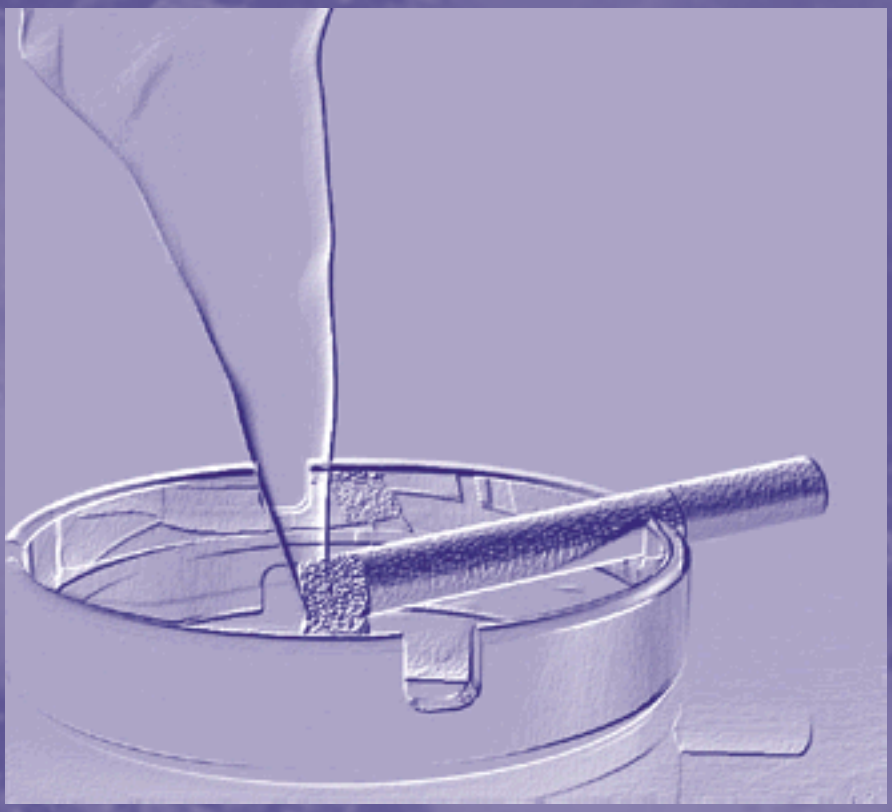
The public health impact of smoking and smoking cessation



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Abstract

Despite the overwhelming evidence that smoking cessation reduces the risk for several chronic diseases, information on the magnitude of these public health benefits is scarce. It has furthermore been suggested that smoking cessation also improves health-related quality of life, but this has not been conclusively shown. The aims of this thesis were to quantify future public health benefits of smoking cessation and to give more insight into the impact of smoking cessation on health-related quality of life.

First, the associations between smoking or smoking cessation and other risk factors for tobacco-related diseases were studied. Using ecological data of the Seven Countries Study, comprising middle-aged men in 16 cohorts in Europe, the United States and Japan, 25-year lung cancer mortality rates among smokers were higher in cohorts with high fat intake than in those with low fat intake, especially for saturated fatty acid. We were not able to conclude whether the effects of smoking and saturated fatty acid intake on lung cancer mortality were independent or that effect modification played a role. In the Doetinchem cohort study among 20-59 year old Dutch men and women, smoking cessation was associated with higher HDL cholesterol levels, which may contribute to the favourable effect of smoking cessation on cardiovascular diseases (CVD). Unfavourable postcessation weight gain partly explained the increase in total cholesterol level and blood pressure after smoking cessation.

The effect of smoking cessation on future morbidity and mortality was estimated with computer simulation modelling. We first estimated that a reduction in smoking prevalence to 20% in 2015 in each member state of the European Union (EU) (WHO's 'Health for All' target) would lead to a reduction in pancreatic cancer patients up to 2015 of 29,500 males and 9,500 females in the EU. Secondly, we observed that this target was expected to reduce the number of total deaths up to 2015 with 2.5% (around 1.1 million deaths) among men and 0.8% (almost 350,000 deaths) among women in the EU. These reductions in mortality were about 30%-50% of those achieved if all smokers would quit instantly. Moreover, applying the Framingham risk function to 40-74 year old Dutch smoking men and women with a high risk for coronary heart disease (CHD), we estimated that smoking cessation, although less or comparably effective in primary prevention of CHD, would lead to a 2-2.5 years larger gain in healthy life expectancy than cholesterol lowering medication.

Finally, Dutch male and female ex-smokers reported higher health-related quality of life scores than current smokers, especially for mental health dimensions, in a cross-sectional study. Generally, the higher the amount of smoking, the larger were quality of life differences between ex- and current smokers.

In conclusion, results in this thesis are one of the first to quantify the effects of smoking cessation on future morbidity and mortality. This information is useful to policy makers, in order to adjust future health care to smoking behaviour changes. Furthermore, this thesis provides evidence that smoking cessation leads to changes in other classical CVD risk factors. This implies that the favourable effect of smoking cessation on CVD risk may partly be mediated by postcessation changes in other CVD risk factors. Finally, our results suggest that smoking cessation also may improve health-related quality of life, especially mental health, but this finding needs to be confirmed in cohort studies.

Contents

1

General introduction

Introduction

Tobacco has been used for many centuries. It was originally cultivated in the Americas and was brought to Europe in the 15th century by Columbus. Initially, tobacco was used in pipes and cigars or as snuff or chewing tobacco.[1,2] In the beginning of the 20th century, tobacco smoking in the form of cigarettes rose dramatically.[1,2] Since the first Surgeon General's Report in the United States in 1964,[3] causally linking cigarette smoking to lung cancer, a huge amount of studies have shown that smoking not only increases the risk for lung cancer, but also the risk for a number of other diseases, including other types of cancer, cardiovascular diseases and chronic obstructive pulmonary disease (COPD).[4-6] Besides the harmful effects of smoking on morbidity and mortality, smoking also leads to poor health-related quality of life.[7,8] This makes cigarette smoking the number one preventable public health problem in western countries.

Numerous studies have shown that smoking cessation decreases the risk for these tobacco-related diseases.[9] Furthermore, it is suggested, although not conclusively shown, that smoking cessation also improves health-related quality of life.[10,11] Despite the overwhelming evidence of the benefits of smoking cessation, information on the magnitude of these public health benefits is scarce. The aim of this thesis, therefore, is to quantify the future public health benefits of smoking cessation. Furthermore, this thesis aims to give more insight into the impact of smoking cessation on health-related quality of life.

Prevalence of smoking behaviour

In western societies, smoking prevalence increased rapidly in the beginning of the 20th century and has been declining for several decades. This trend started among males and was followed by females some decades later.[12,13] The tendency that women generally take up smoking later than men is mainly due to socio-cultural factors, such as a lower income among women or the socially unacceptability for women to smoke in public. Female emancipation and tobacco promotion by the tobacco industry targeted on women are important initiators of female cigarette smoking.[14,15]

Although the trend in smoking behaviour shows similar patterns among western countries, the prevalence of smoking differs. A relatively low percentage of male smokers is found in countries like Sweden (17%), Finland and the United States (both around 27%), whereas a high percentage is seen in Japan (53%), Germany and Spain (both around 44%). Among females, the prevalence of smoking is low in

Portugal (7%), Japan and Italy (both below 20%) and high in Denmark, Germany and Ireland (30% or more). These percentages reflect smoking prevalences in the second half of the 1990's.

In the Netherlands, the smoking prevalence among men and women approached in time (Figure 1). In the 1950's around 90% of the males aged 15 years and over were smokers. This percentage decreased dramatically to around 37% in the late 1980's and stabilised after that period. Among women, smoking prevalence rose during the 1960's from 30% to 40%, followed by a decrease in the following decades and it fluctuates now around 30%. In contrast to older people, among the 15-19 year olds, the smoking prevalence was comparable among men and women in time (Figure 1). The smoking prevalence among 10-14 year olds fluctuates since the 1980's around 10%.[16] Table 1 expresses the current (2000) prevalence of smokers and ex-smokers in the Netherlands among different age classes. Compared to other western countries, current Dutch smoking prevalence is high, especially among women.[13]

Generally, men are more likely to smoke than women.[13] Furthermore, smoking is more prevalent among younger age groups[16,17] and among subjects with low socio-economic status.[12,18] In general, cigarette smoking is associated with several unfavourable lifestyle factors, such as a higher intake of alcoholic beverages,[19] a less healthy diet[20,21] and a lower physical activity level,[22] which may reflect socio-economic status among smokers. Smoking cessation is reported to be associated with male sex,[23] older age,[23,24] and higher socio-economic status.[24]

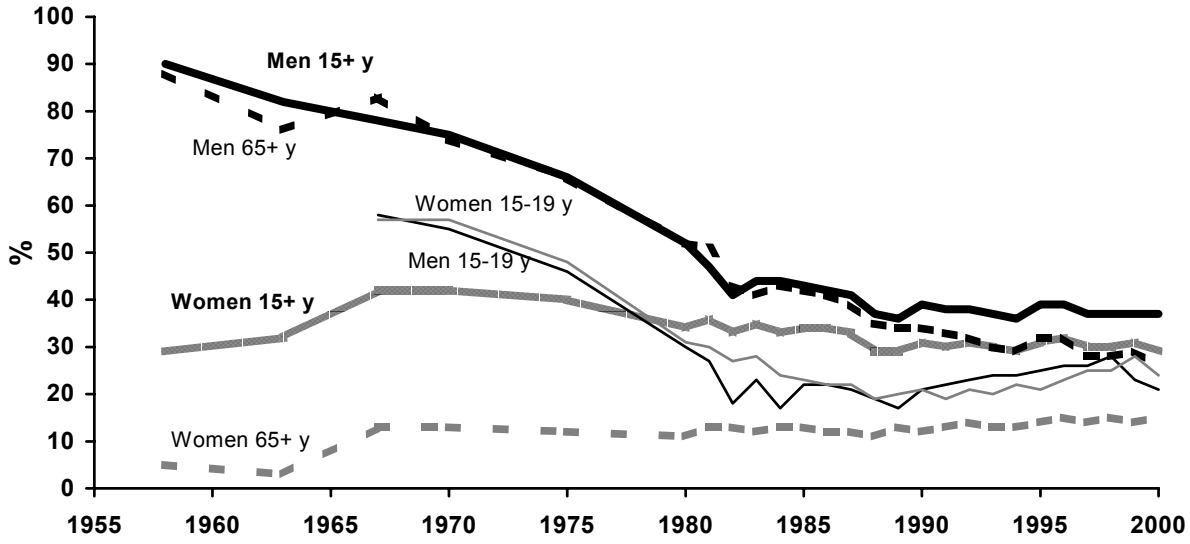

Figure 1 Smoking prevalence in the Netherlands among men and women, from the 1950's up to 2000. Source: Stivoro.[16]

Table 1 Smoking prevalence in 2000 among men and women in different age classes in The Netherlands.

	Men		Women	
Age (y)	Smokers (%)	Ex-smokers (%)	Smokers (%)	Ex-smokers (%)
15-24	32	2	29	4
25-44	42	11	34	13
45-64	37	26	30	19
65-74	29	37	19	14
75+	20	44	11	12
All ages (15+)	37	18	29	13

Source: Stivoro, written communication. Data comprise age range 15 years and over.

Content of cigarette smoke

Tobacco smoke consists of more than 4,000 different chemical components, of which most are formed during burning of the tobacco product.[1] Nicotine is the principal addictive component of smoke.[25] 'Tar', a mixture of all particles in smoke minus water and nicotine, contains several carcinogenic compounds, of which PAHs (polycyclic aromatic hydrocarbons), including benzo[a]pyrene, and N-nitrosamines, including NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) are the most important carcinogens.[26,27] Other chemical components in cigarette smoke include carbon monoxide, carbon dioxide, nitrogen oxides and ammonia. The amount of these components in cigarette smoke depends, among others, on the smoking conditions, the type of tobacco and the design of the cigarette, such as the presence of a filter.[1] Shortly after inhalation of cigarette smoke, a part of these components reaches the blood stream and may induce the development of tobacco-related diseases, through several mechanisms.

Smoking behaviour and public health

Numerous studies have shown that cigarette smoking is a strong risk factor for premature death. About half of those who continue to smoke will eventually be killed by the habit.[28] It is estimated that smoking caused about 4-5 million deaths worldwide by the end of the 1990's, which is expected to increase to at least 10 million each year by 2030, if current smoking patterns remained.[29,30] Shaw et al. estimated that one cigarette may reduce life by eleven minutes.[31] We have

previously shown, using data from the Seven Countries Study, that the elevated mortality risk due to cigarette smoking is independent of culture.[32] Smoking cessation reduces total mortality risk: after 10-15 years of abstinence, the risk is almost reduced to that of never smokers.[9] This section gives a concise overview of the risks of smoking, the benefits of smoking cessation and the underlying mechanisms of the effect of smoking on the two major tobacco-related diseases: cardiovascular diseases and cancer. Furthermore, it reviews the available evidence on the association between smoking, smoking cessation and another important aspect of health status: health-related quality of life.

Smoking behaviour and cardiovascular diseases

Together with serum cholesterol and blood pressure level, cigarette smoking is a major cause for cardiovascular diseases (CVD).[5,33-37] Peto et al.[28] estimated that, in 1995, 13% of all deaths from CVD in developed countries could be attributed to smoking. In the past decades, numerous epidemiological studies estimated the excess risk of smokers for CVD. Results from these studies show that the risk for coronary heart disease (CHD) among smokers is generally about twice the risk among non-smokers.[5] Furthermore, Shinton and Beevers[34] showed in a meta-analysis using 32 studies that smokers have an about 1.5 times higher risk of dying from stroke than non-smokers. Among women, recent studies report higher relative risks of smokers for CVD than earlier studies. This is probably due to the tendency that women nowadays smoke more cigarettes per day and start smoking at an earlier age.[15] Results of a few studies suggest that the relative risk for CVD is higher in women than in men,[34,35,38] but this sex difference was not conclusively reported.[36] A possible higher relative risk in women than in men may be explained, although speculative, by an interaction between smoke components and some female hormonal factors.[34,35] In general, CVD risk increases with the number of cigarettes smoked daily, the number of years smoked, the age at initiation and the degree of inhalation.[5,15,34,35,37]

There is strong evidence that giving up smoking decreases CVD risk.[9] About 1 year after smoking cessation, the risk of dying from CHD is halved, and it becomes similar to that of a never smoker after about 10-15 years. The risk of stroke reaches the risk of a never smoker after about 5-15 years of abstinence. LaCroix et al.[36] showed, in a longitudinal study among subjects aged 65 years and over, that the benefits of smoking cessation on CVD risk continue even at older ages, regardless of the number of years of abstinence.

Mechanism

Several mechanisms for the effect of smoking on CVD have been suggested.[39] One mechanism includes the binding of nicotine to specific acetylcholine receptors, leading to activation of the sympathetic nervous system. Among others, this results in increase in heart rate and blood pressure, coronary vasoconstriction and myocardial contractility, which are all related to CVD.[39] Furthermore, cigarette smoking accelerates atherosclerosis, the underlying process of CHD and stroke. In short, atherosclerosis is caused by endothelial injury, followed by lipid accumulation in the intima and the formation of cholesterol-laden foam cells. Oxidized LDL promotes and HDL cholesterol inhibits the formation of foam cells. As these lesions progress, an atherosclerotic plaque is formed, which may obstruct arterial blood flow or may rupture leading to thrombosis, which causes cardiovascular syndromes.[40-42] Smoking is suggested to affect this process in several ways. First, free radicals in smoke may lead to endothelial dysfunction.[40] Second, smoking may play a role in lipid metabolism associated with atherosclerosis.[39] For instance, smokers have higher LDL and lower HDL cholesterol levels than non-smokers,[43] possibly due to nicotine.[39] Smoking also results in higher levels of oxidized LDL,[44] which activates formation of foam cells. Third, blood coagulates more easily, levels of fibrinogen are higher and platelets are more reactive in smokers compared to non-smokers, which leads to thrombosis. Another suggested mechanism for the effect of smoking on CVD is the effect of carbon monoxide. This binds on haemoglobin in the blood, forming the carboxyhaemoglobin (COHb), which reduces the oxygen transport to the myocardium.[39]

Smoking behaviour and cancer

Cigarette smoking is a risk factor for several types of cancer.[1,4,36,37,45] The most important one is lung cancer. Other established tobacco-related types of cancer include cancer of the oral cavity, pharynx, larynx, oesophagus, pancreas, bladder and kidney. Peto et al.[28] estimated that almost 90% of all lung cancer deaths and 30% of all cancer deaths in the developed world were attributable to cigarette smoking in 1995. A broad range of relative risks for these types of cancer of smokers and ex-smokers compared to never smokers has been reported in the literature.[48] Shopland et al.[45] reported relative risks based on a large prospective cohort study in the United States of America (Table 2). In general, the relative risk for tobacco-related cancers increases with the amount of cigarettes smoked daily, the duration of smoking and the age at initiation.[4,47-52] However, the duration of smoking is thought to have far more impact on at least lung cancer risk than the number of cigarettes smoked.[49] As for CVD, the relative risks for most tobacco-

Table 2 Relative risk of smokers and ex-smokers compared with never smokers for mortality from tobacco-related cancers.

	Men		Women	
	Smokers	Ex-smokers	Smokers	Ex-smokers
Lung	22	9.4	12	4.7
Oral/pharynx	27	8.8	5.6	2.9
Larynx	10	5.2	18	12
Oesophagus	7.6	5.8	10	3.2
Pancreas	2.1	1.1	2.3	1.8
Bladder	2.9	1.9	2.6	1.9
Kidney	3.0	2.0	1.4	1.2

[a] Source: Shopland et al.[45]

related cancers have increased in time in the United States, among female smokers, but for cancer also among male smokers. This is probably because the full effects of cigarette smoking was not visible yet in early studies or due to the change in smoking behaviour over time.[15,45,53]

Cancer risk substantially decreases after smoking cessation, although it is doubted whether cancer risk after cessation ever reaches that of never smokers (Table 2).[9] After 10 years of abstinence, the risk for lung cancer has decreased with about 50%-70%. The risk for cancer of the oral cavity, oesophagus and bladder is halved after a few years of cessation. Some studies have found that pancreatic cancer risk reaches the risk of never smokers after about 10-15 years of abstinence.[54,55] Peto et al.[56] estimated that smokers who quit at age 50 or 60 years, still avoid most of the tobacco-attributable risk for lung cancer of those who continue to smoke and that smoking cessation at 30 years of age may even avoid more than 90% of the tobacco-attributable risk.

Mechanism

Most of the research on the mechanisms of the effect of cigarette smoking on cancer has been conducted for lung cancer. It is thought that carcinogens in tobacco smoke, such as PAH or NNK, are activated by phase I enzymes, such as cytochrome P450, and then converted by phase II enzymes to forms that are highly soluble in water and more readily excretable. During this metabolic detoxification process, metabolites of carcinogens are formed. Some of these metabolites may react with DNA, resulting in the formation of carcinogen-DNA adducts in the lung. In turn, these DNA adducts may be eliminated by DNA repair systems or may lead to

miscoding, resulting in gene mutations. Repeated mutations in critical genes, such as K-ras oncogenes and p53 tumour suppressor genes, may lead to lung cancer. The individual risk for lung cancer depends upon the balance between carcinogen metabolic activation and detoxification and repair rate of DNA (Figure 2).[26,27,57] Besides their effects on lung cancer, PAH and/or NNK are also thought to play a role in the development of other tobacco-related cancers, including cancer of the oral cavity, oesophagus and pancreas.[26,27] Another possible mechanism for the effect of smoking on cancer involves the free radicals in smoke. These free radicals react with molecular oxygen, which causes oxidative DNA damage in the lung.[57] However, the role of this oxidative damage in cancer is not yet understood.[27]

Smoking behaviour and health-related quality of life

The health-related quality of life reflects the self-rated perception of several aspects of physical and mental health, including limitations due to physical functioning, pain, vitality, general health, mental health problems and related role and social functioning. Results of several studies suggest that cigarette smoking is related to poor health-related quality of life. In cross-sectional studies, smokers are reported to have less favourable outcomes on physical functioning,[58] general health[7,58,59] and mental health or depression[7,8,60] when compared with non- or never smokers. Wilson et al.[8] reported less favourable outcomes for all aspects of health-related quality of life, which was more pronounced among heavy and moderate than among

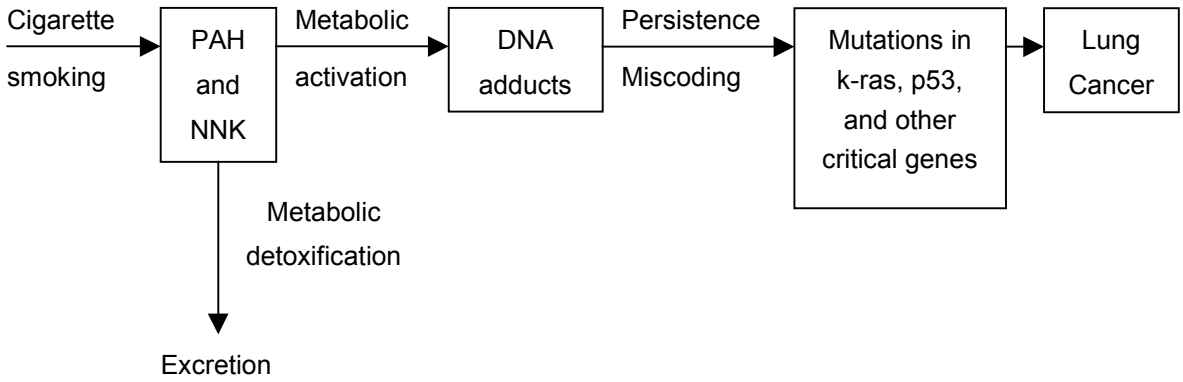

Figure 2 Schematic view of the effect of tobacco smoke carcinogens on lung cancer. Adapted with changes from Cinciripini et al.[26]

PAH=polycyclic aromatic hydrocarbons; NNK=4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.

light smokers. The association between smoking and physical functioning and depression has been confirmed in cohort studies.[61,62]

More research is needed to establish the effect of smoking cessation on health-related quality of life. Only a few studies examined this association. These studies suggested that ex-smokers have more limitations in role functioning due to physical problems,[10] but also have more vitality and experience a better mental health and perceived health than smokers.[10,11,63] However, results were not consistent. The difference between ex- and current smokers tended to be larger for mental health than for physical health.[7,10] Results reported by Díez-Gañán et al.[59] suggested that the frequency of poor subjective health among ex-smokers increased with increasing duration of smoking in the past.

Rationale and aim of this thesis

We can conclude that there is overwhelming evidence that cigarette smoking causes morbidity and mortality from several chronic diseases, independent of culture. Furthermore, there is widespread agreement on the morbidity and mortality risk reduction due to smoking cessation. Based on this knowledge, several projections have been published on the number of future deaths attributable to smoking.[28,30] These numbers strongly underline the worldwide importance of smoking cessation interventions. Public health policy makers more and more realise this and set targets to reduce the smoking prevalence.[64,65] It is now time to quantify the future public health effects of smoking cessation, which are less well described. From a public health point of view, it is important to have insight in the decline in morbidity and mortality following such reductions in smoking prevalence, since this has great impact on the allocation of health care and health care costs. For instance, smoking cessation would decrease the burden of smoking-related diseases. Therefore, the aim of this thesis is to quantify the future public health benefits of smoking cessation. Furthermore, this thesis aims to give more insight into the impact of smoking cessation on health-related quality of life.

Outline of this thesis

In order to quantify future public health benefits of smoking cessation, it is important to have information on the association between smoking or smoking cessation and other risk factors for tobacco-related diseases. For instance, other risk factors may have an intermediate or a modifying effect on the relation between smoking

cessation and disease. Therefore, first, the associations between smoking or smoking cessation and the main risk factors for two of the most important tobacco-related diseases, lung cancer and cardiovascular diseases, were examined. Chapter 2 describes the impact of dietary factors on the effect of smoking on lung cancer. In Chapter 3, the changes in CVD risk factors body weight, total and HDL cholesterol level and blood pressure due to smoking cessation are described.

Then, the benefits of several smoking cessation targets on future smoking-related cancer, cardiovascular diseases and COPD were quantified in Chapters 4, 5 and 6. The results in these chapters are obtained by means of computer simulation modelling. First, in Chapter 4, the reduction in future pancreatic cancer incidence due to smoking cessation in the European Union is estimated. Pancreatic cancer is the most lethal of the tobacco-related cancers. Since smoking is the main avoidable risk factor for this type of cancer, prevention due to smoking cessation is of paramount importance for this cancer site. Then, the impact of several smoking cessation interventions on future total mortality and on future mortality from all currently established tobacco-related diseases (tobacco-related cancer, CHD, stroke and COPD) is estimated for the European Union in Chapter 5. Finally, in Chapter 6, the impact of smoking cessation on CHD and healthy life expectancy in the Netherlands was compared with the impact of another important and frequently used CHD risk reducing intervention, namely cholesterol lowering medication.

As mentioned before, besides a beneficial effect on morbidity and mortality, smoking cessation may also have a positive effect on another public health aspect: health-related quality of life. However, the effect of smoking cessation on this aspect of health is not established yet. Therefore, in Chapter 7, the health-related quality of life is compared between ex- and current smokers, with focus on the impact of amount of smoking and time since quitting. The final chapter, Chapter 8, involves a general discussion of the results described in this thesis.

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2

Role of smoking and diet in the cross-cultural variation in lung cancer mortality: the Seven Countries Study

Abstract

Background and methods - We examined the role of smoking and diet in the cross-cultural variation in lung cancer mortality, using aggregated data of the Seven Countries Study, a follow-up study comprising 12,763 middle-aged men in 16 cohorts in Europe, the United States and Japan, which started around 1960. Smoking habits were assessed with a standardised questionnaire. Dietary intake was collected in random sub-samples of each cohort by the dietary record method. Cohort-specific 25-year lung cancer mortality among all men and among categories of smoking behaviour was related to smoking prevalence and population average dietary intake, respectively, using Poisson regression.

Results - Smoking prevalence was positively associated with lung cancer mortality (risk ratio 1.47, 95% confidence interval (CI) 1.05-2.07, for an increase of 10 percentage points). Lung cancer mortality among smokers, which varied significantly among cultures, was positively associated with average fat intake, especially saturated fat intake (rate ratio 1.10, 95% CI 1.04-1.17, for an increase of 4.6 g) but not with unsaturated fat intake. Average fruit and vegetable intake were not related to lung cancer mortality. Among never smokers, the power to detect associations was low.

Conclusions - In conclusion, both smoking prevalence and average fat intake, especially saturated fat, may play a role in the cross-cultural variation in lung cancer mortality, either independently or by effect modification.

Mulder I, Jansen MCJF, Smit HA, Jacobs DR Jr, Menotti A, Nissinen A, Fidanza F, Kromhout D. Role of smoking and diet in the cross-cultural variation in lung-cancer mortality: the Seven Countries Study. Int J Cancer 2000;88:665-671.

Introduction

Cigarette smoking has been conclusively established as the leading cause of lung cancer mortality within populations.[1] Peto et al. estimated that around 90% of the lung cancer mortality among men in developed countries can be attributed to smoking.[2]

The absolute rate of lung cancer mortality varies across different countries. For instance, the mortality rate was about twice as high in the United States as in Japan in 1990.[3] Besides past and present differences in smoking behaviour, other factors, such as differences in dietary intake, may play an additional role in the cross-cultural variation in lung cancer mortality.

Epidemiological studies based on individuals have consistently found that diets rich in fruits and vegetables protect against lung cancer. It has been suggested that the anti-oxidant micronutrients present in fruits and vegetables are responsible for this protective effect, though evidence for the relation between intake of anti-oxidants and lung cancer mortality is not conclusive. Furthermore, there are weak indications that high fatty acid intake may increase lung cancer risk.[4-6]

Laboratory animal studies[7,8] as well as ecological studies based on national statistics[9-11] suggest that dietary fat may enhance the carcinogenic effect of smoking on lung cancer. Xie et al. showed that the effect of *per capita* cigarette consumption on lung cancer mortality was lower in countries with low average animal fat intake compared to countries with high average animal fat intake.[12] In ecological studies, consumption of plant foods, especially fruits and vegetables, has also been also suggested to modify the effect of smoking on lung cancer mortality.[9]

In the present study, we used data of the Seven Countries Study, a prospective follow-up study performed in 16 cohorts in Europe, the United States and Japan. Previous analyses of the individual data of the Seven Countries Study have shown that, although smoking was harmful in all cultures,[13] the impact of cigarette smoking on lung cancer mortality was stronger in northern Europe than in southern Europe.[13,14] In the present study, we further analysed these data at the ecological level and examined the role of culture-specific dietary intake, in addition to the role of culture-specific smoking prevalence, on the cross-cultural differences in lung cancer mortality. Based on the literature, we focussed on intake of fruits and vegetables and dietary fat. In contrast to national statistics, which are used in most other ecological studies, individual data on smoking and lung cancer mortality allowed us to distinguish lung cancer mortality among different categories of smoking behaviour.

Methods

Study population

In the Seven Countries Study, 12,763 men aged 40 to 59 years were enrolled in 16 cohorts in Europe, the United States and Japan. Ten cohorts consisted of men living in rural parts of Finland (East, West), Italy (Crevalcore, Montegiorgio), Greece (Corfu, Crete), the former Yugoslavia (Dalmatia, Slavonia, Velika Krsna) and Japan (Tanushimaru). One cohort consisted of workers from a large co-operative in Zrenjanin, the former Yugoslavia; one of professors in Belgrade, the former Yugoslavia; and another one of inhabitants of the small commercial town of Zutphen, the Netherlands. Finally, 2 cohorts of railroad employees in Italy (Rome Railroad) and the United States (US Railroad) and 1 in a fishing village in Japan (Ushibuka) were enrolled. Detailed information on the characteristics of these cohorts has been presented elsewhere.[15]

Measurements

Between 1958 and 1964, subjects were examined according to a standardised protocol. Information on smoking habits was collected by means of a questionnaire. Subjects were classified as never, ex- or current smokers. Current smoking was defined as smoking at least 1 cigarette/day at the time of the examination. Information on smoking behaviour was available for 12,699 men. For each cohort, we calculated the percentage of ex-smokers and current smokers and the average number of cigarettes currently smoked per day.

