The impact of cigarette smoking on cardiovascular outcome in women

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Summary
Cigarette smoking should be considered the most important known modifiable risk factor for coronary heart disease (CHD). Globally, it is responsible for 10% of all deaths from cardiovascular disease. An emerging and alarming problem is the growing incidence of smoking among women. Smoking promotes cardiovascular disease and primarily atherosclerosis through multiple direct and indirect mechanisms including increased oxidative stress and vasomotor, rheological and hematological dysfunction. Cigarette smoking also acts by potentiating other risk factors for cardiovascular disease. It is now well documented that women are as vulnerable as men to the dangers of tobacco, if not more so: indeed, women using tobacco face virtually the same risks as men and even greater risks for some diseases. The exact mechanism of gender-related differences is unclear and several possible explanations have been offered. Moreover, the relative risk of CHD associated with smoking seems to be greater for younger women than for older women. All these data suggest that including women in tobacco-control strategies is crucial: an approach with a gender equality policy is the key to winning the battle against smoking.

KEY WORDS: cardiovascular risk, cigarette smoking, estrogen, women

Introduction

Despite its known deleterious effects on health, cigarette smoking remains a widespread habit worldwide. Cigarette smoking is a complex and dynamic mechanism involving different components: *mainstream smoke,* which is the smoke drawn through the tobacco into an active smoker's mouth, *sidestream smoke,* which is the smoke emitted from the burning end of a cigarette, and *enviromental* smoke, which is a fraction of the mainstream smoke exhaled by smokers (1,2). Philip Morris carried out an extensive series of studies of sidestream cigarette smoke in Germany during the 1980s; these studies showed it to be approximately four times more toxic than inhaled mainstream smoke (3) because of its relatively higher concentrations of toxic gaseous components (4).
Smoking is a dangerous worldwide killer, harming not only smokers themselves but also people involuntarily exposed to second-hand smoke (2). Second-hand smoke is mainly made up of sidestream smoke released by smoldering cigarettes (85%), but a small proportion of it is exhaled mainstream smoke (15%) (5). Sidestream smoke, as mentioned, has a higher concentration of toxins, but it is rapidly diluted as it travels away from the burning cigarette. Second-hand smoke is thus a dynamic mixture whose characteristics and concentration change over the time from its formation to its complete dissipation. Because of its dynamic nature, it is not possible to provide a specific quantitative definition of second-hand smoke (2).
Fresh sidestream smoke is 3-4 times more toxic than fresh mainstream smoke (3) and, after entering the air, it becomes 2-4 times more toxic than fresh sidestream smoke. It is thus clearly important to place restrictions on smoking to protect adults and children involuntarily exposed to sidestream smoke.
Another alarming problem is the emerging diffusion of cigarette smoking among women, who already seem to be exposed to second-hand smoke in greater numbers than men, and account for the bulk of deaths (64%) due to second-hand smoke among adult non-smokers (6).
Women are also exposed to residual tobacco smoke pollution after smoking. This "third-hand smoke" (6) includes tobacco-related volatile compounds desorbed from indoor surfaces, such as cushions, carpets and curtains, and smokers' clothing (7).
The pathogenicity of tobacco smoke may be attributed both to biological and behavioral mechanisms that can show different patterns in women and men. Therefore, sex (biological features that differ between males and females) and gender (social behaviors, norms and roles of men and women) are important aspects to consider in order to understand the different use and impact of tobacco in women compared to men (6).

