressure of the arm, and was proposed as an index of subclinical peripheral arterial disease in the early 1980s (Janzon et al. 1981), with lower values indicating disease. It is a consistently strong predictor not only of peripheral arterial disease outcomes but also of coronary and cerebrovascular disease events among adults middle-aged (Zheng et al. 1997) and older (Criqui et al. 1992; Newman et al. 1999). Most of the results in Table 3.4 also show a consistent association between cigarette smoking and the AAI in diverse study populations and in both older and younger adults. These results are also consistent with the association between smoking and clinical peripheral arterial disease (USDHHS 1989, 1990).

The presence of subclinical CVD can be assessed by the presence of cerebral white matter disease or lacunar infarcts in magnetic resonance imaging (MRI) of the brain in asymptomatic persons. Results from studies reporting on the association between smoking status and MRI findings are not consistent for either abnormality, as shown in Table 3.5. Whereas some studies showed an increased prevalence of white matter disease and brain infarcts in smokers compared with nonsmokers (Longstreth et al. 1996, 1998; Liao et al. 1997; Howard et al. 1998b), other studies did not show statistically significant differences (Breteler et al. 1994; Yamashita et al. 1996; Shintani et al. 1998). The studies with the largest samples did find positive trends, but only a few reached conventional levels of statistical significance.

All of the studies of white matter disease are cross-sectional, however, and thus subject to methodologic limitations (e.g., prevalence-incidence bias). For example, even if smoking is truly associated with an increased risk (incidence) of the underlying disease (e.g., subclinical atherosclerosis) and if smoking also affects disease prognosis, the prevalence ratio obtained in a cross-sectional study will be a biased estimate of the RR. If smoking increases the risk of clinical events and mortality in those with atherosclerosis (e.g., by promoting thrombosis [see the section on "Smoking and Thrombosis / Fibrinolysis" earlier in this chapter]), survival of smokers with atherosclerosis will be shorter than that of nonsmokers, and thus the prevalence ratio will underestimate the RR. Because this limitation may have different effects in different settings and populations, it is a possible explanation for some of the inconsistent results across different studies.

A combined index of subclinical atherosclerosis in participants aged 65 years or older in the CHS was constructed using the electrocardiogram, echocardiogram, carotid IMT, AAI, and responses to a questionnaire that asked about symptoms of angina and intermittent claudication (Kuller et al. 1994). Current smokers in this study, excluding persons with a clinical disease, were more than twice as likely to have evidence of a subclinical disease in multivariate analyses that adjusted for other major risk factors. The age-adjusted proportions of current smokers without evidence of CVD were 8 percent in men and 6 percent in women; 16 percent and 14 percent, respectively, had evidence of subclinical disease; and 13 percent and 9 percent, respectively, manifested a clinical disease (these numbers reflect the fact that persons with a clinical disease tend to quit smoking). In the CHS, after excluding those with evidence of clinical CVD, the adjusted odds ratios (ORs) for a subclinical disease comparing smokers with nonsmokers were 2.0 (95 percent CI, 1.5–2.7) in women and 2.4 (95 percent CI, 1.6–3.6) in men (Kuller et al. 1994).

All of the evidence discussed so far in this section pertains to studies of smoking and subclinical atherosclerosis in vascular beds other than coronary arteries. Until recently, direct assessment of subclinical coronary atherosclerosis in epidemiologic studies was not feasible because there were no noninvasive measurements suitable for studies in asymptomatic persons. And although studies using coronary angiography have documented an association between smoking and the presence and degree of coronary artery narrowing (Pearson 1984; Chen et al. 1995), inferences from these studies are limited because of the possibility of selection biases stemming from characteristics of the study participants; even the comparison group (those without angiographic evidence of disease) had some clinical indications on the diagnostic angiography (Pearson 1984).

Evidence from pathology studies on a series of autopsies of adults regardless of the cause of death demonstrated clear and strong associations between smoking histories and the presence of aortic and coronary atherosclerosis (Strong and Richards 1976). These early findings have been strengthened by additional pathology studies of young trauma victims

Table 3.3 Studies on the association between smoking and atherosclerosis using the carotid B-mode ultrasound findings

Study	Design/population	Age/gender
Salonen and Salonen 1990	Community-based Cohort Finland n = 100	42–60 years Men
Bonithon-Kopp et al. 1991	Community-based Cross-sectional France n = 517	45–54 years Women
Heiss et al. 1991	ARIC[†] Study Community-based Case-control United States n = 386 case-control pairs	45–54 years Both genders
Salonen and Salonen 1991	Population-based Cohort Finland n = 1,224	42, 48, 54, or 60 years Men
Bots et al. 1992	Rotterdam Elderly Study Community-based Cross-sectional Netherlands n = 954	≥55 years Both genders
O'Leary et al. 1992	Cardiovascular Health Study Community-based Cross-sectional United States n = 5,201	≥65 years Both genders
Fine-Edelstein et al. 1994	Framingham Heart Study Community-based Cross-sectional United States n = 1,116	66–93 years Both genders

*IMT = Intimal-medial thickness.
[†]ARIC = Atherosclerosis Risk in Communities.
[‡]OR = Odds ratio.
[§]CI = Confidence interval.
[Δ]Cigarette-years = The number of years of smoking multiplied by the number of cigarettes smoked per day.
[¶]Maximum common carotid artery wall thickness.
**Maximum internal carotid artery wall thickness.

Main results	Comments
Progression of IMT* over 2 years: Smokers 0.21 mm increase Nonsmokers 0.09 mm increase	Differences remained significant after adjusting for age, lipids, leukocyte count, and platelet aggregability
Percentage with carotid thickening / Percentage with plaque Smokers 35 / 10 Nonsmokers 28 / 8	The association was significant after adjusting for age, blood pressure, and lipids
Multivariate-adjusted OR‡ of carotid atherosclerosis (high IMT) (95% CI§) Ever vs. never smokers 3.1 (2.1–4.6) Current vs. never smokers 3.9 (2.9–5.9)	Cases and controls were matched for age, gender, race, and center, with additional adjustments for all other major risk factors
Cigarette-years△ were strongly associated with the maximal IMT ($\beta = 0.125$, $p < 0.0001$)	Adjusted for age, ambulatory blood pressure, serum low-density lipoprotein cholesterol, history of ischemic heart disease, pre-exercise systolic blood pressure, and diabetes
Percentage of internal carotid artery stenosis / Percentage of current smokers 0 / 23 1–15 / 26 ≥16 / 32	The increasing percentage of current smoking with higher levels of stenosis remained statistically significant after adjusting for main risk factors
Smoking status Carotid IMT (mm) Never Former Current Maximum common¶ 0.98 1.03 1.03 Maximum internal** 1.39 1.59 1.71 Maximum stenosis (%) 16 20 24	All differences were statistically significant even after adjusting for all main risk factors
Multivariate-adjusted OR for carotid stenosis comparing current with never smokers Men 2.81 ($p = 0.002$) Women 3.07 ($p = 0.0001$)	There was a statistically significant linear dose-response relationship with the amount smoked

Table 3.3 Continued

Study	Design/population	Age/gender
Howard et al. 1994	ARIC† Study Community-based Cross-sectional United States n = 12,953	45–64 years Both genders
Salonen et al. 1994	Cohort (from Seven Countries Study) Finland n = 182	70–89 years Men
Belcaro et al. 1995	Community-based sample Cohort Italy n = 472	40–60 years Both genders
Diez-Roux et al. 1995	ARIC Study (Washington County) Community-based Historical cohort United States n = 2,073	45–64 years Both genders
Bonithon-Kopp et al. 1996	European Vascular Aging Study Community-based Cross-sectional France n = 1,384	59–71 years Both genders
Wei et al. 1996	Community-based Cohort San Antonio, Texas (United States), and Mexico City, Mexico n = 867	35–64 years Both genders
Howard et al. 1998a	ARIC Study Community-based Cohort United States n = 10,914	45–64 years Both genders

*IMT = Intimal-medial thickness.
†ARIC = Atherosclerosis Risk in Communities.
††ETS = Environmental tobacco smoke.
‡‡Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Main results	Comments
Mean IMT* (mm) Never smokers No ETS†† exposure 0.693 With ETS exposure 0.705 Former smokers 0.756 Current smokers 0.761	Among former and current smokers, more pack-years‡‡ of exposure were associated with an increased IMT
In 1989 relative risk for current smoking = 2.46 (95% CI, 0.94–6.45) with nonmineralized atheroma and 1.21 (95% CI, 0.22–6.58) with any mineralization; former smoking = 1.99 (95% CI, 0.99–4.00) with nonmineralized atheroma and 1.15 (95% CI, 0.37–3.62) with any mineralization	Adjusted for age (continuous), cholesterol (mmol/L), and pulse pressure (mm Hg)
The progression of carotid atherosclerosis (change in IMT) was slightly higher in smokers than in nonsmokers, but differences were not statistically significant	Only controlled for age
Carotid IMT was associated with both current smoking and smoking status 15 years before the ultrasound measurement	ETS exposure, either concurrent with or 15 years before the ultrasound measurement, was also associated with carotid IMT
Current smokers (%) Common carotid IMT tertile — No plaque — Plaque Lower (<0.58 mm) 6.4 12.5 Medium (0.58–0.68 mm) 8.7 15.0 Higher (>0.68 mm) 11.1 11.4	Differences were statistically significant
Among current smokers, β = 0.0028 mm (p = 0.84) for IMT for common carotid arteries, and β = 0.0508 mm (p = 0.02) for internal carotid arteries	Adjusted for age, gender, city, diabetes, total and high-density lipoprotein cholesterol, systolic blood pressure, and triglycerides
Adjusted IMT progression (μm/3 years) Never smokers No ETS exposure 25.9 With ETS exposure 31.6 Former smokers No ETS exposure 32.8 With ETS exposure 38.8 Current smokers 43.0	The association between smoking and IMT was strongest among persons with diabetes and persons with hypertension

Table 3.3 Continued

Study	Design/population	Age/gender
Davis et al. 1999	Community-based Cohort United States n = 182 men and 136 women	33–42 years Both genders
Espeland et al. 1999	Case-control Population-based United States n = 280 (141 cases with ≥50% stenosis of ≥1 vessel, 139 controls with no lumen irregularities)	≥45 years Both genders

*IMT = Intimal-medial thickness.

documenting an increased prevalence of advanced lesions and a decreased prevalence of intermediate lesions in young smokers compared with nonsmokers. Data from the Bogalusa Heart Study (Berenson et al. 1998) and from the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study (Strong et al. 1999) show that cigarette smoking by young people remains associated with atherosclerosis. Both studies involved careful assessments of the extent of atherosclerotic lesions found in young victims of trauma. Berenson and colleagues (1998) described the association between atherosclerosis and smoking among 93 participants in the Bogalusa Heart Study who had died and were autopsied. Antemortem risk factor information was available from study records; most died from trauma at a mean age of 21 years. Smoking was associated with fibrous plaques in the aorta and fatty streaks in the coronary vessels even at this young age.