Dietary intake was measured around 1960 in random sub-samples of each cohort (8 to 49 men).[16] In 2 cohorts (Rome Railroad and Ushibuka), dietary intake was measured around 1970. We used the 7-day weighed dietary record method in all but 2 cohorts. In Ushibuka, information on dietary habits was collected for 4 days, and in the United States, a 1-day record was used. In 1985 and 1986, the original dietary records were recoded by one dietician and the average daily intake was calculated for each cohort and summarised into 16 food groups, including fruits and vegetables. Within these groups, specific sub-groups were defined, including citrus and non-citrus fruits and cruciferous, allium, green-leafy, and yellow-orange vegetables. However, by then, the Greek records were no longer available and had to be reconstructed from results of Greek dietary surveys[17] and food balance sheet data from Greece in 1961-1965.[18]

In 1987, food products representing the average daily intake in a cohort were bought locally and transported by air in cooling boxes to the laboratory of the Department of Human Nutrition, Wageningen Agricultural University, the

Netherlands. Within 1 day after arrival, foods were cleaned and the food composites representing the daily intake for each cohort were homogenised, freeze-dried and stored at -20 °C until chemical analysis. Among other components, total fat, saturated and unsaturated fatty acids and cholesterol content were analysed. Total lipids were isolated according to Osborne and Voogt,[19] and fatty acids were determined by gas chromatography.[20] Dietary cholesterol was determined according to the method described by Jonker et al.[21] Based on these data, we calculated the average intake of total fat, saturated fat, mono- and polyunsaturated fats and dietary cholesterol for each cohort.

Mortality

Vital status and cause of death of all subjects in the 16 cohorts were checked during 25 years of follow-up. During follow-up, 5,941 men died. The cause of death was established by 2 central reviewers, based on death certificates and collection of medical information from hospital records, general practitioners or family members. In total, 56 men (0.4%) were lost to follow-up. The end-point was mortality from lung cancer, ICD-8 code 162 as the primary cause of death.[22]

Statistical analysis

Individual data of the Seven Countries Study were used to calculate the age-standardised lung cancer mortality rate for each cohort, in all men, and in never and current smokers separately, using the direct method, with the age distribution of the total population as a standard. To compare lung cancer mortality among different cultures, we pooled the 16 cohorts into 6 areas based on similarities in culture, to obtain more power: northern Europe (East and West Finland, Zutphen), Mediterranean southern Europe (Crete, Corfu, Montegiorgio, Dalmatia), inland southern Europe (Rome Railroad, Crevalcore, Slavonia, Belgrade), Serbia (Zrenjanin, Velika Krsna), the United States (US Railroad) and Japan (Ushibuka, Tanushimaru). For each of the 6 areas, we calculated the age-adjusted relative risk for lung cancer mortality, in all men and among never and current smokers separately, the latter also adjusted for the number of cigarettes smoked per day, using the Cox proportional hazards method. The area with the lowest lung cancer mortality risk (Japan) was taken as a reference.

Because information on dietary intake was available only at the population level, we used aggregated data to examine the association between smoking, diet and lung cancer mortality in the 16 cohorts, using Poisson regression.[23] In all Poisson regression models, the observed number of lung cancer deaths in each of the 16 cohorts was used as a dependent variable and the percentage of smokers or the

population average dietary intake with potential confounders as independent variables. We based the number of lung cancer deaths on the survival time by including the natural logarithm of the survival time as an offset in the model, which is an independent variable with a regression coefficient of 1. First, we examined the association between the percentage of smokers and lung cancer mortality, adjusted for average age and average number of cigarettes currently smoked per day in the cohorts. Because ex-smokers have an elevated lung cancer mortality risk, we additionally adjusted for the percentage of ex-smokers in a cohort. The rate ratio of smoking prevalence was given for a change of 10 percentage points in smoking prevalence. Furthermore, we computed rate ratios for the population average dietary intake on lung cancer mortality among never and current smokers separately, adjusted for population average age, average energy intake and average number of cigarettes smoked per day among current smokers. The rate ratios were given for a change of 10% of the average overall intake of fruits, vegetables, total fat, saturated fat, mono- and polyunsaturated fats and dietary cholesterol in the 16 cohorts. Since the number of statistical units was small, these relations may have been influenced mainly by 1 cohort. To evaluate this effect, we re-analysed the relation between smoking, diet, and lung cancer mortality with 1 cohort removed at a time.

Data were analysed using SAS statistics version 6.12.[24] In all analyses, 2-sided p-values below 0.05 were considered statistically significant.

Results

During the 25 years of follow-up, 424 men (3.3% of the population) died of lung cancer. The age-standardised lung cancer mortality was lowest in Tanushimaru and Montegiorgio (1.0%; 487 and 469 per 10,000 person-years, respectively) and highest in the northern European cohorts, up to 7.3% (4,214 per 10,000 person-years) in East Finland (Table 1). Lung cancer risk in the United States and in the pool of the 3 northern European cohorts were 1.85 (95% confidence interval (CI) 1.11-3.07) and 3.83 (95% CI 2.35-6.24) times higher, respectively, than the risk in the pool of the 2 Japanese cohorts.

The proportion of cigarette smokers in the 16 cohorts of the Seven Countries Study ranged from 44% in Belgrade to 78% in Ushibuka (Table 1). At the population level, the percentage of cigarette smokers in a cohort was positively associated with lung cancer mortality rates in the 16 cohorts. A 10 percentage points increase in the percentage of smokers corresponded to a 47% increase in lung cancer mortality

Table 1 (Chapter 2) Baseline characteristics and age-standardised lung cancer mortality for the 16 cohorts of the Seven Countries Study.

				Cigarette smoking			25-year lung cancer mortality[b]	
				Current smokers		Ex-smokers		
	Area[a]	Number	Age (years) mean ± SD	%	mean number/day ± SD	%	%	Per 10,000 person-years
Tanushimaru	J	492	50.7 ± 5.8	70.7	21.0 ± 6.3	13.0	1.0	487
Montegiorgio	MSE	715	49.5 ± 5.0	58.7	12.0 ± 8.1	15.4	1.0	469
Velika Krsna	S	498	49.9 ± 6.2	49.2	15.8 ± 6.9	9.0	1.7	850
Slavonia	ISE	693	50.4 ± 5.3	60.3	16.3 ± 6.3	13.3	1.9	1,048
Crete	MSE	686	49.2 ± 5.4	57.3	19.7 ± 9.8	19.0	2.0	869
Zrenjanin	S	516	49.2 ± 5.4	63.2	17.7 ± 7.8	17.8	2.1	1,099
Belgrade	ISE	536	47.8 ± 5.7	43.7	21.8 ± 9.9	15.7	2.1	931
Ushibuka	J	495	50.0 ± 5.6	77.8	19.2 ± 7.7	7.3	2.6	1,306
Corfu	MSE	529	49.8 ± 5.7	63.5	16.7 ± 7.9	11.9	2.8	1,329
Crevalcore	ISE	991	50.0 ± 5.1	62.6	14.9 ± 8.4	12.3	3.0	1,594
Rome Railroad	ISE	765	48.7 ± 5.3	65.2	18.2 ± 8.2	16.1	3.3	1,671
US Railroad	US	2,570	49.8 ± 5.8	59.0	17.7 ± 6.3	21.1	3.3	1,679
Dalmatia	MSE	662	50.6 ± 5.0	58.3	17.3 ± 6.5	11.6	3.6	1,748
West Finland	NE	857	50.0 ± 5.5	57.2	14.8 ± 7.2	18.3	4.4	2,394
Zutphen	NE	878	50.1± 5.5	74.5	12.5 ± 7.3	18.2	7.2	3,642
East Finland	NE	816	49.0 ± 5.5	68.5	18.0 ± 7.8	18.4	7.3	4,214

[a] J=Japan, MSE=Mediterranean southern Europe, S=Serbia, ISE=inland southern Europe, US=United States, NE=northern Europe. [b] Age-standardised.

(rate ratio 1.47, 95% CI 1.05-2.07), adjusted for average age, average number of cigarettes currently smoked per day and percentage of ex-smokers in a cohort. When we removed 1 cohort at a time, the rate ratio ranged between 1.28 (95% CI 0.92-1.78), removing East Finland, and 1.58 (95% CI 1.11-2.25), removing West Finland. Figure 1 shows that lung cancer mortality may vary greatly across cohorts with comparable smoking prevalence, *e.g.*, among East Finland and Zutphen in northern Europe, and Tanushimaru and Ushibuka in Japan. Among never smokers, lung cancer mortality was low and the range between the lung cancer mortality rates in the 6 cultural areas was small (0.8% to 1.1%; 263 to 534 per 10,000 person-years) (Table 2). The relative risk for lung cancer mortality among never smokers ranged from 1.2 in Mediterranean southern Europe to 1.7 in inland southern Europe compared to Japan (data not shown), but statistical power to detect differences between the cultural areas was low due to the small number of cases (n=24). Lung cancer mortality among smokers differed between the cultural areas: the mortality risk was statistically significantly higher in northern Europe, the United States and inland southern Europe compared to Japan (Table 2).

Table 3 presents the baseline average daily intakes of fruits, vegetables, total fat, saturated and unsaturated fatty acids and dietary cholesterol for each cohort.

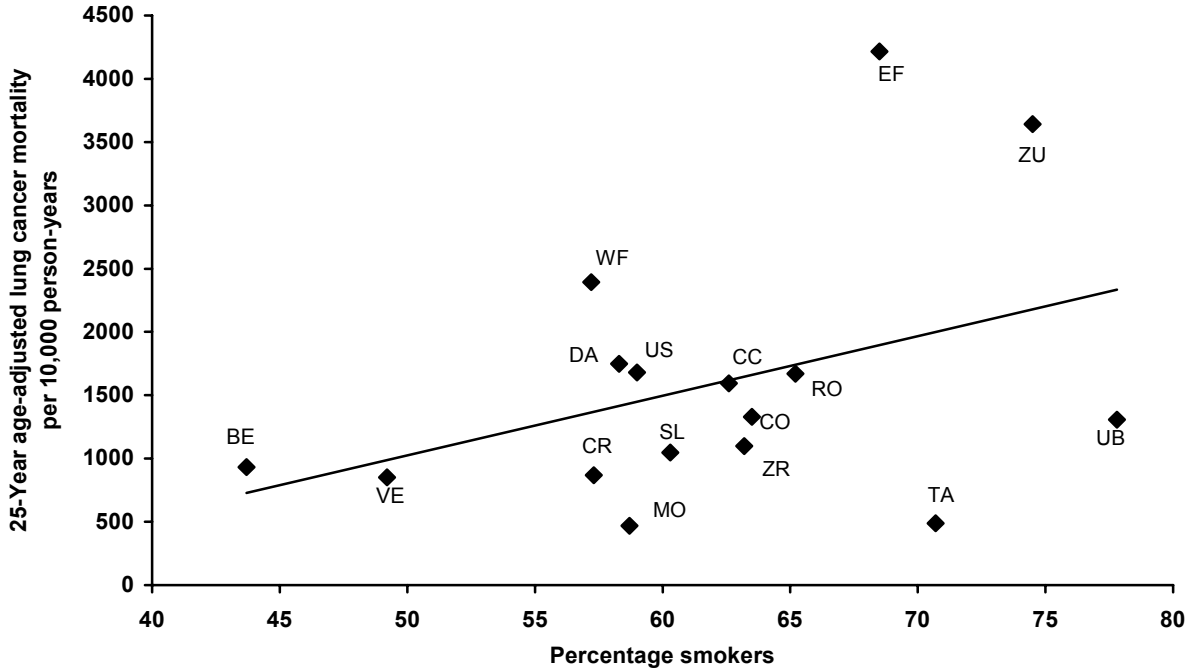

Figure 1 The percentage of smokers and 25-year age-adjusted lung cancer mortality in the 16 cohorts of the Seven Countries Study.

TA=Tanushimaru, MO=Montegiorgio, VE=Velika Krsna, SL=Slavonia, CR=Crete, ZR=Zrenjanin, BA=Belgrade, UB=Ushibuka, CO=Corfu, CC=Crevalcore, RO=Rome Railroad, US=US Railroad, DA=Dalmatia, WF=West Finland, ZU=Zutphen, EF=East Finland.

Table 2 25-Year lung cancer mortality rates among never and current smokers in different areas of the Seven Countries Study.

	Never smokers		Current smokers		
	Number of deaths	Per 10,000 person-years[a]	Number of deaths	Per 10,000 person-years[a]	RR (95% CI)[b]
Japan[c]	1	263	17	1130	1.00
Serbia	3	471	15	1514	1.67 (0.83-3.35)
Mediterranean southern Europe	5	353	51	1588	1.61 (0.93-2.79)
Inland southern Europe	8	534	67	2041	2.08 (1.22-3.54)
United States	4	385	73	2645	2.67 (1.57-4.54)
Northern Europe	3	378	144	4649	5.40 (3.25-8.97)

RR, rate ratio. [a] Age-standardised. [b] Adjusted for age and number of cigarettes/day. [c] Reference.

The population average fruit consumption was low in Velika Krsna and Slavonia and high in the Mediterranean cohorts Crete and Corfu. Low average intake of vegetables was seen in East and West Finland and high average vegetable intake in Rome Railroad and Zrenjanin. The Japanese cohorts were characterised by low average intake of fat, in contrast to Slavonia, where the average intake of fat was relatively high. The northern European cohorts were characterised by high population average intake of saturated fat and dietary cholesterol.

Among never smokers, there was no evidence that the population average intake of fruits, vegetables, total fat, saturated fatty acid, unsaturated fatty acid and dietary cholesterol in a cohort was related to lung cancer mortality (Table 4); but again one must take into account the small number of lung cancer cases among never smokers. Among smokers, a statistically significant positive relation was found between average saturated fat intake and lung cancer mortality (rate ratio 1.10, 95% CI 1.04-1.17, for an increase of 4.6 g in average saturated fatty acid intake) (Table 4, Figure 2). This indicates that the lung cancer mortality rate among smokers was higher in cohorts with high saturated fatty acid intake compared to cohorts with low saturated fat intake. The positive relation between lung cancer mortality among current smokers and average total fat and dietary cholesterol intake was of borderline significance. Analyses with 1 cohort removed at a time did not alter these relations (data not shown). Because average total fat and dietary cholesterol intake were highly correlated with saturated fat intake (r=0.84 and 0.72, respectively), we were not able to examine the independent effects of these dietary factors. Population average fruit and vegetable intake in a cohort were not related to

Table 3 (Chapter 2) Baseline daily dietary intake for the 16 cohorts of the Seven Countries Study.

	Energy (MJ/day)	Fruits (g)	Vegetables (g)	Total fat (g)	Saturated fat (g)	Monounsaturated fat (g)	Polyunsaturated fat (g)	Cholesterol (mg)
Tanushimaru	10.0	26	174	33	10	10	12	170
Montegiorgio	12.1	28	194	101	31	50	15	356
Velika Krsna	14.3	1	115	115	52	42	16	359
Slavonia	15.5	1	198	179	69	81	22	612
Crete	11.8	464	191	131	28	84	13	211
Zrenjanin	13.4	185	245	149	55	65	23	311
Belgrade	11.4	145	179	143	57	54	26	396
Ushibuka	10.2	42	222	46	14	17	13	403
Corfu	11.3	462	191	105	22	63	15	141
Crevalcore	15.2	191	140	155	54	73	21	585
Rome Railroad	11.0	150	260	97	28	54	10	409
US Railroad	9.6	233	170	131	55	49	22	582
Dalmatia	15.8	6	200	148	40	78	24	388
West Finland	14.4	34	104	142	73	49	14	492
Zutphen	11.3	82	227	137	61	50	21	476
East Finland	14.7	40	108	166	89	55	17	537

Table 4 Rate ratio (95% CI) of dietary intake for 25-year lung cancer mortality rates among never and current smokers.

		Rate ratio (95% CI)	
	Unit of change[a]	Never smokers[b]	Current smokers[c]
Fruits	13 g	0.99 (0.93 - 1.04)	1.00 (0.96 – 1.03)
Vegetables	18 g	0.86 (0.67 - 1.08)	0.94 (0.82 - 1.06)
Fatty acids			
Total fat	12 g	0.96 (0.75 - 1.27)	1.13 (0.99 - 1.32)
Saturated fat	4.6 g	1.02 (0.89 - 1.17)	1.10 (1.04 - 1.17)
Monounsaturated fat	5.5 g	0.90 (0.74 - 1.08)	0.98 (0.87 - 1.10)
Polyunsaturated fat	1.8 g	1.08 (0.91 - 1.31)	1.02 (0.90 - 1.15)
Cholesterol	40 mg	0.99 (0.86 - 1.16)	1.08 (0.99 - 1.18)

[a] One unit = change of 10% of the average dietary intake over the 16 cohorts. [b] Adjusted for average age and energy intake in each cohort. [c] Adjusted for average age, energy intake and number of cigarettes smoked per day.

the lung cancer mortality rate among smokers (Table 4), which was also seen for subgroups of fruits (citrus and non-citrus) and vegetables (cruciferous, green leafy and yellow-orange) (data not shown). Our results suggest that allium vegetable intake was negatively related to lung cancer mortality (rate ratio 0.61, 95% CI 0.45-0.82), but this must be interpreted with caution since information on allium vegetable intake was missing for 2 cohorts. Adjustment for average intake of other dietary factors or analyses with 1 cohort removed at a time did not change these results (data not shown).

Discussion

In the Seven Countries Study, ecological analyses in 16 cohorts showed that total lung cancer rate was positively associated with the percentage of smokers. Furthermore, the absolute lung cancer mortality among current smokers, which varied significantly between the 6 cultural areas, was positively associated with average intake of dietary fat, especially saturated fat.

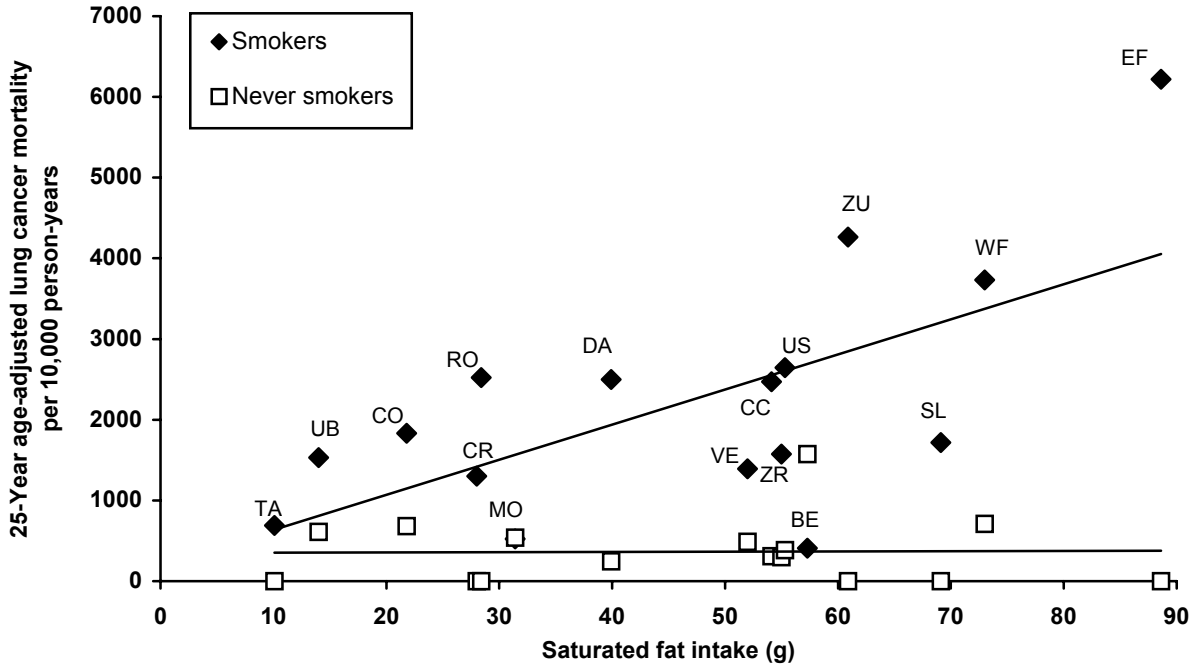

Figure 2 Average intake of saturated fat and 25-year age-adjusted lung cancer mortality among never smokers and current smokers in the 16 cohorts of the Seven Countries Study.
TA=Tanushimaru, MO=Montegiorgio, VE=Velika Krsna, SL=Slavonia, CR=Crete, ZR=Zrenjanin, BA=Belgrade, UB=Ushibuka, CO=Corfu, CC=Crevalcore, RO=Rome Railroad, US=US Railroad, DA=Dalmatia, WF=West Finland, ZU=Zutphen, EF=East Finland.

Some limitations of this study should be mentioned. Firstly, food products representing the average daily intake in a cohort were collected and chemically analysed 25 years after measurement of dietary intake on food group level, to obtain information on fatty acid and micronutrient intake. This may have led to measurement bias of fatty acid intake if the nutrient content of foods included in the food composites had changed during that time. However, intake of saturated, mono- and polyunsaturated fatty acids was also determined at baseline. Since relatively high correlations were found between fatty acid determination at baseline and after 25 years, we expect that changes in food composites did not largely influence our results.[25] Secondly, changes in dietary intake during the follow-up period also may have led to bias. However, although characteristic food-consumption patterns in the cohorts have changed during the 25 years, the characteristic differences in dietary patterns between the cohorts remained.[16] Likewise, smoking habits may have changed during 25 years of follow-up. Additional analysis of smoking prevalence at 5 and 10 years after baseline compared to that at baseline showed that the

characteristic differences in smoking prevalence between the cohorts also remained (correlation coefficient of the percentage of smokers at baseline and after 5 years r=0.87, p<0.0001; after 10 years r=0.83, p<0.0001). Thirdly, in some cohorts, measurement of dietary intake differed from the majority of the cohorts. In 2 cohorts, dietary intake was measured around 1970 in stead of 1960; in 2 cohorts, dietary intake was measured for less than 7 days; and in 2 other cohorts, dietary habits were reconstructed from dietary surveys and food balance sheets. However, exclusion of 1 of these 3 pairs of cohorts at a time did not alter the results. Fourthly, during the 25 years of follow-up, smokers may have quit smoking, which would have reduced the risk for lung cancer. This may have under-estimated the effect of smoking on lung cancer, though this may partly be counterbalanced by the long lag-time of smoking cessation for lung cancer.

Other, mainly smoking-related factors, such as past smoking prevalence, age at smoking initiation or type of cigarettes smoked, are likely to have an important contribution to differences in lung cancer risk between cohorts. Since lung cancer has a long latency period of 30 years or more,[26] smoking prevalence before 1960 may have influenced the lung cancer mortality rate during follow-up. Furthermore, studies based on individuals have shown that early smoking initiation, which is related to a longer duration of smoking, increases lung cancer risk.[1,27] Smoking initiation is dependent on culture. For instance, age at smoking initiation has been reported to be higher in Japan than in the United States.[11] Unfortunately, since information about age at smoking initiation is not available in the Seven Countries Study, we were not able to account for this factor. Next, the type of cigarettes smoked, which also depends on culture, has an effect on lung cancer mortality[1] and could have played a role in our study. In the Mediterranean area, Turkish tobacco was preferred, which is very low in nicotine compared to the Virginia type of tobacco used mainly in northern Europe and the United States. In Japan, a mix of several tobaccos was smoked.[28,29] Besides this, charcoal-containing filter tip cigarettes, which are known to remove several volatile components from smoke, were widely used in Japan compared to, *e.g.*, the United States.[1,30] Finally, a possible genetic influence on the effect of smoking cannot be excluded.[31]

In our analyses to compare lung cancer mortality between different cultures, we pooled the 16 cohorts into 6 areas based on similarities in culture. Nevertheless, divisions between cultures are ambiguous and entail arbitrary choices. Belgrade, *e.g.*, was categorised as a cohort in inland southern Europe, as in other studies using Seven Countries Study data.[32] However, as the capital of Serbia, Belgrade can also be included in the Serbian area. Additional analyses using this division did not influence the results of our study.

Our results suggest that both smoking prevalence and dietary fat intake, especially saturated fat, have an effect on lung cancer mortality in the 16 cohorts of the Seven Countries Study. The percentage of smokers was positively associated with lung cancer mortality in the cohorts. Additionally, the 2 Japanese cohorts, which had a high percentage of smokers but a low lung cancer mortality rate, were characterised by a much lower intake of dietary total and saturated fat compared to East Finland and Zutphen, which had a percentage of smokers comparable to the Japanese cohorts but a high lung cancer mortality rate. Furthermore, the lung cancer mortality rate among smokers was lower in cohorts with low saturated fat intake compared to cohorts with high saturated fat intake. However, due to the small number of cases among never smokers, we were not able to conclude whether the effects of smoking and dietary fat intake on lung cancer mortality were independent or that effect modification played a role.

We found no data on the relation between culture-specific dietary intake and the cross-cultural variation in lung cancer mortality among never and current smokers separately. However, results from animal experiments[7,8] suggest that dietary fat, especially polyunsaturated fat, may enhance the effect of tobacco smoking on lung cancer mortality. Furthermore, ecological studies, mostly based on national statistics data, have found an enhancing effect of total fat,[10,11] saturated and polyunsaturated fats[9] and dietary cholesterol[33] on the impact of smoking on lung cancer mortality. Xie et al. performed an analysis of lung cancer mortality rates of 29 countries and reported an interaction between *per capita* cigarette consumption and average animal fat intake: the effect of cigarette consumption on lung cancer mortality in countries with low animal fat intake was lower compared to countries with high animal fat intake.[12] Additionally, in a case-control study[34] and a prospective follow-up study,[35] a positive relation between dietary fat intake and lung cancer mortality was found among smokers but not among never or ex-smokers.

Some possible underlying mechanisms for a modifying effect of dietary fat are suggested, mainly derived from experimental animal studies. Dietary fat may increase prostaglandin levels, which leads to a suppressed immunosurveillance system.[36] In the presence of polyunsaturated fat, several toxic substances found in tobacco smoke, like benzo[a]pyrene, can be transformed to a carcinogenic derivate in the lung.[7] Furthermore, dietary unsaturated fat may increase the permeability of the cell membrane for carcinogenic compounds.[37]

In the present study, no association was found between population average fruit and vegetable intake in a cohort and lung cancer mortality. Results suggested that allium vegetable intake was negatively associated with lung cancer mortality, but since data on allium vegetable intake were missing for 2 cohorts, this result must be

interpreted with caution. In 1 ecological study, the difference in lung cancer mortality between 2 populations could also not be explained by differences in fruit and vegetable intake.[11] In other ecological studies, however, a protective effect of vegetable foods[9] and yellow-orange vegetables[33] was suggested. Case-control as well as cohort studies have consistently found an inverse relationship between fruit and vegetable intake and lung cancer mortality.[4] In a large prospective cohort study, allium vegetable intake was not related to lung cancer.[38] A protective effect of fruits and vegetables among smokers but not among non-smokers has been reported.[39] However, the opposite has also been found.[40] The small range of average vegetable intake across the cohorts in our study (104 to 260 g/day) may explain the lack of association between average vegetable intake and lung cancer mortality. The range of average fruit intake across the cohorts, however, was much larger (1.2 to 464 g/day). As one of the underlying mechanisms for the protective effect of fruits and vegetables, it is thought that anti-oxidant compounds in fruits and vegetables neutralise oxidants and quench free radicals in tobacco smoke to reduce the carcinogenic process.[4,41]

Despite the limitations of ecological studies,[42,43] our data suggest that, besides differences in smoking prevalence, differences in average dietary fat intake, especially saturated fat, may play a role in the cross-cultural variation in lung cancer mortality, either independently or by effect modification.

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3

The effect of smoking cessation on body weight, total and HDL cholesterol and blood pressure; the Doetinchem cohort study

Abstract

Background - In the general population, it is not clear to what extent the reduction in cardiovascular diseases (CVD) risk after smoking cessation is due to smoking cessation-related changes in other CVD risk factors. We studied the effect of smoking cessation on the CVD risk factors body weight, total and HDL cholesterol level and blood pressure in a general-population cohort.

Methods - The study population consisted of 3,570 subjects from a random sample of 20-59 year old men and women in the Netherlands. Longitudinal data were collected at two examinations. Subjects were classified as persistent smokers, quitters between baseline and re-examination, and never smokers. Six-year changes in body weight, cholesterol level, and blood pressure between baseline and re-examination were estimated. Differences between smoking categories were tested using multivariate analysis of variance.

Results - Compared to persistent smokers, quitters experienced a larger age-adjusted increase in body weight, HDL cholesterol level and diastolic blood pressure among both men and women, and in total cholesterol level and systolic blood pressure among men. However, after adjustment for weight gain, the difference in the increase in total cholesterol level and blood pressure between quitters and persistent smokers lost statistical significance.

Conclusions - Smoking cessation led to a favourable increase in HDL cholesterol level and to unfavourable weight gain which largely explained the postcessation increase in total cholesterol level and blood pressure. These results indicate that, of the major CVD risk factors, only the postcessation increase in HDL cholesterol level may contribute to the beneficial effect of smoking cessation on CVD mortality in the general population.

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Introduction

Numerous studies have shown that giving up smoking reduces the risk for cardiovascular diseases (CVD).[1] This effect may result directly from the elimination of the harmful effects of cigarette smoke, such as increased heart rate and myocardial contractility, decreased oxygen transport of the blood and increased blood coagulation.[2] In addition, smoking cessation may also have an effect on other risk factors for CVD, such as serum total and HDL cholesterol level, blood pressure and body weight.[3]

In turn, this effect of smoking cessation on other risk factors for CVD may result directly from smoking cessation, but may also be caused by changes in other smoking-related determinants. For instance, ex-smokers may adopt a healthier lifestyle, which may result in a decrease in body weight, total cholesterol level or blood pressure. Changes in body weight will consequently alter serum total and HDL cholesterol level and blood pressure levels.[4,5] Since CVD risk is associated with the duration of cessation and the amount of smoking,[6] changes in CVD-risk factors may also be associated with these characteristics of smoking behaviour.