Epidemiology

In 1983, the US Surgeon General conducted the first major review of epidemiological and biological evidence documenting a relationship between smoking and cardiovascular disease (CVD). It was concluded that cigarette smoking should be considered the most important preventable modifiable risk factor for coronary heart disease (CHD) in the United States, given that smokers showed a 70 percent greater cardiovascular mortality than nonsmokers. Tobacco is also a cause of peripheral arterial disease, cerebrovascular disease and aortic disease.
Although this evidence has become increasingly glaring over recent years, cigarette smoking remains the leading behavioral risk factor for a large number of preventable deaths worldwide: a true *"tobacco epidemic*" as it has been defined by the World Health Organization (WHO). Due to the long time that elapses between starting to smoke and the clinical manifestations of smoking, the epidemic of tobacco-related disease and death has only just begun: tobacco caused 100 million deaths in the 20th century, but if current trends continue, it will cause up to one billion deaths in the 21st century. Direct tobacco smoking is currently responsible for the deaths of about 5.4 million people across the world each year and in the next two decades the annual death toll from tobacco is expected to rise to over 8 million, with more than 80% of these deaths expected to occur in low- and middle-income countries (8,9).
Tobacco does not kill only its direct users; indeed, second-hand smoke caused an estimated 603,000 premature deaths in 2004. Of all premature deaths linked to second-hand smoke, 28% occur in children, and 47% in women; the most common causes are ischemic heart disease in adults (63%) and lower respiratory infection in children (27%) (10).
Globally, tobacco use is responsible for 10% of all deaths from CVD. The percentage of smoking-related deaths from CVD varies by region: for example, in 2004, 15% of cardiovascular deaths were attributable to tobacco in Europe, 9% in South-East Asia, and 6% in the Western Pacific. These differences reflect the different smoking prevalence rates in different parts of the world (11).
Unfortunately there is an increased incidence of smoking among females: the WHO is so concerned about this that it made gender and tobacco the theme of the 2010 World No Tobacco Day. One billion men and about 250 million women use tobacco every day around the world, according to a study presented at the 14th World Conference on Tobacco or Health. In the Americas and Europe, the prevalence of female smoking is high, around 17% and 22%, respectively. The disparity between male and female smoking prevalence is greater in low- and middle-income countries where women smoke much less than men: in China, for instance, 61% of men are current smokers, compared with only 4.2% of women. Hovewer, these data may be influenced by some underreporting of smoking among the female population, particularly in countries where it is socially and culturally unacceptable for them to use tobacco. Unfortunately, it is estimated that the proportion of female smokers, particularly girls, will rise from about 12% in the first decade of this century to 20% by 2025 (12), with boys between the ages of 13 and 15 years smoking only two to three times more than girls (13).
The factors leading women to initiate or maintain tobacco use are different; among them, the most common are nicotine addiction, lack of awareness of risk, and difficulty in quitting, the latter due not only to dependence but also to psychosocial and environmental factors. In addition, women are also induced to start smoking by the way cigarettes are marketed (as a symbol of emancipation) by the tobacco industry (14). Indeed, the tobacco industry, suggesting that cigarette smoking symbolizes high fashion, freedom, and modern styles and values, and even promises weight reduction, has long fostered the false idea that smoking empowers women (15).

Gender-related differences in cardiovascular risk and disease

The classic risk factors for coronary atherosclerosis can be divided into those that are potentially modifiable to mitigate risk (diabetes, hypertension, hyperlipidemia, cigarette smoking, obesity, and a sedentary lifestyle) and those that are not modifiable (age and family history). In the INTERHEART study, a large international case-control study of acute myocardial infarction, risk estimates associated with traditional cardiovascular risk factors were, overall, similar in both sexes and across various regions throughout the world. However, although cardiovascular risk rises with age in both sexes, the increase is steeper in women, leading old women to have similar rates of CVD as men. In other words, for CVD, there is a gradual, but striking, loss of the "protective effect" of female gender (Fig. 1). More than 80% of middle-aged women have one or more traditional cardiac risk factors. Although most cardiovascular risk factors are common to men and women, there seem to be differences in terms of their relative risk and there is substantial gender-related variability in their prevalence, outcome and clinical impact. For instance, in women, compared with men, diabetes and hypertension are related to greater adverse differences in the levels of several CVD risk factors. Coronary events and prognosis are substantially worse for diabetic women compared to men affected not only by diabetes but also by insulin resistance and glucose intolerance. Obesity and hypertension appear to have a synergistic effect in the development of left ventricular hypertrophy, whose prognosis is worse in women than in men. Furthermore, risk factors such as smoking, hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-c) levels are also found to have a greater impact in women than in men. Hovewer, increased serum total cholesterol level, body mass index (BMI) and diabetes prevalence explain only 50% of the age-related increase in cardiovascular morbidity and mortality among women. There may be other causes contributing to the high prevalence of CVD in women. Indeed, there exist well-known gender-specific risk factors such as marital stress, hormone deficiency, gestational diabetes and pregnancy-induced hypertension and preeclampsia. The predictive power of these risk factors is largely mediated by traditional risk factors. For

example, polycystic ovary syndrome (a common but often unrecognized hormone disorder affecting women of reproductive age) is associated with type 2 diabetes mellitus and metabolic syndrome, which includes hyperlipidemia, central obesity and hyperglycemia; thus, it can increase cardiovascular risk in young women.

In recent years new risk factors have been identified and suggested to improve cardiovascular risk prediction, especially in patients presenting an intermediate risk. These include C-reactive protein (CRP), homocysteine level, coronary artery calcium score, lipoprotein(a), and carotid intima-media thickness. In particular, inflammatory markers may be particularly useful in the assessment of cardiovascular risk in females. In all ethnic groups, females have higher CRP levels than men, the difference becoming apparent at the time of puberty (16,17); also, CRP and interleukin 6 seem to predict vascular events among apparently healthy women (18).

