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COMMENTARY

Effect of cigarette smoking cessation on CKD: is it a cancer-suppression-like effect or a CVD-suppression-like effect?

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EFFECT OF CIGARETTE SMOKING CESSATION ON CVD INCIDENCE

Cigarette smoking is a well-known and important cardiovascular disease (CVD) risk factor.[1] Cigarette smoking induces CVDs through several key mechanisms. One important mechanism is that the nicotine from cigarette smoke induces sympathetic nervous system stimulation, which results in coronary vasoconstriction. Other mechanisms include endothelial dysfunction, the lowering of the zinc serum/urine quotient, insulin resistance, and oxidative stress.[1–4] Of these mechanisms, vasoconstriction induced by nicotine is a relatively rapid process. The amelioration of endothelial function through the decrease in oxidative stress has been observed only 3 months after smoking cessation.[3] Therefore, cigarette smoking cessation could be expected to rapidly reduce CVD risk. Indeed, a decrease in CVD risk can be observed within 2 years after cessation of cigarette smoking. In 4 years, half of such patients return to a normal level of CVD risk after cessation. Almost all of the CVD risk that is related to cigarette smoking is eliminated within 10 years[5] (see Figure 1a). The effect of cigarette smoking cessation on CVD incidence is a relatively rapid process.

EFFECT OF CIGARETTE SMOKING CESSATION ON CANCER INCIDENCE

It is also well-known that cigarette smoking induces cancer not only in the lungs but also in many other organs. The accumulated effect of smoking on cancer is usually related to the past number of cigarettes smoked, as described by the Brinkman index. After the cessation of cigarette smoking, cancer incidence is expected to decrease. However, recognizing the effect during the first decade after cessation is difficult. For example, the incidence of esophageal cancer during the 2 years after smoking cessation was found to be the same as that of a current smoker.[6,7] Within 10 years after cessation, there was no statistically significant reduction in cancer incidence[6,7] (Figure 1b). Within 11–25 years after cessation, the incidence of esophageal cancer was significantly lower than that of current smokers, but was still approximately twice that of never-smokers. Twenty-five years after cessation, the incidence of esophageal cancer had recovered to the never-smoker level. Obviously, recovering from the cancer-causing effects of smoking takes a longer time than does recovering from the CVD-related conditions induced by cigarettes.[7,8] Cigarette smoking-induced cancers are caused by several major mechanisms: oxidative stress induced by smoking, chemical compounds supplied by smoking, epigenetic changes induced by smoking, and gene mutations induced by stresses. These effects from cigarette smoking accumulate according to the Brinkman index. They are cleared by many biological defensive mechanisms, such as anti-oxidative stress mechanisms. However, this clearance process takes a long time.

EFFECT OF CIGARETTE SMOKING CESSATION ON CKD

Cigarette smoking has been established as a risk factor for chronic kidney disease (CKD) progression. In immunoglobulin A nephropathy, cigarette smoking has been reported to be a strong risk factor for CKD progression (hazard ratio, 2.03 (95% confidence interval, 1.33–3.10)).[9] Moreover, smoking and CKD stage have synergistic effects on CKD progression.[10] In diabetic nephropathy, the situation is more complicated because there are reports that both support and do not support this effect on CKD.[10] However, cigarette smoking is believed to be harmful for kidney disease progression. In terms of proteinuria onset, smoking in Type 1 diabetic patients was reported to be a risk.[11] However, the mechanisms of recovery from the CKD status after quitting smoking remain unknown.

Ohkuma-T *et al.*[12] reported both a dose-dependent association of active smoking and a graded inverse association of the years since quitting smoking with CKD, which enhanced the merits of smoking cessation among 2770 Japanese male patients suffering from Type 2 diabetes. The estimated glomerular filtration rate (eGFR) level in past smokers was the same as that in never-smokers 20 years after smoking cessation. The incidence of albuminuria was also the same as that of never-smokers 20 years after cessation. These results suggested that recovery from the smoking effect after cessation was more similar to cancer than it was to CVD.