The PDAY Study is a multicenter autopsy study of atherosclerosis in trauma victims aged 15 through 34 years. Even among the youngest persons in the study, atherosclerotic lesions were found in the aortas of nearly all persons and in the coronary arteries of the majority (Strong et al. 1999). The extent of atherosclerosis increased with age. Several analyses of the PDAY specimen data have shown that active smoking was associated with the extent of atherosclerosis (PDAY Research Group 1990; Zieske et al. 1999; McGill et al. 2001). McGill and colleagues (2001) reported on the findings in 629 men and 227 women, and they found that smoking was associated with atherosclerosis in the aortas but not in the coronary arteries. Zieske and colleagues (1999) carefully examined coronary arteries from 50 smokers and 50 nonsmokers in the study. They found that smokers were twice as likely to have advanced lesions as nonsmokers, suggesting that lesions progress more rapidly in smokers.

New imaging techniques are now being used to noninvasively assess markers of early coronary artery disease. With recent technological advances, it is now possible to conduct epidemiologic studies of the presence of coronary calcium as a surrogate for the presence of atherosclerosis in coronary arteries of healthy asymptomatic persons. The presence of calcium in plaques is an indicator of atherosclerosis. Using computed tomography (CT) techniques (i.e., helical CT or electron-beam CT [EBCT]), researchers can directly study subclinical atherosclerosis in coronary arteries. Studies measuring coronary calcium in epidemiologic settings (i.e., in population-based samples of asymptomatic persons) are in progress, but only a few studies with selected samples have been published. In two studies with samples that included adults selected because of the presence of cardiovascular risk factors but not necessarily a history of a clinical event (Goel et al. 1992; Wong et al. 1994), a history of smoking was significantly associated with the presence of coronary calcium in multivariate analyses.

In contrast to these results, studies of clinical populations (i.e., patients with acute coronary syndromes) show an inverse association between smoking and the presence of coronary calcium measured by EBCT (Schmermund et al. 1998). Furthermore, another study from an employee screening program of French men (Simon et al. 1995) found no association between current smoking and coronary calcium

Main results	Comments
Pack-years of smoking were significant risk factors for carotid IMT* in men ($\beta = 0.0018$, standard error = 0.0009 [$p < 0.05$])	Adjusted for age, systolic blood pressure, and low-density lipoprotein cholesterol
For all participants, smoking (μm / pack-years) was associated with a 2.25 mm ± 0.49 ($p < 0.0001$) IMT increase, and for cases only a 1.91 mm + 1.04 ($p < 0.0001$) increase for all sites measured	Adjusted for age, blood pressure, glucose, lipids, and body mass index; IMT sites included common segments, bifurcation segments, internal segments, near walls, and far walls

measured with ultrafast CT. In this same group the degree of extracoronary plaque found in carotid, aortic, and femoral arteries based on ultrasound measurements was strongly associated with smoking. The authors interpreted the contrast between the results for coronary calcium and extracoronary plaque in this study as a reflection of the fact that coronary calcification represents a more advanced lesion than uncalcified plaque, and may be influenced by the cumulative, long-term effects of smoking rather than by a current exposure to tobacco smoke (Simon et al. 1995).

Evidence Synthesis

Recently developed techniques can measure markers of subclinical atherosclerosis in healthy persons in community settings. These techniques have now been applied in a number of cohort and cross-sectional studies with repeated findings of a higher frequency of abnormalities in smokers. Consistently, both cross-sectional and cohort studies measuring carotid artery wall thickness or the AAI have demonstrated strong, dose-response associations between smoking and the presence and progression of subclinical atherosclerosis. Results from earlier autopsy studies and the PDAY and Bogalusa studies also suggest that smoking affects the progression of intermediate to advanced atherosclerotic lesions at early ages. Knowledge of the underlying mechanisms by which smoking causes atherosclerosis adds plausibility to these observations. Smoking has immediate adverse effects on the homeostatic balance of the cardiovascular system.

Studies using other markers, such as the presence of silent brain infarcts or white matter disease detected by an MRI or coronary calcium measured with CT, have been less consistent in their findings, possibly because of the limitations imposed by their cross-sectional nature. Longitudinal studies in progress will provide further data for examining the association between smoking and the development and progression of these subclinical markers.

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and subclinical atherosclerosis.

Implications

Cigarette smoking has a causal relationship with the full natural history of atherosclerosis from the time that it can be detected by sensitive, subclinical markers to its late and often fatal stages. The new findings on subclinical disease indicate the potential for preventing more advanced and clinically symptomatic disease through quitting smoking and maintained cessation.

Table 3.4 Studies on the association between smoking and clinical peripheral arterial disease using the ankle-arm index (AAI)

Study	Design/population	Age/gender
Newman et al. 1993	Cardiovascular Health Study Community-based Cross-sectional United States n = 5,201	≥65 years Both genders
Kornitzer et al. 1995	Occupational cohort Cross-sectional Belgium n = 2,023	40–55 years Men
Curb et al. 1996	Honolulu Heart Program Retrospective cohort United States n = 3,450	71–93 years Both genders
Hooi et al. 1998	Limburg Peripheral Arterial Occlusive Disease (PAOD) Study Community-based Cross-sectional Netherlands n = 3,650	40–78 years Both genders
Shinozaki et al. 1998	Occupational cohort Cross-sectional Japan n = 446	43 years (mean)[Δ] Men
Fabsitz et al. 1999	Strong Heart Study Community-based American Indians Cross-sectional United States n = 4,549	45–74 years Both genders

*OR = Odds ratio.
[†]CI = Confidence interval.
[‡]ABI = Ankle/brachial blood pressure index.
[§]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
[Δ]No age range was provided.

Main results	Comments
Adjusted OR* for the AAI <1.0 associated with smoking was 2.55	All differences were statistically significant even after adjusting for all main risk factors (history of diabetes, increasing age, nonwhite race)
AAI ≤0.90 was significantly associated with smoking	In multivariate analyses, the association with smoking was not significant (p = 0.09)
Adjusted OR (95% CI†) for the ABI‡ <0.9 measured in 1991–1993 was associated with current smoking: Cross-sectionally (smoking in 1991–1993): 4.32 (2.92–6.39) Longitudinally (smoking in 1965–1968): 2.82 (2.15–3.69)	Pack-years§ were also associated with AAI in a dose-response fashion
Among persons without intermittent claudication, ABI <0.95 was significantly associated with smoking status	Smoking was more strongly associated with symptomatic than with asymptomatic PAOD
Adjusted OR for AAI <1.0 associated with smoking was 1.74 (95% CI, 1.31–2.99)	None
A low AAI (<0.9) was significantly associated with current cigarette smoking and with pack-years	Associations persisted in multivariate analyses with age, systolic blood pressure, current cigarette smoking, pack-years of smoking, albuminuria (micro and macro), low-density lipoprotein cholesterol level, and fibrinogin level

Table 3.5 Studies on the association between smoking and the presence of subclinical cardiovascular disease using brain magnetic resonance imaging

Study	Design/population	Age/gender
Breteler et al. 1994	Rotterdam Elderly Study Community-based Cross-sectional Netherlands n = 111	65–84 years Both genders
Longstreth et al. 1996	CHS[†] Community-based Cross-sectional United States n = 3,301	≥65 years Both genders
Yamashita et al. 1996	Cross-sectional Japan n = 246	50–75 years Men
Liao et al. 1997	ARIC[§] Study Cross-sectional Community-based United States n = 1,920	51–70 years Both genders
Howard et al. 1998b	ARIC Study Community-based Cross-sectional United States n = 1,737	55–72 years Both genders
Longstreth et al. 1998	CHS Community-based Cross-sectional United States n = 3,660	≥65 years Both genders

*WML = White matter lesion.
[†]CHS = Cardiovascular Health Study.
[‡]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
[§]ARIC = Atherosclerosis risk in communities.
[Δ]HDL = High-density lipoprotein.
[¶]BMI = Body mass index.

