Abstract

Smoking is a major cause of coronary heart disease for both men and women and a positive correlation between tobacco use and cerebrovascular disease has been also described. In addition, cigarette smoking is the most powerful risk factor predisposing to atherosclerotic peripheral artery disease. More recently, passive smoking has been also shown to represent an important risk factor for coronary artery disease. Moreover, the incidence of coronary artery and cerebrovascular diseases in ex-smokers consistently decreases after cessation, further underlying the relevance of smoking as a risk factor for these pathological conditions. The effects of cigarette smoking on atherosclerosis initiation and progression as well on its complications are mostly responsible for the enhanced cardio- and cerebrovascular risk observed in smoking compared to non-smoking subjects. Since hormonal status may also play a role in the development and stability of the atherosclerotic plaque, smoking habits could influence the clinical complications of atherosclerosis in a gender dependent manner. Up to now, however, few studies have investigated the relative importance of smoking as a risk factor for fatal and non-fatal diseases in the two sexes within the same study population. On the basis of available clinical data, this review will discuss the risk of fatal and non-fatal diseases among smoking men and women with special emphasis on cardiovascular and cerebrovascular disease which also represents the most common cause of death among smokers. A description of the mechanisms involved in the tobacco-induced atherosclerotic damage will be also given in order to underline possible gender-related differences. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Atherosclerosis; Endothelial function; Epidemiology

1. Smoking prevalence

In developed countries tobacco is responsible for 24% of all male and 7% of all female deaths, rising to over 40% in some former socialist economies and to 17% in women in the USA [1]. After the rapid spread of tobacco smoking before the 1950s in the United States and Northern European countries among males, the prevalence of cigarette smoking among females started to rise as well. In the 1970s, smoking prevalence among males and females began to decrease, with a stronger decline in males [2,3]. It has been proposed that the less favorable trend in smoking prevalence in women with respect to men may be due to lower cessation rates in women [4].

Together with gender, socioeconomic status emerged as a determinant of smoking: the habit starts among upper social classes or those with a higher educational level and later extends to lower socioeconomic groups [5]. However, it is difficult to classify smoking prevalence by gender or socioeconomic status because many differences between countries and habits may be relevant. Several studies have shown that smoking spreads through populations like an epidemic with four stages [3,6]. In stage 1, smoking is an exceptional behavior and mainly a habit of higher socioeconomic groups. In stage 2, smoking becomes ever more common. Rates among men peak at 50–80% and are equal among socioeconomic groups or higher among higher socioeconomic groups. In women these patterns usually lag 10–20 years behind those of men. Women from higher socioeconomic groups first adopt smoking. In stage 3, the
prevalence rate among men decreases to ~40% since many men stop smoking. Women reach their peak rate (35–45%), and at the end of this stage their rates start to decline too. In stage 4, prevalence rates keep declining slowly for both men and women, and smoking becomes progressively more a habit of the lower socioeconomic groups. There are international variations in smoking-related habits, which may fit with differences between countries according to their smoking stage.

2. Gender- and smoking-related atherosclerotic disease

Smoking causes more deaths from coronary heart disease (CHD) and stroke than any other disease [7] and represents, together with hypercholesterolemia and hypertension, one of the major acquired risk factor for the development of atherosclerotic disease [8]. Cigarette smoking is not only strongly associated with atherosclerosis and ischemic heart disease [9], but is also a major risk factor for acute coronary thrombosis [10]. Indeed, 75% of sudden cardiac deaths due to acute thrombosis are in cigarette smokers [11]. In particular, in younger women, in which the smoking prevalence is currently increasing, cigarette smoking is clearly the most important risk factor for sudden cardiac death [12,13]. That cigarette smoking increases the tendency to thrombosis is also suggested by the strong association between smoking and myocardial infarction compared with a much weaker association with angina pectoris [14]. In fact, among smokers, acute myocardial infarction is most often precipitated by thrombosis at less severe, unstable atherosclerotic lesions [15].