In recent times, in addition to classic cardiovascular risk factors, psychosocial risk factors have been an area of growing interest. Interactions between multiple genetic and environmental/lifestyle factors play an important role in the pathogenesis of atherosclerosis. Recent evidence suggests that depression, more common in females than in males, may be an independent risk factor for the onset of CVD (19-21). Depression can undermine the management of cardiovascular risk factors, leading to a poorer outcome (22). Indeed, it is one of the strongest predictors of non-adherence to treatment (23) and is also strongly linked to smoking, obesity and a sedentary lifestyle. Other factors such as anxiety and marital and work-related stress, again more present in the female world, appear to be associated with CVD (24). Family or work stress, for example, may accelerate atherosclerosis in women (25). This may be linked to increased inflammatory activity, suggested to be a mediator of of the adverse effect of stress on cardiovascular outcomes (26,27). Indeed, gender-specific differences in CRP, an inflammatory marker, are related to the observed two- to 50-fold greater frequency of inflammatory-mediated autoimmune diseases, such as rheumatoid arthritis, SLE, thyroiditis, Raynaud's phenomenon and Takayasu's disease, in women as compared to men.

All this evidence suggests that the pathophysiology of CHD may be different in the two sexes. Sawabe et al. showed less severe epicardial coronary stenosis in women than in men, except at very advanced ages (over 75 years) (28); Jespersen et al. conducted a study that included about 11,000 patients with stable angina undergoing coronary angiography: the presence of non-obstructive coronary artery disease was significantly greater in the women than in the men (65% vs 32%; $p< 0.001$) (29). These data suggest that the mechanisms underlying myocardial ischemia may be different in women than in men. Women's coronary arteries, in fact, undergo "positive remodeling", dilating in order to accommodate plaque, allowing atherosclerosis to occur without focal obstruction. Coronary disease is more extensive in women, in whom myocardial ischemia may more frequently be due to microvascular or endothelial dysfunction. However, positive remodeling does not indicate a good prognosis; it can progress to obstructive coronary disease and increase the risk of acute coronary events.

The substrate of acute coronary events also differs between the sexes, consisting mainly of plaque rupture in men and superficial plaque erosion in women. This differ-

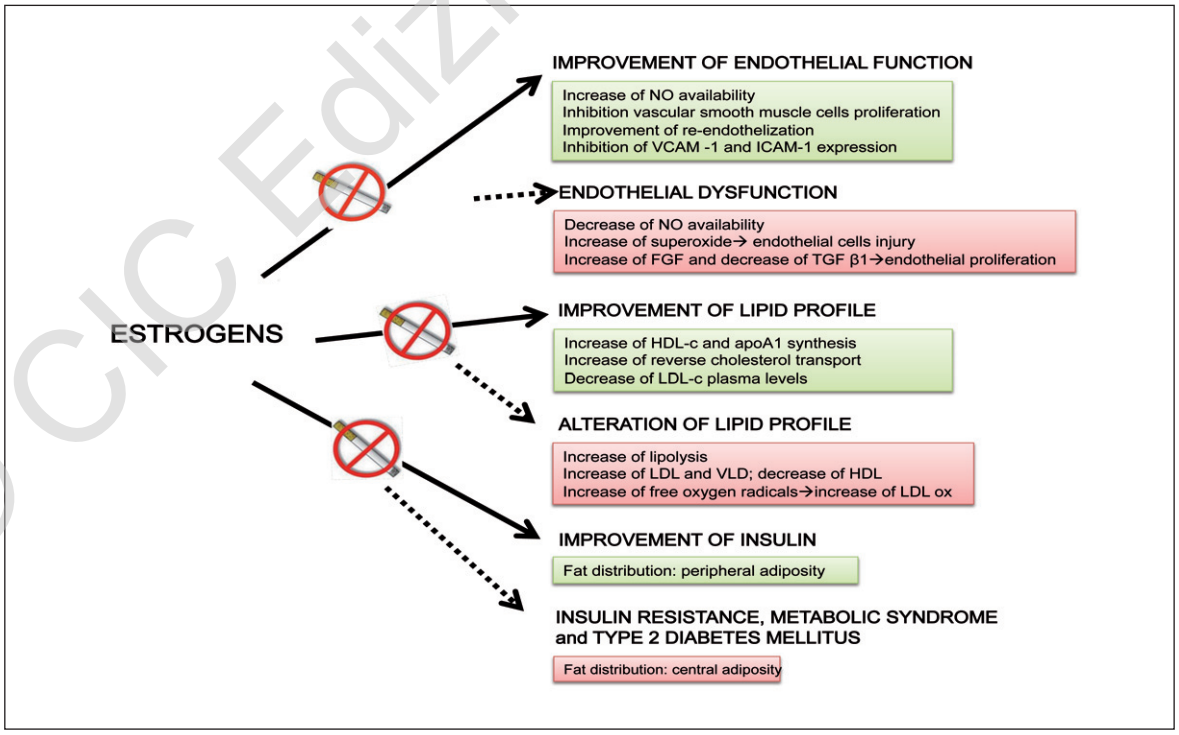

Figure 1 - Interactions between female sex hormones and cigarette smoking.