There are several major mechanisms that can explain how the recovery from CKD status following the effects of smoking after cigarette cessation is similar to cancer rather than to CVD, although CKD has been established as a risk factor for CVD. One mechanism is that an increase in body mass

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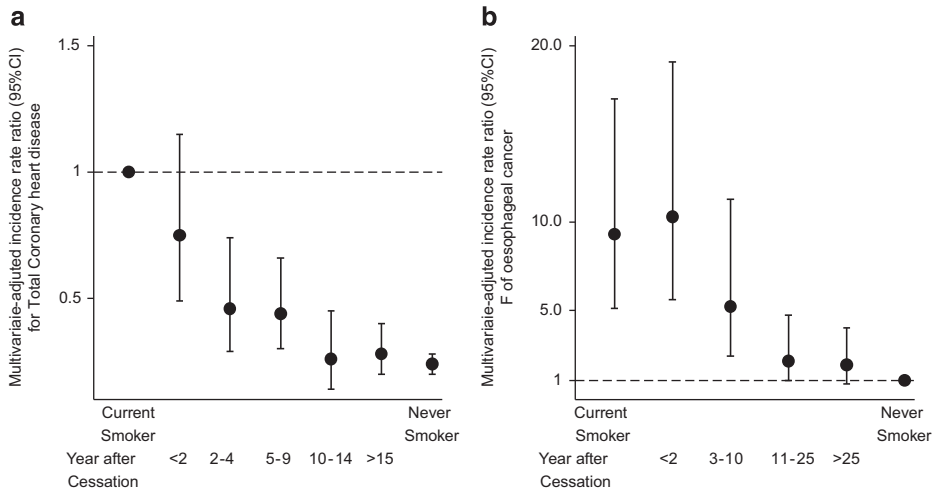

Figure 1 (**a**) Benefits caused by smoking cessation on the incidence of coronary heart diseases. The recovery from an unhealthy condition attributable to cigarette smoking might start immediately after quitting smoking. Half of the recovery could be observed within 4 years. Ten years after quitting smoking, the incidence of coronary heart disease was the same as that of never-smokers. Figure adapted from Kawachi *et al.*[5] (**b**) Benefits caused by smoking cessation on the incidence of esophageal cancer. Recovery from an unhealthy condition with cigarette smoking was not observed within 2 years of quitting smoking. Half of the recovery could be observed 3–10 years after smoking. The incidence of esophageal cancer was the same as that of never-smokers 25 years after smoking cessation. The influence of smoking on the incidence of cancers lasted longer than its influence on coronary heart disease. Figure adapted from Lagergren *et al.*[6] CI, confidence interval.

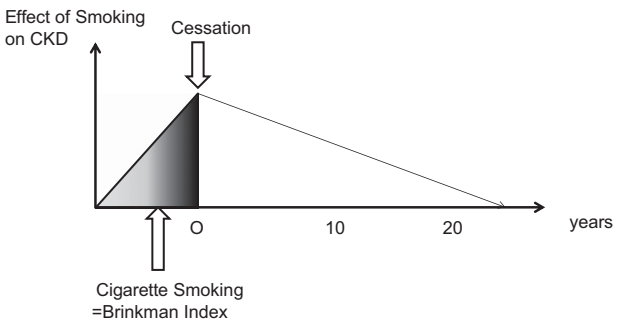

Figure 2 Time course of cigarette smoking effect on CKD. The effect of cigarette smoking on CKD accumulated in proportion to the Brinkman index. After smoking cessation, the effect is cleared. However, the clearance process takes several decades, similar to the recovery time for cancer risk.

index (BMI) after smoking cessation disturbs the recovery from CKD status because BMI is a risk factor for proteinuria[13] and can result in insulin resistance.[4] Fifteen to twenty years after smoking cessation, BMI was shown to return to the level observed before cessation.[4] Another important mechanism is that the clearance of smoking effects that impact CKD, such as oxidative stress and epigenetic changes, take a long time, similar to those that relate to cancer. The effect of cigarette smoking on CKD is proportional to the Brinkman index, and the clearance effect takes several decades, which is more similar to cancer than it is to CVD (see Figure 2). In conclusion, CKD recovery from cigarette smoking takes a long period of time, similar to the time required to recover from cancer risk.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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