In the United States, active cigarette smoking results in ~100,000 deaths due to coronary heart disease each year [16] and the risk of an acute CHD event in smokers has been estimated to be about twice as high as in non-smokers [17]. Men were overall 4.6 times more likely to have a myocardial infarction with respect to premenopausal women and this has been attributed to the beneficial effect on cardiovascular system of female hormones [18]. However, the sex difference in mortality from coronary heart disease varies over time and between countries in a way that cannot be explained solely by endogenous estrogen [19]. Moreover, it appears that smoking has a much larger relative detrimental impact on CHD in women; it should however be stressed that, due to the different absolute risk of the disease observed between women and men, the relative risk associated with cigarette smoke should be interpreted cautiously. Attributable risk, in fact, is in general lower in women than in men.

In a prospective study including both men and women aged 35–52 years, it has been demonstrated that the incidence of myocardial infarction is increased 6-fold in women and 3-fold in men who smoked at least 20 cigarettes per day compared with never smoking. In addition, although the incidence of myocardial infarction is usually greater among men, the rate in female heavy smokers exceeded that of never-smoking men. Current smoking was identified as a stronger risk factor in women than in men (relative risk 3.3 vs. 1.9) and smoking-related gender differences were more pronounced when considering women under 45 years of age [9]. This study is in accordance with the Copenhagen City Heart Study, in which the relative risk of a first myocardial infarction in smokers was 9.4 in women and 2.9 in men with respect to non-smokers and the risk increased by 2–3% for each gram of tobacco smoked [20]. Tverdal and coworkers [21] studied the mortality for different causes in relation to smoking history in men and women aged 35–49 followed for 13.3 years. They found that the relative risk of coronary death per ten cigarettes per day was 1.8 in women and 1.2 in men. An increased susceptibility of female smokers to acute myocardial infarction (33% increase in adjusted relative risk) has been recently confirmed by a large prospective study [22].

The more detrimental effect of smoking in women with respect to men is also evident comparing data obtained in case-control studies among women and in prospective studies where only one sex was considered. In the Nurses' Health Study, CHD incidence was prospectively examined in relation to cigarette smoking in a cohort of females 30–55 years old during 6 years follow-up. The number of cigarettes smoked per day was positively associated with the risk of fatal coronary heart disease (relative risk of 5.5 was observed in women smoking at least 25 cigarette per day), non-fatal myocardial infarction (relative risk 5.8) and angina pectoris (relative risk 2.6) [23]. Rosenberg and colleagues [24] evaluated the influence of individual risk factors on the relationship between non-fatal myocardial infarction and cigarette smoking in a case-control study of women younger than 50 years of age who survived first myocardial infarction. The risk of myocardial infarction increased with the number of cigarettes smoked, both in the presence and the absence of risk factors for CHD (high total serum cholesterol, low HDL cholesterol, hypertension, diabetes mellitus). Moreover, an enhanced number of fatal myocardial infarction cases was reported for smoking women aged 15–44 in a case-control study of risk factors for heart attack [25].

A positive correlation between cigarette smoking and either coronary death or stroke was also found in the MRFIT (Multiple Risk Factor Intervention Trial) study in males. The risk increased with the number of cigarettes smoked and was maximal for 25 cigarettes per day. The relative risk with respect to non-smokers did not exceed 2.5. Substantial differences (34–49% lower) in subsequent CHD mortality were evident for men who reported cigarette smoking cessation by the end of the trial compared with those continuing to smoke [26]. Interestingly, a recently published paper reports that the increased risk of CHD in smoking men may have a genetic component, being more
evident in men carrying the apolipoprotein E epsilon 4 allele [27]. On the other hand, the Framingham study failed to demonstrate a positive correlation between smoking and coronary heart disease among women [28]. When considering the associations between various cardiovascular risk factors such as high systolic blood pressure, high cholesterol level and smoking, however, an increased risk of carotid stenosis was found in women but not in men [29]. In the classic American [30] and British [31,32] studies for coronary mortality, the relative risks associated with smoking were similar in the two genders.