ence is likely due to differences in plaque composition: plaques that tend to rupture have a large lipid core with intimal and adventitial inflammation and a thin fibrous cap; plaques that are more subject to erosion are smooth muscle-cell rich with a thick, intact fibrous cap (30,31).
Recently, sex differences in mortality after acute coronary syndrome have been demonstrated, particularly in patients with ST-segment elevation myocardial infarction (STEMI): women with STEMI have a higher mortality than men. No differences have been found among patients with non ST-segment elevation myocardial infarction (NSTEMI) (32). In addition, sex differences have been demonstrated in young patients with myocardial infarction, with women aged under 50 years showing a higher mortality than age-matched men; this difference disappears in older people (33).
Sex steroid hormones play an important role in determining these gender-related differences, as suggested by an increased occurrence of CVD in women during the menopause and a higher cardiovascular risk in polycystic ovary syndrome and in all women with hyperandrogenism. Estrogens have an antioxidant action and improve lipid profile; they therefore play an atheroprotective role in cardiovascular tissue.
The effects of estrogen on vascular function can be genomic and non-genomic. *In vivo* estrogen administration causes vasodilation through both endothelium-dependent and endothelium-independent pathways. The former are mediated by nitric oxide (NO) activity, while the latter are ion channel-mediated. The genomic effects of estrogens result in an improvement of endothelial function (34). Estrogens stimulate re-endothelialization, but inhibit vascular smooth muscle cell proliferation following arterial injury; moreover, they inhibit inflammatory expression of adhesion molecules VCAM-1 and ICAM-1 in the endothelium, and thus have an essential role in inhibiting the development of atherosclerosis (35).
In addition to their direct effects on vasculature, estrogens can modulate cardiovascular risk factors. In particular, they improve the lipid profile, stimulating HDL-c and apolipoprotein A-1 synthesis and promoting reverse cholesterol transport. In short, these hormones reduce low-density lipoprotein cholesterol (LDL-c) and increase HDL-c. Estrogens play an important role in body fat distribution in women. While premenopausal women show peripheral adiposity, in postmenopausal women body fat tends to redistribute from the periphery to a central location. Central adiposity, measured by abdominal circumference, is associated with an unfavorable cardiovascular risk profile both in males and in females. Finally, the change in glucose metabolism frequently observed during the menopause may be related to lower estrogen blood levels, possibly because estrogens improve insulin sensitivity.

The effects of smoking on the cardiovascular system

Tobacco smoking promotes cardiovascular events through multiple mechanisms, including development of the atherosclerotic process, alteration of atherosclerotic plaque composition, and induction of a hypercoagulable state with a secondary risk of thrombosis. Smoking appears to interact with and potentiate the effects of other risk factors such as hypertension, glucose intolerance, and triglyceride and cholesterol concentrations. Among the components of cigarette smoke, three elements are considered mainly responsible for CVD: nicotine, carbon monoxide and oxidant gases. In addition, polycyclic aromatic hydrocarbons seem to have an impact on atherosclerosis. It is well known that endothelial dysfunction and injury are the first steps towards atherosclerosis. Normally, the endothelium plays an important role in the regulation of vascular tone, hemostasis and inflammation. Hence, endothelial dysfunction results in impaired vasodilation, abnormal adhesion of inflammatory cells to blood vessels and a hypercoagulable state. The relationship between cigarette smoking and endothelial dysfunction can be explained primarily by oxidant chemicals. Oxidant chemicals lead to the formation of reactive oxygen species that interact with NO and reduce its availability. Also, superoxide anion radicals derived from cigarette smoke can lead to the formation of peroxynitrite, a highly reactive intermediate with cytotoxic activity (36). All this results in a reduction of endothelin-dependent vasodilation and an increase in platelet adhesion. NO, in fact, is not just a vasoregulatory molecule; it also takes part in platelet activation and thrombosis (37).
The role of nicotine in endothelial function is controversial. It may impair endothelial function by increasing superoxide production (38); at the same time, it may act either by stimulating the release of fibroblast growth factor or by inhibiting the production of transforming growth factor 1. It has mitogenic effects and results in endothelial proliferation (39).
In addition, the presence of a high number of circulating endothelial cells in smokers suggests that nicotine has the ability to cause endothelial injury.
The high cardiovascular risk associated with cigarette smoking is also linked to the hypercoagulable state which is not due only to altered NO release. Indeed, several studies have shown that cigarette smoke alters platelet function (40,41), although the underlying mechanisms are multiple and unclear. It has been demonstrated that cigarette smoking can modify the structure and thus the fluidity of the platelet membrane, resulting in activation and aggregation. This may explain the high rate of thrombotic events in smokers (42). Moreover, long-term carbon monoxide exposure induces greater red blood cell mass and reduces the oxygen-carrying capacity of red blood cells; this in turn results in relative hypoxemia and a blood viscosity that could contribute to the hypercoagulation state.
Tobacco smoking could promote atherosclerosis also through its direct effect on the lipid profile. Nicotine, in fact, through its symphathomimetic effects, exerts a lipolytic action. High plasma catecholamine levels related to smoking increase lipolysis and circulating free fatty acids (FFAs), which may lower high-density lipoprotein (HDL) plasma levels and increase low density lipoprotein (LDL) and very low density lipoprotein (VLDL) levels. In addition, smoking reduces lecithin-cholesterol acyltransferase activity. The increased levels of free oxygen radicals associated with smoking can lead to the

transformation of LDL into oxidized LDL which is incorporated by macrophages. This is the first step in the development of fatty streaks and subsequent atherosclerotic plaques (43).