To what extent the reduction in CVD risk after smoking cessation is due to smoking-related changes in other risk factors is not established yet in the general population. The effect of smoking cessation on body weight, total and HDL cholesterol levels and blood pressure was examined under controlled circumstances in several smoking intervention trials[7-10] or in several cohort studies among special groups of the population.[11,12,13] Only a few studies, however, examined the effect of smoking cessation on other CVD risk factors in the general population.[14-16] Results obtained from the general population are of greater importance for public health policy makers, since they are derived from a sample of the total population under natural and uncontrolled conditions. In these general-population cohort studies, an unfavourable increase in body weight[14-16] was observed after smoking cessation. To our knowledge, only one study among the general population examined the effect of smoking cessation on total cholesterol level and blood pressure, reporting no effect on these CVD risk factors,[15] and no study examined the effect on HDL cholesterol.

Therefore, in the present study, we used longitudinal data from the general Dutch population to study the change in body weight, serum total and HDL cholesterol level and systolic and diastolic blood pressure in subjects who stopped smoking during follow up. Furthermore, we studied the effect of amount of smoking before cessation and duration of cessation on these changes in CVD risk factors. Finally, we examined whether these changes were influenced by other factors, including body weight change.

Methods

Study population

We used data from the first and second round of the Doetinchem cohort study. In the first round, subjects were examined within the Monitoring Project on Cardiovascular Disease Risk Factors, which was carried out from 1987 through 1991. Every year, a random age- and sex-stratified sample of 20-59 year old men and women from three towns in the Netherlands (Amsterdam, Maastricht and Doetinchem) was invited to participate in the study. Detailed information on this project has been described elsewhere.[17] Respondents from the town of Doetinchem were re-invited six years later within the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN study). The response rate was on average 62% at baseline and 78% at re-examination. Respondents who attended both the baseline examination and re-examination (n=6,118) were included in our study population. Subjects without information on smoking behaviour (n=12), women who were pregnant at either examination (n=115) and subjects using cholesterol or blood pressure lowering medication (n=488) were excluded from the analyses. Weight change due to smoking cessation may not be distinguishable from weight change due to a weight reducing diet or smoking-related chronic diseases, such as CVD, cancer or COPD. However, exclusion of subjects on such a diet or with such diseases did not substantially change our conclusions. Therefore, we chose to include these subjects in our analyses. This left 1,733 never smokers, 1,636 ex-smokers, and 1,466 current smokers at both examinations, 371 quitters between baseline and re-examination, 137 'relapsers' (ex-smokers at baseline who smoked at re-examination) and 160 subjects who were occasional smokers (less than 1 cigarette per day) or who had inconsistent smoking information across the two examinations. Since we focused on the effect of smoking cessation, only persistent smokers, quitters and never smokers (1,618 men and 1,952 women) remained in our final study population. All subjects gave their written informed consent.

Measurements

Subjects were classified as persistent smokers if they reported to smoke 1 cigarette or more per day at both examinations, as quitters if they smoked 1 cigarette or more per day at baseline and reported to have quit smoking at the re-examination, and as never smokers if they did not smoke at both examinations. For persistent smokers and quitters, information on the number of cigarettes smoked per day at baseline was collected and categorised as 1-9, 10-19 and $\geq$ 20 cigarettes per day. For

quitters, the duration of cessation was established at the re-examination and categorised as 0-1 years, 2-3 years and 4-6 years.

Body weight was measured in light indoor clothing without shoes, and 1 kg was subtracted to correct for clothing. Height was measured with a wall-mounted stadiometer in subjects without shoes who stood upright against the wall. Blood pressure was measured twice on the upper arm with the participant in sitting position, with a random-zero sphygmomanometer. Systolic and diastolic blood pressure were recorded at the first and fifth Korotkoff phase, respectively. The average of the two blood pressure measurements was used in the analyses. Total and HDL cholesterol levels were determined at the Clinical Chemistry Laboratory of the University Hospital 'Dijkzigt' in Rotterdam,[18,19] which is the Lipid Reference Laboratory for standardised cholesterol determinations in the Netherlands.

Information on covariates was obtained by means of a questionnaire. Educational level at baseline, as an indicator of socio-economic status, was divided into three categories, according to the highest achieved level of education: low (intermediate secondary education or less), intermediate (intermediate vocational or higher secondary education) and high (higher vocational or university education). Alcohol intake was reported in number of glasses of beer, wine or spirits per week at both examinations. We transposed this into the number of glasses alcohol per day, assuming equal amounts of alcohol in 1 glass of beer, wine and spirits. Then, we calculated the change in alcohol intake between the two examinations. History of myocardial infarction, cerebrovascular accident, diabetes mellitus or cancer at the re-examination was established with four separate questions, presented as 'Have you ever suffered from …?'. Prevalence of asthma and COPD was obtained from information on respiratory symptoms, including chronic cough, chronic phlegm, shortness of breath and wheezing.

Statistical analysis

Differences in characteristics between persistent smokers on the one hand and quitters and never smokers on the other hand were tested by means of a t-test for continuous variables or by means of χ^2-test for categorical variables. Multivariate analysis of variance was used to estimate changes in body weight, total and HDL cholesterol and blood pressure level between baseline and re-examination. These changes were estimated for persistent smokers, quitters and never smokers and for quitters in categories of duration of cessation. Differences in changes between categories were tested with the total group of persistent smokers as the reference group. Furthermore, changes were estimated for persistent smokers and quitters in categories of amount of smoking. In these analyses, differences in changes

between quitters and persistent smokers were tested in subgroups of amount of smoking with persistent smokers as the reference group. A trend in amount of smoking with change in risk factors was tested using linear regression modelling.

All analyses were adjusted for age at baseline. Additional adjustments were made for other covariates, including educational level and number of cigarettes smoked at baseline, change in alcohol intake between the two examinations and history of myocardial infarction, cerebrovascular accident, diabetes, cancer, asthma or COPD at the re-examination. Since changes in body weight affect total and HDL cholesterol and blood pressure levels,[4,5] we further adjusted cholesterol and blood pressure change for the effect of body weight change between baseline and re-examination.

Data were analysed using the GLM-procedure of SAS statistics version 6.12 (SAS Institute, Inc, Cary, NC). Two-sided p-values below 0.05 were considered statistically significant.

Results

There were no significant differences in baseline characteristics between persistent smokers and quitters, except for educational level and for body mass index (BMI) among men and number of cigarettes per day among women (Table 1). At re-examination, quitters reported a lower prevalence of asthma and COPD among men and of cancer and COPD among women.

Table 2 reflects the age-adjusted changes in body weight, total and HDL cholesterol level and blood pressure for categories of smoking behaviour. Compared to persistent smokers, quitters experienced a larger age-adjusted increase in body weight, HDL cholesterol and diastolic blood pressure (DBP) between baseline and re-examination among both men and women (excess gain in quitters compared to persistent smokers: body weight 3.4 kg among men and 3.8 kg among women; HDL cholesterol 0.07 mmol/L among both men and women; DBP 2.8 mm Hg among men and 1.7 mm Hg among women). Furthermore, in men only, quitters experienced a larger age-adjusted increase in total cholesterol and systolic blood pressure (SBP) (excess gain in quitters compared to persistent smokers: total cholesterol 0.17 mmol/L; SBP 2.7 mm Hg).

Quitters who quit smoking 2-6 years before re-examination tended to gain more weight than quitters who quit smoking within 2 years before re-examination, which was most pronounced among women (Table 2). Furthermore, the gain in body weight showed a positive trend with amount of smoking within quitters (p for trend

Table 1 (Chapter 3) Baseline characteristics of the study population (mean (sd) or %).

	Men			Women		
	Persistent smokers	Quitters	Never smokers	Persistent smokers	Quitters	Never smokers
N	709	183	726	757	188	1,007
Age (years)	39.2 (9.6)	39.0 (10.3)	37.3 (9.8)***	38.4 (9.2)	38.0 (10.0)	40.7(11.0)***
Educational level (%):						
Low	67.7	53.6	40.3	76.6	67.2	66.4
Intermediate	20.7	27.3 **	30.8 ***	15.1	20.4 *	20.3 ***
High	11.6	19.1	29.0	8.3	12.4	13.3
Nr of cigarettes per day	15.9 (7.9)	14.7 (8.0)	-	14.2 (6.9)	11.5 (6.1)***	-
Body weight (kg)	79.0 (11.7)	78.5 (10.2)	79.2 (10.0)	64.6 (10.1)	65.3 (9.2)	66.9 (10.6)***
BMI (kg/m^2)	24.7 (3.2)	24.3 (2.7)*	24.5 (2.9)	23.4 (3.4)	23.5 (3.3)	24.4 (3.8)***
Total cholesterol (mmol/l)	5.65 (1.19)	5.48 (1.10)	5.30 (1.04)***	5.41 (1.06)	5.46 (1.04)	5.32 (1.00)
HDL cholesterol (mmol/l)	1.07 (0.26)	1.10 (0.26)	1.16 (0.26)***	1.30 (0.31)	1.29 (0.29)	1.39 (0.28)***
Systolic blood pressure (mm Hg)	124.8 (12.8)	123.5 (12.6)	124.5 (12.9)	115.3 (13.5)	114.4 (13.6)	117.6 (13.8)***
Diastolic blood pressure (mm Hg)	78.5 (9.8)	77.0 (9.8)	78.3 (9.8)	73.7 (9.4)	72.8 (9.4)	75.5 (9.4)***
Alcohol intake:						
% drinkers	83.5	85.8	72.2***	57.5	53.2	37.2***
Nr glasses/day among drinkers	2.3 (1.8)	2.1 (1.6)	1.4 (1.2)***	1.3(1.0)	1.1 (0.9)	0.7 (0.5)***
History of (%):[a]						
Myocardial infarction	1.4	3.3	0.6	0.1	0.5	0.1
Cerebrovascular accident	1.0	1.1	0.7	0.5	0.5	0.5
Diabetes	1.4	0.6	1.1	1.1	1.6	1.3
Cancer	1.4	2.2	0.8	4.9	1.1*	3.7
Asthma	17.2	9.3**	9.2***	14.3	14.4	9.4**
COPD	20.6	12.6*	4.7***	17.6	9.7**	9.2***

* p<0.05, ** p<0.01, *** p<0.001 for a difference with persistent smokers. [a] History of chronic diseases was established at re-examination.

Table 2 (Chapter 3) Age-adjusted change (Δ) (95% confidence interval) between baseline and re-examination in body weight, total and HDL cholesterol, and systolic and diastolic blood pressure for the total groups of persistent smokers, quitters and never smokers, and for quitters in categories of duration of cessation.

	Body weight	Total cholesterol	HDL cholesterol	Systolic blood pressure	Diastolic blood pressure
	Δ (kg)	Δ (mmol/L)	Δ (mmol/L)	Δ (mm Hg)	Δ (mm Hg)
Men					
Persistent smokers	3.1 (2.8-3.4)	-0.04 (-0.10-0.02)	0.05 (0.03-0.06)	2.1 (1.1-3.0)	1.9 (1.2-2.7)
Quitters	6.5 (5.9-7.2)***	0.13 (0.01-0.24)*	0.12 (0.10-0.15)***	4.8 (2.9-6.6)*	4.7 (3.2-6.1)**
Never smokers	3.8 (3.5-4.1)**	0.07 (0.01-0.13)**	0.06 (0.05-0.08)	2.5 (1.6-3.5)	2.6 (1.8-3.3)
Duration of cessation (years)[a]					
0-1	5.5 (3.9-7.1)***	0.10 (-0.12-0.32)	0.09 (0.03-0.15)	2.8 (-0.7-6.3)	2.4 (-0.2-5.1)
2-3	7.1 (5.4-8.8)***	0.31 (0.07-0.55)**	0.15 (0.09-0.22)***	4.3 (0.5-8.2)	3.3 (0.4-6.2)
4-6	6.7 (5.5-8.0)***	0.01 (-0.17-0.18)	0.14 (0.09-0.18)***	6.9 (4.1-9.8)**	7.0 (4.8-9.1)***
Women					
Persistent smokers	3.0 (2.6-3.4)	0.05 (-0.002-0.11)	0.12 (0.10-0.14)	4.9 (4.0-5.9)	2.9 (2.2-3.6)
Quitters	6.8 (6.1-7.5)***	0.03 (-0.08-0.14)	0.19 (0.15-0.23)***	5.7 (3.8-7.7)	4.6 (3.2-5.9)*
Never smokers	4.0 (3.7-4.4)***	0.12 (0.07-0.16)	0.12 (0.10-0.14)	4.3 (3.5-5.2)	2.8 (2.2-3.4)
Duration of cessation (years)[a]					
0-1	5.2 (3.5-6.8)**	-0.02 (-0.23-0.20)	0.22 (0.15-0.29)**	5.9 (1.9-9.8)	4.1 (1.3-6.9)
2-3	8.0 (6.3-9.6)***	0.02 (-0.19-0.23)	0.19 (0.13-0.26)*	5.3 (1.4-9.1)	6.0 (3.3-8.7)*
4-6	7.5 (6.1-9.0)***	0.04 (-0.15-0.23)	0.17 (0.11-0.23)	4.3 (0.8-7.8)	3.6 (1.2-6.1)

* p<0.05, **p<0.01, ***p<0.001 for difference with persistent smokers. [a] Among quitters.

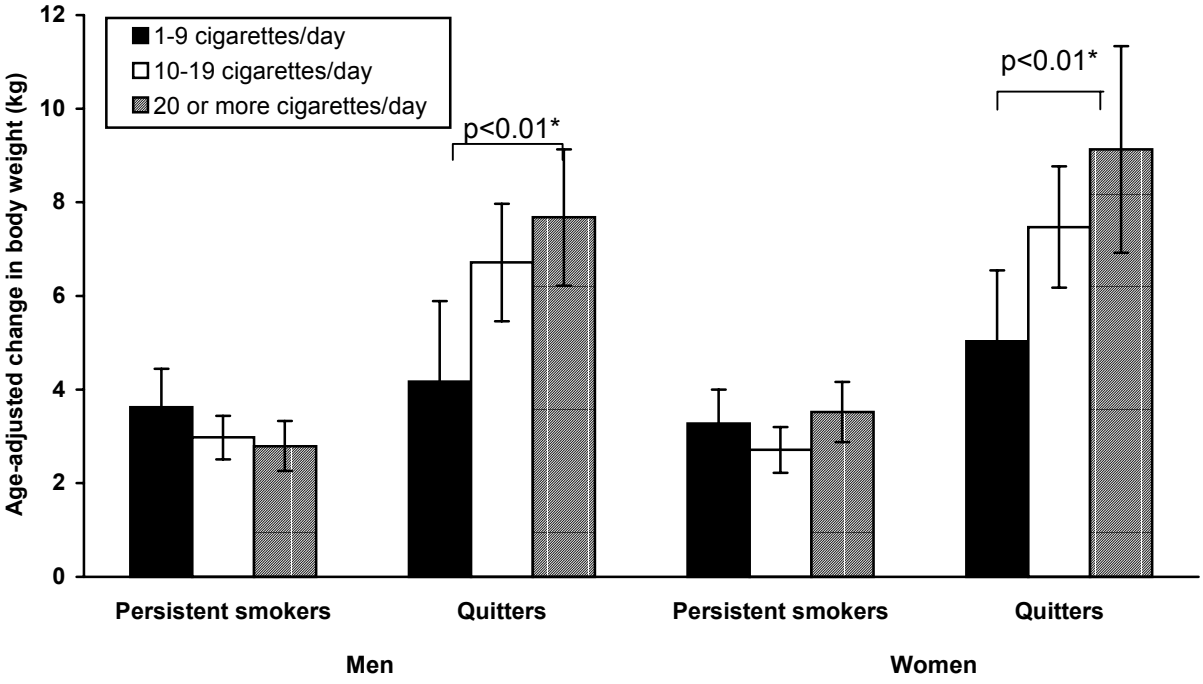

Figure Age-adjusted change in body weight between baseline and re-examination, for persistent smokers and quitters in categories of amount of smoking at baseline. *p for trend.

<0.01), but no trend within persistent smokers, which implies that heavy smokers who quit smoking gained more weight than light smokers who quit smoking (Figure). No clear effect of duration of cessation and amount of smoking was observed on the change in total and HDL cholesterol level and blood pressure between baseline and re-examination. Among men, but not among women, the increase in HDL cholesterol level tended to be largest after at least 2 years of cessation. Furthermore, in men, change in both systolic and diastolic blood pressure seemed to be larger among long-term quitters than among quitters who quit within 4 years before the re-examination, but this was not observed in women (Table 2). Among women, but not among men, HDL change among quitters tended to be largest from 10 cigarettes per day onward (data not shown).

So far, we expressed the change in risk factors as the age-adjusted, actual observed change. This change in risk factors after smoking cessation may be explained by several factors. We examined the effect of several demographic and lifestyle factors, disease history, and weight gain, which are shown in Table 3. Adjustment for age, educational level, number of cigarettes per day at baseline, change in alcohol consumption and disease history did not substantially alter our

Table 3 (Chapter 3) Change (Δ) (95% confidence interval) between baseline and re-examination in body weight, total and HDL cholesterol, and systolic and diastolic blood pressure, adjusted for several factors,[a] for persistent smokers, quitters and never smokers.

	Body weight	Total cholesterol	HDL cholesterol	Systolic blood pressure	Diastolic blood pressure
	Δ (kg)	Δ (mmol/L)	Δ (mmol/L)	Δ (mm Hg)	Δ (mm Hg)
Men					
Adjustment I					
Persistent smokers	3.0 (2.6-3.5)	-0.002 (-0.08-0.07)	0.05 (0.03-0.07)	1.4 (0.2-2.7)	1.5 (0.5-2.5)
Quitters	6.5 (5.8-7.2)***	0.14 (0.02-0.26)*	0.12 (0.09-0.15)***	4.2 (2.2-6.2)*	4.4 (2.9-6.0)***
Never smokers	3.9 (3.4-4.3)*	0.03 (-0.05-0.11)	0.06 (0.04-0.08)	3.0 (1.7-4.3)	2.9 (1.9-4.0)
Adjustment II					
Persistent smokers		0.02 (-0.05-0.10)	0.04 (0.02-0.06)	1.9 (0.7-3.1)	1.9 (0.9-2.8)
Quitters	-	0.04 (-0.08-0.16)	0.15 (0.12-0.18)***	2.6 (0.6-4.6)	3.2 (1.6-4.8)
Never smokers		0.03 (-0.05-0.11)	0.06 (0.04-0.08)	3.0 (1.7-4.2)	2.9 (1.9-3.9)
Women					
Adjustment I					
Persistent smokers	2.7 (2.2-3.3)	0.07 (-0.01-0.15)	0.11 (0.09-0.14)	4.2 (2.8-5.6)	2.3 (1.3-3.3)
Quitters	6.6 (5.8-7.4)***	0.04 (-0.08-0.16)	0.18 (0.14-0.22)**	5.3 (3.2-7.4)	4.4 (2.9-5.9)*
Never smokers	4.3 (3.8-4.7)***	0.11 (0.04-0.18)	0.13 (0.10-0.15)	4.7 (3.5-5.9)	3.3 (2.5-4.2)
Adjustment II					
Persistent smokers		0.09 (0.02-0.17)	0.10 (0.08-0.13)	5.0 (3.6-6.3)	2.8 (1.8-3.8)
Quitters	-	-0.02 (-0.13-0.10)	0.20 (0.17-0.24)***	3.6 (1.5-5.6)	3.2 (1.8-4.7)
Never smokers		0.10 (0.03-0.17)	0.13 (0.11-0.15)	4.5 (3.3-5.6)	3.2 (2.3-4.0)

*p<0.05, **p<0.01, ***p<0.001 for difference with persistent smokers. [a] Adjustment I includes age, educational level and number of cigarettes per day at baseline, change in alcohol consumption between baseline and re-examination and history of myocardial infarction, cerebrovascular accident, diabetes, cancer, asthma and COPD at re-examination; adjustment II includes adjustment I plus changes in body weight between baseline and re-examination.

age-adjusted results (Adjustment I). After adjustment for weight gain, the increase in total cholesterol level, systolic and diastolic blood pressure among quitters tended to become smaller for both men and women, and the difference in total cholesterol (among males) and blood pressure change between quitters and persistent smokers lost significance (Adjustment II). The increase in HDL cholesterol level tended to become slightly larger after adjustment for weight gain.

Discussion

In this general-population study, quitters experienced a larger increase than persistent smokers in body weight, HDL cholesterol level and diastolic blood pressure between baseline and the 6-year follow-up re-examination, among both men and women. Men also experienced a larger increase in total cholesterol level and systolic blood pressure. Heavy smokers gained more weight after cessation than light smokers. Weight gain largely explained the larger increase in total cholesterol and blood pressure among quitters compared with persistent smokers and slightly counteracted the favourable increase in HDL cholesterol among quitters.

Our results were derived from population based data, and thus reflect the change in CVD risk factors among the general population in which smoking behaviour changes under natural circumstances. From a public health point of view, this is an advantage over results from several other studies on this topic, such as trials in which smokers quit smoking under controlled experimental conditions, or studies in selected groups of the population, since public health policy asks for information on health effects in the general, uncontrolled population.

In our study, we reported the age-adjusted, observed changes in CVD risk factors after smoking cessation and examined to what extent confounding factors such as demographic and lifestyle factors, were responsible for these changes. Limitations of our study include the possibility that quitters may have adopted other healthy lifestyle habits affecting body weight, cholesterol level and blood pressure, which we were not able to account for. For instance, non-smokers usually are more physically active than current smokers.[20,21] Furthermore, non-smokers generally consume a healthier diet compared to smokers, especially heavy smokers[22,23] Although information on physical activity and dietary intake was obtained at both baseline and re-examination in our study, we were not able to adjust for changes in these factors, because of differences between questionnaires used in the two examinations. Additional analysis within each examination round showed that

quitters were equally active as persistent smokers at baseline, but more active at the re-examination. If these analyses imply that quitters became more active during follow up compared with persistent smokers, adjustment for physical activity change may have given a larger increase in body weight, total cholesterol level and blood pressure and a smaller increase in HDL cholesterol level among quitters, since physical activity is associated with lower weight, total cholesterol and blood pressure and higher HDL cholesterol. Dietary intake at both baseline and re-examination did not substantially differ between quitters and persistent smokers. Information on intake of alcoholic beverages, which also differs between heavy smokers and ex-smokers,[22] was comparable between the two examinations and the change in alcohol consumption between baseline and re-examination was included in our analyses.

A gain in body weight following smoking cessation has been widely reported.[7-16,24] On average, male and female quitters gained 3.4 kg and 3.8 kg respectively more than persistent smokers in our study with six years of follow-up, which did not substantially change after adjustment for relevant variables. These excess gains were smaller than those found in a smoking cessation trial[7] (6.3 kg and 6.8 kg for men and women respectively after 5 years of follow-up), but larger than those found in other smoking cessation trials,[8] in cohort studies among specific groups of the population,[11,13] or in other cohort studies among the general population,[14-16] which reported excess gains from around 2 kg to 3.8 kg after 4-16 years of follow up. Larger excess gains in our study may be explained by the longer duration of follow-up in some other studies, since it is suggested that, after an initial increase, body weight may decrease later in the follow-up period.[14,25] Williamson et al. reported in a study among the general population that the peak risk for severe weight gain occurred 4-6 years after smoking cessation. Our data are in line with these results. The largest weight gain was found after 4 years of cessation and the excess weight gain decreased afterwards. Besides this, the larger postcessation weight gain among heavy smokers compared with light smokers also confirmed the results found in other general population cohorts.[14]

Mechanisms for weight gain after smoking cessation are not fully established, but several have been suggested.[24] Some studies,[26,27] but not all,[28] have found an increase in dietary intake following cessation which may be responsible for weight gain. Besides an increased dietary intake, metabolic changes resulting in decreased energy expenditure may cause energy imbalance after cessation.[24,29]

Our results confirm the postcessation increase in HDL cholesterol after quitting reported in smoking cessation trials.[8,10] The nicotine in tobacco smoke stimulates the adrenal cortex, leading to consecutive releases of free fatty acids and very low

density lipoprotein, which in turn results in lower HDL cholesterol levels.[30] The absence of nicotine after smoking cessation may reverse this process. HDL cholesterol has been identified as a protective factor against cardiovascular diseases. It is estimated that the excess gain of quitters compared to persistent smokers of 0.07 mmol/L, as we found in our study, would decrease CVD mortality with around 5.5% among men and 8% among women.[31] This indicates that this postcessation change in HDL cholesterol may contribute to the positive effects of smoking cessation on CVD.

Smoking cessation increased total cholesterol levels in men and systolic (significant in men only) and diastolic blood pressure levels in both men and women. Most trials,[8,10] cohort studies among a specific population,[13] or other general population studies[15] reported no change in total cholesterol and blood pressure after cessation. However, after adjustment for change in body weight in our study, the increase in total cholesterol level among men and blood pressure among men and women diminished and lost significance. Weight gain is known to increase total cholesterol and blood pressure levels.[4,5] This indicates that the increase in body weight may mediate between smoking cessation on the one hand and total cholesterol and blood pressure change on the other hand.

These results suggest that quitters should prevent postcessation weight gain as much as possible in order to gain the maximum health benefits from smoking cessation. However, results on the effect of weight control on smoking cessation attempts are inconsistent. Some studies showed a higher cessation rate in subjects on a slimming diet compared to subjects not on a diet,[32] but others failed to show a benefit from weight interventions on smoking cessation[33] and suggest that simultaneously giving up smoking and losing weight may undermine the attempt of quitting.[34] Nevertheless, since smoking is the most important preventable risk factor for CVD and the health benefits of smoking cessation far exceed the small increase in CVD risk due to the temporary postcessation weight gain,[1] less favourable postcessation changes in some CVD risk factors should not discourage smokers to quit.

In conclusion, our data among the general population showed that smoking cessation led to a favourable increase in HDL cholesterol level. Furthermore, giving up smoking predominantly resulted in unfavourable changes in other major CVD risk factors. Weight gain following smoking cessation largely explained the unfavourable increase in total cholesterol level and blood pressure. These results imply that, of the major CVD risk factors, only the postcessation increase in HDL cholesterol may contribute to the beneficial reduction in CVD risk following smoking cessation in the general population. Far more important seem to be the direct effects of smoking

cessation on CVD, which includes the elimination of the harmful effects of cigarette smoke on the sympathetic nervous system, the oxygen transport of the blood and blood coagulation, among others.[2]

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4

Smoking cessation would substantially reduce the future incidence of pancreatic cancer in the European Union

Abstract

Background - Since pancreatic cancer is one of the most rapidly fatal cancers, prevention is of paramount importance to reduce the future burden of this disease. We studied the impact of ceasing smoking on the future incidence of pancreatic cancer in the European Union (EU).

Methods - We developed a computer simulation model, Markov multi-state type, using country-specific published data on population sizes, smoking behaviour, pancreatic cancer incidence and total mortality rates, corresponding relative risks for ex- and current smokers, and estimated probabilities of starting and ceasing smoking (transition rates), with which we refined previously reported preliminary results. We simulated a scenario based on theoretically maximal smoking reduction, a more feasible scenario based on the World Health Organization's 'Health for All' target in which smoking prevalence is reduced to 20% in 2015, and scenarios based on reductions in smoking prevalence in 20 steps of 5% (from 0% to 100% reduction) in 2015. Simulations were based on changes in transition rates for smoking behaviour. We estimated the absolute and relative reduction of pancreatic cancer patients in the EU, for each scenario compared to a reference scenario in which the current transition rates remained unchanged, for the period 1994-2015.

Results - Theoretically, if all smokers would quit instantly, the estimated number of new pancreatic cancer patients up to 2015 in the EU could be reduced by 15% (around 150,000 patients). The more feasible scenario would lead to a reduction of almost 29,500 male and 9,500 female patients. These results corresponded to a reduction in smoking prevalence with around 45% and 30% among men and women, respectively, in each EU country.

Conclusions - Giving up smoking would substantially reduce the future incidence of pancreatic cancer. This emphasizes the importance of prevention in the reduction of the future pancreatic cancer burden.

Mulder I, Hoogenveen RT, van Genugten MLL, Lankisch PG, Lowenfels AB, de Hollander AEM, Bueno de Mesquita HB. Smoking cessation would substantially reduce the future incidence of pancreatic cancer in the European Union. Eur J Gastroenterol Hepatol 2002;14:1343-1353.

Introduction

Pancreatic cancer is one of the most rapidly fatal cancers. For several decades, clinical researchers have made an effort to improve treatment for pancreatic cancer patients. However, despite advances in diagnostic and curative methods, so far without satisfying success: the survival rate of pancreatic cancer has hardly changed during the last decades[1] and nowadays 85% of the patients still die within 1 year.[2] This makes prevention of pancreatic cancer of paramount importance for the reduction of the future burden of this disease.

In the literature several risk factors for pancreatic cancer have been reported, including dietary factors, history of diabetes mellitus and chronic pancreatitis.[3] However, the most consistently reported risk factor, and also the best avoidable one, is cigarette smoking.[4-12] Of all deaths from tobacco related cancer in the European Union (EU), pancreatic cancer is the second leading cause of death among both men and women.[13] Epidemiological studies have shown that giving up smoking approximately halves the risk for pancreatic cancer.[5,8,9] This indicates that encouraging smokers to quit may play an important role in the prevention of pancreatic cancer, which, among other reasons, should stimulate clinicians to advise their patients to quit smoking.

Although giving up smoking is established to be beneficial for the prevention of pancreatic cancer, studies on the quantity of the preventive effect of smoking cessation on future pancreatic cancer are scarce. Therefore, in the present study, we estimated the absolute and relative reduction in the number of future pancreatic cancer patients in the EU which can be achieved by smoking cessation, by means of a mathematical computer simulation model. We simulated several scenarios based on smoking reduction, including a scenario which is based on the 'Health for All' target for future public health policy in the European region with respect to tobacco smoking, as formulated by the World Health Organization.[14] In 1999, we reported preliminary results of this study using a preceding, crude version of our simulation model.[15] Now, our mathematical simulation model is refined, with a more sophisticated method of computer simulation based on the Markov multi-state model, with adjustments for competing causes of death and with new data on smoking behaviour, and we are now able to report more precise estimates on the number of preventable pancreatic cancer patients due to smoking cessation.