There are some discrepancies between studies in demonstrating a different ‘penetrance’ of smoking as a risk factor for atherosclerotic disease in women. Conflicting results between studies may be related to many factors such as sex differences in smoking habits and cessation during follow-up (in general more men than women quit smoking) [17,33], different age distribution of women included into the studies [9], oral contraceptive use [24] and end points of the study. In fact, the relative increase in risk was generally greater, the lower the underlying predisposition to myocardial infarction. In particular, among women aged 45–49, smokers of at least 35 cigarettes daily were estimated to have a risk of MI five times that of women who never smoked, while among women aged 25–29 the corresponding increase was 3-fold. Nevertheless, the absolute increase in risk attributable to smoking is usually greater among those whose baseline risk is higher, that among older women [24]. Moreover, if all cardiovascular disease cases are included in a single end-point, the difference between sexes may be diluted thus leading to misclassification [34].

The association between smoking and cardiovascular disease was first recognized in the 1950s [35] but more recent evidence suggests the existence of a relationship between number of cigarettes smoked daily and stroke risk [36]. Cigarette smoking is responsible for up to one quarter of all strokes and several large cohort and case-control studies have consistently found the relative risk of stroke among current smokers to be higher (between two and four times) than among non-smokers [37]. A population-based study followed for 14 years in men and women 35–52 years of age found that daily smoking increased the risk of stroke in both men and women, the relative risk being non-statistically different in the two sexes (1.6 and 2.1, respectively) [38]. Kawachi and colleagues [39] found a 2.6-fold increase in the relative risk of total stroke in middle-aged female nurses who were current smokers compared with never smokers. The risk of stroke increased along with the number of cigarettes smoked daily from 1.8 among light smokers to 4.2 among heavy smokers. In middle-aged men, current smoking was associated with a nearly 4-fold increased relative risk of stroke compared with never smokers in a follow-up period of ~13 years [40]. A dose-dependent increased risk of ischemic stroke was also reported in male physicians [41], with a relative risk of 2.0 when smoking 1–19 cigarettes per day and 2.7 when smoking more than 20 cigarettes per day. Overall, differently from that observed for CHD, only a small difference in the risk of stroke was observed between sexes, with a greater increase in women compared with men current smokers [36] (Table 1). Some confounding factors such as the concurrent use of contraceptives in women and the small protective effect of alcohol use in men who smoke may be at least in part responsible for the differences observed between the sexes in the prevalence of stroke in current smokers.

Atherosclerotic peripheral arterial disease (PAD) is a common and probably underdiagnosed disease, affecting ~8–10 million people in the United States [42] with a higher incidence in men compared to women [43]. The occurrence of PAD is attributable to classical cardiovascular risk factors. For symptomatic PAD in older subjects, smoking has a more deleterious impact in women than in men, with relative risks of 4.6 and 2.5, respectively [44].

A positive relationship between smoking and diabetes mellitus, a major independent risk factor for atherosclerotic disease, has also been recently confirmed by a large prospective cohort study. Among those who smoked ≥2 packs per day at baseline, men had a 45% higher diabetes rate than men who had never smoked; the corresponding increase for women was 74% [45].

Table 1

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<th>Smoking</th>
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<td>Ex-smokers</td>
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<td>Passive smokers</td>
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3. Gender-related mechanisms in atherosclerotic lesions in smokers

Clinical manifestation of atherosclerosis may result in unstable angina, myocardial infarction and sudden death. Indeed, arterial atherosclerotic lesions by themselves may produce stable symptoms such as angina pectoris precipitated by increased oxygen demand, while physical disruption of vulnerable atherosclerotic plaque may lead to occlusive thrombus formation causing acute coronary syndromes [46]. Inflammation plays a pivotal role in the pathophysiology of such acute thrombotic events and infectious agents might potentiate the complications of existing atheroma [46–48]. Interestingly, Burke et al. [12] found that traditional risk factors such as smoking have distinct mechanisms of plaque instability and sudden coronary death in women, which vary by menopausal status.