In addition, several studies have demonstrated an association between cigarette smoking and impaired insulin action, insulin resistance, and type 2 diabetes mellitus (45,46). This may be due to the abovementioned FFA overload and to direct effects of nicotine or other components of tobacco on pancreas beta cells (46,47). The development of insulin resistance in smokers may also be linked to obesity. There is evidence that the number of cigarettes smoked per day is positively associated with central fat accumulation and thus with metabolic syndrome, especially in women (48,49). Both smoking and central obesity are linked to an increased cardiovascular risk; when they are combined, they increase mortality risk (50).

Smokers often assume that smoking few cigarettes per day has no consequences. Light and intermittent smoking is widespread especially among young people, women and educated people. Social smoking is intermittent smoking that is limited to a particular social context. The dose-response relationship between smoking and cardiovascular mortality is not linear (51). In both sexes, smoking 1-4 cigarettes per day was associated with a significantly higher mortality risk for ischemic heart disease and for all causes (52); even using as little as 3-5 grams of tobacco per day or smoking without inhaling is associated with an increased risk of myocardial infarction (53).

In addition, cigarette smoking has acute effects. Inhaled nicotine is released rapidly, in high concentration, into arterial blood causing increases in heart rate, blood pressure and myocardial contractility. Thus, nicotine-induced sympathetic activity causes an increase in myocardial work, which in turn increases myocardial blood flow demand. Also, carbon monoxide exposure has adverse hemodynamic effects. Unfortunately, in smokers affected by coronary artery disease there is no increase in blood flow, and therefore oxygen supply, to the heart because of the nicotine-indiced coronary vasoconstriction. This can result in symptoms of ischemia, particularly in smokers with established coronary artery disease.

The effects of cigarette smoking on women

Women, compared with men, have lower absolute rates of coronary artery disease. However, cigarette smoking has been associated with a higher relative risk of both myocardial infarction and cardiovascular mortality in women (12). Smoking is the single most important preventable cause of CHD in women and the leading cause of CHD in women younger than 50 years old. Moreover, smoking can cause additional female-specific cancers (cervical cancer, ovarian cancer, breast cancer) and it can compromise pregnancy and reproductive health (12). In fact, cigarette smoking has been correlated with delayed conception (54,55), miscarriage risk (56), and early onset of the menopause (57-61).

Data suggest that the risk of early menopause increases with the number of cigarettes smoked (60,62,63).

Several authors have highlighted hormonal alterations induced by cigarette smoking, which could be involved in the onset of early menopause and reduced fertility and, consequently, in increased cardiovascular risk. These alterations concern the levels of numerous hormones and their metabolites such as: estradiol, progesterone, follicle-stimulating hormone, luteinizing hormone, and glycoprotein sex-hormone binding globulin (64-66). Conflicting data on the impact of tobacco on endogenous hormones could be due to differences in the timing of biospecimen collection (65).

Several mechanims may underlie the negative effects of smoking on sex hormone function: polycyclic hydrocarbons may injure ovarian cells causing early exaustion of ovarian follicles and falling blood estrogen levels; alkaloids, such as nicotine, may inhibit conversion of androstenedione to estrogen (59,60,67). An increase in estrogen inactivation associated with a change in the activity of cytochrome P450 systems could also be involved (68). It has also been assumed that smoke does not act directly on the ovaries, but through effects on thyroid (69) or adrenocortical function (70). Thus, the underlying mechanisms could be multiple and still need to be defined.

Studies investigating the ability of passive smoking to alter ovarian function have yielded conflicting results (58,61).

Impaired ovarian function and low blood estrogen levels associated with direct tobacco use could contribute to greater cardiovascular risk, especially in young female smokers. Indeed, before the menopause, females have a lower cardiovascular risk than males, thanks to the protective effects of estrogens, however these effects are reduced or canceled by cigarette smoking. Therefore, cigarette smoking influences cardiovascular risk and promotes CVD in different ways: directly, by acting on the mechanisms common to both sexes, albeit probably by different pathways in females, and indirectly, by reducing estrogen levels.