Main results	Comments
No association was observed between the presence of WMLs* and current or former smoking after adjusting for age and gender	No substantial change in the results was found after further adjustments for a previous stroke and myocardial infarction
In analyses adjusted for age and gender, ever smoking cigarettes ($p < 0.001$) and more pack-years‡ of smoking ($p < 0.05$) were associated with WML grade	None
Cigarette smoking was not related to silent brain infarctions	No adjustments were mentioned
Age, race, and gender were adjusted proportionally by WML grade WML grade: Normal 0; Mild 1; Moderate 2; Severe 3–9 Smoking status Current smokers: 12.3; 45.0; 24.5; 18.2 Former smokers: 13.4; 52.5; 22.9; 11.3 Never smoked: 16.5; 49.8; 22.7; 10.9	Linear trend was statistically significant ($p = 0.004$)
Odds ratios (OR) for silent cerebral infarctions: Smoking status Nonsmokers: OR 1; OR when adjusted for other risk factors 1 Smokers exposed to environmental tobacco smoke: 1.03; 1.06 Former smokers: 1.32; 1.16 Current smokers: 2.13; 1.88	Cigarette smoking had a significant ordinal association ($p = 0.029$); other risk factors included demographics, cerebrovascular disease risk factors (HDL△, triglycerides, hypertension, and diabetes), and lifestyle factors (fat and alcohol intake, BMI¶, and physical activity)
In analyses adjusted for age and gender, pack-years were associated with silent lacunar infarcts ($p < 0.05$)	None

Table 3.5 Continued

Study	Design/population	Age/gender
Shintani et al. 1998	Hospital-based Cross-sectional Japan n = 270	40–87 years Both genders

Smoking, Coronary Heart Disease, and Sudden Death

Epidemiologic Evidence

Coronary Heart Disease

CHD results from atherosclerosis of the coronary arteries. Atherosclerosis is evident in persons as young as 20 years of age but becomes more severe with clinically evident manifestations in middle to older adulthood. The category of CHD includes MI, ischemic heart disease, and angina pectoris. MI results from an interruption of blood flow through the coronary arteries to the myocardium, with acute injury and then scarring and permanent damage to the heart muscles. Ninety percent of those who die from sudden cardiac death have at least two coronary arteries with about 90 percent occlusion. Angina pectoris refers to the chest pain a person experiences resulting from a lack of blood flow to the heart muscle.

The United States has experienced an epidemic of CHD for the past 50 years, and CHD remains the leading cause of death for Americans. In 2003, an estimated 1.1 million Americans had a new or recurrent coronary attack (AHA 2002). In spite of treatment advances, the prognosis after a coronary event is still poor, as 25 percent of men and 38 percent of women die within one year after a recognized MI. Due to primary and secondary prevention interventions and better quality of care for CHD, age-specific death rates from CHD have been substantially declining during the last four decades (Gillum 1994). However, compared with a decline of approximately 25 percent in rates between 1978 and 1997 in the United States, the actual number of deaths has only declined by approximately 9 percent over the same period because the American population is aging. Although 85 percent of those who die of CHD are 65 years or older, CHD also affects younger adults. In Americans younger than 65 years of age, approximately 80 percent of CHD mortality occurs during the first coronary event (AHA 2002).

Previous Surgeon General's reports have reviewed the evidence firmly establishing that smoking is a major cause of CHD (USDHHS 1990). Since these reports, there have been several additions to the large body of evidence previously considered. First, the new data support a causal association between smoking and MI across various racial and ethnic groups (USDHHS 1998). Second, smoking has been identified as a strong risk factor for MI in women younger than 50 years of age (Rosenberg et al. 1985; Croft and Hannaford 1989), even though the incidence of MI is very low in this population. A case-control study of women younger than 44 years of age (mean age 41 years) found that the OR for MI showed a strong dose-response relationship, with a risk of 2.47 (95 percent CI, 1.12–5.45) for those smoking 1 to 5 cigarettes per day and rising to 74.6 (95 percent CI, 33–169) for those smoking more than 40 cigarettes per day compared with nonsmokers (Dunn et al. 1999). The reported population attributable risk for tobacco use and MI in this group was 73 percent. Third, in data on female

Main results	Comments
There was no association between silent lacunar infarctions and smoking habits with or without adjusting for other main risk factors (serum levels or total cholesterol, HDL cholesterol, triglycerides, lipoprotein(a), hemoglobin A1c, age, gender, systolic blood pressure, diastolic blood pressure, duration of hypertension, family history, alcohol intake, obesity [BMI], and atrial fibrillation)	None

smokers from the study by Prescott and colleagues (1998), the highest risk (6.8) for MI was in women younger than 55 years of age. Fourth, prospective cohort results based on approximately 1,100 coronary disease events observed in a 14-year follow-up of about 86,000 women from the Nurses Health Study (Stampfer et al. 2000) showed strong dose-response relationships between the number of cigarettes smoked per day and the risk of CHD. The adjusted RRs of CHD for former smokers, for women smoking 1 to 14 cigarettes per day, and for those smoking 15 or more cigarettes per day were 1.55, 3.12, and 5.48, respectively, compared with lifetime nonsmokers. A further analysis of the Nurses Health Study suggests that the reduction in smoking observed in this cohort from 1980–1994 explains about 13 percent of the concurrent decline in CHD incidence (Hu et al. 2000). Finally, whereas most of the earlier evidence has come from studies in populations of predominantly European origin, recent studies have also demonstrated that the association between smoking and CHD is of a similar magnitude in other ethnic groups, such as African Americans (Liao et al. 1999; Rosenberg et al. 1999).

A recent meta-analysis summarized the cohort studies that measured the effect of smoking cessation on mortality after having an MI (Wilson et al. 2000). Thirteen studies meeting the analysis criteria were reviewed. The combined OR in former smokers compared with current smokers, based on a random effects model for death after MI, was 0.54 (95 percent CI, 0.46–0.62), with no significant heterogeneity among the studies. There was no difference in the OR for studies published before and after 1980. The results did not vary by gender, age, country in which the study took place, or the quality of the study.

The beneficial impact of smoking cessation on survival after acute MI is well established. Several recent studies show that cessation is beneficial at the time of and after percutaneous coronary artery vascularization for CHD. At the time of revascularization, substantial differences between risk factor profiles in smokers and nonsmokers have been observed. About one-third of those who receive percutaneous coronary artery vascularization are current smokers, and 50 to 60 percent continue to smoke after the procedure. Probably because of the thrombogenic properties of tobacco smoking, smokers are usually younger, have had angina for a shorter period of time, and have more favorable profiles for other traditional cardiac risk factors, such as hypertension and hypercholesterolemia, than their nonsmoking counterparts. This more favorable risk factor profile may explain the better outcomes for smokers found in several studies (Barbash et al. 1995).

For studies of outcomes after percutaneous coronary artery vascularization, careful consideration needs to be given as to which measure to use. Because cigarette smoking may increase the rate of restenosis, using repeat percutaneous coronary artery vascularization procedures or coronary artery bypass surgery as the outcome is problematic. However, many physicians are reluctant to recommend invasive procedures for patients who continue to smoke, even if their symptoms return (Underwood and Bailey 1993). One of the largest studies with a broad assessment of outcomes is based on 5,437 patients who had a successful percutaneous coronary artery revascularization and were followed for a mean of 4.5 years (Hasdai et al. 1997). Persistent smokers were at significantly greater risks for electrocardiographically confirmed infarctions

and death than were nonsmokers, and this trend was evident when compared with those who quit smoking after the vascularization. Persistent smokers were less likely to have a repeated percutaneous procedure or coronary bypass surgery than were nonsmokers, but this difference could be due to a reluctance by clinicians to recommend invasive procedures for those who are still at a higher risk for atherogenesis as a consequence of smoking (Hasdai et al. 1997).

Dose-response relationships between tobacco smoking and CVD have been readily established for the highest levels of cigarette smoking, but most studies have not had a sufficient sample size to assess the level of risk for those smoking only a few cigarettes per day. A recent report assessed 25-year mortality rates for the 12,763 men in the Seven Countries Study. Compared with nonsmokers, those smoking one to nine cigarettes per day had a hazard ratio of 1.2 (95 percent CI, 0.99–1.44) for CHD, 1.3 (95 percent CI, 0.51–3.28) for other arterial diseases (Jacobs et al. 1999), and 1.3 (95 percent CI, 1.17–1.43) for total deaths. All of these results were adjusted for baseline cohort of residence, age, BMI, serum cholesterol, systolic blood pressure, and the presence of clinical CVD.

During the past 40 years, there have been numerous changes in cigarette design and manufacturing, with sharp declines in tar and nicotine yields according to measurements based on the Federal Trade Commission protocol (National Cancer Institute [NCI] 1996). During this same interval, a number of case-control studies have assessed cigarette type or tar and nicotine yields and the risk for CVD including MI, CHD mortality, and stroke. The possibility that lower-yield products might be associated with lower risks for CHD draws plausibility from the postulated roles of both nicotine and carbon monoxide in increasing the risks for MI.

However, studies conducted since the 1960s have not consistently found lower risks for CHD in smokers of lower-yield cigarettes (Table 3.6). For acute MI, large case-control studies show that risk does not vary with measures of tar, nicotine, or carbon monoxide yields. Several cohort studies do show lower mortality rates from CHD among users of lower-yield products, but the effects are small. The American Cancer Society Cancer Prevention Study I (CPS-I) found that smokers of lower-tar cigarettes had slightly lower mortality rates from heart disease compared with smokers of high-tar cigarettes (Hammond et al. 1976). In contrast, neither a case-control study of men (Kaufman et al. 1983) nor that of women (Palmer et al. 1989) found any association between cigarette tar yields and the risk of nonfatal MI, and a case-control study from Italy conducted in the late 1980s also failed to identify a clear trend between cigarette tar yields and risks of acute MI (Negri et al. 1993).