As previously discussed, cigarette smoking increases the risk of atherosclerosis in coronary, cerebral and peripheral arteries. Several autopsy studies have demonstrated that smoking is associated with more severe coronary lesions and that the effect of smoking on atherosclerosis is more pronounced in the aorta than in the coronary arteries of adults. These results have been recently confirmed in a multicenter cooperative study demonstrating a higher prevalence of advanced lesions in 15–34-year-old patients who smoked with respect to non-smokers [49]. Moreover, both past and current active and passive smoking are associated with increased carotid intimal-medial wall thickness [50]. Smoking is postulated also to cause both ischemic and hemorrhagic stroke by promoting atherogenesis [51,52]. Consumption of cigarettes exposes the smokers to a range of harmful substances, several of which have a potential impact on the process of atherosclerosis [53], but the mechanisms of the increase in coronary and cerebrovascular disease risk associated with smoking are not completely understood (Fig. 1).

Endothelial dysfunction, an early phenomenon in atherogenesis, has been described in brachial and coronary arteries of healthy chronic and acute smokers [54–56]. It has been suggested that this may be related to reduced plasma NO concentration and enhanced oxidant injury [57–59]. Cigarette smoking is strongly associated with atherosclerotic complications as well, being a major risk factor for acute coronary thrombosis [10]. Indeed, smoking may promote arterial thrombotic complications by impairing endothelial cell function, increasing the concentration of fibrinogen and altering platelet activation [60–62]. The impact of smoking on the risk of thrombotic complications was evaluated retrospectively in both men and women with essential thrombocytosis. Among women 60% of the smokers and 15% of the non-smokers experienced arterial thrombosis. Men had a significantly higher risk of arterial

Fig. 1. Differential effects of smoking and estrogen on atherosclerotic disease.
thrombotic complications than women, but no difference between smokers and non-smokers could be found [63]. Hormonal differences may explain these findings to some extent: among women, an additional factor, such as smoking, may in many cases be needed for the development of thrombosis.

However, few studies have investigated the possible mechanism(s) underlying sex differences in CHD related to smoking. The antiestrogenic effect of cigarette smoking could be related, at least in part, to the increased risk of CHD in young female smokers, which is relatively higher than in men. Smoking appears to alter estradiol metabolism, leading to enhanced formation of inactive catechols [64] (Fig. 1). This may be related to induction of estrogen-metabolising cytochrome P450 isoenzymes CYP1A1 and CYP1A2 [65]. Recently, it has been also published that in smoking women under oral estrogen replacement therapy plasma levels of estrogen were 40–70% lower than in non-smoking women [66]. Moreover, a decrease in both estradiol and testosterone concentrations in men currently smoking has also been reported, but the interpretation of these results is still difficult [67].

HDL cholesterol was more reduced in absolute and relative terms in female than in male smokers [9,68] and this could be associated with sex hormone concentrations. Stratified by serum HDL cholesterol, the smokers to non-smokers ratio of myocardial infarction incidence was higher in women than in men, suggesting that mechanisms other than HDL reduction may be responsible for the gender-related difference observed. Indeed, the PROCAM study reported similar HDL cholesterol and triglyceride levels in men and women current smokers. The mean increase in total cholesterol in women, however, was twice that of men and that of LDL cholesterol was almost four times as great, leading to a 1.5-fold greater increase in the LDL/HDL cholesterol ratio in female versus male smokers [69]. These differences may reflect variations between the population studied.

### 4. The impact of passive smoking on atherosclerotic disease

Passive cigarette smoking is associated with a smaller increase in the relative risk of coronary heart disease than is active cigarette smoking, but this increase is nevertheless relevant. Epidemiological studies have shown that the risk of ischaemic heart disease in non-smokers exposed to tobacco is increased by 30%, almost half that of smoking 20 cigarettes per day [70–72].

In a meta-analysis of epidemiologic studies, non-smokers exposed to environmental smoke had a relative risk of CHD (including myocardial infarction and death due to CHD), of 1.25 as compared with non-smokers not exposed to smoke, after adjustment for important confounding factors (age, sex, body weight, blood pressure and serum cholesterol level). The authors found a significant dose–response relationship, with relative risks of 1.23 and 1.31 for exposure to the smoke of 1–19 or more than 20 cigarettes per day, respectively [73]. Accordingly, the meta-analysis by Law and colleagues [70] reported that the relative risk of ischaemic heart disease associated with exposure to environmental tobacco smoke was 1.30 at age 65. In a large prospective study of male and female never smokers enrolled in the Cancer Prevention Study II, the relative risk of coronary heart disease was 1.22 higher in non-smoker men married to currently smoking wives compared with those married to wives who had never smoked. The corresponding rate ratio for women was 1.10 [74]. A 12-year study evaluating total mortality associated with passive smoking reported a relative risk of death from all causes of 1.17 for men and 1.15 for women with passive exposure [75]. Interestingly, compared to never smokers, the odds ratio (OR) for exposure to environmental tobacco smoke during childhood was 0.97 for men and 0.92 for women, whereas the adjusted OR associated with adult exposure was 1.5, although no trend was observed with the number of years of exposure [76]. A review by Wells et al. on heart disease from passive smoking in the workplace indicated that morbidity risk was twice the mortality risk, and both types of risk were higher in women [77].