Hence, despite the protective effects of female gender against CVD, smoking may be especially harmful to women (26-30). Compared with males, middle-aged female smokers have a 50% increased relative risk of myocardial infarction and an increased risk of vascular mortality. The age-adjusted risk of CVD seems to correlate with the amount of cigarettes smoked per day up to 45 or more and remains even when it is adjusted for the levels of other risk factors.

As regards the development of coronary thrombosis, in women the acute effects of smoking are greater than the effects of chronic exposure. Heavy smoking in women is associated with a four-fold increased risk of sudden cardiac death, similar to that conferred by a history of myocardial infarction (31).

In 1998, Prescott et al. found that women had a significantly higher relative risk of vascular disease associated with smoking than did men (71), with a relative risk of myocardial infarction in female smokers that exceeded that of male smokers by more than 50%, even after adjustment for major cardiovascular risk factors (72).

A recently published meta-analysis, including 86 prospective trials, showed that women, compared with men, have a significant 25% increased risk of CHD conferred by cig-

arette smoking, after allowing for classic cardiovascular risk factors (73).

In the IMPROVE study, the entity of lifetime tobacco exposure significantly correlated with carotid arterial wall thickness (an index of atherosclerosis) in both genders. However, the effect in women was more than twice that in men. Furthermore, in women the effect of the progression of the disease over time was more than five-fold that observed in men (74) and the association, in both sexes, was independent of other factors.

Some authors affirm that the female excess risk of CHD could be an artifact because men who smoke might die from other smoking-related disease such as lung cancer before they have the chance to develop CHD (73).

However, the exact mechanism underlying gender-related differences remains unclear and several possible explanations have been offered: as mentioned above, tobacco smoke could interact with sex hormones, lowering estrogen blood levels and thus increasing the risk of ischemic heart disease relatively more in female than in male smokers (72); women, compared with men, might extract a greater quantity of carcinogens and other toxic agents from the same number of cigarettes (75) increasing the oxidative stress, endothelial dysfunction and inflammatory process; interactions with smoking may promote risk factors, such as diabetes and hypertension, which are more deleterious in women than in men; also, differences in smoking behavior between women and men could be taken into account (73). The increased cardiovascular risk in young female smokers could also be attributed to a chronic activation of the sympathetic nervous system (SNS), particularly influenced by nicotine, a sympathomimetic drug which promotes the release of catecholamines, both locally from neurons and systemically from the adrenal gland. It has been demonstrated that smoking alters the normal pattern of SNS activity with the ovarian cycle. In premenopausal women, SNS activity noramally falls during the early follicular phase but female smokers do not show this decline: constant SNS overactivity might contribute to the pathogenesis of CVD (76). A tobacco-mediated dysautonomic mechanism may contribute to the deleterious effects on the cardiac and vascular system. In particular, women, compared with men, are known to show a more marked age-related increase in sympathetic drive, independently of BMI, waist-to-hip ratio and menopause, which contributes to hypertension and metabolic, hemodynamic, trophic and rheological abnormalities.

A strong association between cigarette smoking and increased risk of CHD has also been demonstrated among women with type 2 diabetes mellitus, in whom it seems to amplify the excess of cardiovascular risk associated with this condition (77). Diabetes in premenopausal women appears to abrogate the cardiovascular protective effects of endogenous estrogen through different mechanisms: enhanced platelet aggregation, relatively greater coagulation and decreased fibrinolytic activity, lipoprotein abnormalities, endothelial dysfunction, enhanced oxidative stress, vascular protein glycation, and enhanced growth factor stimulation. Hyperglycemia could determine these effects, decreasing estradiol-mediated NO production from endothelial cells (78).

Moreover, cigarette smoking seems to be an independent risk factor for the development of type 2 diabetes (46,79), whose increased rate in women smokers versus non-smokers has been shown to be higher (74%) than the corresponding difference in men (45%) (80). Tobacco is also thought to increase insulin resistance and aggravate metabolic disturbances in diabetic people (81,82).

In women, in particular, starting smoking has been shown to be associated with the intention to diet and to lose weight (83,84). Indeed, given the metabolic effect of smoking, it is expected that the more cigarettes smoked, the lower the smoker's body weight will be. But, although smoking has been associated with lower BMIs (albeit with some reservations as regards heavy smokers, who seem to be more likely to be overweight) (85), as mentioned above, smoking also appears to affect fat distribution, favoring visceral accumulation (85-87). In women, hormonal alterations could play a role in visceral accumulation of fat: female smokers in fact show higher androgen concentrations and lower bioavailability of estrogens, associated with higher fasting plasma cortisol concentrations, determined by the stimulation of SNS activity (85,88). Generally, smokers have a lower BMI than non-smokers. However, heavy smoking is frequently found to be associated with less physical activity and often with general and abdominal obesity, particularly in men. A recent analysis showed that the highest mortality risks were among current smokers with BMI >35 kg/m and with the largest waist circumference. Both tobacco smoking and central obesity predispose to CVD and their combination is related to an especially high mortality risk (50).