Several more recent studies have found that low-tar cigarettes appear to slightly lower the risks of CHD associated with tobacco smoking (Tang et al. 1995). Four cohorts of British men (n = 56,255) first enrolled in 1967 and followed for an average of 13 years were assessed for all-cause and CHD mortality. An estimated 18 percent of the cohort who smoked manufactured cigarettes reported smoking primarily plain (unfiltered) cigarettes. The RR for CHD (0.76 [95 percent CI, 0.56–1.03]) was lower among filter-tipped cigarette smokers compared with smokers of plain cigarettes. Point estimates for mortality from each smoking-related disease were consistently lower for filter-tipped cigarette smokers than for plain cigarette smokers, but only the relative mortality for all smoking-related diseases was significantly different (RR = 0.83 [95 percent CI, 0.68–1.00]). Another major study investigating the impact of low-tar cigarettes on CHD was based on 13,926 cases and 32,389 controls in the United Kingdom sample of the International Studies of Infarct Survival clinical trial (Parish et al. 1995). Tar yield was classified based on self-reports of the brand of cigarettes usually smoked. For this cohort, almost all smoked filter-tipped cigarettes, and 25 percent used low-tar brands. Because a reduction in tar yields had already occurred by the time of the study, no participants were classified in the high-tar category. With standardization for age, gender, and the daily number of cigarettes smoked, the incidence of MI was 10.4 percent higher in medium-tar compared with low-tar cigarette smokers ($p = 0.06$). Among persons aged 30 through 59 years, the incidence was 16.6 percent higher ($p = 0.02$).

There has been a continued suggestion that the association of smoking with CVD risk and with CHD risk specifically could reflect an inadequate control of confounding by lifestyle-related risk factors. Countering this argument are the findings of many studies showing that carefully controlling for these other risk factors does not substantially change the strength of the smoking-CVD association. A recent analysis from the Cancer Prevention Study II (CPS-II) of more than 900,000 adults examined the changes in relative and attributable risks for CHD associated with smoking, comparing models that only adjusted for age with models that also adjusted for other risk factors (Thun et al. 2000). The risk estimates for CHD outcomes were unchanged with multivariate adjustments for potential confounders in both men and women and younger and older persons. The total number of annual CHD

deaths in the United States attributable to smoking changed from an estimated 91,500 in the age-adjusted only model to an estimated 94,200 in the multivariate model that controlled for aspirin use, alcohol consumption, BMI, physical activity, and dietary fat consumption. Thus, controlling for major risk factors had little consequence, and it is doubtful that there would be substantial residual confounding by other factors, whether known or still unknown. In fact, it seems unlikely that there are still unknown risk factors that have both sufficiently strong associations with cigarette smoking and sufficiently strong effects on CHD risk to be important confounders of the smoking-CHD association.

Sudden Death

Sudden death is the sudden, abrupt loss of heart function in a person who may or may not have a diagnosed heart disease, for whom the time and mode of death are unexpected, and for whom death occurs instantly or shortly after the onset of symptoms (AHA 2002). Sudden cardiac death is usually due to cardiac arrest from untreated cardiac arrhythmias, and it may have been the first manifestation of CHD.

Cigarette smoking might increase the risk of sudden cardiac death by increasing platelet adhesiveness, releasing catecholamines, causing acute thrombosis, and promoting ventricular ectopy (arrhythmias). The morphology of cardiac vessels is different in smokers than in nonsmokers who die suddenly from coronary disease. Smokers are more likely to have acute thrombosis than stable plaques at the time of death, but the frequency of plaque rupture and eroded plaque that cause thrombosis is the same in smokers and nonsmokers (Burke et al. 1997). Evidence also indicates that nicotine affects the conductance of myocardial cell channels, providing a plausible mechanism for the putative association of cigarette smoking (and smokeless tobacco use) with arrhythmias and sudden death (Wang et al. 2000).

Cigarette smoking has been associated with sudden cardiac death of all types. During 26 years of follow-up in the Framingham Heart Study, there were 177 sudden deaths in men and 50 in women. One-half of the deaths in men and 75 percent of those in women occurred without evidence of prior CHD. Smokers had a RR of 2.5 compared with nonsmokers ($p < 0.001$), and men had a higher RR for smoking than women (Kannel et al. 1975). In the Nurses Health Study, women who smoked more than 25 cigarettes per day died of CHD at a much higher rate than nonsmokers (RR = 5.4 [95 percent CI, 3.0–10.4]), but the risk was similar for nonfatal MI (RR = 5.8 [95 percent CI, 4.2–8.0]) (Willett et al. 1987). A case-control study of Tasmanian men found a threefold increase in the risk of sudden, unexpected cardiac death from current smoking (Sexton et al. 1997). In a study based on the National Mortality Followback Survey, current smoking was associated with an adjusted OR of 1.8 (95 percent CI, 1.2–2.7) for sudden death in those without a history of CHD (Escobedo and Caspersen 1997). Although many studies document the relationship between tobacco smoking and sudden cardiac death, the association does not seem to be stronger than the relationship between tobacco smoking and MI or CHD in general.

Nicotine has well-characterized effects on the cardiovascular system and increases heart rate through activiation of the sympathetic nervous system (USDHHS 1988). Smoking is associated with increased risk for sudden cardiac death in men and women (USDHHS 1983; Albert et al. 2003). This association might reflect underlying artherosclerosis caused by smoking and possibly an effect of nicotine itself.

Congestive Heart Failure

Smoking-caused CHD may contribute to CHF. In contrast to CHD and stroke, the incidence of CHF is increasing. An estimated 4.6 million Americans have CHF, and 43,000 persons die from CHF every year. In the third National Health and Nutrition Examination Survey (NHANES), the prevalence of CHF ranged from 6.2 percent for men between 55 and 64 years of age to 9.8 percent for men over 75 years of age. The corresponding figures are 3.4 percent and 9.7 percent, respectively, for women (AHA 2002).

Since tobacco smoking has been causally linked to MI and CHD, it is reasonable to consider the extent to which smoking may contribute to causing CHF. Within six years of a recognized MI, 22 percent of men and 46 percent of women will be disabled with heart failure (Ho et al. 1993). Survival after the onset of CHF is poor. According to Framingham Study data collected between 1948 and 1988, five-year survival rates are 25 percent for men and 38 percent for women with CHF (Ho et al. 1993). In the first NHANES Epidemiologic Follow-up Study, cigarette smoking was an independent risk factor (RR = 1.59 [95 percent CI, 1.39–1.83]) for the development of CHF over the 19-year follow-up (He et al. 2001). The estimated population attributable risk for tobacco smoking was 17.1 percent, higher than any other risk factor with the exception of pre-existing CHD. This estimate may be low because the contribution of tobacco smoking to pre-existing CHD was not included in this estimate. Since CHD is

Table 3.6 Studies on the association between smoking low-yield cigarettes and the risk of cardiovascular disease (CVD)

Study	Design/population	Variable analyzed
Hammond et al. 1976	Cohort study of 1 million volunteers in the American Cancer Society Cancer Prevention Study followed from 1960–1972	Tar content (high: 25.8–35.7 mg/cigarette, medium: 17.6–25.7 mg/cigarette, low: <17.6 mg/cigarette)
Hawthorne and Fry 1978	Prospective follow-up study of 18,786 persons attending a multiphasic screening examination from 1965–1977; Scotland	Filter-tipped vs. plain cigarettes
Todd et al. 1978	Prospective cohort study of 10,063 persons aged 35–69 years in a 12.4 year follow-up period from 1965–1977, from a random sample in Great Britain	Filter-tipped vs. plain cigarettes
Lee and Garfinkel 1981	Prospective mortality study of >1 million men and women in a 12-year follow-up period from 1960–1972; United States	Tar yield: low/high
Higenbottam et al. 1982	Cohort study of 17,475 male civil servants aged 40–64 years, and a sample of 8,089 male British residents aged 35–69 years	Current cigarette smoking habits
Borland et al. 1983	Prospective cohort of the Whitehall Study of 4,910 men who smoked cigarettes with known carbon monoxide (CO) yields, followed from 1976–1979; Great Britain	CO yields
Kaufman et al. 1983	Case-control study of 1,337 men aged 30–54 years; northeastern United States	Nicotine and CO yields

*CHD = Coronary heart disease.
†RR = Relative risk.
‡CI = Confidence interval.
§MI = Myocardial infarction.

Outcome	Results
CHD* mortality	Compared with high-tar smokers: CHD standardized mortality ratio = 1.03 for medium-tar smokers and 0.82 for low-tar smokers
CVD mortality	RR† of CVD mortality = 1.05 for smokers of filter-tipped cigarettes compared with smokers of plain cigarettes
CHD mortality	RR for men = 0.75 for smokers of filter-tipped cigarettes compared with smokers of plain cigarettes; and 1.03 for women who smoked filter-tipped cigarettes compared with women who smoked plain cigarettes
CHD mortality	RR for men = 0.90 for smokers of low-tar yield cigarettes compared with smokers of high-tar yield cigarettes; and 0.81 for women smokers of low-tar yield cigarettes compared with women smokers of high-tar yield cigarettes
CHD mortality	Ten-year CHD mortality rates per 100 deaths standardized for age; employment grade among inhalers = 4.29 for consuming 1–9 cigarettes / day, 5.98 for 10–19 cigarettes / day, 6.56 for ≥20 cigarettes / day; among noninhalers, 3.48 for 1–9 cigarettes / day, 5.73 for 10–19 cigarettes / day, and 5.18 for ≥20 cigarettes / day; coronary deaths were more common among inhalers; effects of tar / nicotine yields were confined to inhalers
CHD mortality	RR = 1.47 in those smoking cigarettes with <18 mg CO yield compared with smokers of cigarettes with ≥20 mg CO yield, adjusted for age, grade of employment, cigarettes / day, and tar yield; persons smoking high CO-yield cigarettes (>20 mg) smoked fewer cigarettes / day
MI§	RR = 2.8 (95% CI‡, 2.0–4.0) for current smokers compared with nonsmokers; risk varied with number of cigarettes smoked (up to 7.5 [95% CI, 3.7–15.3] for men aged 30–44 years who smoked ≥45 cigarettes / day); little or no significance was found comparing lower with higher nicotine yields: 3.0 (95% CI, 1.9–4.9) for <0.8 mg / cigarette to 2.6 (95% CI, 1.5–4.4) for ≥1.5 mg / cigarette; or in CO levels: 2.7 (95% CI, 1.5–4.8) for <10 mg / cigarette to 2.8 (95% CI, 1.5–5.1) for ≥19 mg / cigarette

