Effects of Tobacco Smoking on Cardiovascular Disease

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Tobacco smoking continues to be a major risk factor for cardiovascular disease (CVD) and the leading avoidable cause of death worldwide. Tobacco smoking has declined in high-income countries, but the average smoking rate in Japan remains high: 29.4% for men and 7.2% for women in 2017. Of note, the average smoking rate among middle-aged men remains approximately 40%, indicating that a high incidence of smoking-related CVD will continue for a couple of decades in Japan. The adverse effects of tobacco smoking on CVD are more extensive than previously thought. Physicians should be particularly alert to the development and progression of heart failure, atrial fibrillation, and venous thromboembolism, as well as ischemic CVD among tobacco smokers. Increasing use of heat-not-burn tobacco as cigarette alternatives is an emerging issue. Harmful effects do not disappear just by changing the delivery system of tobacco.

Key Words: Atrial fibrillation; Cardiovascular disease; Heart failure; Tobacco smoking; Venous thromboembolism

Tobacco smoking is the leading preventable cause of death, responsible for more than 6 million deaths annually worldwide. On average, smokers lose 10 years of life compared with people who never smoke, and smoking was the leading determinant of adult deaths from non-communicable diseases in 2007. Among smoking-related deaths, cardiovascular disease (CVD) accounts for approximately one-third of cases in both Japan and worldwide.

Even smoking only a single cigarette daily increases the risk of developing coronary artery disease (CAD) and stroke. People who smoke just 1 cigarette daily have 40–50% of the increased CVD risk of those who smoke 20 cigarettes daily, this risk in low-use smokers is much greater than ever suspected.

Recently, the use of heat-not-burn tobacco products has increased in Japan as cigarette alternatives (Figure). Although the present review focuses on cigarette smoking, because of the vast information available in the literature, what is said regarding cigarette smoking might also be said regarding heat-not-burn tobacco products – the problems are associated with the agent, not its delivery method.

The effects of tobacco smoking are not restricted to atherosclerotic CVDs. Smoking, especially current smoking, is associated with increased risk of hospitalization for incident heart failure (HF). Smoking was previously considered to be a nonsignificant predictor of atrial fibrillation (AF), but now accumulating evidence shows that smoking is a major risk factor for AF, including among Japanese men and women. The association between smoking and the risk of venous thromboembolism (VTE) is an as-yet-unsolved clinical question. Because VTE events occur after censoring the data to evaluate deaths caused by cancer or CVD, data regarding VTE events have not been counted and thus excluded from analysis. However, when VTE events are analyzed as the only outcome, heavy smoking is associated with provoked VTE.

Prevalence of Tobacco Smoking

The estimated global prevalence of tobacco smoking in 2010 was 36.6% for men and 7.5% for women. In Japan, smoking prevalence rates in 2017 were 29.4% for men and 7.2% for women. Although the average smoking rate in Japan has declined by half during the past 30 years, the rate among middle-aged men remains high, at approximately 40%. This fact indicates that a high incidence of smoking-related CVDs will continue for several more decades in Japan.

Effects of Constituents of Tobacco Smoke

Tobacco smoking, both active and passive (i.e., secondhand smoke), increases the incidence of all phases of atherosclerosis, from endothelial dysfunction to various types of CVD. More than 7,000 chemicals, including nicotine, tar, and carbon monoxide, contribute to the development of CVD through increases in heart rate and myocardial contractility, inflammation, endothelial impairment, thrombus formation, and a decrease in the serum levels of...
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Endothelial Dysfunction