Increased intra-abdominal subcutaneous fat is known to be correlated with insulin resistance. Consequently, through this mechanism, smoking may cause, contribute to, and/or trigger metabolic abnormalities, especially in overweight individuals, resulting in the metabolic syndrome (89). It has been shown that metabolic syndrome-related risk factors contribute to the risk of myocardial infarction more in women than in men (90).

Thus, the higher incidence of obesity and metabolic syndrome among women might explain the greater impact on cardiovascular outcome of cigarette smoking in women. Cigarette smoking has also been shown to potentiate the physiological increase in fibrinogen that occurs in postmenopausal women; hemostasis is well known to play an important role in the pathogenesis of CHD (91,92). Another possible cause of the stronger effect of tobacco smoking on women may be inflammation. Female gender seems to afford protection against the detrimental effects of systemic inflammation, as testified by the relationship between arterial wall thickening and indexes of inflammation, which is very strong in men, but absent in women; however, when women smoke they lose this protection and the relationship between CRP and arterial wall thickening becomes similar to that observed in men (74,93).

Smoking may be implicated in increasing cardiovascular risk both in young and in older women: in the former it seems to eliminate the physiological protection afforded by estrogens, while in postmenopausal women it enhances alterations that occur at this stage of a woman's

life and that promote the development of atherosclerotic disease.

However, the relative risk of CHD associated with smoking is greater for younger than for older women. Data from the American Cancer Society's Cancer Prevention Study II (CPS II) for 1982-1986 indicate that the age-adjusted relative risk of CHD was 3% in women from 35 to 64 years old and 1.6% in women aged 65 years or older (94).

Furhermore, Burke et al. have shown that cigarette smoking is implicated in sudden cardiac death, especially in young, as opposed to older, women without significantly elevated cholesterol levels, BMI or glycohemoglobin levels; the mechanism involved could be plaque rupture facilitated by toxic molecules present in smoke (95).

Non-obstructive coronary artery disease diagnosed by angiography appears to be emerging as a predictor of mortality in women, *adding microvascular disease to the causes of myocardial ischemia and necrosis.* Numerous data underline the prominent role of inflammation in sex-related differences in coronary artery disease.

Researchers have found that plaque rupture and ulceration are common in *women* with myocardial infarction without angiographically demonstrable obstructive coronary artery disease*;* occult plaque disruption with distal embolization of atherosclerotic debris or platelet aggregates and/or vasospasm is the potential etiology. As described above, smoking cigarettes could promote and influence *all the components of the different mechanisms involved.*

*F*emale smoking has also been associated with a higher risk of subarachnoid hemorrhage as well as with ischemic stroke; this association is similar to that observed in men and increases with the amount of cigarettes smoked per day (96,97). Thus, cigarette smoking appears to increase the incidence of CHD more in women than in men, but a similar pattern has not emerged for stroke.

In postmenopausal women, smoking, in addition to all its other negative effects, can also jeopardize the success of hormone replacement therapy (HRT). Clinical studies have demonstrated that in smokers the estrogen activity of orally administered HRT may be impaired or even completely canceled, along with its protective effects on the cardiovascular system (98). Girdler et al. in 2000 published the first double-bind placebo-controlled study showing oral hormone replacement benefit to be reduced by smoking (99).

The main "antiestrogenic effect" of smoking in the context of estradiol or estrogen treatment is usually attributed to a decrease in estradiol levels and an increase in estrogen inactivation, closely associated with the number of cigarettes smoked and smoking duration (98,100,101). With regard to treatment with estradiol, the effect of smoking seems to be dependent on the estrogen dose and the estrogen levels achieved (100). For this reason, the loss of efficacy induced by smoking cannot be compensated for by increasing the dosage (also because it cannot be ruled out that a higher dose might increase the production of potentially toxic metabolites), however the negative effect of smoking can be avoided when HRT is given transdermally (102). The dose of transdermally administered estradiol is actually only a fraction of the oral dose and transdermal application makes it possible to avoid high distribution levels in the liver, where the most significant estrogen-inactivating process is presumed to take place (98).

Another important aspect to be considered is the interaction between smoking and oral contraceptives (OCs): women who smoke and use OCs have an incresed risk of thrombotic disease and CVD and a higher mortality than non-OC users; the mortality rate is even higher for women who smoke 15 or more cigarettes per day (103-105). OC use alone has been associated with a moderate increase in CHD risk and this risk has been found to be 20- to 40-fold greater among OC users who also smoke heavily, compared with women who neither use OCs nor smoke (106,107). The overall risk of CHD associated with lower-dose formulations of OCs has been shown to be less than that observed with the first-generation formulations; however, the relative risk among smokers, especially heavy smokers, is still markedly higher than that among non-smokers who do not use OCs (108-110).