Table 3.6 Continued

Study	Design/population	Variable analyzed
Alderson et al. 1985	Case-control study of 12,693 in-patients from 1977–1982; Great Britain	Always filter-tipped vs. plain cigarettes
Petitti and Friedman 1985	Prospective cohort study of 16,270 current regular cigarette smokers and 42,113 persons who never used any form of tobacco, from 1979–1983; United States	Low-yield cigarette use
Palmer et al. 1989	Case-control study of 910 women <65 years of age with incident MI, and 2,375 hospital controls; United States	Low-yield cigarette use
Kuller et al. 1991	Prospective cohort study of a 10-year follow-up of the Multiple Risk Factor Intervention Trial of men from 1972–1985; United States	Tar and nicotine levels
Negri et al. 1993	Multicenter case-control study, 916 patients with acute MI without a history of IHD[¶] and 1,106 controls admitted to the hospital for acute conditions unrelated to risk factors for IHD, between September 1988 and June 1989, from over 80 coronary care units in various regions of Italy	Cigarette tar and nicotine yields
Parish et al. 1995	Hospital-based, case-control study of 4,923 recently discharged MI cases and 6,880 controls, all current smokers of cigarettes with known tar yields, early 1990s, United Kingdom	Tar yields of manufactured cigarettes were assessed at the beginning of the study

[Δ]OR = Odds ratio.
[§]IHD = Ischemic heart disease.

Outcome	Results
CHD mortality	Aged 35–54 years: OR[Δ] = 1.78 for men who always smoked filter-tipped cigarettes compared with men who always smoked plain cigarettes; 0.24 for women who always smoked filter-tipped cigarettes compared with women who always smoked plain cigarettes; aged 55–74 years: OR = 2.67 for men who always smoked filter-tipped cigarettes compared with men who always smoked plain cigarettes; 1.32 for women who always smoked filter-tipped cigarettes compared with women who always smoked plain cigarettes; all ORs were adjusted for the number of cigarettes / day
CVD and MI[§]	RR = 1.15 (95% CI, 1.05–1.27) for CVD per 5.0 mg increase in tar among current cigarette smokers compared with nonsmokers, adjusted for age, gender, and race; RR = 1.22 (95% CI, 1.00–1.50) for acute MI per 5.0 mg increase in tar among current cigarette smokers compared with nonsmokers, adjusted for age, gender, and race; CVD risk was consistently higher in smokers of higher-yield cigarettes compared with smokers of lower-yield cigarettes (small differences in magnitude)
Nonfatal MI risk	RR = 4.7 (95% CI, 2.8–8.0) for current smokers who smoked brands with the lowest nicotine levels (<0.40 mg / cigarette) compared with lifetime nonsmokers; 4.2 (95% CI, 2.4–7.2) for smokers of higher-yield brands (>1.30 mg)
CHD mortality	Compared with men who smoked cigarettes with nicotine levels ≤1 mg, RR = 1.04 (95% CI, 0.8–1.35) for men who smoked cigarettes with 1.1–1.4 mg and 1.27 (95% CI, 0.92–1.77) for men who smoked cigarettes with ≥1.5 mg; compared with men who smoked cigarettes with tar levels ≤15 mg, RR = 1.08 (95% CI, 0.8–1.45) for men who smoked cigarettes with 16–19 mg and 1.19 (95% CI, 0.86–1.65) for men who smoked cigarettes with ≥20 mg; estimates were adjusted for age, serum cholesterol, diastolic blood pressure, and cigarettes / day; low-tar and low-nicotine cigarette smokers smoked more cigarettes / day
MI risk	Compared with nonsmokers, RR = 3.8, 4.3, 3.2, and 3.7 for the four categories of tar yield (<10, 10–15, 16–20, and >20 mg / cigarette, respectively); there was no trend in risk across yields when the analysis was restricted to smokers; RR = 1.2, 0.8, and 1.0 for higher-yield categories, respectively, compared with the lowest-yield category; RR = 9.3–12.6 for persons aged <50 years but no trend was observed with increasing yields; thus, lower-tar yields were not effective for reducing MI morbidity
Incident nonfatal MI	After standardization for age, gender, and amount smoked, the rate was 10.4% higher (standard deviation = 5.4) in medium-tar (≥10 mg / cigarette) than in low-tar (<10 mg / cigarette) cigarette smokers ($p = 0.06$)

Table 3.6 Continued

Study	Design/population	Variable analyzed
Tang et al. 1995	Four cohort studies of 56,255 men between 1967 and 1982 from the British United Provident Association Study (London), Whitehall Study (London), Paisley-Renfrew Study (Scotland), and United Kingdom Heart Disease Prevention Project	Tar yields of manufactured plain and filter-tipped cigarettes were assessed at the beginning of the study
Powell et al. 1997	Case-control study, 291 smokers with newly referred peripheral arterial disease, 828 controls without the disease, from outpatient clinics, 1988–1992, London, United Kingdom	Tar and nicotine yields and carboxyhemoglobin levels

the underlying cause for roughly 65 percent of CHF cases, the risk of CHF from smoking is probably mediated through CHD.

Evidence Synthesis

These new data reaffirm the already well-documented causal association of smoking with the risk for CHD. Compared with lifetime nonsmokers, the RR in smokers rises with the number of cigarettes smoked and falls after cessation. The type of cigarette smoked has little influence on CHD risk. The association cannot be explained by confounding.

Conclusions

1. The evidence is sufficient to infer a causal relationship between smoking and coronary heart disease.

2. The evidence suggests only a weak relationship between the type of cigarette smoked and coronary heart disease risk.

Implications

Because of its prevalence, smoking is a major cause of CHD, particularly among younger smokers. While CHD mortality rates have continued to fall, a substantial proportion of the population's burden of CHD could be avoided with smoking prevention and cessation. Products with lower yields of tar and nictotine, as measured by a smoking machine, have not been found to reduce CHD risk substantially and they are not a lower-risk alternative for smokers who cannot quit. By causing CHD and MI, smoking may also contribute to the development of CHF, an increasingly frequent disease that is disabling and has a poor prognosis.

Outcome	Results
Mortality from CHD and stroke	Compared with lifetime nonsmokers, RR for CHD = 1.21 (95% CI, 1.06–1.38) for former smokers, 2.05 (95% CI, 1.73–2.42) for current smokers of plain cigarettes, and 1.94 (95% CI, 1.70–2.21) for current smokers of filter-tipped cigarettes; RR for stroke = 1.0 (95% CI, 0.73–1.36) for former smokers, 1.98 (95% CI, 1.36–2.88) for current smokers of plain cigarettes, and 1.62 (95% CI, 1.19–2.21) for current smokers of filter-tipped cigarettes; risk of IHD and stroke showed an interaction with age; relative mortality in cigarette smokers of a 15 mg decrease in tar yield / cigarette was 0.77 (95% CI, 0.61–0.97) for CHD and 0.86 (95% CI, 0.50–1.50) for stroke
Peripheral arterial disease	OR = 1.75 for smokers of cigarettes with ≥14 mg tar compared with smokers of cigarettes with <9 mg; 1.54 for smokers of cigarettes with ≥1.2 mg nicotine compared with smokers of cigarettes with <0.8 mg; 1.62 for whole blood carboxyhemoglobin ≥4.5% among cases compared with whole blood carboxyhemoglobin <2.7% among controls; all ORs were adjusted for age, gender, and depth of inhalation

Smoking and Cerebrovascular Disease

Cerebrovascular disease is a syndrome of neurologic deficits resulting from interruptions in the arterial blood flow to the brain. Deficits range from mild to severe, depending on the zone of the brain that is affected, and can be transitory (transient ischemic attack) or permanent (stroke). In the United States, the incidence of stroke is an estimated 600,000 cases per year. The one-year, case-fatality rate is about 30 percent, and strokes caused an estimated 160,000 deaths in the United States in 1996 (the third leading cause of death after CHD and malignant neoplasms). According to estimates from the AHA (2002), there are approximately 4.6 million stroke survivors in the United States, with cases equally distributed between women and men.

The causes of strokes are either ischemic (brain infarction stemming from a reduction of blood flow because of local atherothrombosis or emboli from the heart or extracranial arteries) or hemorrhagic (either subarachnoid or parenchymal). Many of the pathophysiologic mechanisms discussed in preceding sections for atherosclerosis and CHD also apply to cerebrovascular disease, particularly for ischemic stroke.

The epidemiologic association between cigarette smoking and stroke is well established. The 1964 Surgeon General's report summarized studies conducted in the 1950s describing the increase in mortality from strokes in smokers compared with nonsmokers (USDHEW 1964). Subsequent Surgeon General's reports reviewed further evidence indicating that (1) smoking is clearly associated with an increase in both the incidence of and mortality from cerebrovascular disease; (2) smoking is associated with the risk of both ischemic stroke and subarachnoid hemorrhage; (3) the smoking-associated risk of stroke is particularly elevated in younger persons, and the smoking-associated risk of subarachnoid hemorrhage is elevated in women (USDHHS 1990); and (4) as with many other smoking-related diseases, later studies (e.g., CPS-II 1982–1986) tend to show a higher RR of stroke in relation to smoking than did earlier studies (e.g., CPS-I 1959–1965). These more recent findings may be explained by cohort effects related to smoking duration and earlier smoking initiation in birth cohorts who reached middle to older ages (Garfinkel and Stellman 1988).