Endothelial dysfunction is considered to be the first step in vascular disease. Components of cigarette smoke provoke endothelial injury and dysfunction long before clinical events. Healthy endothelium produces vasodilatory substances, including nitric oxide (NO), prostacyclin, and endothelium-derived hyperpolarizing factor. When the endothelium becomes injured, the synthesis and bioactivity of these vasodilators are impaired, and the balance between vasodilators and vasoconstrictors is destroyed. At present, oxidative stress and the upregulation of inflammatory cytokines, both of which are caused by reactive oxygen species in cigarette smoke, are considered to play critical roles in endothelial dysfunction by reducing the bioavailability of NO. In particular, superoxide anion reduces NO availability through the formation of peroxynitrite, which also causes the oxidation of low-density lipoprotein. Inflammatory cytokines enhance the process of atherosclerotic change, which leads to endothelial dysfunction. Moreover, exposure to cigarette smoke results in platelet activation, stimulation of the coagulation cascade, and impairment of anticoagulative fibrinolysis. These effects lead to the formation of vascular disease.

Impairment of Endothelial Progenitor Cells (EPCs)

Normal endothelium plays an important role in the regulation of vascular tone. When the endothelium is injured, the damaged endothelial cells must be removed and replaced to maintain vascular tone. We and other researchers have revealed that the capacity for endothelial repair is reduced in smokers compared with nonsmokers. In particular, smokers have both fewer circulating EPCs and impaired endothelial-dependent vasodilation. One mechanism by which injured vessel walls undergo repair is through the recruitment of circulating EPCs. Smoking, by increasing the oxidative stress level and reducing NO activity, impairs the mobilization of EPCs and decreases their half-life. Other findings also support the connection between smoking and endothelial dysfunction in terms of EPCs. For example, smoking cessation is associated with a rebound in the number of circulating EPCs and improvement of endothelium-dependent vasodilation.

Smoking and Metabolic Disorders

Because nicotine causes short-term increases in energy expenditure, smokers tend to weigh less than nonsmokers initially. However, over time, smoking increases insulin resistance and is associated with central fat accumulation, leading to the development of metabolic syndrome (MetS) and diabetes mellitus (DM). In Japanese cohorts, subjects with MetS or DM, even when detected at an early stage, were at increased risk for CVDs. Furthermore, cigarette smoking may be the first step towards unhealthy high-density lipoprotein cholesterol.

Figure. Potential pathways and mechanisms by which cigarette smoking and heat-not-burn tobacco products cause cardiovascular disease, VTE, and hospital admission for HF. ACS, acute coronary syndrome; CAD, coronary artery disease; EPC, endothelial progenitor cell; HF, heart failure; VTE, venous thromboembolism.
habits, including excess alcohol consumption and caloric intake, which are linked to future metabolic disorders.

**Smoking and Hypertension**

The effects of smoking on blood pressure (BP) are complex. Smoking just a 1 cigarette increases BP acutely and transiently through sympathetic nervous activation. In 1 study, the average transient elevation in systolic BP after the first cigarette was approximately 20 mmHg. The half-life of nicotine after smoking is approximately 2 h. Therefore, when smoking continues, BP remains elevated.

The chronic effects of smoking on BP are unclear. However, current smokers with normal to high-normal BP (120–139/75–89 mmHg) are known to be at increased risk for CVD compared with nonsmokers with normal to high-normal BP. In addition, daytime ambulatory BP tends to be higher than the in-clinic measurement in smokers. Therefore, medical practitioners should be alert to masked hypertension when they care for smokers with normal to high-normal BP. Furthermore, tobacco smoking increases arterial stiffness that persists for a decade after smoking cessation; this persistent arterial stiffness also is related to increased risk for CVD events.

**Smoking and CVD**

Exposure to tobacco smoke increases the risk of coronary plaque rupture, thus promoting thrombus formation at the lesion, and leading to sudden onset of acute coronary syndrome (ACS), including sudden cardiac death. Moreover, tobacco smoking elicits coronary artery spasm with or without apparent significant coronary narrowing. Compared with Caucasians, Japanese patients exhibit a greater incidence of coronary spasm and vasospastic angina. The risk for coronary spasm caused by smoking shows some genetic predisposition in East Asians.