Recent studies have shed some light on the effect of passive smoking on CHD. To study the acute effects of passive smoking on coronary circulation, Otsuka and colleagues [78] assessed coronary flow velocity reserve, a measure of endothelial function, before and after a 30-min exposure to environmental tobacco smoke, using trans-thoracic Doppler echocardiography of the left anterior descending coronary artery. Before exposure to environmental tobacco smoke, coronary flow velocity reserve was significantly higher in non-smokers than in smokers. After exposure to environmental tobacco smoke, however, coronary flow velocity reserve in non-smokers decreased and was not significantly different from that of smokers. The effect of passive smoking on cardiac morbidity and mortality may be as high as one third of the effect of active smoking, emphasizing the importance of protection from even short-term exposure to secondhand smoke. Overall, even if there are to date no clinical studies specifically designed to answer the question of whether passive smoking differently influences CAD between males and females, it seems that, as for active smoking, passive smoking may have a more detrimental impact on women with respect to men (Table 1). Although it can not be ruled out that confounding factors such as lifestyle and diet are responsible for the enhanced CHD risk observed between passive smokers compared to non-smokers [79], the high prevalence of passive cigarette smoking at home and in the workplace should make the population aware of its possible relevant impact in terms of cardiovascular mortality.
5. Smoking cessation and atherosclerotic disease

It is largely accepted that smoking cessation has favorable effects on total mortality as well as on cardio- and cerebrovascular morbidity and mortality. Moreover, it has been observed that stopping smoking delays the onset of atherosclerotic disease by about a decade [8].

There is no general consensus on the relative risk reduction in former compared to current and never smokers and the excess risk of CAD does not seem to completely disappear a few years after cessation. Moreover, the time required for former smokers to reduce the risk of death to baseline differs across studies, ranging from 2 to up to 20 years for coronary heart disease mortality.

In particular, there are few data on how gender may influence the risk of cardio- and cerebrovascular diseases in ex-smokers compared to current smokers, because most large prospective studies with data on smoking cessation were based on men.

Data from the Framingham study reported that men under the age of 65 who were cigarette smokers at entry and subsequently stopped had CHD attack rates which were half those experienced by those who continued to smoke [80].

Qiao and colleagues [81] found that adjusted ratios for 35-year CHD mortality were 1.63 and 1.39 in current and former smokers, respectively. In addition, the relative risk for 10-year mortality was stronger in both groups, given the same amount of cigarettes smoked. On the other hand, data from the Copenhagen City Heart Study have shown that ex-smokers have the same risk of developing their first myocardial infarction as those who have never smoked, regardless of duration of smoking and time elapsed since quitting [20]. In a 13-year follow-up study, Tverdal et al. [21] reported that among men who had quit cigarette smoking, the CHD mortality decreased with time since quitting smoking to almost the level of the never smokers after 5 years.

In a prospective cohort study with female nurses [82] (Table 2), a 24% reduction in the mortality from CHD was apparent within 2 years of giving up cigarettes; however, only after 10–14 years following cessation did the risk drop to the level of never smokers, irrespective of the age at starting smoking. A population-based control study conducted in order to investigate the risk of myocardial infarction or coronary death in ex-smokers has shown that odds ratios declined rapidly after quitting and were not statistically different from unity within ~3 years. The short time reported in this study may support the view that smoking acts mainly on thrombogenesis rather than as a promoter of atherosclerosis. However, even if women had consistently and significantly higher mean relative risk values than men, fibrinogen concentrations were not significantly different between sexes in this study [83]. Accordingly, Rosenberg et al. [84] found that the risk of a first myocardial infarction in ex-smoking women (25–65 years) who had not smoked for 3 or more years was indistinguishable from that of women who had never smoked, regardless of age, duration of smoking and presence or absence of other predisposing factors.