Methods

Simulation model

We used a mathematical simulation model to estimate the reduction in the number of pancreatic cancer patients due to smoking cessation in the EU. This model was based on the Markov multi-state model, which uses transition rates to indicate the probability of a subject moving from one state to another,[16] for example the probability of dying or the probability of giving up smoking.

In our model, in each of the 15 EU member states, the population at the beginning of our simulation (1994) consisted of male and female never, ex- and current smokers, in 1 year age classes, starting from age 15 up to age 85 and over. Each age class had specific transition rates, i.e. specific probabilities of starting and ceasing smoking and specific total mortality rates. We formulated several scenarios based on a reduction in smoking prevalence during the successive years of our simulation period, which led from 1994 to 2015. Each scenario had its specific transition rates for smoking behaviour. A schematic representation of our model is given in Appendix I. In this Appendix, arrows represent the yearly transitions of subjects in each age class from one state to another, i.e. either to remain in the same state, to start or quit smoking, or to die. In 1994, for each scenario, the number of subjects in each state of smoking behaviour, i.e. the number of never, ex- and current smokers, was estimated using published data on population sizes and on the prevalence of ex- and current smokers. In the subsequent years of our simulation, the number of 15-year-old never, ex- and current smokers, which can be considered as 'new' members of our population, were estimated similarly. For the remaining age classes, for each scenario, the number of never, ex- and current smokers and the total number of deaths in a subsequent simulation year depended on the numbers in the preceding year, the scenario specific transition rates for smoking behaviour and the total mortality rates (see Appendix II-2). During simulation, the group of ex-smokers consisted of subjects who were ex-smokers at the start of our simulation plus subjects who quit smoking during simulation (see Appendix II-2). Each year, in each state of smoking behaviour, new pancreatic cancer patients arose. To estimate the yearly age- and sex specific number of future pancreatic cancer patients in each scenario, we used the incidence rate among the separate smoking categories, the scenario specific number of never, ex- and current smokers, and the lag time of smoking cessation (see Appendix II-3).

Table 1 (Chapter 4) Population size, age-standardised[a] pancreatic cancer incidence rate and prevalence of smoking behaviour among men and women aged 15 years and over in the European Union.

	Population size in 1994 (x1000)[b]		Pancreatic cancer incidence rate (100,000/year)[c]			Prevalence of smoking behaviour (%)[d]				
							Ex-smokers		Current smokers	
Member state	Men	Women	Year	Men	Women	Year	Men	Women	Men	Women
Austria	3,164	3,402	1988-1992	10.1	8.2	1995	15	12	37	25
Belgium	4,019	4,272	Not available			1987-1995	24	14	37	27
Denmark	2,113	2,194	1988-1992	11.3	9.3	1987-1995	23	18	37	43
Finland	1,978	2,136	1987-1992	13.7	10.1	1994-1995	28	18	32	23
France	22,378	24,141	1988-1992	7.2	4.0	1987-1995	26	14	43	30
Germany	32,804	35,296	1988-1992	10.5	6.5	1987-1995	24	14	39	25
Greece	4,200	4,414	Not available			1987-1995	19	6	55	27
Ireland	1,315	1,344	1988-1992	11.2	6.6	1987-1995	21	16	34	30
Italy	23,317	25,153	1988-1992	11.6	7.7	1987-1995	24	11	37	26
Luxembourg	161	171	Not available			1987-1995	22	15	33	27
The Netherlands	6,174	6,393	1989-1992	9.8	6.7	1987-1995	27	21	41	36
Portugal	3,821	4,224	Not available			1987-1995	21	5	43	12
Spain	15,915	16,885	1986-1992	8.0	4.6	1987-1995	22	8	48	27
Sweden	3,488	3,630	1988-1992	10.2	8.3	1995	31	25	21	28
United Kingdom	22,631	24,178	1988-1992	10.8	7.7	1987-1995	29	24	32	31

[a] On the world standard population. Source: [b] United Nations,[17] [c] IARC,[19] [d] Eurobarometer.[18]

Sources of information

The sex specific population sizes in each EU member state in 1994 were derived from the United Nations (Table 1).[17] From these data, which are given in 5-year age classes, we estimated the population sizes for each 1 year age class in 1994 (S-Plus 2000, Professional Release 2. MathSoft Inc., Seattle, 2000). For the subsequent years of our simulation period (1995-2015), the population sizes of the 15-year-olds, the youngest age class in our population, were estimated by the same method, except that the UN population sizes were population size projections. The population size of all other age classes in the subsequent simulation years depended on the scenario specific estimated number of never, ex- and current smokers.

Age- and sex specific prevalences of ex- and current cigarette smoking (manufactured and hand-rolled) in the EU member states were derived from ten Eurobarometer surveys carried out from 1987 to 1995 (Nos. 27, 29, 30, 31, 32, 34.1, 36, 38, 41 and 43) (Table 1).[18] In each survey, a random sample was drawn from the population aged 15 years and over in each country. Per country, approximately 1,000 subjects were interviewed in their homes, except for the United Kingdom (1,000 in Great Britain and 300 in Northern Ireland), Germany (1,000 in both former West and East Germany), and in survey No. 32 (1989) (twice as many subjects in each country). Since 1990, Germany includes East Germany. Data were weighted by sex, age, region and size of neighbourhood to obtain representative data for the whole country. Per country, we averaged the weighted age- and sex specific prevalences over the ten Eurobarometer surveys. For both men and women, ex- and current smoking prevalences were then smoothed over 1 year age categories (S-Plus 2000). These data were assumed to be the smoking prevalence at the beginning of our simulation (1994). From these prevalences of smoking behaviour, we estimated the age- and sex specific transition rates for smoking behaviour, i.e. the probability of moving from one state of smoking behaviour to another during 1 year (Mathematica Version 4.1. Wolfram Research, Champaign, USA, 2000). The transition rates included the start rate, which is the probability of a never smoker becoming a smoker within 1 year, and the stop rate, which is the probability of a smoker ceasing to smoke within 1 year. The stop rate is the net rate, incorporating the rate of quitting and relapse after quitting. Because sufficient time series of past smoking prevalence were not available for all countries, we assumed no trend in the start and stop rates.

Information on the age- and sex specific pancreatic cancer incidence rate (ICD-9 157) in each EU member state was obtained from the International Agency for Research on Cancer (IARC) (Table 1).[19] Data reflect all newly diagnosed pancreatic

cancer patients per 100,000 person years in 5-year age classes in periods centred on 1990. Data were derived from national cancer registries (Denmark, Finland, the Netherlands, Sweden) or from one (Austria, Ireland) or more than one (France, Italy, Spain, Germany, the United Kingdom) regional cancer registry. For Belgium, Luxembourg, Portugal and Greece, information on the incidence of pancreatic cancer was not available. For these countries, we estimated the incidence rate by applying the mean pancreatic cancer incidence rate among never smokers of adjacent or geographically comparable countries (Germany, France, and the Netherlands for Belgium and Luxembourg; Spain for Portugal; Spain and Italy for Greece) to the never smokers in these countries. The national age- and sex specific total mortality rate for each member state of the EU was obtained from the World Health Organization (WHO) Databank. These data reflect all deaths per 100,000 in 5-year age classes in 1994. We smoothed both the pancreatic cancer incidence rates and the total mortality rates over 1 year age classes (S-Plus 2000). Since pancreatic cancer incidence and total mortality rates among never, ex- and current smokers separately were not available, we estimated these rates using data on prevalence of smoking behaviour, pancreatic cancer incidence or total mortality rates in the total population at the beginning of simulation (1994), and data on the relative risk of ex- and current smokers (see Appendix II-1). We assumed the age-specific pancreatic cancer incidence and total mortality rates in each category of smoking behaviour to be constant over time.

The relative risks of ex- and current smokers for pancreatic cancer incidence were taken from the study of Fuchs et al.[8] These authors reported a relative risk for smokers of 3.0 for men and 2.4 for women and a relative risk for ex-smokers of 1.3 for men and 1.1 for women. We chose this study because relative risks were derived from large cohort studies, were reported for pancreatic cancer incidence, which are usually more accurate than for mortality, and were reported for men and women separately. Fuchs et al. calculated the relative risks for men with data from the Health Professionals Follow-up Study, a cohort study among over 50,000 American males aged 40-75 years, which started in 1986. The relative risks for women were derived from the Nurses' Health Study, a cohort study among over 120,000 American female nurses aged 30-55 years, which started in 1976. In these analyses, follow-up for both studies ended in 1992. The lag time of smoking cessation, i.e. the period of decrease in risk after smoking cessation towards the risk of a never smoker, is reported to be 10-15 years.[5,7,8] We used the most conservative, upper value of 15 years in our model. The relative risks of ex- and current smokers for total mortality were taken from the Cancer Prevention Study II (CPS II),[9] which is a large cohort study among 1.2 million American men and

women aged 35 years and over, started in 1982 with a 4 year follow up. In this study, the relative risk for total mortality of a smoker was 2.3 and 1.9 and the relative risk of an ex-smoker was 1.6 and 1.3, among men and women respectively. For both pancreatic cancer incidence and total mortality, we assumed that an individual who started smoking directly experienced the relative risk of an average smoker. We furthermore assumed that an individual who quit smoking experienced a decrease in relative risk for pancreatic cancer incidence from the relative risk of a smoker to 1, proportionally within 15 years after cessation, and directly experienced the relative risk of an average ex-smoker for total mortality.

Scenarios

We formulated a 'reference scenario' in which the transition rates for smoking behaviour at the beginning of the simulation and all other factors influencing pancreatic cancer incidence, except ageing, remained unchanged in the subsequent years.

We formulated several alternative scenarios based on two approaches: a reduction of the prevalence of smokers in each EU member state *to* a fixed percentage and a reduction of the prevalence of smokers *with* a fixed percentage. These reductions were achieved by varying the age- and sex specific start and/or stop rates. In these scenarios, we assumed that all other factors influencing pancreatic cancer incidence, except ageing, remained unchanged in the subsequent years.

First, we simulated a reduction of the smoking prevalence *to* a fixed percentage in a theoretical maximum scenario and a more feasible scenario. In the 'maximum scenario', we simulated that in each country no individual would start smoking and that all smokers would quit instantly, i.e. a reduction of the smoking prevalence to 0% by the year 1995. This was achieved by assuming the start rate to be 0 and the stop rate to be 1 for each age class and each simulation year, from 1995 onward. With this scenario, the theoretical maximum reduction in pancreatic cancer incidence following smoking cessation can be estimated. The more feasible scenario ('HFA scenario') is based on the Health for All (HFA) target of the World Health Organization with respect to tobacco smoking, which implies that the prevalence of non-smoking should be at least 80% in each country of the EU by the year 2015.[14] In the HFA scenario, we simulated a reduction of the percentage of smokers (male and female) to 20% in each country by the year 2015. This was achieved by increasing the age- and sex specific stop rate with the same proportion for each age class and simulation year, from 1995 onward. Since the percentage of

smokers was already around 20% among men in Sweden and among women in Portugal, in these cases the stop rate was not changed.

We then simulated reductions in the smoking prevalence *with* a fixed percentage for each country. In 20 consequent simulations, we reduced the smoking prevalence with steps of 5%: from a 0% to a 100% reduction, relative to the smoking prevalence in 1994, achieved by the year 2015. Also in these scenarios, the age- and sex specific stop rate increased with the same proportion for all age classes and successive simulation years, from 1995 onward.

Model outcome variables

The number of pancreatic cancer patients in each country was cumulated over time to obtain the estimated total number of incident pancreatic cancer patients from 1994 through 2015 among men and women aged 15 years and over, in each scenario. For each alternative scenario, we estimated the absolute and relative reduction in incident pancreatic cancer patients as compared to the reference scenario. Since country specific smoking prevalence was available only for the EU population aged 15 years and over, results were estimated for this age group. For each scenario, the number of pancreatic cancer patients in the European Union, as a whole, was estimated by adding up the number of patients in all 15 member states in the EU.

The information we used in our model incorporates some degree of uncertainty. To evaluate the sensitivity of our model to this uncertainty, we performed additional sensitivity analyses by varying the relative risk of ex- and current smokers and the lag time for pancreatic cancer. In these analyses, we estimated the number of preventable pancreatic cancer patients using a relative risk of current smokers of 1.5, which is the lowest value in the range of published relative risks for both men and women, and using a relative risk of 4.5 among men and of 3.6 among women, which is a theoretical 50% larger relative risk of current smokers. Additionally, we varied the relative risk of ex-smokers with 50%, with a minimum of 1. Furthermore, we used the relative risks of smokers (2.1 for both men and women) and ex-smokers (1.3 for men and 1.8 for women) reported by Lund Nilsen and Vatten, which are based on a large cohort study in Norway.[20] Finally, we examined the impact of a lag time for smoking cessation of 10 years, which is also mentioned in the literature.

Table 2 Estimated number of new pancreatic cancer patients cumulated up to the year 2015 among men and women in the reference scenario in the member states of the European Union; rounded off to the nearest 10.

Member state	Men	Women
Austria	10,210	15,200
Belgium	12,820	11,080
Denmark	8,110	8,770
Finland	9,510	10,870
France	55,080	42,300
Germany	118,550	109,050
Greece	19,400	13,800
Ireland	4,260	3,230
Italy	97,230	97,410
Luxembourg	470	450
The Netherlands	20,260	18,380
Portugal	9,120	8,680
Spain	43,820	38,990
Sweden	13,660	14,340
United Kingdom	87,830	86,550
European Union	510,320	479,100

Results

The estimated cumulative numbers of new pancreatic cancer patients arising in each EU member state up to the year 2015, in the reference scenario, are presented in Table 2. If smoking behaviour would remain unchanged in the future decades, in the EU around 510,000 and 480,000 new pancreatic cancer patients would be diagnosed among men and women, respectively.

If all smokers would give up smoking instantly, among men, the number of new pancreatic cancer patients up to 2015 could be reduced by 15%-25% in most countries, as compared to the reference scenario (Figure 1A). The lowest relative reduction in male patients would appear in Sweden (12%). Among women, the estimated relative reduction in pancreatic cancer patients in the maximum scenario was lower than among men, mainly because of the lower prevalence of smoking among women (Figure 1B).

More feasible is the HFA scenario (Figure 1A and 1B). This scenario would lead to no reduction in pancreatic cancer patients among men in Sweden and among

women in Portugal, since the percentage of smokers among these groups was already around 20% or less. In the other EU member states, the estimated relative reduction of cancer patients up to 2015 in this scenario ranged from around 3% in Ireland and the United Kingdom to almost 13% in Greece among men, and from 0.9% in Finland to 7% in Denmark among women.

The estimated absolute and relative number of preventable pancreatic cancer patients in the EU, as a whole, are presented in Figure 2A and 2B. In the maximum scenario, more than 100,000 male and 50,000 female pancreatic cancer patients could be prevented up to the year 2015, which corresponded to 20% and 10.5% respectively. The HFA scenario would lead to a reduction of almost 29,500 male and 9,500 female pancreatic cancer patients up to 2015. This corresponded to a relative reduction of 5.7% and 2.0% for men and women, respectively.

Figure 3 reflects the estimated absolute reduction of pancreatic cancer patients up to 2015 for a relative reduction in smoking prevalence in 20 steps of 5% by the year 2015 in the European Union. The figure indicates that, for example, a 25% reduction in smoking prevalence in each country of the EU from 1994 up to 2015 (for instance from a smoking prevalence of 40% in 1994 to a prevalence of 30% in 2015) would reduce the estimated number of pancreatic cancer patients by more than 15,000 men and 7,500 women. A reduction of almost 29,500 male and 9,500 female pancreatic cancer patients, as estimated with the HFA scenario, could be achieved by a reduction in smoking prevalence with around 45% among men and almost 30% among women in each EU member state.

We additionally evaluated the sensitivity of our model to uncertainty in relative risk of smokers and ex-smokers and in lag time for pancreatic cancer incidence (data not shown). These analyses indicated that a relative risk of 1.5 would lead to a 70%-77% lower estimated number of preventable pancreatic cancer patients in the HFA scenario, although not greatly influencing the cumulated number of patients (1%-3%). Furthermore, a theoretical 50% larger relative risk among smokers would increase the number of preventable pancreatic cancer patients by around 50%-80%. Values were lower for a 50% change in the relative risk among ex-smokers, up to a 14% larger estimated number of preventable patients among men. Using the relative risks reported by Lund Nilsen and Vatten[20] would decrease our results in the HFA scenario by 26%-30%. A lag time of 10 years would lead to a 25% increase in preventable patients among men and women.

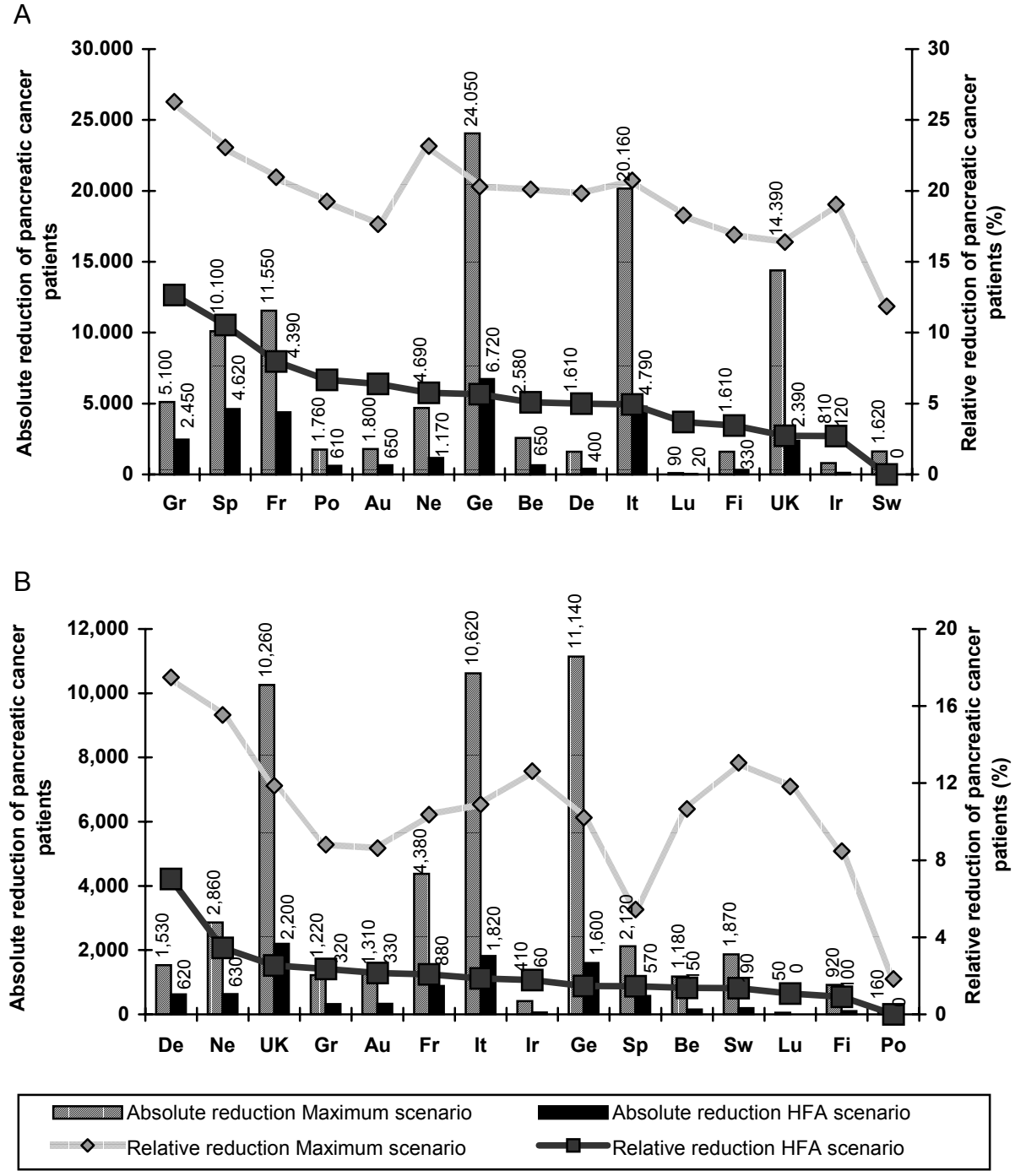

Figure 1A and **1B** Absolute and relative reduction of the cumulated number of pancreatic cancer patients up to the year 2015, among men (A) and women (B), in each member state of the European Union, in the maximum and the World Health Organization 'Health For All' (HFA) scenario compared to the reference scenario; rounded off to the nearest 10. Au=Austria, Be=Belgium, De=Denmark, Fi=Finland, Fr=France, Ge=Germany, Gr=Greece, It=Italy, Ir=Ireland, Lu=Luxembourg, Ne=the Netherlands, Po=Portugal, Sp=Spain, Sw=Sweden, UK=United Kingdom.

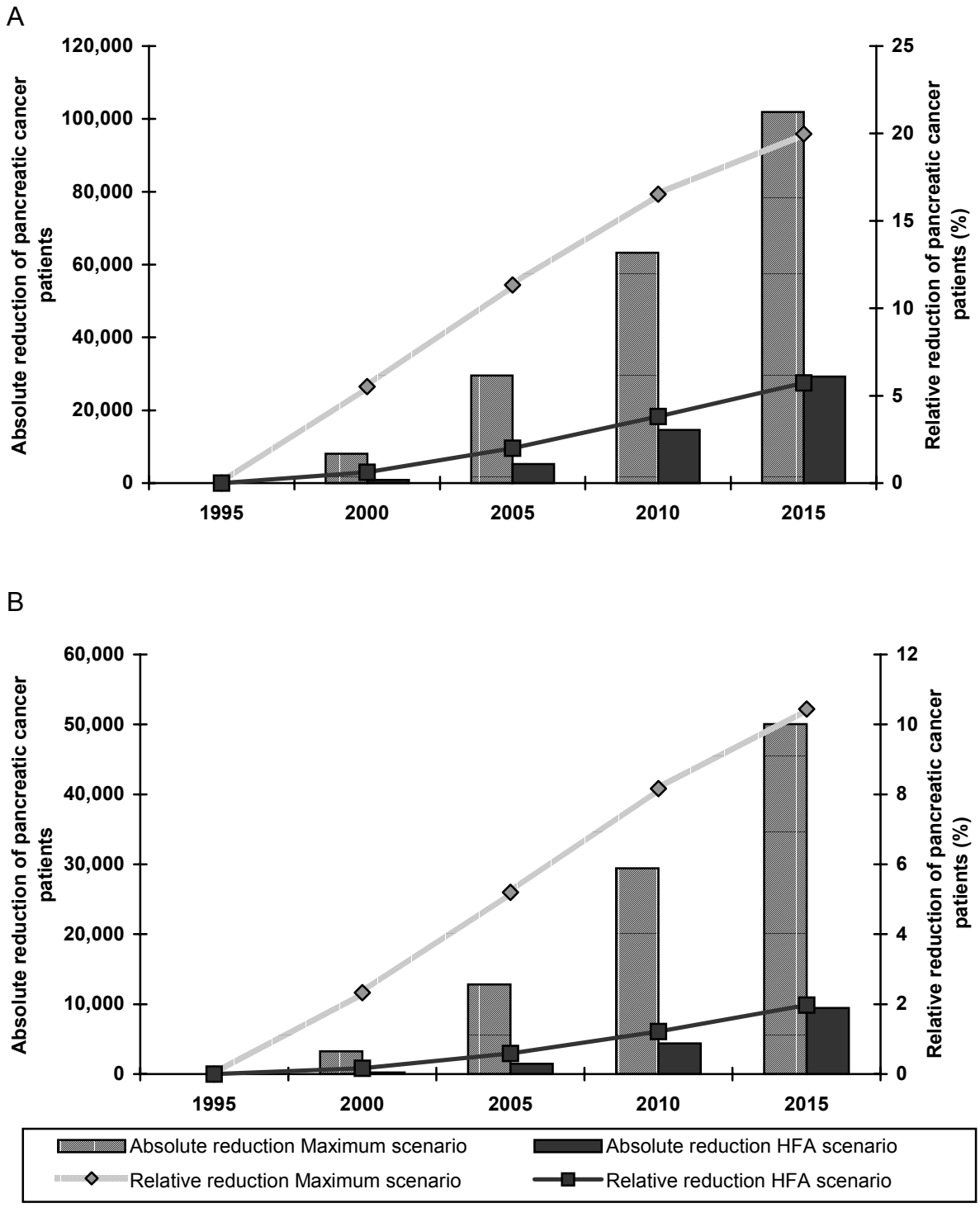

Figure 2A and **2B** Absolute and relative reduction of the cumulated number of pancreatic cancer patients up to the years 1995, 2000, 2005, 2010 and 2015, among men (A) and women (B), in the European Union as a whole, in the maximum and the HFA scenario compared to the reference scenario.

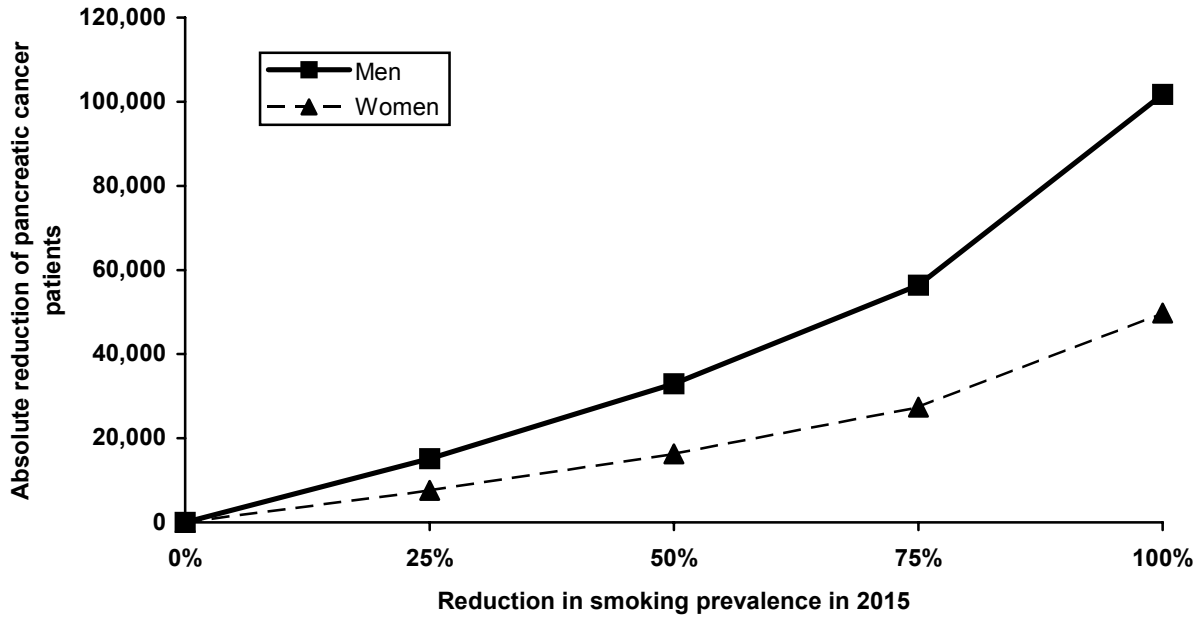

Figure 3 Absolute reduction of the cumulated number of pancreatic cancer patients up to the year 2015 for each 5% reduction in smoking prevalence in the European Union as a whole.

Discussion

The results of this study on the estimated number of preventable pancreatic cancer patients in the EU indicated that, theoretically, up to the year 2015, a maximum of more than 100,000 and around 50,000 pancreatic cancer patients could be prevented among men and women, respectively. When a more feasible scenario, based on the Health for All targets of the WHO, was simulated, a reduction of up to almost 29,500 male and 9,500 female pancreatic cancer patients would be achieved. These results corresponded to a reduction in smoking prevalence with around 45% and 30% among men and women respectively in each EU country.

Since we did not include other possible risk factors for pancreatic cancer incidence into our model, our results can not be interpreted as absolute predictions of future pancreatic cancer incidence, but rather as an indication of the reduction in future pancreatic cancer due to smoking cessation. Obviously, the expected maximum reduction of around 15% (around 150,000 patients) in future pancreatic cancer is purely theoretical. However, even a more feasible scenario like the Health For All target of the WHO would lead to a substantial reduction in the number of

pancreatic cancer patients. In this scenario, future pancreatic cancer was expected to decline by around 4% (almost 39,000 patients), which corresponded to 26% of the estimated maximum reduction if all smokers would cease smoking instantly. Each successive year will, of course, further increase the number of cancers prevented. Although several studies examined the impact of smoking cessation on lung cancer,[21-23] to our knowledge, besides our previously reported preliminary results using a preceding, crude version of our model,[15] no other studies investigated the reduction in future pancreatic cancer incidence due to smoking cessation.

In public health modelling, one intends to develop a model which reflects real life as close as possible. With a more sophisticated method of simulation, based on the Markov multi-state model, with new data on smoking behaviour, inclusion of ex-smokers and adjustments for competing causes of death, our model presents a more precise reflection of real life than our preceding, crude simulation model. However, although Markov models are often used in public health modelling,[16] simplifications of reality in these models still are inevitable. For instance, we assumed the group of smokers to be homogeneous with respect to the relative risk for pancreatic cancer, independent of amount and duration of smoking, whereas in reality this relative risk increases with increasing number of cigarettes smoked per day and number of years smoked.[5-7] However, since we used average group estimates of the relative risk for current smoking, we expect that the differences in relative risk within the group of current smokers will partly be averaged out. Moreover, smoking prevalence seems to reduce in time among men in the United Kingdom, Denmark, France and Spain, and among women in Denmark and the Netherlands. Since sufficient historical age-specific data on both cigarette smoking and pancreatic cancer incidence were not available for all member states of the EU, however, we were not able to account for a possible trend in these variables.