A meta-analysis reviewed 32 case-control and cohort studies and documented that cigarette smoking increased the risk of stroke by an estimated 50 percent, although the effect differs according to stroke subtype: the RR for ischemic stroke was 1.9, and 2.9 for subarachnoid hemorrhage, but no elevation in risk was found for cerebral hemorrhage (Shinton and Beevers 1989).

Based on the wealth of epidemiologic, biologic, and laboratory evidence available at the time, the 1989 Surgeon General's report concluded that there was a causal association between smoking and cerebrovascular disease (USDHHS 1989). Using estimates of prevalence and RR from the large CPS-II study, the report estimated that among persons younger than 65 years of age, smoking was responsible for 51 percent of cerebrovascular disease deaths in men and 55 percent in women.

The 1990 Surgeon General's report on smoking cessation examined all previously published studies comparing the risk of stroke for lifetime nonsmokers with both current and former smokers (USDHHS 1990). The report confirmed previous conclusions of a twofold to fourfold increase in risk associated with current smoking and concluded that the risk decreases steadily after smoking cessation, becoming indistinguishable in former smokers from that of lifetime nonsmokers after 5 to 15 years, depending on the study.

Epidemiologic Evidence

Both case-control and cohort studies published since the 1990 Surgeon General's report have confirmed the epidemiologic association of cigarette smoking with the main subtypes of stroke (i.e., ischemic stroke and subarachnoid hemorrhage). One of the most important publications provides results from the British Doctors Study, reporting an association between smoking and stroke (among other disease outcomes) in more than 30,000 male British physicians followed for over 40 years, from 1951–1991 (Doll et al. 1994). These findings confirmed previous reports of a strong and consistent epidemiologic association between smoking and mortality from stroke subtypes. Compared with lifetime nonsmokers, current smokers at baseline had RRs of 1.31 for thrombotic stroke, 1.37 for hemorrhagic stroke, and 2.14 for subarachnoid hemorrhage. Dose-response relationships with an increasing number of cigarettes smoked per day were reported for both thrombotic and hemorrhagic subtypes, and were particularly strong for subarachnoid hemorrhage (RR = 1.43, 1.71, and 3.43 for smokers of 1–14, 15–24, and >24 cigarettes per day, respectively; p for trend <0.001).

Another report addressed the association between smoking and stroke mortality in the Multiple Risk Factor Intervention Trial (MRFIT) (Kuller et al. 1991). Among the more than 360,000 people initially screened, current smokers had a RR for overall stroke mortality of 2.5 (p <0.001) during a 10-year follow-up, with a clear dose-response relationship between an increased risk and an increase in the average number of cigarettes smoked per day.

In addition to the risk for stroke mortality, other studies have reported on the effects of smoking on stroke incidence. Data from a 10-year follow-up of more than 22,000 participants in the United States Physicians Study showed that, compared with lifetime nonsmokers, current smokers of 1 to 19 cigarettes per day had an age-adjusted RR for stroke incidence of 2.02 (95 percent CI, 1.23–3.31), and smokers of 20 or more cigarettes per day had an adjusted RR of 2.52 (95 percent CI, 1.75–3.61; p for trend <0.0001) (Robbins et al. 1994). Similar dose-response associations between the amount smoked and stroke incidence were reported in the British Regional Heart Study, a population-based cohort study of about 7,700 middle-aged men (Shaper et al. 1991). In subsequent analyses of this study (Wannamethee et al. 1995), stroke risks for former smokers fell to the lowest levels around five years after smoking cessation; the remaining risk levels depended on the amount smoked: former heavy smokers fell to a level similar to that of light smokers, and former light smokers fell to a level similar to that of lifetime nonsmokers. Switching to a pipe or cigar had little effect on risk. Benefits from smoking cessation were observed after controlling for all possible relevant confounders and were present in both normotensive and hypertensive persons, although the benefit seemed to be more marked in the latter group. This study also confirmed the conclusions of the 1990 Surgeon General's report on the benefits of smoking cessation on stroke risk (Wannamethee et al. 1995).

The above studies were all conducted on men of mostly European origin. However, there is a wealth of evidence demonstrating that smoking is also associated with strokes in women and in all ethnic groups and countries where the hypothesis has been tested. In contrast to some earlier studies that suggested that the RR for stroke (especially subarachnoid hemorrhage) was more elevated in female smokers than in male smokers, recent cohort studies of a variety of population samples tend to show similar RRs in both men and women. In a large cohort study of more than

42,000 participants in a health survey in Finland, RRs for the incidence of subarachnoid hemorrhage were 2.4 (95 percent CI, 1.6–3.7) in men and 2.5 (95 percent CI, 1.5–4.1) in women, independent of other known stroke risk factors (i.e., age, hypertension, and body weight) (Knekt et al. 1991). Another issue of particular concern to women is the possible synergism between oral contraceptives and smoking on the risks of stroke. Whereas earlier studies suggested that possibility (Kannel 1987), it was recently argued that low-dose oral contraceptive combinations may not interact with smoking to substantially increase these risks (Mishell 1999). However, a report based on a large cohort of reproductive-aged women in the Kaiser Permanente study (Petitti et al. 1996), where 408 strokes were observed among 1.1 million women (>3.6 million person-years of observation), found that the RRs for ischemic stroke and for hemorrhagic stroke among current smokers compared with nonsmokers were 2.66 (95 percent CI, 1.65–4.30) and 2.70 (95 percent CI, 1.71–4.27), respectively. The combination of smoking and low-dose oral contraceptives was associated with an overall stroke RR of 3.64 (95 percent CI, 0.95–13.87).

Even though few studies have published ethnic- or minority-specific data on the relationship between smoking and stroke risks, there is consistent evidence of an association in African Americans, a group with a particularly high risk for cerebrovascular disease (Gillum 1999). Furthermore, in ecologic analyses conducted with data from the World Health Organization's MONICA (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease) project, smoking and hypertension were the main factors explaining the variability of stroke mortality rates across populations (Stegmayr et al. 1997). Similar conclusions were reached in analyses based on persons from the multinational Seven Countries Study (Jacobs et al. 1999).

In a cohort study of a Korean population with low cholesterol levels, the risk for stroke was linearly associated with increasing amounts of cigarette smoking (Jee et al. 1999). Another large cohort study in an Asian population was conducted in a cohort of approximately 265,000 Japanese men and women (Hirayama 1990). The RRs for nonhemorrhagic strokes were only slightly elevated in current smokers compared with lifetime nonsmokers (1.08 in men and 1.18 in women), whereas for subarachnoid hemorrhage the corresponding RRs were 1.82 and 1.71.

The higher RRs for a subarachnoid hemorrhage compared with other stroke subtypes are consistent with the observations summarized in previous Surgeon General's reports as well as in most recent studies. Among those screened for the MRFIT, the smoking-related RR for a nonhemorrhagic stroke was 2.1, whereas the RR for a subarachnoid hemorrhage was 3.0 (Neaton et al. 1993). Teunissen and colleagues (1996) reviewed the data and consistently found smoking to be an independent risk factor for subarachnoid hemorrhage. The mechanisms for this increased risk are likely due to damage to the cerebral artery wall associated with one or more components of cigarette smoke (Weir et al. 1998). Cumulative damage to the arterial elastica layer can result in an aneurysmal dilatation, and the presence of this dilatation with the additional impact of smoking on vasoactivity, especially in the presence of hypertension, may create high risks for a hemorrhagic event.

Most of the recent studies described in this section adjusted for risk factors that could possibly confound the association between smoking and stroke. From the epidemiologic standpoint, only hypertension appears as consistently related to stroke risks as smoking does. However, controlling for blood pressure or hypertension status has very little effect on the observed strength of the smoking-stroke association seen in most studies. This finding would be expected, given the weak and inverse relationship of smoking with hypertension. In the analysis by Thun and colleagues (2000) of the CPS-II cohort, the estimate of stroke deaths for the United States based on the age-adjusted risk estimate was 21,400. With adjustment for several potential confounding factors there was a slight drop to about 17,800.

Evidence Synthesis

The more recent evidence remains fully consistent with a causal effect of smoking on risk for cerebrovascular disease. The recent evidence extends the range of populations in which an association with smoking has been demonstrated and shows consistent associations of smoking with all major types of stroke.

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and stroke.

Implication

Cigarette smoking remains a major cause of stroke in the United States.

Smoking and Abdominal Aortic Aneurysm

Aortic aneurysm refers to the dilatation or expansion of the aorta between the arch and the division into the iliac arteries, while AAA occurs in the abdominal portion of the aorta. The aorta has a high pressure across its wall and rupture can quickly lead to death. Most AAAs are the result of atherosclerosis, although other conditions can cause them (Davies 1998). Evidence of pathogenesis includes atherosclerosis, degradation of elastin in the aorta's wall, and inflammation (Blanchard 1999). In the young trauma victims in the PDAY study, smoking was associated with the extent of atherosclerosis in the abdominal aorta (McGill et al. 2001). In the smaller sample from the Bogalusa Heart Study, the findings were similar (Berenson et al. 1998). The natural progression of AAAs is to grow increasingly larger, and when they become greater than 4 cm in diameter there is a substantial risk for rupture. Most persons do not have any symptoms until the aneurysm ruptures; at that point, sudden death can occur. Surgical repair is much less successful once the aneurysm begins to leak. Estimates for 2003 were that AAAs caused more than 15,000 deaths and 60,000 hospitalizations in the United States (AHA 2002).