Cigarette smoking is a potent risk factor for stroke in both men and women. A meta-analysis of 32 studies revealed that smoking increases the risk of developing cerebral aneurysms and subarachnoid hemorrhage (relative risk, 2.93; 95% confidence interval, 2.48–3.46) and cerebral infarction (relative risk, 1.92; 95% confidence interval, 1.71–2.16). The smoking-induced sudden rupture of cerebral plaques and abrupt onset of cerebral aneurysms together account for the increase in intrinsic sudden death among smokers.

**Cigarette Tobacco Use in Terms of CVD**

The number of cigarettes smoked daily shows a dose-response relationship with CVD risk, but the relationship is non-linear for CAD, for which risk increases after exposure to even a low level of smoke. Consequently, no level of smoking is safe in terms of CVD — remember that smoking just 1 cigarette daily accounts for half of the excess risk for CAD caused by smoking 20 cigarettes daily. The occurrence of vasospasm, or a non-linear relationship between the amount of fine particulates in cigarette smoke and their pronounced effects on platelet aggregation, may account for the associated high risk for CVD.

**Beneficial Health Changes From Smoking Cessation**

Smoking cessation improves endothelium-dependent vasodilation and reduces the risk of morbidity and mortality of CVD. Several favorable changes occur after quitting smoking. In particular, BP decreases within 20 min, and within 2–12 weeks the number and function of circulating EPCs rebound and endothelium-dependent vasodilation improves. In addition, the risk of CAD and risk of death at 1 year after quitting are about half that of current smokers; at 5–15 years after smoking cessation, the risk of stroke is reduced to that of nonsmokers.

We previously showed that smoking cessation for more than 4 years reduced total mortality (hazard ratio, 0.57; 95% confidence interval, 0.34–0.91), stroke (hazard ratio, 0.52; 95% confidence interval, 0.24–1.01), and total CVD events (hazard ratio, 0.27; 95% confidence interval, 0.13–0.50) among middle-aged Japanese men. In a 10-year cohort study of 94,683 Japanese (41,782 men and 52,901 women), the risk for CAD and CVD overall declined within 2 years after smoking cessation and the risk for stroke decreased at 2–4 years afterward.

**Abdominal Aortic Aneurysm (AAA) and Peripheral Arterial Disease**

Smoking is a strong risk factor for AAA. Meta-analysis revealed that the risk of AAA was about 5-fold greater in current smokers and 2-fold greater in former smokers compared with nonsmokers. In addition, a positive dose-response relationship emerged between the number of cigarettes smoked daily and the risk of AAA. In a community-based cohort study, 1 in 9 middle-aged current smokers developed clinical or asymptomatic AAA in their lifetime, and quitting smoking reduced the lifetime risk by 29%. Therefore, one-time ultrasonography to screen for AAA is recommended for male smokers and ex-smokers.

Peripheral arterial diseases associated with smoking include arteriosclerosis obliterans (ASO) and Buerger’s disease (thromboangiitis obliterans). ASO is an occlusive arterial disease that affects the abdominal aorta and the small and medium-sized arteries of the lower extremities. ASO is about 3-fold more common among smokers than nonsmokers, and the association between smoking and ASO may be even stronger than that between smoking and CAD. The severity of ASO tends to increase with the number of cigarettes smoked.

Buerger’s disease is a rare disease of the arteries and veins in the arms and legs. The strong association between Buerger’s disease and cigarette smoking cannot be overemphasized; most patients with Buerger’s disease are heavy smokers. Patients with Buerger’s disease must stop smoking completely, because smoking cessation is the ultimate effective treatment. One of the mechanisms underlying Buerger’s disease may involve impaired circulating EPCs, and autologous EPC transplantation is an effective strategy for no-option patients with critical limb ischemia caused by Buerger’s disease.

**Hospitalization for HF Among Current Smokers**

An estimated 1.0 million people (1% prevalence) have HF in Japan, and this number will continue to rise. Avoiding readmission for HF is important in terms of prognosis, quality of life, and medical expenses. Quitting smoking is a key way to avoid HF, because current smoking is a significant risk factor for death and hospitalization for incident HF.