Some remarks on the input variables of our model should be made here. First, we used standard Eurobarometer survey data on the prevalence of smoking behaviour instead of national survey data. Eurobarometer survey data have several advantages over national survey data. For instance, data are obtained according to a standard protocol in each member state, which is not the case in national survey data. Since the sampling method, the method of data collection and interpretation, and the definition of smoking are standardized, smoking data are comparable across the EU countries. Nevertheless, the size of the study population of the Eurobarometer survey data amounts to approximately 1,000 subjects per member state per survey, which is relatively small. This may have led to an inaccurate estimation of smoking prevalence, if these subjects were not representative for the

whole country. However, data were weighted by age, sex, region, and size of neighbourhood in each member state to obtain representative data for the whole country. Furthermore, for each country we averaged the weighted percentage of ex- and current smokers over the ten Eurobarometer surveys, which increased the study population and improved the smoking prevalence estimate.

Second, the quality of the cancer incidence data has been evaluated by IARC, using, among other criteria, the percentage of morphological verified patients (MV%) and the mortality/incidence ratio (M/I). Although all cancer registries need to provide incidence data with overall adequate quality, four out of eight cancer registries in France showed an unfavourably high M/I for pancreatic cancer of more than 200%. This may indicate that the incidence registration was incomplete. Exclusion of these cancer registries gave an increase in the number of preventable patients in France of 16%-19%. Furthermore, in several countries, only regional incidence data were available. To approximate the national pancreatic cancer incidence rate in these countries, we averaged the incidence rate over the different regions, weighted by the size of the populations in the specific regions. This could have led to inaccurate estimates if the regional registries were not representative for the whole country. Other studies estimated the national pancreatic cancer incidence in these countries from national mortality data[13,24,25] and reported higher rates in Austria and Ireland, and among males in France, and lower rates in Italy, and among males in Germany and Spain.[24] However, mortality data on pancreatic cancer are considered to be less accurate than incidence data.

Although cigarette smoking is the most consistent risk factor for pancreatic cancer, a high percentage of smokers in a population does not necessarily result in a high pancreatic cancer incidence rate. For instance, Spain, with high smoking rates, has one of the lowest pancreatic cancer incidence rates in the EU. In contrast, Finland with quite low smoking rates showed the highest incidence rates. This contradiction may be explained by differences in past smoking prevalences or differences in the prevalence of other pancreatic cancer risk factors, such as dietary factors, history of diabetes mellitus, chronic pancreatitis[3] and variation in genetic susceptibility.

In this paper we estimated that smoking cessation would substantially reduce the number of pancreatic cancer patients, if all smokers would quit instantly, but also if the WHO's Health for All target concerning tobacco smoking could be achieved. Although results from public health modelling do represent uncertainty due to the inevitable simplifications and should be interpreted as an indication of the magnitude of the effect, our results emphazise the importance of prevention of pancreatic cancer. Since cigarette smoking is also a risk factor for other diseases, including

lung cancer and cardiovascular diseases,[4,26] which both largely contribute to the disease burden, the impact of ceasing smoking on the total burden of disease would be much greater.

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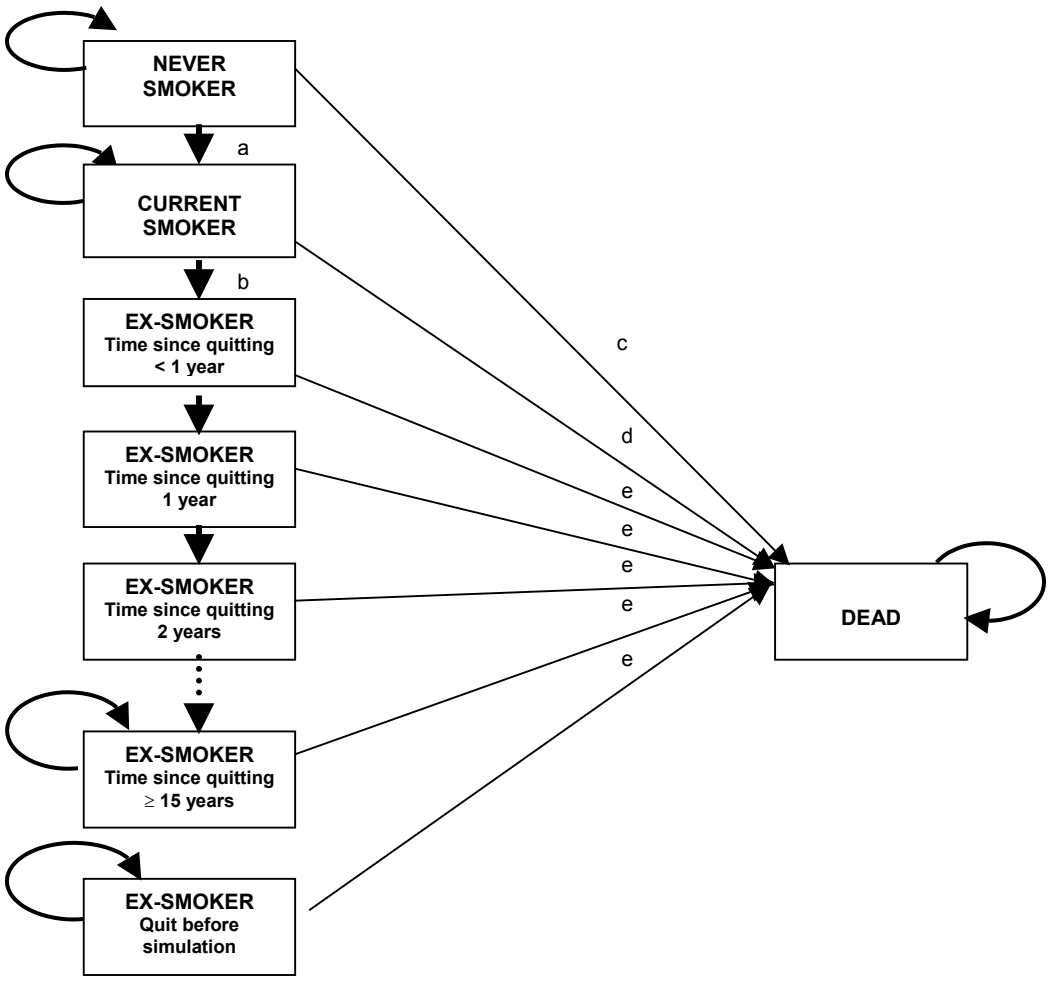
Appendix I Schematic representation of the computer simulation model



In the above figure, a = start rate, b = stop rate, c = total mortality rate of never smokers, d = total mortality rate of current smokers, and e = total mortality rate of ex-smokers.

The interpretation of this schematic representation of the simulation model is as follows. Each year, the population of each EU member state consists of subjects in several mutually exclusive states, represented by blocks, i.e. never smoker, current smoker, ex-smoker with different years since quitting or dead. Arrows represent the yearly transitions of subjects in each age class from one state to another, i.e. to remain in the same state (curved arrows), to start or cease smoking, with the start and stop rate as corresponding transition rates or to move into a group of ex-smokers with one extra year since quitting (thick arrows), or to die, with the total mortality rate as corresponding transition rate (thin arrows). Each year, in each of the smoking behaviour states, new pancreatic cancer patients arise, which depends, among others, on the state specific pancreatic cancer incidence rate (see Appendix II-3).

Appendix II Formulas used to model the impact of smoking cessation on future pancreatic cancer incidence

The following descriptors are used in the equations:

never	=	never smokers
ex	=	ex-smokers
current	=	current smokers
s	=	sex
a	=	1 year age class: 15 years up to 85 and over
RR	=	relative risk
N	=	number
t	=	year of simulation: 1994 up to 2015
mort	=	total mortality rate
start	=	start rate
stop	=	stop rate
inc	=	pancreatic cancer incidence rate
r	=	number of years since quitting

1. Calculation of the age-specific pancreatic cancer incidence rate and total mortality rate among never, ex- and current smokers

Pancreatic cancer incidence and total mortality rates among never, ex- and current smokers separately are not available. We therefore estimated these rates using published age- and sex specific data on the pancreatic cancer incidence and total mortality rates in the total population and the prevalence of smoking behaviour at the beginning of our simulation (1994), and on corresponding relative risks of ex- and current smokers, by means of the following formulas.

$$x_{never,s,a} = \frac{x_{total\ population,1994,s,a}}{(RR_{current,s}*\%current_{1994,s,a} + RR_{ex,s}*\%ex_{1994,s,a} + \%never_{1994,s,a})}$$

$$x_{ex,s,a} = RR_{ex,s} * x_{never,s,a}$$

$$x_{current,s,a} = RR_{current,s} * x_{never,s,a}$$

where x represents either the pancreatic cancer incidence rate or the total mortality rate and RR represents the corresponding relative risk.

2. Age-specific number of never, ex- and current smokers in a specific simulation year

The number of subjects in each category of smoking behaviour at the beginning of our simulation (1994) is estimated using the age- and sex specific prevalence of smoking behaviour and population size. For the remaining simulation years, the number of 15-year-old never, ex- and current smokers, the youngest age class which each year may be assumed as 'new' subjects in our simulation, was estimated similarly.

t = 1994 or age = 15:

$N\ never_{t,s,a} = \%never_{1994,s,a}/100 * population\ size_{t,s,a}$

$N\ ex_{t,s,a} = \%ex_{1994,s,a}/100 * population\ size_{t,s,a}$

$N\ current_{t,s,a} = \%current_{1994,s,a}/100 * population\ size_{t,s,a}$

The number of never, ex- and current smokers in each other age class in each of the remaining simulation years (1995-2015) was the result of the number of subjects in the preceding year and the transition rates. In these estimations, the group of ex-smokers was divided into several subgroups, based on the number of years since quitting.

t = 1995 up to 2015 and age > 15:

$N\ never_{t,s,a} = N\ never_{t-1,s,a-1} * (1- mort_{never,s,a-1}) * (1-start_{s,a-1})$

$N\ ex_{quit\ before\ simulation\ t,s,a} = N\ ex_{quit\ before\ simulation\ t-1,s,a-1} * (1- mort_{ex,s,a-1})$

$N\ ex_{time\ since\ quitting\ <\ 1\ year\ t,s,a} = N\ current_{t-1,s,a-1} * (1- mort_{current,s,a-1}) * stop_{s,a-1}$

$N\ ex_{time\ since\ quitting\ 1\ year\ t,s,a} = N\ ex_{time\ since\ quitting\ <\ 1\ year\ t-1,s,a-1} * (1- mort_{ex,s,a-1})$

$N\ ex_{time\ since\ quitting\ 2\ years\ t,s,a} = N\ ex_{time\ since\ quitting\ 1\ year\ t-1,s,a-1} * (1- mort_{ex,s,a-1})$

.. .. ..

$N\ ex_{time\ since\ quitting\ r\ years\ t,s,a} = N\ ex_{time\ since\ quitting\ r-1years\ t-1,s,a-1} * (1- mort_{ex,s,a-1})$

$N\ current_{t,s,a} = N\ current_{t-1,s,a-1} * (1- mort_{current,s,a-1}) * (1-stop_{s,a-1}) + N\ never_{t-1,s,a-1} * (1- mort_{never,s,a-1}) * start_{s,a-1}$

The total mortality rate and the start and stop rates in these estimations are expressed as probability variables between 0 and 1.

3. Calculation of the age-specific absolute number of pancreatic cancer patients in a specific simulation year

The number of pancreatic cancer patients in each scenario was estimated by adding up the number of pancreatic cancer patients in each category of smoking behaviour. The estimation of the number of patients among never, ex- and current smokers was based on the number of subjects in each category multiplied by the smoking behaviour-specific pancreatic cancer incidence rate.

$$\begin{aligned} N\ \text{pancreatic cancer patients}_{t,s,a} = {} & N\ never_{t,s,a} * inc_{never,s,a} + \\ & N\ ex_{\text{quit before simulation } t,s,a} * inc_{ex,s,a} + \\ & N\ ex_{\text{time since quitting < 1 year } t,s,a} * inc_{current,s,a} + \\ & N\ ex_{\text{time since quitting r years } t,s,a} * inc_{\text{ex time since quitting r years},s,a} + \\ & N\ current_{t,s,a} + inc_{current,s,a} \end{aligned}$$

where $inc_{\text{ex time since quitting r years},s,a} = inc_{never,s,a} * RR_{\text{ex time since quitting r years},s}$

and
$$RR_{\text{ex time since quitting 1 year },s} = RR_{current,s} * decrease$$
$$RR_{\text{ex time since quitting 2 years},s} = RR_{current,s} * decrease^2$$
$$\ldots \qquad \ldots$$
$$RR_{\text{ex time since quitting r years},s} = RR_{current,s} * decrease^r$$

where $decrease = (1/RR_{current,s})^{1/\text{lag-time}}$

5

Modelling future mortality reduction through smoking cessation in the European Union

Abstract

Background - To assess public health relevance of targets on tobacco smoking, information is needed on the decline in future mortality following smoking cessation. WHO's Health for All (HFA) and other targets on tobacco smoking in the European Union (EU) were therefore simulated.

Methods - A computer simulation model, Markov multi-state type, was developed using published age- and sex-specific information on population sizes, smoking prevalences, total and cause-specific mortality rates and corresponding relative risks for ex- and current smokers. The probabilities to start and quit smoking (transition rates) were estimated. Targets on smoking cessation included WHO's HFA target (country-specific smoking prevalence is reduced to 20% by 2015), and a theoretical maximum target (all smokers quit instantly). Simulation of these targets was based on changes in transition rates for smoking behaviour. For each target, the cumulated number of all-cause and cause-specific deaths between 1994 and 2015 was estimated for each EU member state. Then, the absolute and relative reduction in the number of deaths compared to a reference scenario, in which transition rates for smoking behaviour remained constant, were estimated for the EU as a whole.

Results - WHO's HFA target was expected to give a total mortality reduction by 2015 of 2.5% (around 1.1 million deaths) among men and 0.8% (almost 350,000 deaths) among women in the EU. Overall, the expected mortality declines in the HFA target were about 40-50% (men) and 30% (women) of the expected declines in the maximum target. The largest impact of the HFA target would be reached for lung cancer mortality.

Conclusions - These results emphasize the need for policymakers in each EU member state to put strong effort into encouraging smokers to quit smoking.

Mulder I, Hoogenveen RT, Smit HA, Bueno de Mesquita HB. Modelling future mortality reduction through smoking cessation in the European Union. Eur J Public Health. *Accepted for publication*.

Introduction

It is well known that cigarette smoking is the number one preventable risk factor for mortality in the European Union (EU). Established smoking-related causes of death include several forms of cancer, cardiovascular diseases and chronic obstructive pulmonary disease (COPD).[1,2] Peto et al.[3] estimated that 15% of all deaths in 1995 in the EU could be attributed to cigarette smoking. A reduction in smoking prevalence may thus be of great importance in the efforts to reduce future mortality in the EU.

In the Health for All (HFA) policy document, the World Health Organization has formulated several targets for future health policy in the European Union.[4] One of these targets implies a reduction in future prevalence of cigarette smoking, to a maximum of 20% by the year 2015. To assess the public health relevance of such smoking-cessation-based targets, one should have information on the estimated decline in future mortality following such a reduction in smoking prevalence. We therefore simulated this HFA target and other smoking-cessation-based targets by means of a computer simulation model, and estimated the future reduction in the number of deaths from cancer, cardiovascular diseases and COPD and the number of deaths from all causes through smoking cessation in the European Union.

Methods

Simulation model

We used a mathematical computer simulation model to estimate the reduction following smoking cessation in the number of deaths from all causes and in the number of deaths from smoking-related cancer (lung, oral cavity and pharynx, larynx, oesophagus, pancreas, bladder and kidney), coronary heart disease (CHD), stroke and chronic obstructive pulmonary disease (COPD) in the European Union. Our model was based on the Markov multi-state model, using transition rates to indicate the probability of subjects moving from one state to another, for example the probability of dying or the probability of starting or quitting smoking.[5]

At the beginning of the simulation (1994), the model's population in each of the 15 EU member states consisted of male and female never, ex- and current smokers, in 1-year age classes starting from age 15 up to age 85 and over, each with specific probabilities of starting and quitting smoking and specific total and cause-specific mortality rates (transition rates). Several smoking-cessation-based targets were formulated, each with target-specific transition rates for smoking behaviour during successive years of the simulation period, which led from 1994 up

to 2015. In 1994, for each scenario, the number of subjects in each state of smoking behaviour, i.e. the number of never, ex- and current smokers, was estimated using published data on population sizes and on the prevalence of ex- and current smokers. In subsequent years of the simulation, the number of 15-year-old never, ex- and current smokers, who can be considered as 'new' members of our population, were estimated similarly. For the remaining age classes, the number of never, ex- and current smokers in each age class in a subsequent simulation year depended on the numbers in each smoking stratum of the preceding year, the target-specific transition rates for smoking behaviour, and the total mortality rates. The yearly number of future deaths from all causes and from each smoking-related disease was estimated for each target, using the target-specific number of never, ex- and current smokers and the total and cause-specific mortality rates among the separate smoking categories.

Input data

The population sizes for men and women in each EU member state in 1994 were derived from the United Nations (Table 1).[6] From these data, which are given in 5-year age classes, the population sizes were estimated for each 1-year age class in 1994 (S-Plus 2000, Professional Release 2. MathSoft Inc., Seattle, 2000). For the subsequent years of the population (1995-2015), the population sizes of the 15-year-olds, the youngest age class in the population, were estimated by the same method, except that the UN population sizes were population size projections. The population size of all other age classes in the subsequent simulation years depended on the estimated number of never, ex- and current smokers.

Age- and sex-specific prevalences of ex- and current cigarette smoking (manufactured and hand-rolled) in the EU member states were derived from ten Eurobarometer surveys carried out from 1987 to 1995 (Nos. 27, 29, 30, 31, 32, 34.1, 36, 38, 41 and 43) (Table 1).[7] In each survey, a random sample was drawn from the population aged 15 years and over in each country. For each country, approximately 1,000 subjects were interviewed in their homes, except for the United Kingdom (1,000 in Great Britain and 300 in Northern Ireland), Germany (1,000 in both former West and East Germany), and in survey No. 32 (1989) (twice as many subjects in each country). Since 1990, Germany includes East Germany. Data were weighted by sex, age, region and size of locality to obtain representative data for the whole country. For each country, the weighted age- and sex-specific prevalence were averaged over the ten Eurobarometer surveys. For both men and women, ex- and current smoking prevalences were then smoothed over 1-year age categories (S-Plus 2000). These data were assumed to be the smoking prevalences at the

beginning of the simulation (1994). From these prevalences of smoking behaviour, the age- and sex-specific transition rates for smoking behaviour were estimated, i.e. the probability to move from one state of smoking behaviour to another during one year (Mathematica Version 4.1. Wolfram Research, Champaign, USA, 2000). These transition rates included the start rate, which is the probability of a never smoker becoming a smoker within 1 year, and the stop rate, which is the probability of a smoker quitting smoking within 1 year. The stop rate is the net rate, incorporating the rate of quitting and relapse after quitting. Because sufficient time series of past smoking prevalences were not available, it was assumed that the transition rates for smoking behaviour had not changed over time.

Information on the national age- and sex-specific mortality rates for total mortality and for smoking-related cancer, CHD, stroke and COPD in each member state of the EU was obtained from the World Health Organization (WHO) Databank, in 5-year age classes. The mortality rates were smoothed over 1-year age classes (S-Plus 2000). In each member state, these data were collected in 1994 (Table 2A and 2B). Since mortality rates among never, ex- and current smokers separately were not available from published databases, these rates were estimated for each member state using the prevalences of smoking behaviour, the total and cause-specific mortality rates in the total population, and the relative risks of ex- and current smokers. It was assumed that the age-specific mortality rates in each category of smoking behaviour were constant over time.

The relative risks of ex- and current smokers for total mortality and for mortality from smoking-related diseases were taken from the Cancer Prevention Study II (CPS II) (Table 3).[1] The CPS II is a large cohort study which started in 1982. In this study, among other information, smoking habits and 4-year mortality data were collected from 1.2 million men and women aged 35 years or older from all states in the United States of America. It was assumed that an individual who started smoking experienced directly the relative risk of an average smoker and that an individual who quit smoking directly experienced the relative risk of an average ex-smoker. It was further assumed that these relative risks remained constant in the subsequent years.

Targets

A ‘reference scenario’ was formulated in which the transition rates for smoking behaviour at the beginning of the simulation remained unchanged in subsequent years.

Several alternative targets were formulated based on two approaches: a reduction of the prevalence of smokers in each EU member state to a fixed

Table 1 (Chapter 5) Population size and prevalence of smoking behaviour around 1994 among men and women in the 15 EU member states.

	Population size aged 15 and over in 1994[a] (x 1000)		Prevalence of smoking behaviour[b] (%)				
				Ex-smokers		Current smokers	
	Men	Women	Year	Men	Women	Men	Women
Austria	3,164	3,402	1995	15	12	37	25
Belgium	4,019	4,272	1987-1995	24	14	37	27
Denmark	2,113	2,194	1987-1995	23	18	37	43
Finland	1,978	2,136	1994-1995	28	18	32	23
France	22,378	24,141	1987-1995	26	14	43	30
Germany	32,804	35,296	1987-1995	24	14	39	25
Greece	4,200	4,414	1987-1995	19	6	55	27
Ireland	1,315	1,344	1987-1995	21	16	34	30
Italy	23,317	25,153	1987-1995	24	11	37	26
Luxembourg	161	171	1987-1995	22	15	33	27
The Netherlands	6,174	6,393	1987-1995	27	21	41	36
Portugal	3,821	4,224	1987-1995	21	5	43	12
Spain	15,915	16,885	1987-1995	22	8	48	27
Sweden	3,488	3,630	1995	31	25	21	28
United Kingdom	22,631	24,178	1987-1995	29	24	32	31

Source: [a] United Nations,[6] [b] Eurobarometer.[7]

Table 2A (Chapter 5) Standardized[a] mortality rates[b] per 100,000 among men aged 15 and over in the in the 15 EU member states in 1994.

	Lung	Oral cavity/pharynx	Larynx	Oesophagus	Pancreas	Kidney	Bladder	CHD	Stroke	COPD	Total
Austria	79.1	10.2	5.6	6.5	19.1	11.3	10.6	270.6	120.2	37.2	1239.1
Belgium	134.4	9.9	7.4	10.7	14.1	8.7	16.3	157.8	90.9	79.2	1242.9
Denmark	95.4	8.4	4.2	11.1	15.4	9.8	18.1	291.3	93.0	65.5	1316.2
Finland	80.3	3.9	1.7	5.0	16.9	10.7	7.8	377.9	121.2	36.6	1274.5
France	86.7	20.0	10.5	17.9	14.4	8.9	13.8	106.9	73.7	35.5	1131.6
Germany	88.6	11.8	4.6	9.4	16.1	12.2	14.1	284.1	122.3	58.0	1311.3
Greece	82.1	2.7	5.2	2.2	10.1	4.0	11.3	133.5	121.7	10.0	870.7
Ireland	87.7	8.1	3.5	16.7	16.7	6.2	9.5	379.8	96.5	90.9	1315.9
Italy	102.8	10.0	8.3	7.3	14.6	8.7	17.5	159.5	117.0	50.2	1114.2
Luxembourg	99.0	12.8	5.2	7.9	15.0	6.7	9.6	189.4	127.2	67.5	1238.0
The Netherlands	124.2	5.2	3.5	11.8	14.5	9.9	13.0	208.8	88.0	67.1	1166.2
Portugal	53.4	11.4	10.1	9.4	11.4	4.4	11.5	129.8	255.3	43.0	1325.4
Spain	92.1	12.7	11.9	10.3	11.5	6.2	17.9	128.7	101.1	64.4	1099.9
Sweden	44.1	4.5	1.4	5.6	14.8	10.1	8.2	287.9	86.3	26.2	1014.9
United Kingdom	98.3	5.7	3.0	16.7	12.6	7.5	13.7	337.0	98.0	65.4	1198.3

[a] According to the standard European population. [b] Source: WHO, 1994.

Table 2B (Chapter 5) Standardized[a] mortality rates[b] per 100,000 among women aged 15 and over in the 15 EU member states in 1994 .

	Lung	Oral cavity/pharynx	Larynx	Oesophagus	Pancreas	Kidney	Bladder	CHD	Stroke	COPD	Total
Austria	19.4	1.8	0.3	0.9	13.3	5.6	3.0	144.8	105.1	14.1	782.0
Belgium	17.9	1.9	1.1	1.8	9.2	4.4	3.4	77.7	80.2	20.2	758.4
Denmark	51.2	3.0	0.9	3.1	12.2	5.0	5.6	153.2	82.6	42.5	891.2
Finland	13.3	1.8	0.1	2.2	12.9	5.0	2.2	183.6	100.4	8.4	730.6
France	10.9	2.4	0.6	2.1	8.2	3.6	2.6	49.3	59.5	14.5	636.8
Germany	17.1	2.3	0.4	1.8	11.1	5.3	3.7	148.3	104.0	18.6	807.4
Greece	13.4	0.9	0.5	0.9	7.1	2.0	2.2	71.7	161.1	4.6	724.5
Ireland	35.6	2.5	1.3	8.1	10.2	3.2	4.0	184.0	94.2	40.9	856.5
Italy	14.8	1.7	0.4	1.4	9.7	3.1	2.7	79.8	101.7	15.2	681.1
Luxembourg	21.1	2.4	0.0	1.8	8.9	4.5	5.7	89.3	106.6	25.0	734.0
The Netherlands	24.2	1.8	0.5	4.0	10.6	5.2	3.5	96.5	77.1	20.1	730.9
Portugal	8.8	1.8	0.4	1.9	6.6	1.7	2.5	67.4	206.9	13.7	802.2
Spain	7.2	1.7	0.2	0.9	7.3	2.0	2.6	58.7	90.4	15.5	631.3
Sweden	20.3	1.8	0.1	1.7	13.2	5.1	2.5	136.9	77.0	14.3	666.0
United Kingdom	39.3	2.3	0.7	6.8	9.6	3.5	4.6	168.2	97.0	29.8	806.9

[a] According to the standard European population. [b] Source: WHO, 1994.

Table 3 Relative risk[a] of ex- and current smokers for mortality from smoking-related diseases and total mortality.

	Ex-smokers		Current smokers	
	Men	Women	Men	Women
Oral cavity/pharynx	8.8	2.9	27.5	5.6
Oesophagus	5.8	3.2	7.6	10.3
Pancreas	1.1	1.8	2.1	2.3
Larynx	5.2	11.9	10.5	17.8
Lung	9.4	4.7	22.4	11.9
Bladder	1.9	1.9	2.9	2.6
Kidney	2.0	1.2	3.0	1.4
CHD				
< 65 years	1.8	1.4	2.8	3.0
≥ 65 years	1.3	1.3	1.6	1.6
Stroke				
< 65 years	1.4	1.4	3.7	4.8
≥ 65 years	1.3	1.0	1.9	1.5
COPD	8.8	7.0	9.7	10.5
Total mortality	1.6	1.3	2.3	1.9

[a] Source: Shopland et al.[1]

percentage and a reduction of the prevalence of smokers by a fixed percentage. These reductions were achieved by varying the age- and sex-specific start and/or stop rates.

In the 'HFA target' and the theoretical 'maximum target', a reduction of the smoking prevalence to a fixed percentage was simulated. The HFA target was based on the Health for All (HFA) target of the World Health Organization with respect to tobacco smoking, which implies that the prevalence of non-smoking should be at least 80% in each country of the EU by the year 2015.[4] In the HFA target, a reduction of the percentage of smokers (male and female) to 20% in each country by the year 2015 was simulated. This was achieved by increasing the age- and sex-specific stop rate with the same proportion for each age class and simulation year. Since the percentage of smokers was already around 20% among men in Sweden and among women in Portugal, in these cases the stop rate was not changed. In the maximum target, it was simulated that in each country no individual would start smoking and that all smokers would quit instantly, i.e. a reduction of the smoking prevalence to 0% by the year 1995, achieved by assuming the start rate to be 0 and the stop rate to be 1 for each age class and simulation year, from 1995

onwards. Using this target, the theoretical maximum reduction in mortality following smoking cessation can be estimated.

For each EU member state, reductions in the smoking prevalence by a fixed percentage were then simulated. In 20 consequent simulations, the smoking prevalence was reduced in steps of 5%: from a 0% reduction to a 100% reduction, relative to the smoking prevalence in 1994, achieved by the year 2015. Also in these targets, the age- and sex-specific stop rate was increased in the same proportion for all age classes and successive simulation years, from 1995 onwards.

Model outcome variables

The yearly number of deaths in each country were cumulated over time to obtain the total number of deaths from each smoking-related disease and from all causes between 1994 and 2015, among men and women aged 15 years and over. For each alternative target, the absolute and relative reduction in mortality compared to the reference scenario was computed. For each target, the number of deaths from each cause in the European Union as a whole was estimated by cumulating the number of deaths in all 15 member states in the European Union. In the estimations, the number of deaths from smoking-related cancer, other than lung cancer, were presented as one group, ‘other cancers’.

Results

Table 4 reflects the country-specific cumulated number of deaths from lung cancer, other smoking-related cancers, CHD, stroke, COPD and all causes that was expected in the reference scenario, among men and women, over the period 1994-2015. In all countries, cardiovascular diseases, especially coronary heart disease (CHD), were the number one cause of death. In general, the lowest number of deaths was expected for COPD among men and for lung cancer among women. The most important types of cancer within the group of ‘other cancers’ were bladder cancer and pancreatic cancer among men and pancreatic cancer among women (data not shown).

Table 4 (Chapter 5) Estimated number of deaths (x 1,000; rounded to the nearest 100) in the reference scenario, cumulated up to the year 2015, among men and women aged 15 and over.