Also third-generation OCs seem to be associated with an incresed risk of arterial thrombosis, which is strengthened by smoking status. An exponential increase with age has been demonstrated; in fact, the relative effect of smoking on arterial thrombosis becomes significant when smoking is combined with OC use in women older than 40 years (111). For these reasons the American College of Obstetricians and Gynecologists has recommended that physicians prescribe combination OCs with caution to smoking women, particularly those older than 35 years (112).

All these data suggest that including women in tobacco-control strategies is crucial: an approach with a gender equality policy is the key to winning the battle against smoking.

Smoking cessation

Smoking cessation is associated with reduced total mortality and cardio and cerebrovascular morbidity and mortality. Jiang et al. found that smoking cessation is beneficial in attenuating the risk of carotid atherosclerosis (113). Furthermore, it has been demonstrated that after smoking cessation the risk of myocardial infarction declines following an exponential delay curve. In women, researchers have found quitting compared with continuing smoking to be associated with a significant reduction in the risk of all-cause mortality; in particular, compared with other causes, a more rapid decline was observed in mortality from coronary artery disease and cerebrovascular disease in the first five years. The atherogenic effect of tobacco, in fact, appears to be partly reversible among former smokers.

These findings are also supported by Bakuru et al. who found a reduction in inflammatory markers, used as indicator of atherosclerotic disease, in former smokers; the inflammatory component returns to baseline levels within five years of stopping smoking (114).

The reduction in cardiovascular risk may be due to the improvement in lipid profile after smoking cessation as testified by the rapid increase in HDL concentration regardless of baseline smoking intensity. This evidence shows

that even light smokers can benefit from stopping smoking. Instead, data regarding the benefit on LDL-c profile improvement are not equivocal (43). It is possible that the absence of LDL and triglyceride reduction could be due to the weight gain, which can be as much as 9.7 kg after five years (115). The main mechanisms explaining weight gain after quitting smoking include increased energy intake, decreased resting metabolic rate, and decreased physical activity. An increase in body weight is associated with atherogenic alterations in lipid profile, blood pressure and insulin sensitivity; nevertheless, the epidemiological evidence suggests that the benefits of smoking cessation far exceed any health risks that may result from smoking cessation-induced body weight gain (116). But the prospect of an increase in body weight often represents a barrier to quitting, especially in women.

The vast majority of smokers are chronically dependent on tobacco. This dependence arises from the rituals and sensations associated with smoking and particularly from the nicotine content of cigarettes. Quitting is hard: people usually have two or three attempts, or even more, before finally succeeding. Pharmacotheraphy can increase the success rate. The severity of withdrawal symptoms which patients find distressing, and in some cases unacceptable, can be controlled by nicotine replacement therapy (NRT) to reduce the urge to smoke cigarettes (117).

The first type of NRT to become widely available was chewing gum; other forms of NRT include transdermal nicotine patches, intranasal nicotine spray, and nicotine inhaler devices. Other pharmacotheraphy options are bupropion and varenicline. Bupropion was developed and first marketed as an antidepressant. Its assumed mechanism of action is inhibition of re-uptake of dopamine and noradrenaline (118). However, it has been demonstrated that bupropion in women does not prevent smoking cessation-related weight gain, unless it is associated with weight concerns counseling (119). Varenicline, a nicotine receptor partial agonist, has been shown to be twice as effective as bupropion in maintaining smoking abstinence (120,121). Recently, King et al. suggested that genetic loci influence smoking cessation and therapeutic response; different genetic signals may be associated with varenicline and bupropion treatment response. In the future, genetic markers should be identified to guide treatment decisions, resulting in improved smoking cessation rates overall, and in a reduction in smoking prevalence (122). In the most complicated cases second-line therapy may be used, including clonidine and nortriptyline (120).

Gender-related differences have also been found with regard to treatments: NRT seems to be less effective in women than in men. A meta-analysis found that the increase in quitting due to the nicotine patch versus placebo was only about half as great in women as in men at six months (4.6% vs 9.3%) (123). This gender difference in response to NRT may be partly due to genetic differences (124). Instead, varenicline and bupropion appear to be equally effective in women and men, although absolute quit rates were higher with varenicline at one year (RR: 1.52) (125,126).

However, no form of pharmacotherapy is a substitute for motivation.

Concluding remarks

This literature review highlights the great negative impact that cigarette smoking has on women's cardiovascular health. The effects of tobacco smoking seem to be considerably higher in females than in males but paradoxically cigarette smoking in on the increase among females, whereas it is clearly declining among males. Possible explanations for this trend are an unawareness of just how harmful smoking is and a widespread belief in its slimming properties (often the main reason for starting to smoke) among the female population. Another aspect to be considered is that women may need more intensive behavioral and pharmacological support when quitting. Particular emphasis should be placed on addressing stress, the need for social support, and women's concerns about weight gain.

All these considerations suggest that including women in tobacco-control strategies is crucial: an approach with a gender equality policy is the key to winning the battle against smoking.

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