Epidemiologic Evidence

Evidence linking tobacco smoking and aortic atherosclerosis has been available for several decades (Table 3.7). In 1983, the Surgeon General's report suggested that cigarette smoking aggravates or accelerates aortic atherosclerosis (USDHHS 1983), and several epidemiologic studies indicated that smokers had elevated death rates from ruptured abdominal aneurysms compared with nonsmokers. A literature review published in 1999 found a positive, strong, and independent association between smoking and AAA in 10 studies of cohort, case-control, and cross-sectional designs (Blanchard 1999).

The findings of the long-term cohort studies provide clear evidence for an association of smoking with AAA. During the 40 years of follow-up of the British physicians cohort, the risk for death from AAA was increased more than fourfold in current smokers compared with lifetime nonsmokers and was increased twofold in former smokers (Doll et al. 1994). In the U.S. veterans cohort, there was a fivefold increase for current smokers and a more than doubling of mortality for this cause of death in former smokers (Rogot and Murray 1980). In CPS-I, the increased risk for current smokers was of a similar magnitude (Burns et al. 1997).

Recent studies not included in the 1999 review also confirm this association. For example, in a case-control study using state-of-the-art clinical and epidemiologic methods (Blanchard et al. 2000), smoking was strongly associated with AAA with adjustment for all known risk factors. A dose-response relationship was evident. Compared with lifetime nonsmokers, the adjusted OR was 2.75 (95 percent CI, 0.85–8.91) for 1 to 19 pack-years, 7.31 (95 percent CI, 2.44–21.9) for 20 to 34 pack-years, 7.35 (95 percent CI, 2.40–22.5) for 35 to 49 pack-years, and 9.55 (95 percent CI, 2.81–32.5) for 50 or more pack-years. Other recent case-control studies have also found dose-response relationships (Wilmink et al. 1999), as have earlier cohort studies.

As in other cohort studies published in recent years, the Edinburgh Artery Study, a population-based cohort study of men and women 55 through 74 years of age, found that current (or recent) smoking also was strongly associated with AAA (OR = 3.1 [95 percent CI, 1.5–6.2]) (Lee et al. 1997). This association can be partially explained by atherosclerosis (Reed et al. 1992), although cohort data from the Edinburgh Artery Study suggest an increased risk for aortic aneurysm associated with smoking beyond that from underlying atherosclerosis (Lee et al. 1997). Lee and colleagues (1997) found that smoking remained associated with a risk for incident aneurysm after adjusting for CVD and the AAI at baseline. In a cohort of Finnish males, risk for AAA was positively associated with the number of years of smoking (Törnwall et al. 2001) and with the number of cigarettes smoked in a 33-year cohort study in Sweden (Nilsson et al. 2001).

The CHS is a multicenter prospective cohort study of cardiovascular disease in older Americans (Alcorn et al. 1996). In the fifth year of follow-up, ultrasound was used to evaluate the abdominal aortas of all participants. The prevalence rates for aneurysm by smoking were 6.8 percent, 11.5 percent, and 14.4 percent for never, former, and current smokers, respectively.

Evidence Synthesis

Smoking causes atherosclerosis in arteries, including the abdominal aorta. Autopsy studies show that even young adults who smoke have more plaque in their aortas than do lifetime nonsmokers. Other mechanisms by which smoking might injure the abdominal aorta include inflammation and damage to elastin.

The epidemiologic evidence, coming from multiple studies of differing design and location, shows a strong association of smoking with risk for AAA. Dose-response relationships with the amount and duration of smoking have been reported and risks are lower in former than in current smokers. Uncontrolled confounding cannot explain the findings.

Conclusion

1. The evidence is sufficient to infer a causal relationship between smoking and abdominal aortic aneurysm.

Implication

Smoking is one of the few currently avoidable causes of this frequently fatal disease.

Summary

Research during the past decade has produced further evidence that tobacco smoking is causally related to all of the major clinical cardiovascular diseases. A large body of evidence coming from multiple populations, age groups, and both genders outlined in previous Surgeon General's reports indicates that tobacco smoking causes atherosclerosis and associated clinical syndromes. A dose-response relationship has been repeatedly demonstrated with higher levels of cigarette smoking and a longer duration of smoking. Evidence now suggests that light smokers (fewer than 10 cigarettes per day) have moderate but measurable increases in the risks for CVD, and passive smoking has been causally associated with CHD (California Environmental Protection Agency 1997; Scientific Committee on Tobacco and Health 1998). New evidence also documents that tobacco smoking is associated with subclinical or very early atherosclerosis. Multiple potential confounding factors have been considered, and none account for the association between tobacco smoking and CVD. Most large prospective studies of the association between smoking and cardiovascular outcomes conducted in recent years controlled for other known cardiovascular risk factors that could be proposed as possible confounders (e.g., diet, physical exercise, BMI, and other lifestyle habits).

The temporal relationship between tobacco smoking and CVD has never been in doubt due to the extensive data from carefully conducted prospective cohort studies. A large body of research documents the impact of tobacco smoke on a wide range of biologic processes related to atherosclerosis, establishing biologic plausibility. New evidence also documents that tobacco smoking is associated with subclinical atherosclerosis (i.e., with the presence of atherosclerosis) earlier in its natural history, before it manifests clinically. The cross-sectional and prospective evidence summarized in this chapter consistently demonstrates that tobacco smoking is related to the thickness of the intimal-medial layers of the carotid and popliteal arteries as well as to the presence of coronary atherosclerosis (by angiographic and pathology studies) and subclinical markers of cerebrovascular disease (white matter disease and subclinical infarcts). This conclusion is entirely consistent with the strong evidence linking tobacco smoking and clinical cardiovascular disease manifestations as reviewed in this and in previous Surgeon General's reports. Atherosclerosis is a complex disease process that progresses slowly across different vascular beds and involves multiple metabolic, inflammatory, and homeostatic pathways.

Table 3.7 Studies on the association between smoking and the risk of abdominal aortic aneurysm (AAA)

Study	Design/population	Tobacco exposure	Outcome
Kahn 1966	U.S. veterans cohort study 293,658 persons aged 31–84 years (mainly white male World War I [WWI] veterans) who held active U.S. government life insurance policies in December 1953 Questionnaires were administered in 1954 and 1957 with 198,834 and 49,361 responses, respectively 8.5 years of follow-up United States (nationwide)	• Cigarettes / day • Pipes and cigars only	Death from nonsyphilitic aneurysm of the aorta
Weir and Dunn 1970	Cohort study 68,153 men aged 35–64 years 482,658 person-years of observation California Began in 1954	• Nonsmokers / all smokers • Packs / day	Death from aortic aneurysm
Rogot and Murray 1980	U.S. veterans cohort study (update) 293,658 persons aged 31–84 years (mainly white male WWI veterans) who held active U.S. government life insurance policies in December 1953 Questionnaires were administered in 1954 and 1957 with 198,834 and 49,361 responses, respectively 16 years of follow-up United States (nationwide)	• Never smoked • Former cigarette smokers • Current cigarette smokers • Cigarettes / day • Cigars only • Pipes only	Death from aortic aneurysm
Strachan 1991	Whitehall Cohort Study of 18,403 male civil servants examined at the ages of 40–64 years 18-year follow-up England	• Nonsmokers • Manufactured cigarettes • Hand-rolled cigarettes • Pipes or cigars only	Death from aortic aneurysm

*CI = Confidence interval.
†RR = Relative risk.

Findings	Risk estimates (95% CI*)		Comments
• Significant mortality rate for current and former cigarette smokers (greater than expected) • Dose-response relationship was observed	Mortality ratios Total current smokers 10–20 cigarettes / day 21–30 cigarettes / day Current pipe and cigar smokers only Former cigarette smokers	 5.15 (significant) 5.58 (significant) 6.55 (significant) 1.76 2.75 (significant)	Never smokers were the comparison group; age distributions were standardized using the 1960 distribution of the U.S. male population by single years; p values and 95% CIs were not provided
• Increased risk was associated with cigarette smoking	RR[†] Nonsmokers All smokers About 1 / 2 pack or less About 1 pack About 1 1 / 2 or more packs	 1.0 (referent) 2.64 2.44 2.88 2.54	Nonsmokers included pipe and cigar smokers; p values and 95% CIs were not provided
• Dose-response relationship was observed with more cigarettes / day	Mortality ratios Former cigarette smokers All current cigarette smokers <10 cigarettes / day 10–20 cigarettes / day 21–39 cigarettes / day ≥40 cigarettes / day Cigars only Pipes only	 2.58 5.23 2.29 5.46 6.36 7.18 2.04 2.07	Never smokers were the comparison group; p values and 95% CIs were not provided
• 99 outcome events • All forms of tobacco use in this study were associated with increased mortality rates	Mortality ratios Manufactured cigarettes Hand-rolled cigarettes Pipes or cigars only	 5.3 (3.1–9.1) 20.1 (9.2–43.8) 5.4 (1.9–15.3)	Mortality ratios were calculated against nonsmokers at entry; mortality ratios were adjusted for diastolic blood pressure, and were adjusted by analysis of matched sets using conditional logistic regression

Table 3.7 Continued

Study	Design/population	Tobacco exposure	Outcome
Doll et al. 1994	Cohort study 34,439 British male doctors who replied to a postal questionnaire in 1951 United Kingdom 1951–1991	• Nonsmokers • Former smokers • Current smokers • Cigarettes / day	Death from aortic aneurysm
Alcorn et al. 1996	Cross-sectional study 656 persons aged 65–90 years from a Pittsburgh subgroup of the Cardiovascular Health Study Pittsburgh 1990–1992	• Never smoked • Former smokers • Current smokers	AAA was defined as an infrarenal aortic diameter ≥3 cm, an infrarenal to suprarenal diameter ratio ≥1.2, or a history of AAA repair
Powell et al. 1996	Screening cross-sectional study of patients with peripheral arterial disease 44 AAA patients 244 hospital controls matched for age and gender London 1989–1992	• Pack-years[‡] • Cigarettes / day	NR[§]

[‡]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
[§]NR = Data were not reported.
[Δ]OR = Odds ratio.