	Men						Women					
	Lung	Other cancers	CHD	Stroke	COPD	Total	Lung	Other cancers	CHD	Stroke	COPD	Total
Austria	52.7	44.8	197.1	87.4	23.4	898.3	22.4	29.0	197.0	148.7	20.3	1,026.4
Belgium	131.6	66.5	162.4	96.6	79.2	1,260.6	25.8	33.0	131.4	145.2	34.6	1,284.4
Denmark	47.0	33.6	151.5	48.8	33.0	678.6	31.7	20.5	129.1	68.1	30.7	691.1
Finland	38.9	22.0	182.8	57.2	17.6	607.5	10.4	18.8	164.7	88.8	6.8	620.6
France	477.5	475.1	632.4	442.1	203.9	6,645.7	88.9	166.2	508.6	623.1	140.0	6,392.7
Germany	708.3	540.0	2,237.9	950.1	446.0	10,208.2	216.0	307.7	2,162.5	1,559.6	280.6	11,197.4
Greece	98.4	44.9	167.5	185.5	15.2	1,184.1	21.2	21.6	123.8	314.5	8.9	1,265.2
Ireland	23.2	16.4	105.2	27.1	24.3	368.3	12.4	10.9	76.2	40.2	15.6	349.9
Italy	608.5	399.4	1,003.6	791.6	336.0	7,003.6	134.7	176.8	867.9	1,167.8	181.7	7,134.1
Luxembourg	3.9	2.2	7.5	5.0	2.7	48.6	1.1	1.4	6.1	7.7	1.7	47.8
The Netherlands	180.4	83.8	302.2	128.0	99.6	1,694.9	46.1	53.0	218.5	188.1	49.0	1,701.5
Portugal	47.7	52.7	122.6	256.8	39.7	1,253.2	12.2	20.4	103.8	355.9	21.6	1,232.2
Spain	350.9	274.5	534.9	457.6	280.5	4,612.2	45.4	89.3	418.8	710.6	122.9	4,447.3
Sweden	39.5	43.1	305.3	96.5	26.6	1,066.4	21.3	31.0	236.4	137.3	18.6	1,078.4
United Kingdom	536.9	333.1	2,003.1	609.1	385.7	7,097.8	287.9	218.4	1,559.2	958.3	252.5	7,408.3
European Union	3,345.3	2,432.0	8,115.7	4,239.2	2,013.4	44,628.1	977.6	1,197.8	6,904.0	6,513.7	1,185.8	45,877.4

In the HFA target, the largest effect of smoking cessation would be reached for lung cancer mortality. Lung cancer mortality would decrease by around 11% among men and 8% among women, accounting for a reduction of about 372,000 and 78,000 male and female lung cancer deaths respectively over the simulation period (Figure 1). Among men, the group of 'other cancers' would be reduced by 6.4%, stroke by 2.1%, CHD by 1.3% and total mortality by 2.5% (around 1.1 million deaths), from 1994 up to 2015. Due to the decrease in total mortality, which results in a higher number of people at risk, mortality from COPD would increase among men by 0.8% (16,000 deaths). Among women, mortality from COPD would decrease by 2.0% (24,000 deaths) in the HFA target (Figure 1). Overall, the expected decline in mortality after smoking cessation was lower among women than among men, due to the lower smoking prevalence among women (Figure 1). Although the expected absolute reduction in 'other cancers' (25,500 deaths) was lower than that in stroke (37,500 deaths) and similar to that in CHD (24,000 deaths) among women, the expected relative reduction was higher (2.1% for 'other cancers' compared to 0.6% and 0.3% for stroke and CHD respectively). Total mortality would be reduced by 0.8% (almost 350,000 deaths) from 1994 to 2015 in the HFA target.

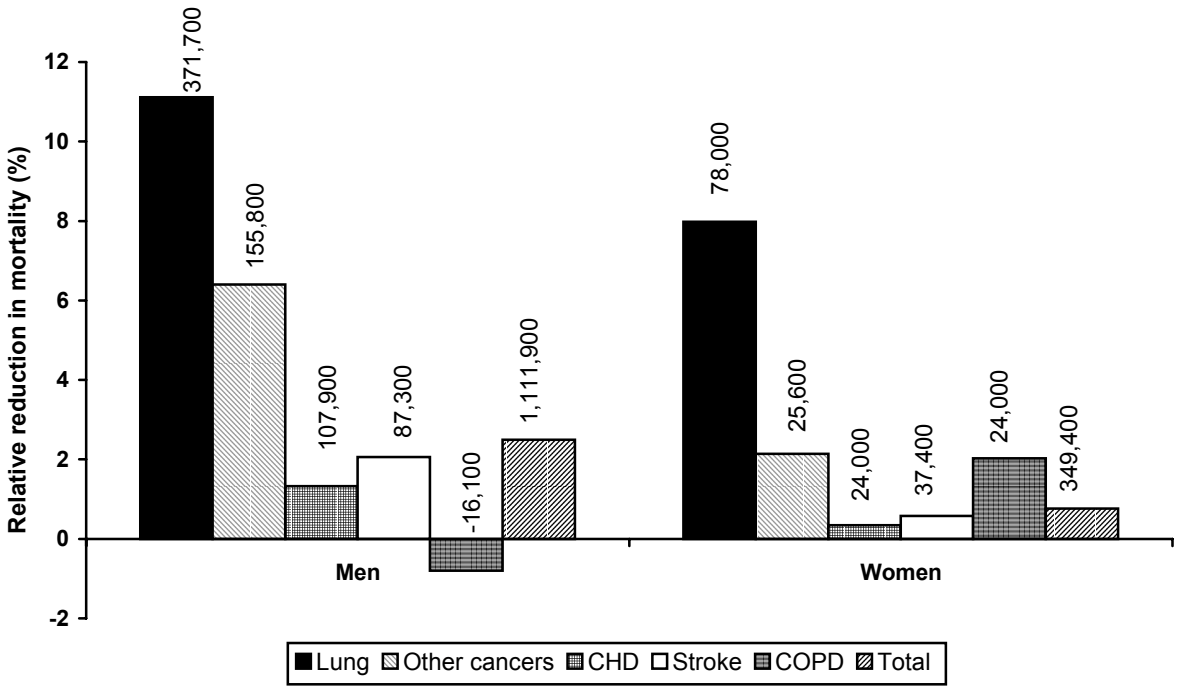
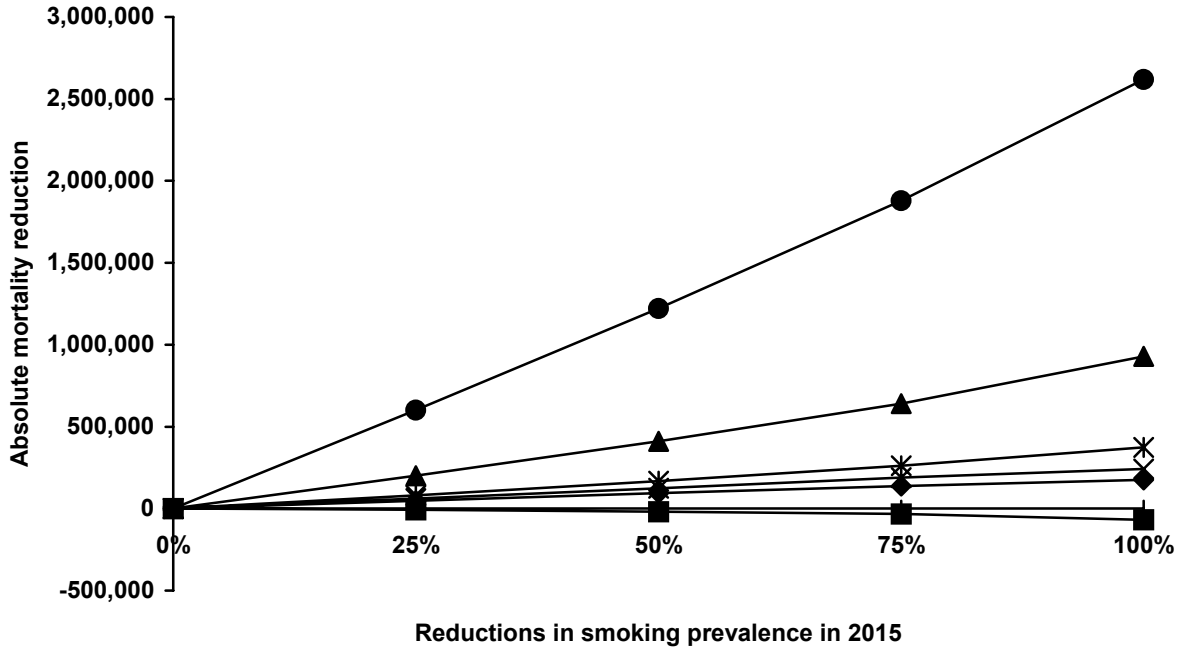


Figure 1 Estimated relative reduction (absolute reduction above bars, rounded to the nearest 100) in mortality from lung cancer, other smoking-related cancers, CHD, stroke, COPD and total mortality in the EU following smoking cessation in the HFA target, cumulated between 1994 and 2015, among men and women aged 15 and over.

A



B

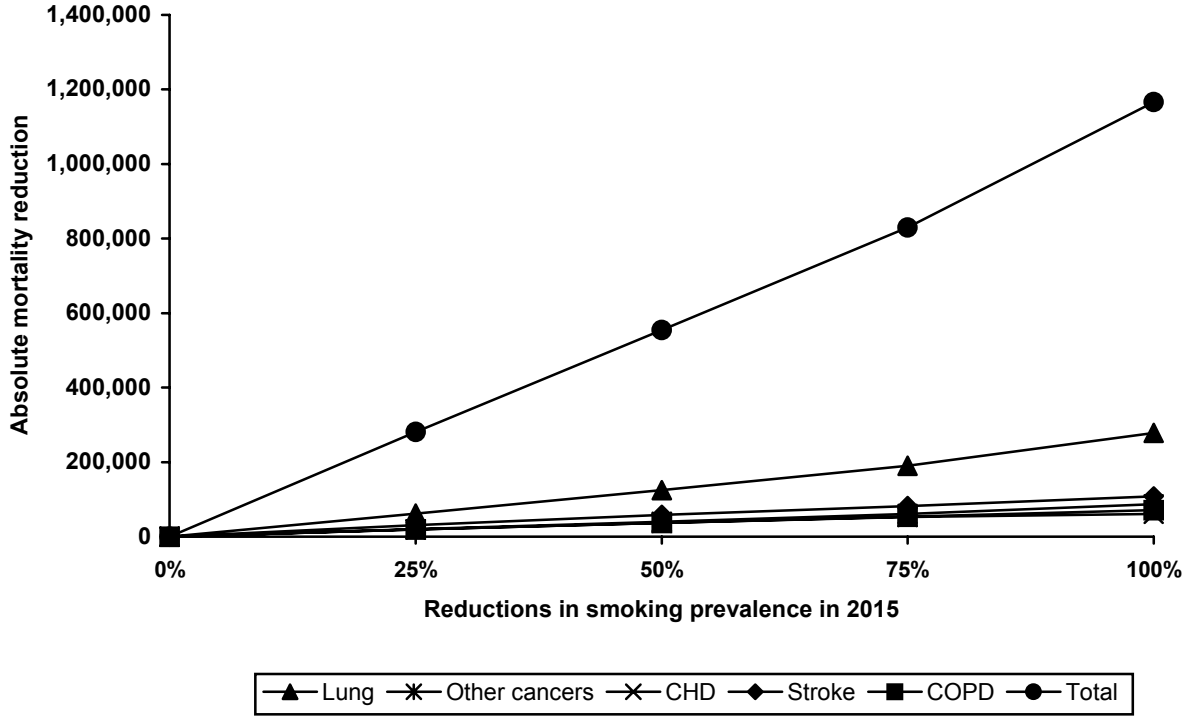


Figure 2 Absolute reduction in mortality from lung cancer, other smoking-related cancers, CHD, stroke, COPD and total mortality in the EU following a reduction in smoking prevalence by the year 2015 in 20 steps of 5%, cumulated between 1994 and 2015, among men (A) and women (B) aged 15 and over.

Obviously, the expected effect of the theoretical maximum target on mortality was larger than that of the HFA target, but the relative position of the causes of death in the expected decline in number of deaths was similar (data not shown). If all smokers would quit smoking instantly, the cumulated lung cancer mortality from 1994 to 2015, among men and women respectively, would be reduced by 28% and 29%, 'other cancers' by 16% and 7.4%, stroke by 4.3% and 1.7%, CHD by 2.9% and 0.8% and total mortality by 6.3% and 2.6%. As for the HFA target, an increase in COPD was expected among men (3.8%) and a decrease in COPD was expected among women (6.3%) (data not shown).

The reduction in the number of deaths by reducing the smoking prevalence in each EU member state *by* a fixed percentage, in 20 steps of 5% from 0% reduction to 100% reduction relative to the smoking percentage in 1994, achieved by the year 2015 (Figure 2A and 2B) was then estimated. For instance, a relative reduction in smoking prevalence of 35% between 1994 and 2015 in each EU member state (for example from a smoking prevalence of 40% in 1994 to 26% in 2015) would reduce the expected lung cancer mortality by 283,000 deaths among men and 87,000 deaths among women. This figure also indicates that a reduction of 372,000 deaths among men and 78,000 lung cancer deaths among women, as was expected in the HFA target, would be reached if the percentage of smokers was decreased by around 45% among men and around 30% among women in each EU member state.

Discussion

These results showed that the WHO's Health for All target on smoking cessation would give an expected total mortality reduction of 2.5% (around 1.1 million deaths) among men and 0.8% (almost 350,000 deaths) among women in the European Union, over the period 1994-2015. These and the expected cause-specific mortality declines in the HFA target were about 40-50% and 30% of the expected declines in the maximum target, among men and women respectively. The largest impact of the HFA target would be reached for lung cancer mortality. A comparable reduction in lung cancer mortality would be reached with a decrease in smoking prevalence in each EU member state of around 45% among men and 30% among women.

In public health modelling, Markov multi-state models are often used to model diseases or to estimate the effect of specific interventions on public health.[5,8,9] However, these models are a simplified reflection of real life and several assumptions were inevitable in these analyses. For instance, it was assumed that the groups of ex- and current smokers in the study were homogeneous groups with

respect to mortality risk, whereas in reality, the relative risk for smoking-related mortality increases with increasing amount and duration of smoking and decreases with the duration of abstinence. However, since average group estimates of the relative risks for ex- and current smoking were used, it is expected that the differences in risk within ex- and current smokers will be partly averaged out in the analyses. There are several reasons why we were not able to incorporate the heterogeneity of smokers and ex-smokers into the model. First, information on the duration of smoking in EU member states was not available. Second, the time span over which risk increases after taking up smoking or decreases after abstinence is unclear for some causes of death.[2] And third, published relative risk estimates by amount and duration of smoking for the specific smoking-related causes of death would have been derived from different sources and would therefore have been difficult to compare.

Moreover, it was assumed that the reduction in smoking prevalence in all but the maximum target, was due to smoking cessation alone and not to a reduction in the number of people who start to smoke. This assumption was made to make these targets comprehensible, since it would have been arbitrary which part of the reduction was due to smoking cessation and which part to not starting. People who start smoking are mostly young people, who still experience a low mortality risk over the simulation period. Although preventing those people from smoking would have a much larger impact on the mortality rate in the long run, within the time span of the simulation, this would have less impact on the mortality rate than encouraging older smokers to quit. If we had reduced the smoking prevalence in the HFA target (to 20% in each country) by a combination of smoking cessation and a reduction in the number of people who start smoking, the mortality reduction would have been smaller. Additional analyses of the data indeed showed that, in the extreme case that no one starts smoking, the HFA target would result in a reduction of total mortality up to 2015 of 1.8% and 0.4% among men and women respectively.

Finally, it was assumed that the situation in the base population remained constant during the simulation period and that the only factor that could change was the transition rates for smoking behaviour, whereas in reality several other factors may have changed. For instance, smoking behaviour may change spontaneously in the future without any smoking cessation intervention. Furthermore, treatment for several smoking-related diseases may improve in future years, which may reduce mortality rates. Therefore, and because simplifications are inevitable, results from public health modelling and thus from this study are uncertain and should be interpreted only as an indication of the magnitude of the effect.

However, these results are comparable to the scarce estimates from other studies. For instance, the International Agency for Research on Cancer (IARC) projected cancer mortality in 2015.[10] Although estimated differently, in general, there was a less than 10% difference between the IARC data and our reference scenario, with the exception of oral cavity/pharynx, larynx, and lung cancer mortality. For these types of cancer, the difference was larger, up to around 25% for larynx cancer. Furthermore, in the maximum target, results showed that, after instant elimination of cigarette smoking, within 21 years the number of all deaths would have been reduced by 6.3% among men and 2.6% among females. Peto et al.[3] estimated that yearly 24% of all male deaths and 6% of all female deaths are attributable to cigarette smoking. In the light of these estimations, the present results may seem disappointing. However, for the simulation that all smokers and ex-smokers in the population would have been never smokers, as Peto simulated, the number of all deaths within the simulation period decreased by 20.5% among men and 6.5% among women, which is comparable to the results Peto estimated. The differences between Peto's estimates and the results estimated in our targets are due to the fact that, in reality, giving up smoking reduces but does not immediately eliminate mortality risk, due to the remaining elevated risk of ex-smokers. For some causes of death, smoking cessation may eliminate risk only in the long run, after several decades. The maximum benefits of the elimination of cigarette smoking on mortality can thus only be seen when all ex-smokers with an elevated mortality risk have died, leading to a population of never smokers. This is a long-lasting process, which in theory may take over half a century, but in reality will never happen.

Obviously, our maximum target is purely theoretical, since it is not realistic that all smokers quit smoking and no individual starts smoking. However, results indicate that even in the more feasible HFA target, smoking cessation would lead to a substantial reduction in mortality. Specifically, it is estimated that the HFA target would lead to a reduction of almost 1.5 million deaths (1.6%) in the EU, which is slightly more than the male population of Ireland in 1994. Overall, among men and women, the expected reductions in mortality from several causes of death in the HFA target were still around 40-50% and 30% of the expected declines in the maximum target, respectively.

Among both men and women, the beneficial impact of smoking cessation appeared to be largest on lung cancer mortality. This finding is due to the high risk of smokers to die from lung cancer and to the large difference in relative risk for lung cancer mortality between smokers and ex-smokers, which was less pronounced for other causes of death. The lung cancer mortality risk among smokers is 12 to 22 times higher than that of never smokers and giving up smoking more than halves

this risk.[1] On the contrary, among men, the number of deaths from COPD increased following smoking cessation in our estimations. This may be explained by the small difference in relative risk between smokers and ex-smokers for COPD mortality. Giving up smoking reduced the relative risk for COPD mortality by only around 9%.[1] This reduction in COPD mortality following smoking cessation was apparently too small to counterbalance the increase in COPD mortality as a result of a higher number of people at risk due to the reduced total mortality. Among women, the difference in relative risk for COPD mortality between smokers and ex-smokers was large enough to counterbalance the effect of competing causes of death.

The decreased mortality from smoking-related diseases due to smoking cessation has great impact on the allocation of health care costs. In the UK, it is estimated that the health care costs for smoking-related diseases were around 1,400-1,500 million pounds per year.[11] It is obvious that smoking cessation would reduce these costs dramatically. Since non-smokers live longer than smokers,[12,13] it is uncertain whether the lower costs for smoking-related diseases among non-smokers are balanced out by the higher costs for other diseases at older ages.[14-16] However, from an ethical point of view, the beneficial public health impact of smoking cessation for such a large part of the population should be of far more importance than the economic effects.

In conclusion, these results indicate that, if the Health for All target of the WHO with respect to smoking cessation could be achieved, the expected total mortality from 1994 to 2015 would be reduced by about 1.6% among men and women in the European Union, with the reduction in lung cancer mortality being the most important. Although this target may be difficult to realize, these results emphasize the need for policymakers in each member state of the European Union to put strong effort into encouraging smokers to quit smoking.

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6

The health effects of cholesterol lowering medication versus smoking cessation in smokers with a high risk for coronary heart disease

Abstract

Objective - The Dutch Minister of Public Health proposed not to refund smokers cholesterol lowering medication for primary prevention of coronary heart disease (CHD). We compared the health effects of cholesterol lowering medication and smoking cessation in smokers with a high absolute risk for CHD.
Method - 10-Year absolute CHD-risk was estimated with the Framingham risk function, in 40-74 year old smokers without hyperlipidemia, cardiovascular diseases or diabetes, derived from two Dutch population studies. We selected those smokers who were eligible for cholesterol lowering medication, based on their absolute CHD risk. We estimated the reduction in CHD events and the gain in healthy life expectancy in a cholesterol lowering medication intervention and three smoking cessation interventions, compared to a reference strategy. In the smoking cessation interventions, we furthermore estimated the reduction in the number of people eligible for cholesterol lowering medication. The results were extrapolated to the total Dutch population with the characteristics mentioned.
Results - If all smokers in our population would quit smoking, the number of people eligible for cholesterol lowering medication would decrease by about 75%. Compared to using cholesterol lowering medication, giving up smoking led to a less strong (men; difference 11%-22%) or comparable (women) reduction in the expected number of CHD events. However, smokers would gain 2-2.5 healthy life years more by quitting smoking than by using cholesterol lowering medication.
Conclusions - Giving up smoking would lead to a reduction in the number of people eligible for cholesterol lowering medication. Although smoking cessation was less or comparably effective in the primary prevention of CHD, it would lead to a larger gain in healthy life expectancy, compared to cholesterol lowering medication. However, these effects can only be reached with strong smoking cessation interventions.

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Introduction

In the 1990's, several large trials showed that cholesterol synthesis inhibitors (statins) substantially lowered the risk for coronary heart disease (CHD).[1] These findings led to an increase in prescription of statins, which initiated a tremendous change in the discussion on the indication for cholesterol lowering therapy. Since the costs of statins are high (about 225 million euros on material costs in 2001 in the Netherlands[2]), choices had to be made on the eligibility of subjects for cholesterol lowering therapy. This led to the second revision of the Dutch 'Consensus Cholesterol', with guidelines for cholesterol lowering therapy, in which the indication for therapy in primary prevention is no longer based on the cholesterol concentration alone, but on the absolute CHD risk, based on the total risk profile.[3,4]

In 2000, the Health Council of the Netherlands advised the Dutch Minister of Public Health on the indication for cholesterol lowering therapy.[5] In their advice, patients with familial hypercholesterolaemia, a history of cardiovascular diseases or diabetes mellitus who have a total cholesterol concentration above 5 mmol/L are eligible for cholesterol lowering treatment. For subjects with a high absolute CHD risk without the diseases mentioned, based on the opinion of the minority of the Health Council which is based on the latest revision of the Consensus Cholesterol, the Minister proposed not to refund smokers cholesterol lowering therapy for primary prevention, in order to stimulate smokers to take their own responsibility and quit smoking. It was expected that giving up smoking would decrease CHD risk to a level at which statin treatment is not indicated anymore.

Several studies reported on the separate health effects of smoking cessation and cholesterol lowering medication.[1,6] However, to our knowledge, comparisons between both interventions are scarce. Therefore, we compared the health effects of our Minister's proposal, which is based on smoking cessation, with that of cholesterol lowering therapy in smokers with a high CHD risk, without hyperlipidemia, cardiovascular diseases and diabetes mellitus in the Netherlands. Health outcomes were number of people eligible for cholesterol lowering therapy, number of CHD events and healthy life expectancy.

Methods

Indication for cholesterol lowering therapy

The indication for cholesterol lowering treatment for primary prevention in the Netherlands, according to the recent second revision of the Dutch Consensus Cholesterol,[3,4] is based on the absolute CHD risk according to the Framingham risk

function.[7] In this risk function, CHD risk was estimated using sex, age, systolic blood pressure, smoking behaviour, ratio of total and HDL cholesterol level, diabetes mellitus and left ventricular hypertrophy as independent variables. According to the Consensus Cholesterol, medication is recommended in subjects with a 10-year absolute CHD risk above 25% at ages younger than 60 years, above 30% at age 60-69 years and above 40% (men) and 35% (women) in subjects aged 70 years and over. In each age group, these cut-off points were lowered with 5% in subjects with a family history of coronary heart disease. The above mentioned guidelines are to be applied for primary prevention in those with a cholesterol level above 5 mmol/L and below 8 mmol/L. Subjects with a cholesterol level above 8 mmol/L are referred to a lipid clinic to examine the presence of familial hypercholesterolemia.

Study populations

The study populations consisted of subjects who participated in the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN study) for 40-59 year olds and the Rotterdam Study for 60-74 year olds. The MORGEN study is a cross-sectional study among more than 21,000 men and women aged 20-59 and was conducted from 1993 though 1997. The Rotterdam Study is a longitudinal study among almost 8,000 men and women aged 55 years and over, living in an urban district in Rotterdam, the Netherlands.[8] We used the baseline data, collected from 1990 through 1993.

For our analyses, we selected from these study populations all 40-74 year old smokers eligible for cholesterol lowering therapy for primary prevention according to the Dutch Consensus Cholesterol.[3,4] Smokers were subjects who reported to smoke more than 1 cigarette per month and ex-smokers who quit less than one year ago. A total of 178 men and 40 women with a total cholesterol level between 5 and 8 mmol/L, no cardiovascular diseases and diabetes mellitus, who were not treated at baseline were selected.

Measurements

Information on smoking behaviour was obtained through a standardised questionnaire in both studies. Systolic blood pressure was measure twice with the participant in sitting position using a random zero sphygmomanometer. We used the mean of the two measurements in our analyses. Nonfasting serum total and HDL cholesterol level was determined[9,10] in two laboratories, which are permanent members of the international Cholesterol Reference Method Laboratory Network. In the MORGEN study, use of cholesterol lowering medication was self-reported and in the Rotterdam Study it was obtained by asking the subjects to bring their

medication. Prevalence of diabetes mellitus in the MORGEN study was self-reported or based on a random nonfasting serum glucose level ≥ 11.1 mmol/L. In the Rotterdam Study, diabetes mellitus was based on use of antidiabetic medication or a random or post-load serum glucose level ≥ 11.1 mmol/L. In both studies, data on left ventricular hypertrophy (LVH) was not available at the present time. Therefore, we assigned LVH aselect using age-specific LVH prevalences from the Framingham study,[11] by means of the Monte Carlo method.[12] Information on family history of premature coronary heart disease in first degree relatives was collected in the MORGEN study for premature (<60 years) myocardial infarction in parents only and in the Rotterdam Study for premature (<65 years) myocardial infarction in parents, siblings and children. Missing values on family history were imputed using linear regression and the Monte Carlo method.[12] To exclude subjects with cardiovascular disease, in the MORGEN study, self-reported information on history of myocardial infarction, stroke, heart surgery and intermittent claudication (Rose questionnaire) was obtained. In the Rotterdam Study, verified diagnoses on myocardial infarction and stroke and self-reported history of heart surgery and of intermittent claudication and angina pectoris (Rose questionnaire) was obtained.

Interventions

In the 'reference strategy', we assumed that no interventions on smoking behaviour were carried out.

We formulated a medication intervention and three smoking cessation interventions. In the 'medication intervention', all subjects in our study population (smokers at high CHD risk) were considered to be put on cholesterol lowering medication, leading to a 31% lower absolute CHD risk for each person.[1]

In the 'maximum smoking cessation intervention', we assumed that all smokers quit smoking. This intervention estimates the maximum health gain by smoking cessation.

The '50% smoking cessation intervention' assumed that half of the smokers with a high CHD risk quit smoking. This intervention is based on the finding that about half of the smokers quit smoking after a cardiovascular event,[13] which suggests that, in theory, such a reduction in the percentage of smokers may maximally be feasible.

The third smoking cessation intervention, the 'MIS intervention', is an existing intervention in Dutch tobacco control. This minimal contact behavioural intervention (MIS) is a method to assist smokers in a general practice to quit smoking,[14] which takes minimal effort of the general practitioner. The Dutch Minister of Public Health recommended this method as a useful method to stimulate smoking cessation. Evaluation of the effectiveness of the MIS showed that 13.4% of smokers using this

method quit smoking within one year.[14] We assumed that all general practitioners in the Netherlands implemented the MIS in their practice and that 74%-85% of the smokers visits the general practitioner each year, based on information from Statistics Netherlands.

Health outcomes

For each subject, we estimated the 10-years risk for a (non-)fatal CHD event, using the Framingham risk function. Then, for each intervention, we estimated the number of subjects eligible for cholesterol lowering medication, based on the Consensus Cholesterol. The number of CHD events within 10 years was estimated by adding the individual risks. With the life table method, we calculated the life expectancy of smokers. To estimate the healthy life expectancy, the remaining life years were multiplied by weighing factors for the main smoking-related chronic diseases:[15] lung cancer, other smoking-related cancers, CHD, stroke and COPD (chronic obstructive pulmonary disease), in order to adjust for quality of life.

The reduction in the number of people eligible for cholesterol lowering therapy in the smoking cessation interventions, and the reduction in the number of CHD events and the gain in healthy life expectancy in the medication and the smoking cessation

Table 1 Characteristics of the study populations[a] obtained from the MORGEN study and the Rotterdam Study. Data are means ± sd or percentages.

	Men		Women[b]
	MORGEN study	Rotterdam Study	Rotterdam Study
	40-59 years	60-74 years	60-74 years
N	71	107	40
Education (%)			
Low	76.1	53.3	80.0
Middle	12.7	37.4	17.5
High	11.3	9.4	2.5
Systolic blood pressure (mmHg)	144.0 ± 17.9	144.4 ± 18.3	148.2 ± 17.5
Total cholesterol (mmol/L)	6.39 ± 0.65	6.75 ± 0.78	7.03 ± 0.75
Total/HDL cholesterol	7.20 ± 1.37	6.53 ± 1.37	6.13 ± 1.37
BMI (kg/m^2)	27.9 ± 3.2	25.6 ± 2.6	26.0 ± 3.7
Family history of cardiovascular diseases (%)	24.7	34.6	55.0

[a]Smokers without hypercholesterolaemia, history of cardiovascular diseases or diabetes mellitus, who are eligible for cholesterol lowering therapy, based on their absolute CHD risk. [b]No women aged 40-59 years in the MORGEN study fulfilled the inclusion criteria for cholesterol lowering medication.

Table 2 Reduction in the number of smokers in the Netherlands who are eligible for cholesterol lowering medication, in the smoking cessation interventions compared to the reference strategy.

	Men		Women
	40-59 years	60-74 years	60-74 years
Reference strategy	30,918	60,496	21,347
Reduction in smoking cessation interventions[a] (N (%))			
Maximum smoking cessation intervention	24,458 (79%)	44,002 (73%)	16,628 (78%)
50% smoking cessation intervention	12,229 (40%)	22,001 (36%)	8,314 (39%)
MIS intervention	2,434 (8%)	4,472 (7%)	1,838 (9%)

[a] Compared to the reference strategy.

interventions are expressed compared to the reference strategy. Our results were extrapolated to the total 40-74 year old Dutch population of smokers in 1994, with a high CHD risk and without the diseases mentioned, using population data of Statistics Netherlands.