In a prospective study, the relative risk of mortality from all and cardiovascular causes was evaluated in subjects aged 65 years or older during 5-year follow-up [85]. Among former smokers, risk of cardiovascular mortality was similar to that observed in never smokers, irrespective of the number of years since quitting smoking, and no differences between sexes were detected. Gender-related differences in the relative risk may have faded because of the fact that women in that age range are entering their years of higher absolute risk.

Differences observed between studies may be related to several factors such as age of cessation, duration of the smoking habit before the start of the study, number of cigarettes consumed and presence of confounding factors (other risk factors, illness status as a cause for quitting smoking). Moreover, recidivism among ex-smokers in prospective studies may produce differences in the time required to lower the relative risk to unity.

As for CHD, stopping smoking reduced the relative risk of stroke in both men and women. In the Framingham study stopping smoking reverted the risk of stroke to the level of non-smokers within 5 years, but no separate comparison was made between ex- and never smokers [86].

In general, case-control and observational studies consistently show that ex-smokers have relative risks of stroke that are intermediate between those of non-smokers and current smokers and greater than people who have never smoked [39,40,87–89] (Table 2). Similarly, the rate of progression of atherosclerosis measured by ultrasound technique is intermediate between rates of non-smokers and current smokers [90].

In a population of middle-aged female nurses during a 12-year follow-up the excess risk for total and ischemic stroke among former smokers largely disappeared between 2 and 4 years after cessation. Within 2 years of stopping smoking, the relative risk of stroke was reduced by 22% compared with continuing smoking, and within 4 years it was reduced by 54%, being 1.2 times the risk of never smokers and 0.5 that of current smokers [39]. The same
patterns of decline were observed regardless of number of cigarettes smoked, age at starting and presence of other risk factors. On the contrary, in a 12.75-year follow-up study of middle-aged British men, the benefit of giving up smoking was seen within 5 years of quitting, but this was dependent on past levels of smoking. Light-moderate smokers (less than 20 cigarettes/day) reverted to the risk level of those who had never smoked, whereas heavy smokers (more than 20 cigarettes/day) retained a 2.2 relative risk compared to never smokers [40]. Overall, the findings warrant efforts to encourage smokers to stop at any age, although the best public health advice remains to not start smoking at all.

6. Drugs, smoking and gender

Smoking might influence the plasma concentration of several drugs primarily by interfering with their metabolism, as previously discussed for estrogens [65].

Gender differences in drug metabolism have also been described and involve multiple metabolic pathways. Indeed, pharmacokinetic differences may be responsible for alterations in pharmacodynamic responses. For example, β-blockers and calcium channel blockers have been demonstrated to have gender-specific responses [91,92]. Pharmacokinetics in metabolic pathways have been associated with greater drug exposure in female subjects. To our knowledge, there are no studies designed to identify the influence of medication on both gender and smoking. However, if a smoker takes a drug that is metabolized primarily by the CYP1A2 system, an increased dose may be required [93].

7. Conclusions

In view of its high prevalence and the increased risk as discussed in this review, both passive and active smoking should be considered among the most important known modifiable risk factors for CHD and stroke. The analysis of gender-related differences in the risk of smoking-related disease is relevant in order to make the population aware of the health impact of smoking. Whereas gender-specific cardioprotective effects of female hormones have been widely recognized, it is important to underline that smoking women, due to both the antiestrogenic effect and the unfavorable lipid profile of smoking, apparently lose their ‘natural’ protection against CHD. The impact of smoking as a risk factor for coronary artery disease may be more detrimental in postmenopausal women due to the lack of natural estrogen protection, or in subjects at risk of thrombosis such as women taking oral contraceptives. The less favorable trend in smoking prevalence and cessation in women compared to men calls into question the priority of smoking prevention among women.

References