Findings	Risk estimates (95% CI)		Comments
• Significant association; p <0.001 for trend	Annual mortality per 100,000 men		Mortality rates were standardized for age and calendar period
	Nonsmokers	15	
	Former smokers	33	
	Current smokers	62	
	1–14 cigarettes / day	38	
	15–24 cigarettes / day	74	
	≥25 cigarettes / day	81	
• AAAs were more prevalent among smokers	Prevalence among those with AAA		p values were calculated using logistic regression and were adjusted for age, gender, height, and weight
	Never smoked	6.8%	
	Former smokers	11.5%	
	Current smokers	14.4%	
	p value for trend <0.0001		
• Pack-years p value for trend = 0.174 • Cigarettes / day p value for trend = 0.008 • No association was found between AAA risk and type of tobacco used	OR[Δ]		Matched analyses were carried out using conditional logistic regression
	<35 pack-years	1.0 (referent)	
	35–55 pack-years	2.07 (0.95–4.52)	
	>55 pack-years	1.84 (0.61–3.42)	
	0–10 cigarettes / day	1.0 (referent)	
	11–20 cigarettes / day	3.03 (1.29–7.22)	
	≥21 cigarettes / day	1.99 (0.97–3.73)	

Table 3.7 Continued

Study	Design/population	Tobacco exposure	Outcome
Burns et al. 1997	Cohort study Cancer Prevention Study I Approximately 68,000 American Cancer Society volunteers Questionnaires administered: 1959–1960, 1961, 1963, 1965, and 1972 United States (nationwide) 1959–1972	• Cigarettes / day stratified by age	Death from aortic aneurysm
Hrubec and McLaughlin 1997	U.S. veterans cohort study 293,658 persons aged 31–84 years (mainly white male WWI veterans) who held active U.S. government life insurance policies in December 1953 Questionnaires were administered in 1954 and 1957 with 198,834 and 49,361 responses, respectively 26-year follow-up (1954–1980) United States (nationwide)	• Former regular cigarette smokers	Death from aortic aneurysm

Findings	Risk estimates (95% CI)		Comments
• For men, there was a dose-response relationship in every age category	Mortality risk ratios		None
	Men		
	Aged 50–64 years		
	1–19 cigarettes / day	3.1	
	20 cigarettes / day	4.2	
	≥21 cigarettes / day	5.3	
	Aged 65–79 years		
	1–19 cigarettes / day	4.4	
	20 cigarettes / day	6.1	
	≥21 cigarettes / day	8.2	
	Aged ≥80 years		
	1–19 cigarettes / day	3.0	
	20 cigarettes / day	3.9	
	≥21 cigarettes / day	4.5	
	Women		
	Aged 35–49 years		
	1–19 cigarettes / day	6.2	
	20 cigarettes / day	6.1	
	≥21 cigarettes / day	NR	
	Aged 50–64 years		
	1–19 cigarettes / day	3.4	
	20 cigarettes / day	7.5	
	≥21 cigarettes / day	12.4	
	Aged 65–79 years		
	1–19 cigarettes / day	2.4	
	20 cigarettes / day	4.4	
	≥21 cigarettes / day	1.4	
	Aged ≥80 years		
	1–19 cigarettes / day	4.5	
	20 cigarettes / day	4.2	
	≥21 cigarettes / day	NR	
• Significant risk was associated with former regular smoking	RR		RR was calculated using Poisson regressions
	Never regular smokers	1.0 (referent)	
	Former regular smokers	2.6 (2.2–3.1)	

Table 3.7 Continued

Study	Design/population	Tobacco exposure	Outcome
Wilmink et al. 1999	Nested case-control study From a population-based screening program for AAA Men aged >50 years 210 cases (infrarenal aortic diameter >29 mm) 237 controls Huntington, United Kingdom	• Duration of smoking • Cigarettes / day	NR
Blanchard et al. 2000	Case-control study 98 incident diagnoses of AAA 102 hospital controls Winnipeg, Manitoba (Canada) 1992–1995	• Pack-years	NR
Nilsson et al. 2001	Cohort study Questionnaire replies from 16,458 men and 25,086 women aged 18–69 years, chosen from the 1960 census population Analysis was done in 1996 Sweden 1963	• Never smoked • Former smokers • Current smokers	Death from aortic aneurysm

Findings	Risk estimates (95% CI)		Comments
• When cigarettes / day ORs were adjusted for duration of smoking, associations became insignificant	Duration of smoking 0 years ≤20 years 21–40 years >40 years Cigarettes / day 0 cigarettes / day 1–5 cigarettes / day 6–10 cigarettes / day 11–15 cigarettes / day 16–20 cigarettes / day >20 cigarettes / day	OR 1.0 (referent) 1.4 (0.6–3.4) 3.6 (1.6–8.2) 5.8 (2.6–13.0) OR 1.0 (referent) 2.1 (0.7–6.1) 5.1 (2.0–13.0) 3.4 (1.3–8.8) 4.2 (1.7–10.5) 7.0 (2.7–18.0)	ORs were calculated using multivariate unconditional regression and were adjusted for age, family history of AAA, history of ischemic heart disease and treated hypertension, and the presence of peripheral arterial occlusive disease
• Smoking was significantly associated with AAA in women but not in men	Men 1–19 pack-years 20–34 pack-years 35–49 pack-years ≥50 pack-years Women 1–19 pack-years 20–34 pack-years 35–49 pack-years ≥50 pack-years	OR 1.21 (0.22–6.66) 2.45 (0.51–11.7) 2.96 (0.63–14.0) 3.83 (0.84–17.5) OR 5.81 (0.95–35.5) 21.7 (3.87–121.5) 18.2 (3.01–110.5) 28.9 (2.30–362.1)	ORs were calculated using unconditional logistic regression; risk estimates were adjusted for age, diastolic blood pressure, diabetes mellitus status, and family history of AAA
• Risk associated with current smoking was significant for both men and women	Men Never smoked Former smokers Current smokers Women Never smoked Former smokers Current smokers	RR 1.00 (referent) 1.57 (0.94–2.63) 3.30 (2.08–5.23) RR 1.00 (referent) 0.42 (0.06–3.02) 3.43 (2.11–5.59)	RRs were calculated using Cox proportional hazards regression model; risk estimates were adjusted for age and place of residence

Table 3.7 Continued

Study	Design/population	Tobacco exposure	Outcome
Törnwall et al. 2001	Cohort study 29,133 male smokers aged 50–69 years Participants in an alpha-tocopherol, beta-carotene cancer prevention study Enrollment: 1985–1993 Ended: spring 1993 Finland	• Cigarettes / day • Duration of smoking	AAA, ruptured or unruptured
American Cancer Society, unpublished data, 2002	Cohort study Cancer Prevention Study II (CPS-II) Approximately 77,000 American Cancer Society volunteers Initial questionnaire: 1982 United States (nationwide and Puerto Rico)	• Nonsmokers • Former cigarette smokers • Current cigarette smokers	Death from aortic aneurysm

As reviewed above, there is very strong evidence from animal and laboratory experiments documenting the potential for tobacco products to have multiple detrimental effects at different stages of the natural history of atherosclerosis, both in its subclinical evolution and in the precipitation of its clinical manifestations.

The new conclusion regarding tobacco smoking and heart disease in this report relates to subclinical disease.

Findings	Risk estimates (95% CI)		Comments
• 181 outcome events • Duration of smoking was a stronger risk factor than cigarettes / day	Cigarettes / day ≤14 cigarettes / day 15–24 cigarettes / day ≥25 cigarettes / day Duration of smoking ≤32 years 33–40 years >40 years	RR 1.00 (referent) 1.01 (0.70–1.46) 0.81 (0.52–1.27) RR 1.00 (referent) 1.45 (0.88–2.39) 2.25 (1.33–3.81)	RRs were calculated using Cox proportional hazards model; comparisons were limited to smokers only; risk estimates were adjusted for age, body mass index, systolic blood pressure, diastolic blood pressure, serum total cholesterol, serum high-density lipoprotein cholesterol, serum alpha-tocopherol, serum beta-carotene, total energy intake, alcohol consumption, history of diabetes mellitus, education, and exercise performed in leisure time
• 1,275 outcome events in men • 413 outcome events in women • Significantly increased mortality among both men and women who were current cigarette smokers	Death rate ratios Men Nonsmokers Former smokers Current smokers Women Nonsmokers Former smokers Current smokers	 1.00 (referent) 2.42 (2.03–2.88) 5.97 (5.03–7.09) 1.00 (referent) 1.81 (1.41–2.32) 6.82 (5.66–8.22)	Death rates were standardized to the CPS-II population

Conclusions

Smoking and Subclinical Atherosclerosis

1. The evidence is sufficient to infer a causal relationship between smoking and subclinical atherosclerosis.

Smoking and Coronary Heart Disease

2. The evidence is sufficient to infer a causal relationship between smoking and coronary heart disease.
3. The evidence suggests only a weak relationship between the type of cigarette smoked and coronary heart disease risk.

Smoking and Cerebrovascular Disease

4. The evidence is sufficient to infer a causal relationship between smoking and stroke.

Smoking and Abdominal Aortic Aneurysm

5. The evidence is sufficient to infer a causal relationship between smoking and abdominal aortic aneurysm.

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