Results

The characteristics of our study population from the MORGEN study and the Rotterdam Study are shown in Table 1. No women in the MORGEN study fulfilled the inclusion criteria for cholesterol lowering medication.

If all smokers in the Netherlands with a high CHD risk would quit smoking (the maximum smoking cessation intervention), the number of people eligible for cholesterol lowering medication in this group would be reduced by 75% among 40-74 year old men and 78% among 60-74 year old women (Table 2). Half of this reduction would be obtained if 50% of the smokers would quit smoking. Obviously, the reduction was smaller in the MIS intervention: around 8% among both men and women (Table 2).

Figure 1 shows the expected reduction in the number of CHD events in the medication intervention and the three smoking cessation interventions compared to the reference strategy. The reduction in CHD through cholesterol lowering medication was 31% by definition. Reduction in the number of CHD events in the maximum smoking cessation intervention was 27.5% among 40-59 year old men and 24% among 60-74 year old men. Smoking cessation therefore yielded a relative reduction in the number of CHD events that was 11% (40-59 year old men) and 22% (60-74 year old men) less than that obtained through cholesterol lowering

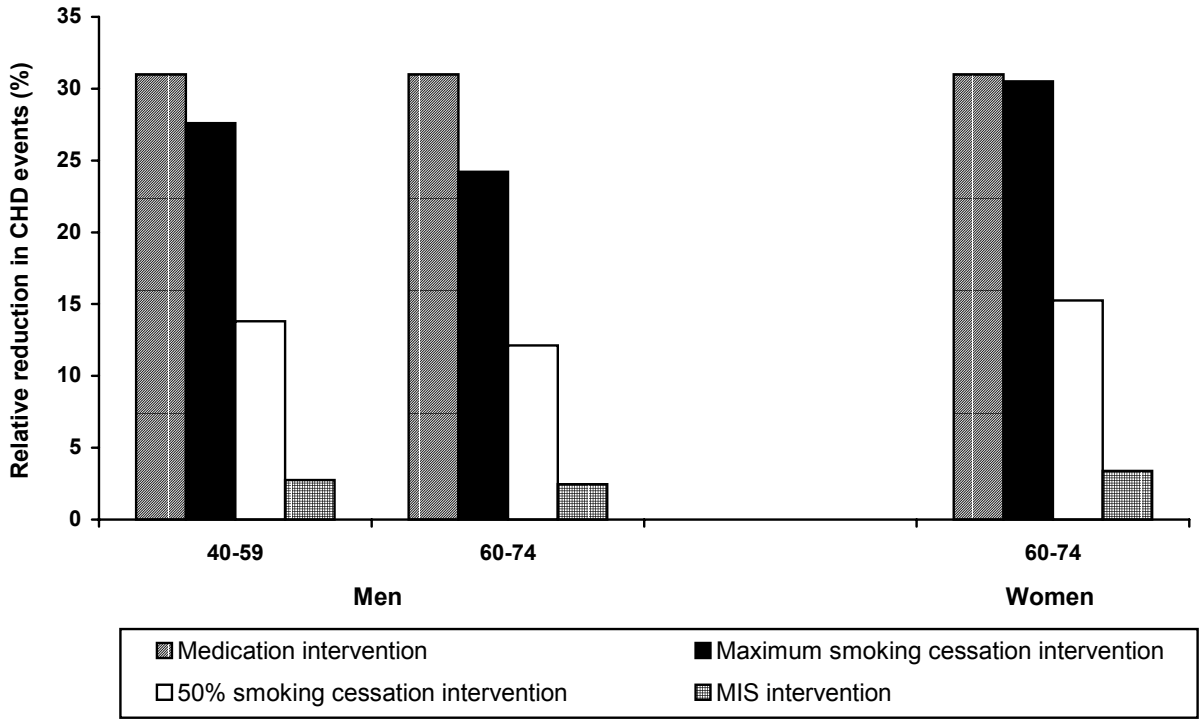

Figure 1 Relative reduction in fatal and non-fatal CHD events in 10 years, in the medication intervention and the smoking cessation interventions compared to the reference strategy in the Dutch smoking, high CHD risk population. Number of CHD events in the reference strategy: 8,896 and 22,604 among men aged 40-59 and 60-74 years respectively and 8,260 among women aged 60-74 years.

medication. Among 60-74 year old women, the expected reduction in the maximum smoking cessation intervention (30.5%) was comparable to the medication intervention (31%). If 50% of the smokers would quit smoking, half of the maximum reduction in the number of CHD events would be observed. The MIS intervention would lead to a reduction in the number of CHD events of 2.5% among elderly men to 3.4% among elderly women.

The expected gain in healthy life expectancy in the medication intervention was 1.6 years among the 40-59 year old men and 1.2 years among both the 40-59 year old men and women (Figure 2). If all smokers would quit smoking, 40-59 year old men would gain more than 2.5 healthy life years extra and 60-74 year old men and women would gain almost 2 healthy life years extra compared with the situation that these smokers would use cholesterol lowering medication (Figure 2). If 50% of the smokers would quit smoking, the gain in healthy life expectancy would be 2.1 years among the youngest men and 1.5 years among the oldest men and women. In the MIS intervention, a gain in healthy life expectancy of approximately 4 months among men and women was estimated.

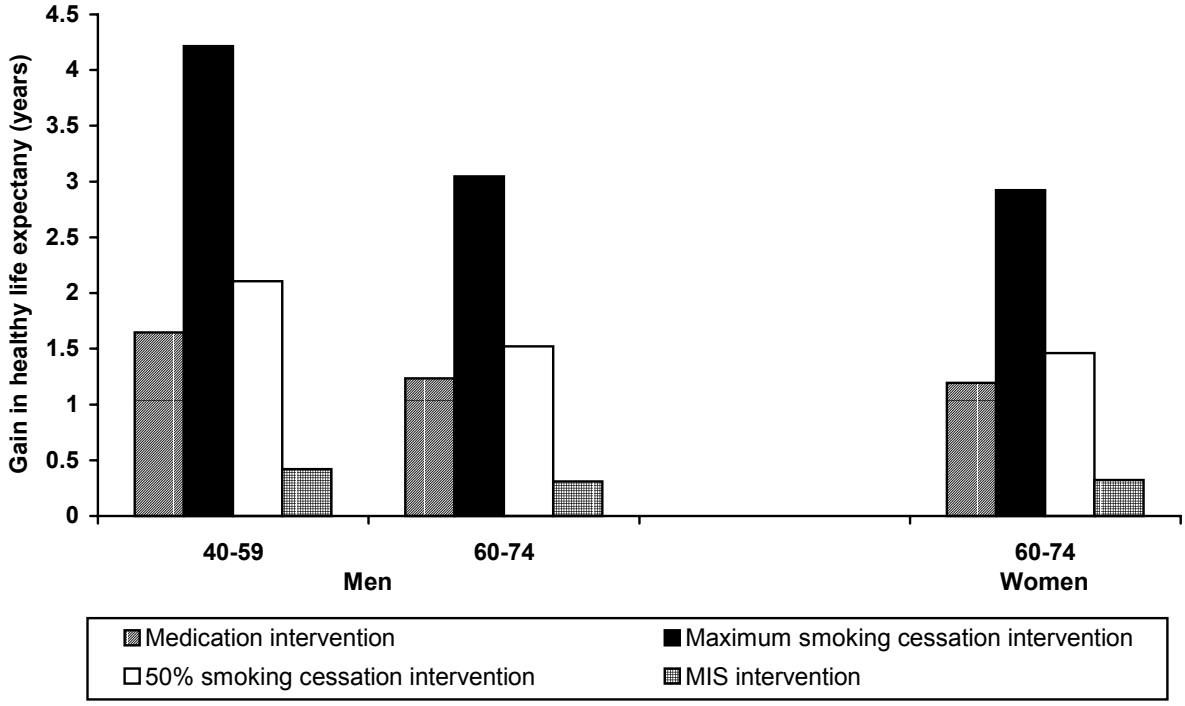

Figure 2 Gain in healthy life expectancy, in the medication intervention and the smoking cessation interventions compared to the reference strategy in the Dutch smoking, high CHD risk population. Healthy life expectancy in the reference strategy: 15.5 years and 9 years among men aged 40-59 and 60-74 years respectively and 11 years among women aged 60-74 years.

Discussion

Our study showed that among smokers with a high CHD risk, smoking cessation reduces the number of people eligible for cholesterol lowering therapy by about 75%. Compared to using cholesterol lowering medication, giving up smoking led to a less strong reduction in the expected number of CHD events among men (difference 11%-22%) and a comparable reduction among women. However, when smokers quit smoking, they would gain 2-2.5 healthy life years extra compared to continuing to smoke and using cholesterol lowering medication.

Smoking cessation reduces the number of people eligible for cholesterol lowering therapy, according to the Consensus Cholesterol, due to the fact that the indication for cholesterol lowering therapy is based on a person's absolute CHD risk. This risk decreases after smoking cessation. Our results showed that after smoking cessation, only a quarter of the smokers at high CHD risk remained eligible for cholesterol lowering medication.

The relative reduction in the number of CHD events after smoking cessation was larger among women than among men and larger at younger ages than at older ages. This may be due to the higher absolute CHD risk among men compared to women and to the increasing CHD risk with age. The relative effect of smoking cessation on the absolute CHD risk decreases with an increasing initial absolute risk.

In our medication intervention, we assumed that all smokers in our population received cholesterol lowering medication (and compliance was 100%). To compare the health effects of cholesterol lowering therapy and smoking cessation, the medication intervention should be compared with the maximum smoking cessation intervention, in which all smokers quit smoking. In practice, however, it is not feasible that all smokers quit smoking and thus the maximum smoking cessation intervention is purely theoretical. After a cardiovascular event, only about half of the smokers quit smoking.[13] This suggests that, in theory, this may be the maximum feasible reduction in the percentage of smokers.

Our data showed that, even if all smokers quit smoking, smoking cessation among men would not outnumber the reduction in CHD events through cholesterol lowering medication. However, the gain in healthy life expectancy was 2-2,5 years more due to smoking cessation than due to cholesterol lowering medication, among both men and women. Even if half of the smokers would quit smoking, the expected gain in healthy life years in this population was still a few months larger compared to the gain from the use of cholesterol lowering medication. This is due to the fact that, besides the risk on CHD, smoking cessation also lowers the risk for other chronic diseases, including stroke, lung cancer, other smoking-related cancers and COPD. In the United Kingdom, it is estimated that smoking cessation is 17 times more cost-effective per life year gained than statin use.[16]

The Dutch Minister of Public Health stated that the MIS is a useful method to stimulate smoking cessation. However, our results showed that the MIS resulted in a relatively small health gain compared to the use of cholesterol lowering medication. The current application of the MIS in the general practice would thus not be sufficient to make enough smokers quit to obtain a health gain comparable to or larger than that resulting from the use of cholesterol lowering medication. As the Minister also advised, the application of the MIS should be increased (at present less than 30% of the general practitioners use the MIS)[14] and stronger smoking cessation interventions should be developed especially targeted on this group of smokers at high CHD risk.

Some limitations of our study need attention. First, we used two different study populations for the two age groups. The methods used in these two studies were

comparable for most variables. However, for some, such as the prevalence of diabetes mellitus, differences occurred. Furthermore, both studies were conducted in different time periods: the Rotterdam Study before 1994, the MORGEN study mainly after 1994. Since the total cholesterol concentration declined in the Netherlands in the 1990's, the total cholesterol level in the MORGEN study is lower than the level in the Rotterdam Study. Therefore, both age groups should be compared with caution. Secondly, because of the small proportion of the MORGEN study and the Rotterdam Study eligible for cholesterol lowering therapy according to the current guidelines, our results are based on relatively small numbers. However, although this implies that the absolute numbers mentioned for each intervention should be interpreted with caution, we expect that this did not greatly affect the estimated difference between the different interventions. Finally, one may doubt whether the Framingham risk function can be generalised to the Dutch population. However, it is shown that the Framingham risk function is reasonably accurate for northern European populations as well.[17]

From this population of smokers with a high CHD risk, without hypercholesterolaemia, history of cardiovascular diseases or diabetes mellitus, we can conclude that, based on a reduction in absolute CHD risk, smoking cessation would lead to a substantial decrease in the number of subjects eligible for cholesterol lowering medication, according to the Consensus Cholesterol, which reduces medical costs. Despite the substantial reduction in absolute CHD risk, smoking cessation would be less (men) or comparably (women) effective in the prevention of CHD events than cholesterol lowering therapy. Nevertheless, in a broader public health perspective, smokers would gain more healthy life years by quitting smoking than by using cholesterol lowering therapy. However, these effects can only be achieved with strong smoking cessation interventions.

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7

Smoking cessation and quality of life: the effect of amount of smoking and time since quitting

Abstract

Background - Knowledge of the impact of smoking cessation on health-related quality of life may be important in encouraging smokers to quit. We determined whether the difference in quality of life between ex- and current smokers is influenced by amount of smoking or time *since quitting.*

Methods - Data were collected within a cross-sectional study among a random sample of the general population in The Netherlands. Health-related quality of life was measured with the RAND-36 questionnaire (adapted from SF-36). Smoking behavior was assessed with a self-administered questionnaire. Adjusted differences in quality of life scores between ex- and current smokers were tested with multivariate analysis of variance, among 9,660 men and women aged 20-59 years, without history of tobacco-related chronic diseases.

Results - Ex-smokers reported significantly higher quality of life scores than current smokers. This was more pronounced for mental health, especially for role functioning limitations due to emotional problems (difference 6.5 points; $p<0.0001$), than for physical health dimensions. Differences were generally larger between ex- and current heavy smokers than between ex- and current light or moderate smokers (p trend<0.05 when ex-smokers had quit <5 or ≥10 years ago). No significant trend was observed with time since quitting.

Conclusions - Generally, the higher the amount of smoking, the higher were quality of life differences between ex- and current smokers.

Mulder I, Tijhuis M, Smit HA, Kromhout D. Smoking cessation and quality of life: the effect of amount of smoking and time since quitting. Prev Med 2001;33:653-660.

Introduction

In general, the most important reason to give up smoking is concern about one's health.[1,2] The beneficial effects of giving up smoking on morbidity and mortality have been widely known for many years.[3] In contrast, the effects of smoking cessation on other aspects of health status, such as the quality of life, are less well described. Health-related quality of life reflects a person's self-rated perception of aspects of health, such as limitations in physical functioning, pain, vitality, mental health problems, and related role and social functioning. Knowledge of the impact of smoking cessation on health-related quality of life may be important in encouraging smokers to quit, since possible beneficial effects on quality of daily living may be seen readily.

Several studies investigated the relation between smoking behavior and health-related quality of life, suggesting that cigarette smoking relates to poor quality of life.[4-8] Ex-smokers are reported to have more limitations in role functioning due to physical problems, but also to have more vitality and to experience a better mental and perceived health than current smokers.[9-11] However, results were not consistent. Associations between smoking behavior and quality of life were more pronounced for mental health than for physical health.[4,9] Amount of smoking and time since quitting show a dose-response relationship with morbidity and mortality risk.[3] Wilson et al.[8] also found a clear dose-response relationship between amount of smoking and quality of life, showing lower quality of life scores among heavy and moderate smokers compared with light smokers. However, the effect of time since quitting on the health-related quality of life among ex-smokers is not understood yet. Furthermore, it is not clear whether time since quitting or amount of smoking influence the difference in quality of life between ex- and current smokers.

We studied the association between smoking behavior and health-related quality of life, in a cross-sectional study among the general Dutch population aged 20-59 years without history of tobacco-related chronic diseases. We focused on the effect of time since quitting and amount of smoking on the difference in quality of life between ex- and current smokers. Based on the available literature, we hypothesized that (1) ex-smokers experience a better quality of life than current smokers; (2) differences in quality of life between ex- and current smokers are more pronounced for dimensions reflecting mental health than for dimensions reflecting physical health; (3) time since quitting and amount of smoking show a dose-response relationship with quality of life among ex- and current smokers, analogous to morbidity and mortality; and (4) the difference in quality of life between ex- and

current smokers increases with increasing time since quitting and increasing amount of smoking.

Methods

Study population

The Monitoring Project on Risk Factors for Chronic Diseases (MORGEN study) was a cross-sectional study, conducted from 1993 through 1997 among 20- to 59-year-old men and women in a random stratified sample of the general Dutch population. In the present study, data from 1995 through 1997 were used, since information on quality of life was collected only in these years. Data were collected in three Dutch towns. In Amsterdam and Maastricht, subjects were randomly chosen from the civil registries. In Doetinchem, the study population consisted of individuals aged 26-59 years who participated from 1989 through 1991 in the previous Monitoring Project on Cardiovascular Disease Risk Factors, supplemented with a random sample of 20- to 25-year-olds. From 1995 through 1997, 31,750 invitations to participate in the study were sent by municipal health services. The response rate of the three towns varied between 40 and 44% during the course of the study and was higher among women (46%) than among men (39%). Subjects without information on health-related quality of life (n=437) or smoking behavior (n=91), or on the covariates age, gender, educational level, and town of investigation (n=62), were excluded from the analyses. Furthermore, to minimize the influence of tobacco-related chronic diseases on the association between smoking behavior and quality of life, we excluded subjects with history of cancer, myocardial infarction, cerebrovascular accidents, asthma, or COPD or with missing values on these variables (n=3,149). The final study population consisted of 4,348 men and 5,312 women. All subjects gave their written informed consent.

Measurements

Data were collected by means of a self-administered questionnaire. The health-related quality of life was measured by the standardized RAND-36 questionnaire, Dutch version,[12] which was adapted from the standardized SF-36 Health Survey.[13] The questionnaire included 36 items, 1 item on health change in the past year and 35 items on eight dimensions of quality of life: physical functioning (10 items), role functioning limitations due to physical problems (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role functioning limitations due to emotional problems (3 items), and mental health (5

items). The subjects rated each item on a 2-, 3-, 5-, or 6-point scale. The total score for each dimension was calculated according to the method described by the Medical Outcomes Trust[13] and ranged from 0 to100. With factor analytic methods, Ware et al.[14] constructed two summary scores: the physical component summary and the mental component summary, which reflect the physical and mental components of health.

Subjects were classified as never, ex-, or current smokers. The group never smokers consisted of subjects who had never smoked (90%), subjects smoking less than 1 cigarette a month (3%) and subjects who smoked between 1 cigarette a month and one cigarette a day (7%). Ex-smokers were classified in three categories of time since quitting: subjects who quit smoking < 5 years, 5-9 years, or ≥ 10 years ago. Within these three categories, ex-smokers were further categorized as ex-light (1-9 cigarettes per day), ex-moderate (10-19 cigarettes per day), or ex-heavy (≥ 20 cigarettes per day) smokers, based on the amount of smoking in the past. Current smoking was defined as currently smoking at least 1 cigarette a day. In concordance with ex-smokers, we further categorized current smokers as light, moderate, or heavy smokers.

Educational level, as an indicator of socioeconomic status used as a covariate, was divided into three categories, according to the highest achieved level of education: low (intermediate secondary education or less), intermediate (intermediate vocational or higher secondary education), and high (higher vocational or university education).

For exclusion of subjects with history of tobacco-related chronic diseases, having a history of cancer, myocardial infarction, cerebrovascular accidents, or asthma was operationalized as ever having the specific disease, based on the answers to four separate questions, presented as ‘Have you ever suffered from …?’ The presence of COPD was measured by means of a FEV_1 measurement during physical examination. Subjects with a FEV_1 of less than 70% of the predicted FEV_1, based on the FEV_1 among never smokers without any respiratory complaints, were considered to have COPD.

Table 1 Characteristics of the study population (% (absolute number) or mean ± sd).

	Never smokers	Ex-smokers	Current smokers
N	3,707	2,856	3,097
Age	38.0 ± 11.3	44.2 ± 9.2	40.2 ± 10.3
Gender (% men)	42.3 (1,567)	48.6 (1,389)	45.0 (1,392)
Educational level			
Low	33.3 (1,234)	41.5 (1,185)	51.1 (1,581)
Intermediate	34.6 (1,281)	27.3 (779)	29.3 (908)
High	32.2 (1,192)	31.2 (892)	19.6 (608)
Town of investigation			
Amsterdam	34.4 (1,276)	31.1 (888)	38.0 (1,176)
Maastricht	31.3 (1,160)	31.1 (887)	29.2 (903)
Doetinchem	34.3 (1,271)	37.9 (1,081)	32.9 (1,018)
Time since quitting[a]			
< 5 years		25.6 (721)	
5-9 years	NA	18.1 (509)	NA
≥ 10 years		56.3 (1,583)	
Amount of smoking[a, b]			
Light		28.8 (804)	20.3 (630)
Moderate	NA	31.8 (888)	41.9 (1,298)
Heavy		39.4 (1,100)	37.8 (1,169)
Dimensions of quality of life			
Physical functioning	91 ± 14	90 ± 15	88 ± 17
Role limitations physical	85 ± 29	84 ± 31	82 ± 32
Bodily pain	82 ± 21	79 ± 22	78 ± 23
General health	75 ± 16	74 ± 17	71 ± 18
Vitality	66 ± 17	67 ± 17	63 ± 18
Social functioning	87 ± 20	86 ± 20	83 ± 23
Role limitations emotional	85 ± 30	86 ± 30	78 ± 35
Mental health	75 ± 15	76 ± 15	71 ± 18
Physical component summary	52 ± 7	51 ± 8	51 ± 8
Mental component summary	49 ± 9	50 ± 9	47 ± 11

NA, not applicable. [a] Added absolute numbers among ex-smokers are lower than total number of ex-smokers due to missing values on time since quitting (43 subjects) and amount of smoking (64 subjects). [b] Among ex-smokers, amount of smoking in the past; among current smokers, amount of current smoking.

Statistical analyses

We calculated mean scores for the eight dimensions of quality of life and for the physical and mental component summary among never, ex-, and current smokers, adjusted for age, gender, educational level, and town of investigation, using multivariate analysis of variance. Furthermore, we used linear regression modelling to test for a dose-response relationship of quality of life with time since quitting and amount of smoking in the past among ex-smokers and, consequently, with amount of current smoking among current smokers. Adjusted regression coefficients were presented for every extra 5 years since quitting and for every extra 10 cigarettes smoked per day, based on continuous data. Then, we used multivariate analysis of variance to study the impact of time since quitting and amount of smoking on the difference in mean scores between ex- and current smokers, by means of stratification. In these analyses, we computed the adjusted difference in mean score between ex-smokers who smoked light, moderate, or heavy in the past on the one hand and current smokers with corresponding amount of smoking on the other hand, within each category of time since quitting (< 5 years, 5-9 years or ≥ 10 years ago). Finally, linear regression modeling was used to test for a possible trend in the difference in the quality of life between ex- and current smokers with time since quitting and amount of smoking.

Data were analyzed using the GLM-procedure of SAS version 6.12 (SAS Institute, Inc, Cary, NC). In all analyses, adjustments were made for age, gender, educational level, and town of investigation. Two-tailed p values below 0.05 were considered statistically significant.

Results

Table 1 shows characteristics of the study population. Crude mean scores on the eight health-related quality of life dimensions ranged from 66 to 91, from 67 to 90, and from 63 to 88 among never, ex-, and current smokers, respectively. Figure 1 presents mean health-related quality of life scores, adjusted for age, gender, educational level, and town of investigation. Except for bodily pain ($p<0.0001$), adjusted mean scores on the quality of life dimensions did not significantly differ between never smokers and ex-smokers (Figure 1). Current smokers reported lower scores than never smokers for all eight dimensions ($p<0.001$), and lower scores than ex-smokers for all dimensions ($p<0.05$) except bodily pain (Figure 1). Differences in mean scores between never and ex-smokers on the one side and current smokers on the other side were most pronounced for dimensions concerning

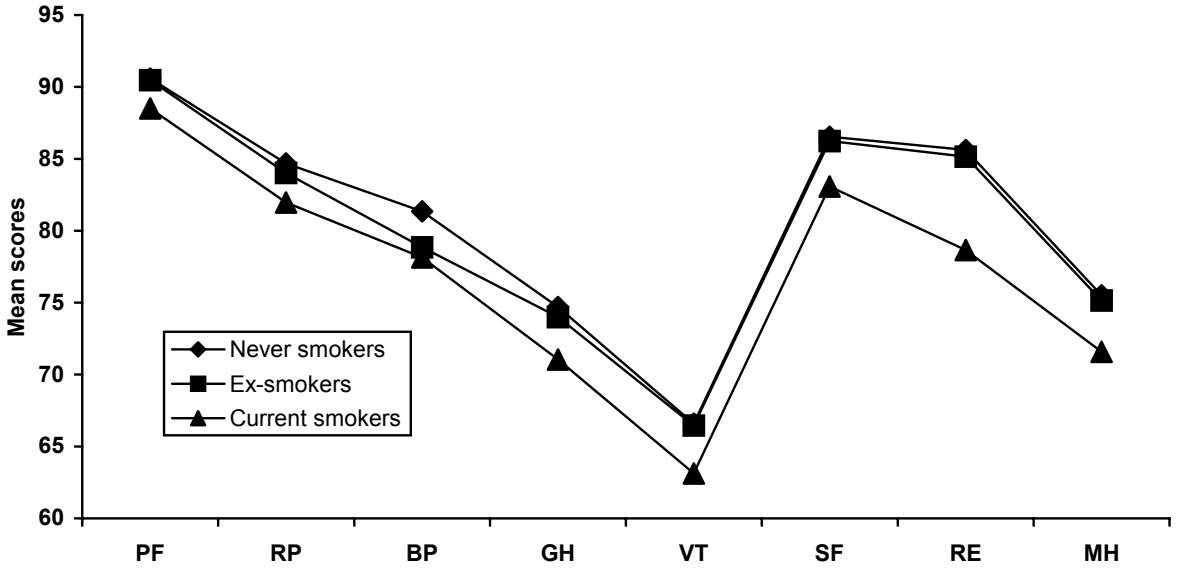

Figure 1 Mean scores of eight dimensions of quality of life among never, ex-, and current smokers, adjusted for age, gender, educational level, and town of investigation.

PF=physical functioning, RP=role functioning limitations due to physical problems, BP=bodily pain, GH=general health, VT=vitality, SF=social functioning, RE=role functioning limitations due to emotional problems, MH=mental health.

mental health, especially for role limitations due to emotional problems (difference 6.5 points; $p<0.0001$). The adjusted mean component summary scores among never, ex-, and current smokers amounted to 52.0, 51.6, and 51.4, respectively, for the physical component summary and to 49.3, 49.2, and 46.9, respectively, for the mental component summary. The physical component summary score among never smokers was higher compared with ex- ($p<0.05$) and current smokers ($p<0.001$), the mental component summary among current smokers was lower compared with both never and ex-smokers ($p<0.0001$). The covariates age, gender, educational level, and town of investigation, did not interact with these associations.

We further explored the impact of time since quitting and amount of smoking on the health-related quality of life. We first studied the effect of these two factors among ex- and current smokers. Among ex-smokers, a higher number of years since quitting was associated with higher scores on three of the eight dimensions and on the mental component summary (Table 2). Furthermore, among ex-smokers, a higher amount of smoking in the past was related to lower scores on four quality of life dimensions and on the physical component summary (Table 2). But the effect of

both time since quitting and amount of smoking on quality of life among ex-smokers was weak. Among smokers, however, the inverse association between amount of smoking and mean quality of life scores was stronger and was apparent for all dimensions and the two component summaries (Table 2). In general, associations were stronger for dimensions reflecting mental health than for dimensions reflecting physical health. The strongest associations were observed for role limitations due to emotional problems (among ex-smokers, β=0.62, p=0.10 for every extra 5 years since quitting; β=-1.11, p<0.05 for every extra 10 cigarettes per day smoked in the past; among smokers, β=-3.60, p<0.0001 for every extra 10 cigarettes per day smoked currently). The covariates age, gender, educational level, and town of investigation interacted with a few of these associations. However, no consistent pattern could be observed.

We then examined the impact of time since quitting and amount of smoking on the difference in quality of life scores between ex- and current smokers, by means of stratification. Figures 2A and 2B reflect the differences in quality of life scores between ex- and current light and between ex- and current heavy smokers, in each strata of time since quitting. Results for ex- and current moderate smokers are not shown here, but were generally in between results for ex- and current light and

Table 2 Association[a] (coefficient; p) between health-related quality of life and time since quitting and amount of smoking among ex- and current smokers.

	Ex-smokers				Current smokers	
	Time since quitting		Amount of smoking		Amount of smoking	
	β[b]	p	β[c]	p	β[c]	p
Physical functioning	0.33	0.07	-0.74	0.002	-1.89	<0.0001
Role limitations physical	-0.12	0.75	-0.97	0.07	-3.05	<0.0001
Bodily pain	0.05	0.85	-0.64	0.09	-2.51	<0.0001
General health	0.49	0.02	-0.57	0.048	-2.25	<0.0001
Vitality	0.48	0.03	-0.65	0.03	-2.32	<0.0001
Social functioning	0.41	0.10	-0.62	0.07	-2.28	<0.0001
Role limitations emotional	0.62	0.10	-1.11	0.03	-3.60	<0.0001
Mental health	0.48	0.01	-0.33	0.19	-1.76	<0.0001
Physical component summary	0.02	0.85	-0.28	0.03	-0.81	<0.0001
Mental component summary	0.29	0.01	-0.26	0.11	-1.12	<0.0001

[a] Adjusted for age, gender, educational level, and town of investigation. [b] For every extra 5 years since quitting. [c] For every extra 10 cigarettes smoked per day.

heavy smokers. Figure 2A shows that ex-smokers who smoked lightly in the past and who had quit smoking less than 5 years ago (shaded bars) or 5-9 years ago (black bars) did not score significantly different from current light smokers. Quality of life among long-term light quitters (≥10 years ago; white bars) was significantly better than among current smokers for the dimensions role limitations due to emotional problems and mental health, and substantially but not significantly better for vitality and social functioning (2.1 (95% confidence interval (CI) –0.05 to 4.3) and 2.4 (95% CI –0.2 to 5.0), respectively). In contrast, subjects who smoked heavily in the past (Figure 2B) scored significantly higher on roughly all dimensions than current heavy smokers, regardless of the time since quitting. An increase in time since quitting did not result in a significant increase in the difference in quality of life between ex- and current light, moderate (except for physical functioning, p trend<0.05), nor heavy smokers (except for mental health, p trend<0.01). Furthermore, the difference in quality of life between ex- and current smokers significantly increased with increasing amount of smoking for all (p trend<0.05) but three dimensions (vitality, role limitations due to emotional problems, and mental health), among short-term quitters, and for all (p trend<0.05) but one dimension (role limitations due to emotional problems) among long-term quitters. No trend with amount of smoking could be observed among subjects who had quit 5-9 years ago. Again, differences in quality of life score between ex- and current smokers were more pronounced for dimensions reflecting mental health, especially for role limitations due to emotional problems, compared with dimensions reflecting physical health. The covariates age, gender, educational level, and town of investigation interacted with a few associations, but again, a consistent pattern could not be observed.