Current smoking elicits vasoconstriction and increases BP and heart rate through the effects of nicotine on sympathetic nerve activation. The increased carbon monoxide levels in current smokers leads to chronic...
ischemia in the heart and other organs by hindering the ability of hemoglobin to carry oxygen, thus further worsening HF. In addition, increased inflammatory cytokine levels, endothelial dysfunction, and impaired kidney function contribute to the high readmission rate for HF among current smokers.64

**AF**
The association between smoking and AF development is inconsistent in Japanese populations. In the second cohort of the Hisayama Study, which began in 1974, smoking was not associated with the development of AF in either men or women.65 However, in a recent study, current smoking was independently associated with AF in Japanese men and women, as well as other ethnic populations.9

Tobacco smoking promotes the development of AF in several ways. The nicotine in cigarette smoke stimulates sympathetic neurotransmission and may increase vulnerability to AF.66 In addition, nicotine contributes to the development of atrial fibrosis, which favors the occurrence of atrial arrhythmia.7 Furthermore, smoking may indirectly predispose to AF through effects on ischemic heart disease and hemodynamic changes.

Risk for stroke and thromboembolism is high in people with AF. The CHA2DS2-VASc score is useful for identifying stroke risk in affected people,68 and anticoagulation therapy typically is initiated when the CHA2DS2-VASc score is ≥2. Given that the vast majority of smokers also have vascular disease, the CHA2DS2-VASc score inevitably is higher in smokers than in nonsmokers. Consequently, smokers with AF are at high risk for thromboembolic stroke.69

**VTE**
VTE, including both deep vein thrombosis and pulmonary embolism, is a considerable cause of morbidity and mortality worldwide. The association between tobacco smoking and VTE is somewhat unclear because of competing risk for cancer and myocardial infarction. In heavy smokers, VTE will likely occur after the development of cancer or myocardial infarction, thus complicating assessment of the isolated effects of smoking on VTE.12 In an analysis of more than 1.1 million participants in 76 cohorts, smoking was clearly associated with an increased risk of VTE.70

**Secondhand Smoke and Risk for CVD**
So-called ‘secondhand smoke’ is the cigarette smoke that fills restaurants, offices, and other enclosed spaces when people burn tobacco products. Nonsmokers exposed to secondhand tobacco smoke have increased risks of CVD morbidity and mortality. A meta-analysis has indicated a 25–30% increase in risk of CAD caused by exposure to secondhand smoke.71 There is no safe level of exposure to secondhand tobacco smoke and smoke-free legislation in Japan has reduced the incidence of ACS. In particular, the incidence of ACS decreased by 15% after tobacco smoking was legally banned from all public venues, including bars.72 Regions that had partial restriction of smoking or low implementation of the smoking ban did not show the reductions in ACS that were associated with the comprehensive ban.73,74

**Heated Tobacco Products**
Heated tobacco products, also known as heat-not-burn tobacco products, are battery-operated devices that heat tobacco to a maximum of 350°C, compared with 600°C when a conventional cigarette is burned. At present, 3 tobacco companies promote these products by claiming that, because the tobacco leaves are only heated and not burned, these products are less harmful than conventional tobacco cigarettes. However, the mainstream aerosol of heated tobacco contains the same acrolein, formaldehyde, benzaldehyde, acenaphthylene, nicotine, carbon monoxide, and particulates that are harmful constituents of conventional cigarette smoke.79 No evidence currently available demonstrates that heated tobacco products are less harmful than conventional tobacco products.

**Conclusions**
Smoking is a major cause of CVD, including AF and VTE. Current smoking increases hospitalization for HF. Smoking promotes hypertension and MetS, which both increase the risk for CVD. Evidence indicates that even smoking just 1 cigarette daily and secondhand smoke increase the threat of CVD. No evidence to date demonstrates that heat-not-burn tobacco products are safer than conventional cigarette smoking. Completely smoke-free environments protect both smokers and nonsmokers from CVD.

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