Discussion

In this study among subjects without history of tobacco-related chronic diseases, ex-smokers experienced a better health-related quality of life than current smokers, which was more pronounced for mental than for physical health dimensions. Amount of smoking showed a dose-response relationship with quality of life among ex- but especially among current smokers. Time since quitting was only weakly related to quality of life among ex-smokers. Finally, in general, the difference in quality of life between ex- and current smokers significantly increased with increasing amount of smoking. No trend in the difference in quality of life was observed with time since quitting.

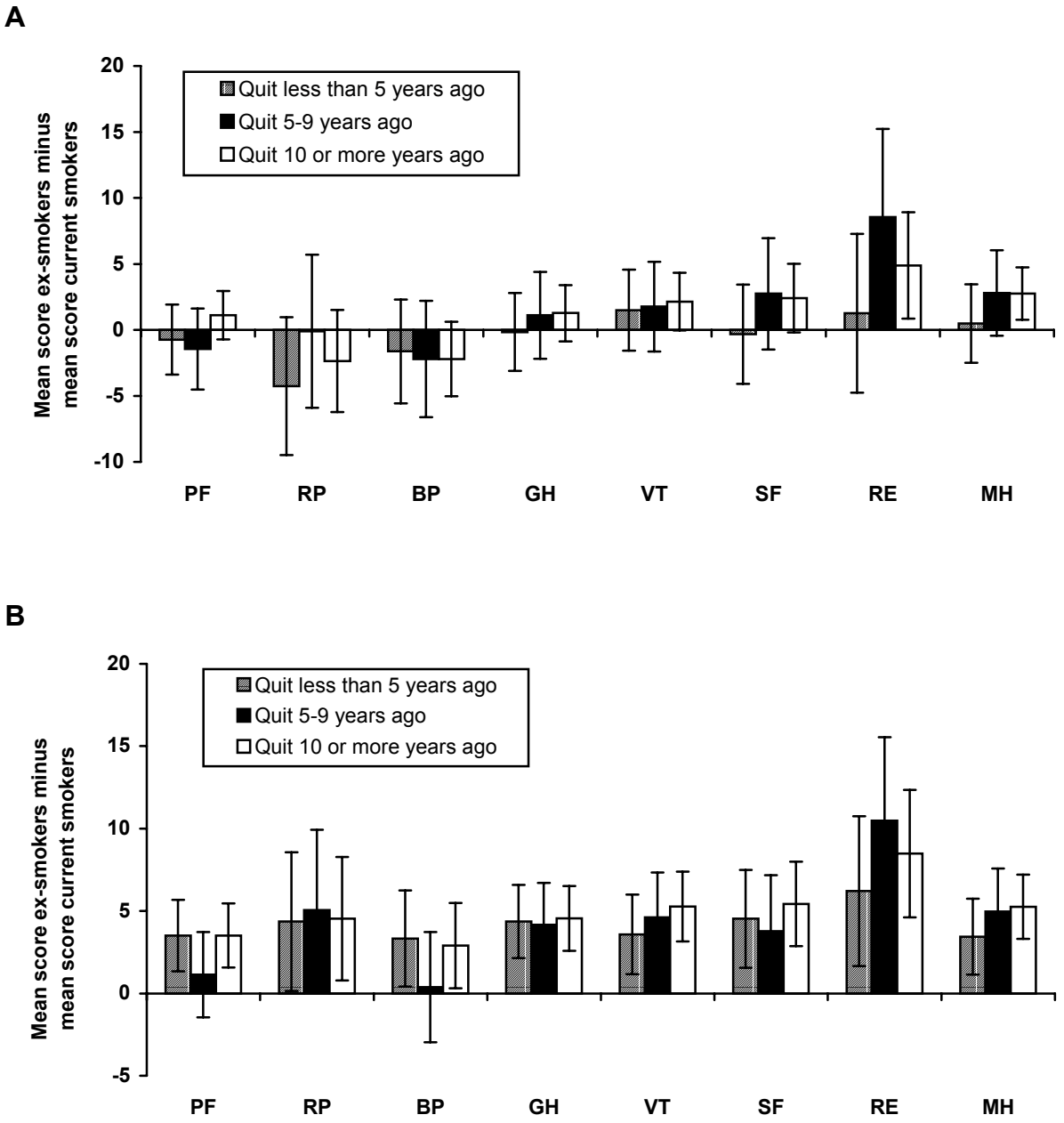

Figure 2 (A) Difference in mean scores (95% CI) on eight dimensions of quality of life between ex-smokers who were light smokers in the past and quit smoking < 5 years ago, 5-9 years ago, or ≥ 10 years ago and current light smokers, adjusted for age, gender, educational level, and town of investigation. (B) Difference in mean scores (95% CI) on eight dimensions of quality of life between ex-smokers who were heavy smokers in the past and quit smoking < 5 years ago, 5-9 years ago, or ≥ 10 years ago and current heavy smokers, adjusted for age, gender, educational level, and town of investigation.

PF=physical functioning, RP=role functioning limitations due to physical problems, BP=bodily pain, GH=general health, VT=vitality, SF=social functioning, RE=role functioning limitations due to emotional problems, MH=mental health.

In our study, the crude values of the quality of life scores on the eight dimensions ranged from 67 to 90 among ex-smokers and from 63 to 88 among current smokers. These values were slightly lower (range 77-91 and 73-94, respectively, adjusted values, in a subset of dimensions)[9] or higher (range 53-79 and 47-69[4] and 61-83 and 56-79, respectively)[10] than scores reported in other studies using the SF-36 measure. Another study (range 63-89 and 61-85 among ex- and current smokers, respectively) reported lower scores for the physical health dimensions, but higher scores for mental health dimensions.[8] Higher quality of life scores in our study may be due to the exclusion of subjects with history of tobacco-related chronic diseases. We excluded subjects with these conditions to minimize the influence of tobacco-related chronic diseases on the association between smoking behavior and quality of life. For instance, smokers may quit smoking if a tobacco-related disease has been diagnosed. This group of ex-smokers may have poor quality of life because of the underlying disease and not because of their smoking status, which would affect the relation between smoking behavior and quality of life. Generally, in our study, subjects with chronic conditions were older, were slightly more likely to be heavy smokers, had a lower educational level, and had lower mean quality of life scores than our study population.

In the literature, several other studies reported an association between smoking habits and health-related quality of life. Cross-sectional studies suggest that cigarette smoking is associated with poor physical functioning and poor perceived general health among elderly[5,6] and with poor mental health or depression among the general population,[15-17] compared with non- or never smoking. Cohort studies confirmed the association between cigarette smoking and poor physical functioning among elderly subjects[7] and poor mental health and depression among young and middle-aged subjects.[11,18,19]

Just a few studies examined the association between smoking habits and health-related quality of life by means of the standardized SF-36 or a subset of items of this measure. Some studies reported the difference between non- or never smokers and current smokers. In a cross-sectional study among patients visiting primary care practices, Woolf et al.[4] found significantly higher scores among nonsmokers than among current smokers for general and mental health and not for other dimensions. Wilson et al[8] reported lower scores among current smokers compared with never smokers for all quality of life dimensions among a general population. Stafford et al.[20] focused on physical functioning and reported higher scores among never than among current smoking men in a cohort study among middle-aged subjects. Some studies focused on the difference in quality of life between ex- and current smokers. A cross-sectional study reported significantly

higher scores among ex-smokers for general health, vitality, and mental health only and borderline significantly higher scores for social functioning.[10] In a smoking cessation trial, ex-smokers who had quit smoking for 6 months reported higher scores for mental health and lower scores for role limitations due to physical functioning than continuing smokers.[9] These results are partly in line with results found in our study, since we report significantly lower scores among current smokers for almost all dimensions when compared with never or ex-smokers. Generally, the differences in quality of life scores between ex- and current smokers found in these studies (range –6 to 5,[9] 3.1-5.4,[10] 7.0-15.6)[4] were larger than differences found in our study, which ranged from around 0.7 to 3.6, with the exception of role limitations due to emotional problems (6.5 points). However, our sizes of the difference were in line with those observed by Wilson et al.[8] (range 0.7-3.9 with the exception of role limitations due to emotional problems (7.5 points)). In our study, the difference between ex- and current smokers was larger for mental than for physical health, which is in line with results reported in other studies.[4,9] To our knowledge, no other study investigated the impact of time since quitting or amount of smoking on the difference in quality of life between ex- and current smokers.

The largest differences in quality of life in this study were found between ex- and current heavy smokers, which roughly ranged between 3 and 5 points, dependent on dimension and time since quitting, with the exception of role limitations due to emotional problems (10.5 and 8.5 points for the two highest categories of time since quitting, respectively). The magnitude of these differences is only slightly lower than differences in quality of life between subjects with and without asthma in the MORGEN study,[21] which indicates the relevance of the values found in this study.

A causal relation between cigarette smoking and poor physical health is suggested to be biologically plausible, since cigarette smoking may lead to, for example, osteoporosis due to lower bone mass[22,23] or losses in pulmonary functioning.[24] The weak associations between smoking and physical health in our study might indicate that losses in physical functioning due to cigarette smoking only marginally influence the quality of daily living. The causal relationship between smoking behavior and poor mental health is debated. Several studies explored the relation between smoking and depression. In these studies, three pathways are suggested by which smoking and mental health may be related.[18,19] First, smoking may cause depression, by means of nicotine exposure to depression-related neurobiologic systems. Results from a Japanese cohort study, in which mental health improved more among subjects who quit smoking during follow-up than among persistent smokers, support this pathway.[11] Furthermore, depression may

cause smoking, since smoking may act as self-medication to regulate the mood of the depressed. This may explain the finding that depressed smokers are less likely to give up the habit than smokers who are not depressed.[17] Finally, both smoking and depression may be influenced by a shared environmental or genetic factor.

Some limitations of our study should be mentioned. First, since our study is cross-sectional, no conclusions on causality can be drawn from our results. Furthermore, bias may have occurred in our study. For instance, the percentage of smokers found in the MORGEN study (1995-1997) was slightly lower than values found in other Dutch population-based studies, which indicates selective response of smokers. If nonresponding smokers differ in quality of life compared to responding smokers, this may introduce selection bias. However, we expect that nonresponse bias did not greatly influence our results, since the association between smoking and subjective health did not differ between responders and nonresponders in an extension of the MORGEN study. Furthermore, recall bias in our data on smoking behavior may have influenced our results. If, for example, especially smokers who do not feel well underestimate the amount of cigarettes smoked, the relation between heavy smoking and quality of life may have been underestimated. Additionally, ex-smokers were asked about their smoking behavior in the past (e.g., age at quitting and amount of cigarettes smoked), which also may have led to differential recall bias.

In conclusion, in this study among subjects without history of tobacco-related chronic diseases, ex-smokers experienced a better quality of life than current smokers, in physical health, but especially in mental health. In general, the higher the amount of smoking, the higher was the difference between ex- and current smokers. Although no conclusions on causal relationships can be drawn from this cross-sectional study, these results underline again the importance of giving up smoking and may play a role in encouraging smokers to give up this habit.

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8

General discussion

Main findings

The aims of this thesis were to quantify the future public health benefits of smoking cessation and to give more insight into the impact of smoking cessation on health-related quality of life.

In order to quantify future public health benefits of smoking cessation, it is important to have information on the association between smoking or smoking cessation and other risk factors for tobacco-related diseases. Results from a longitudinal study in 16 different cohorts in Europe, the United States and Japan showed that lung cancer mortality among smokers varied among cultures (Chapter 2). Ecological data indicated that the lung cancer mortality among smokers was higher in cohorts with high average saturated fatty acid intake than in cohorts with low average saturated fatty acid intake, which may suggest that saturated fatty acid intake may increase lung cancer risk among smokers. However, since power to detect associations among never smokers was low, we were not able to conclude whether the effects of smoking and dietary fat intake on lung cancer mortality were independent or that effect modification played a role. The population average intake of fruits and vegetables was not related to lung cancer mortality rate among smokers.

The changes of other main risk factors for cardiovascular diseases (CVD) (body weight, total and HDL cholesterol level and systolic and diastolic blood pressure) due to smoking cessation were studied in a 6-year follow up study among 20-59 year old Dutch men and women (Chapter 3). Results showed a postcessation increase in body weight, HDL cholesterol level and diastolic blood pressure among both men and women, and in total cholesterol level and systolic blood pressure among men, compared to persistent smokers. Adjustment for change in body weight showed that weight gain largely explained the postcessation increase in total cholesterol and blood pressure level. The results of this study suggest that a postcessation increase in HDL cholesterol may contribute to the beneficial effect of smoking cessation on CVD.

The effect of several smoking cessation targets on future tobacco-related morbidity and mortality were quantified in three studies, using computer simulation modelling (Chapters 4, 5 and 6). In two studies, involving the effects of smoking cessation in the European Union (EU), the WHO's Health for All target concerning smoking prevalence was simulated, which implied that smoking prevalence was reduced to 20% in 2015 in all member states of the EU. If this target would be reached, it was expected that 4% of all pancreatic cancer patients could be prevented between 1994 and 2015, which corresponds to 29,500 male and 9,500

female patients (Chapter 4). Furthermore, this scenario was expected to reduce mortality up to 2015 from all causes with 2.5% (around 1.1 million deaths) and 0.8% (almost 350,000 deaths), from coronary heart disease (CHD) with 1.3% and 0.3%, from stroke with 2.1% and 0.6%, from lung cancer with 11% and 8%, and from other tobacco-related cancers with 6.4% and 2.1%, among men and women respectively (Chapter 5). Chronic obstructive pulmonary disease (COPD) mortality was estimated to increase by 0.8% among men. This may be explained by the small difference between the relative risks of smokers and ex-smokers for COPD, which makes the reduction in COPD mortality too small to counterbalance the increase in COPD through a higher number of people at risk. Among women, the number of deaths from COPD was expected to decrease by 2.0% following smoking cessation. These studies indicated that these declines in morbidity and mortality were about 30%-50% of the declines if, theoretically, all smokers would quit instantly.

In Chapter 6, the effect of smoking cessation on coronary heart disease and on healthy life expectancy was compared with that of cholesterol lowering medication, in smokers without familial hypercholesterolaemia, cardiovascular diseases or diabetes, who were eligible for cholesterol lowering medication according to the Dutch Consensus Cholesterol. Results showed that complete smoking cessation would lower the number of smokers eligible for cholesterol lowering medication with 75%. Furthermore, smoking cessation led to a less strong (men; difference 11%-22%) or comparable (women) reduction in coronary heart disease compared with cholesterol lowering medication. However, smokers who quit smoking would gain 2-2.5 healthy life years more than smokers who use cholesterol lowering therapy.

Finally, ex-smokers experienced a better quality of life than current smokers in a cross-sectional study among 20-59 men and women in the Netherlands, which was more pronounced for mental health than for physical health (Chapter 7). The difference between ex- and current smokers increased with increasing amount of smoking, but not with increasing time since quitting.

Smoking behaviour and other public health risk factors

Most research on the public health impact of smoking and smoking cessation involved the effect of smoking behaviour itself. Numerous studies, for instance, reported relative risks for smokers and ex-smokers compared to never smokers for tobacco-related diseases. However, results from several studies have indicated that other public health risk factors, such as diet or body weight, may have a modifying or intermediate effect in the pathway of smoking or smoking cessation and smoking-

related diseases. These associations between smoking behaviour and other risk factors on health have not been fully understood.

Smoking, fat intake and lung cancer mortality

Although smoking is in each culture a risk factor for several causes of death,[1] the magnitude of the effect of smoking may not be similar across cultures.[2,3] This suggests that other factors may modify the effect of smoking. Most data on culture-specific effects of smoking have been published for lung cancer. Stellman et al.[3] reported that the odds ratio of smoking on lung cancer was about 10 times larger in the United States than in Japan, using data from a multicentre case-control study. Keys et al.[2] found that the impact of smoking on lung cancer was stronger in northern than in southern European cohorts of the Seven Countries Study. Furthermore, in an ecological study comprising 29 countries, Xie et al.[4] showed that the effect of per capita cigarette consumption on lung cancer mortality was lower in countries with low average animal fat intake compared to countries with high average animal fat intake. The interaction between cigarette smoking and animal fat intake was significant in that study, leading to the hypothesis that fat intake enhances the carcinogenic effect of smoking on lung cancer mortality.

In Chapter 2 of this thesis, this topic was further examined, using ecological data of the Seven Countries Study. In this study, we found that lung cancer rates among smokers were higher in cohorts with high average fat intake than in cohorts with low average fat intake, which was most pronounced for saturated fatty acids. For instance, lung cancer rates among smokers were higher in Finland, the Netherlands and the United States, where average saturated fatty acid intake was high, than in Japan and Greece, where saturated fatty acid intake was lower. Unfortunately, power to study the impact of fat intake on lung cancer mortality among never smokers was low and the number of cohorts was small. Therefore, we were not able to conclude whether the effect of smoking and saturated fatty acid intake on the variation in lung cancer across cultures was an independent effect or effect modification.

Published data on the association between smoking, fat intake and lung cancer may help to get an indication on which of these types of effect would be most plausible in our study. However, further insight could not be obtained from the literature for three reasons.

First, data on the association between fat intake and lung cancer in never smokers is not clear. In general, information on lung cancer in never smokers may be difficult to obtain due to the low incidence of lung cancer among never smokers.

In a review, Koo et al.[5] concluded that never smoking is exceedingly rare among male lung cancer patients, regardless of ethnicity. If this would imply that lung cancer among never smokers is similarly rare in each culture, regardless of the average saturated fatty acid intake, it would support the hypothesis of effect modification between saturated fatty acid intake and cigarette smoking. However, it can not be concluded from this finding alone that lung cancer mortality among never smokers is similar across cultures. Furthermore, few case-control studies[6-9] and cohort studies[10,11] examined the effect of fat intake on lung cancer among never smokers. The results of these studies were not consistent, although, generally, the number of lung cancer patients among never smokers was small in studies in which an inverse or no association was observed.

Second, the literature does not give consistent evidence on the possible modifying effect of fat intake on the effect of cigarette smoking on lung cancer. This topic was studied at the ecological level as well as the individual level. Some of the ecological studies support the hypothesis that fat intake may enhance the carcinogenic effect of cigarette smoking on lung cancer,[4,12-14] but another study did not.[15] None of these studies examined the effect of fat intake on lung cancer mortality among never and current smokers separately. Yet, some limitations of ecological studies, including the study described in Chapter 2, should be mentioned. In general, no conclusions about causal pathways can be drawn from ecological studies. Furthermore, information about some important factors in the etiologic pathway of lung cancer, that differ considerably across populations, are often not available. Finally, associations found at the ecological level can not be generalised to the individual level and vice versa.[16,17] Thus, although ecological studies are useful in determining possible associations, studies at the individual level are needed to fully express the plausibility of associations.

In studies based on individuals, the effect of diet on lung cancer mortality was merely studied in the total population, adjusting for smoking behaviour, or in never smokers. Results, mainly derived from case-control studies, weakly suggest that high fat intake, may increase lung cancer.[18-20] This effect was more consistent for saturated fatty acid intake. Only few studies reported the relation between fat intake and lung cancer for the separate smoking behaviour categories,[10,21,22] but results were inconsistent. A recent pooled analysis of 8 cohort studies showed no association between fat intake and lung cancer, among the total population nor among the smoking categories separately.[22] Results from other studies suggested that an association between fat intake and lung cancer was restricted to smokers,[10,21] which would support our hypothesis. However, the number of lung cancer cases among never smokers was small in these studies and, as we

mentioned before, a positive association between fat intake and lung cancer among never smokers was also reported.[6,8,9,11]

Third, most of these studies, including the one described in Chapter 2, were not able to exclude the effect of other lung cancer risk factors, which are suggested to partly explain variation in lung cancer across cultures. For instance, differences in smoking-related factors across cultures are suggested to play a role, including the type of tobacco blend and filters, inhalation practices, age at smoking initiation, amount of cigarettes smoked and past smoking prevalence.[3,14,23] Furthermore, a protective effect of fruit and/or vegetable intake has been suggested in some ecological studies,[12,24] but not in all,[14] including the study described in Chapter 2 of this thesis. In case-control[25-27] and cohort[28,29] studies, fruit and/or vegetable intake was consistently found to be protective for lung cancer. Green tea consumption is suggested to play a role in the low lung cancer mortality in Japan.[30] Finally, variation in occurrence of P450 genetic polymorphisms between Japanese and Caucasian populations[31] underline the suggestion that variation in metabolism of smoke carcinogens or in DNA repair capacity may play a role in the variation of lung cancer across cultures.[31-34] It may be possible that mean saturated fatty acid intake is closely correlated with one or more of these factors and thus that the effect of saturated fatty acid intake on the association between smoking and lung cancer mortality merely reflects the effect of other factors, especially in ecological studies.

In conclusion, although our results are in line with results from other ecological studies and some studies based on individual data, the role of fat intake on the carcinogenic effect of smoking on lung cancer is still unclear and remains speculative. However, the hypothesis that fat intake may enhance the effect of cigarette smoking on lung cancer is supported by animal studies[35-37] and by possible underlying mechanisms,[38,39] which indicates that a possible role of dietary fat intake can not be ruled out. Further study is needed to explore the relation between smoking and other risk factors on mortality from lung cancer.

Smoking cessation and other risk factors for cardiovascular diseases

Besides possible modifying effects, other public health risk factors may also mediate between smoking behaviour and morbidity or mortality risk. For instance, changes in smoking behaviour may lead to changes in other risk factors, which accordingly may affect risk. In Chapter 3, the change in cardiovascular disease (CVD) risk factors after smoking cessation has been studied among a general Dutch population, in order to get an indication to what extent changes in other risk factors may influence CVD risk after smoking cessation. The results indicated that smoking cessation

increased HDL cholesterol level and body weight and that this weight gain in turn resulted in an increase in total cholesterol level and blood pressure. A postcessation weight gain has been widely reported[40-42] and an increase in HDL cholesterol level after smoking cessation was reported in smoking cessation intervention studies.[43,44] The smoking cessation induced increase in total cholesterol level and blood pressure level in our study, which is generally not found in the literature, was largely explained by postcessation weight gain. These results suggest that the favourable decrease in CVD risk after smoking cessation would be the resultant of a CVD risk decrease due to smoking cessation itself and a consequent rise in HDL cholesterol level and a CVD risk increase due to postcessation weight gain and a consequent rise in total cholesterol and blood pressure level.

This indicates that smoking cessation not only reduces cardiovascular disease risk directly, for instance by reducing the oxidation of LDL, which is one of the major causes for atherosclerosis, but that it also may play a role in the underlying mechanisms of atherosclerosis through changes in other classical CVD risk factors. A smoking cessation induced increase in HDL cholesterol level, for instance, protects against atherosclerosis by removing excess cholesterol from peripheral tissue to the liver and inhibits oxidation of LDL. On the other hand, higher blood pressure and unfavourable lipid profiles due to weight gain after smoking cessation contribute to the development of lesions in the vessel wall or to formation of foam cells and atherosclerotic plaques, which increase the risk for atherosclerosis. Several interactions between these risk factors have been reported, which illustrates the complexity of the association between the CVD risk factors and atherosclerosis.[45]

It is estimated that the excess weight gain of quitters compared to persistent smokers of 3.4 kg among men and 3.8 kg among women in 6 years, reported in Chapter 3, which corresponds to about 1 and 1.4 unit of BMI respectively in our study, would increase CVD mortality by around 8% and 4% respectively.[46] Furthermore, HDL cholesterol level increased by 0.07 mmol/L for both men and women, which was estimated to decrease CVD mortality by around 5.5% and 8% respectively.[47] Thus, roughly, the smoking cessation induced change in weight and HDL cholesterol level would result in a net increase in CVD mortality among men and a net decrease in CVD mortality among women. However, compared to the substantial risk reduction after smoking cessation, the excess risk of CVD may be halved already after one year of cessation, the effects of smoking-related changes in other risk factors on CVD risk would be minor. Far more important seem to be the favourable direct effects of smoking cessation on CVD development, which includes

elimination of the harmful effects of cigarette smoke on oxidation of LDL, blood coagulation, the sympathetic nervous system and oxygen transport in the blood.[48]

Results in Chapter 3 showed that the peak weight gain occurred within 4 years after cessation and that excess weight gain decreased afterwards, which was in line with another study.[40] For HDL cholesterol, no clear effect of duration of smoking cessation was observed, although HDL cholesterol level increase tended to become less pronounced after a few years of cessation among women. This suggests that the role of changes in other CVD risk factors would diminish with increasing years of smoking cessation.

It is possible that smokers who quit smoking, also adopt other healthy lifestyle factors associated with smoking behaviour, such as consuming a healthier diet[49] or increasing their physical activity level.[50] Since these factors are also associated with weight, cholesterol and blood pressure level, and since we were not able to fully adjust for these factors, they may account partly for the reported changes in body weight or HDL cholesterol level.

An unfavourable increase in body weight after smoking cessation suggests that the favourable effects of smoking cessation would be largest in quitters who gain the least weight. Results reported by Jousilahti et al.[51] even suggest that smoking and body weight interact in their association with coronary mortality. They reported that the relative risk of CHD mortality among ex-smokers compared to never smokers was larger in obese (BMI $\geq$ 30 kg/m^2) men than in lean (BMI < 25 kg/m^2) and moderately overweight (BMI 25-29 kg/m^2) men. The association between smoking behaviour and body weight may differ by socio-economic status. Molarius and Seidell[52] have reported that among subjects with low education, ex-smokers have significantly higher BMI than light and heavy smokers. Among subjects with high or intermediate education, however, the difference in BMI between ex-smokers and light smokers was less pronounced and there was no difference between ex-smokers and heavy smokers, except for intermediately educated men. This effect of education was not explained by physical activity, fat intake, alcohol consumption or smoking related factors. This may indicate that quitters with low education may gain more weight than quitters with a higher level of education. Subjects at high educational level may be more concerned about their weight and may be more likely to control postcessation weight gain. Johansson et al.[53] illustrated that physical activity may play a role in the association between smoking behaviour, body weight and health. They showed that the odds ratio of ex-smokers for self-reported poor health status largely depended on their physical activity level. Active ex-smoking women, for example, showed an odds ratio for poor health of 1-1.5, in normal

weight, overweight or obese subjects, compared to active never smoking women with normal weight. In inactive ex-smoking women, however, the odds ratios were 3.2 among women with normal weight, 4.7 in overweight women and 10 in obese women, compared to active never smoking women with normal weight.

Currently, there is a great interest in the so-called global risk concept, in which the combined effect of different risk factors on CVD is estimated. Most research on this topic has been performed for cardiovascular diseases and all-causes mortality.[54-58] Yusuf et al.[54] examined the effect of having 1, 2, 3, or more risk factors on CVD development and all-causes mortality in the NHANES I study. Risk factors included current smoking, high total cholesterol level, high blood pressure, diabetes and overweight. They reported that the relative risks of the separate factors for coronary heart disease were 1.5, 1.4, 1.4, 2.2 and 1.3 respectively, compared to the absence of the specific factor. Prevalence of one of these risk factors was associated with a relative risk of 1.6 compared to the absence of all factors. The risk increased with increasing number of risk factors and was 2.2, 3.1 and 5.0 times the risk of no factors, for 2, 3 and 4 or more risk factors respectively. The same pattern was seen for stroke and all-causes mortality.

In a study from the US among the MRFIT and the CHA population, it was estimated that CHD and all CVD mortality was 77%-92% and 72%-85%, respectively, lower among subjects with a low risk profile (no smoking, blood pressure $\leq$ 120/80 mmHg, total cholesterol level < 5.17 mmol/L, no history of diabetes or MI and no ECG abnormalities) compared to all other subjects combined.[55] Houterman et al.[56] examined the combined effects of smoking, systolic blood pressure and total cholesterol level on CHD, all CVD and all-causes mortality among Dutch young and middle-aged men and women. They reported that the relative risk for CVD mortality among smokers with low blood pressure and cholesterol level was 2.3 among men and 1.8 among women, compared to subjects with a low risk factor profile (no smoking, blood pressure < 120 mmHg, cholesterol level < 5.2 mmol/L). At low cholesterol level, the additional effect of smoking was larger than the additional effect of elevated blood pressure. When smoking was accompanied by elevated levels of blood pressure ($\geq$ 140 mmHg) and cholesterol ($\geq$ 6.5 mmol/L), relative risks increased up to 14 and 9.3, among men and women respectively, compared to the low risk factor profile. Similar results were found for CHD and all-causes mortality. Thus, the total risk profile seems to be more important than the presence or level of risk factors separately.

Smoking cessation and future public health benefits

Smoking cessation and future morbidity and mortality

The decreased risk for tobacco-related diseases after smoking cessation has a large impact on the allocation of health care services. In order to adjust the health care system to these changes in smoking behaviour one should have an indication of the future change in morbidity and mortality after smoking cessation. However, studies on the effect of smoking cessation on future morbidity and mortality are scarce. Peto et al.,[59] for instance, predicted the number of future deaths attributable to smoking, in other words the number of deaths that could have been prevented if all smokers would never have smoked. Although these results are crucial in the understanding of the effect of smoking, it does not give insight in the future effects of smoking cessation. Moreover, the effects of several smoking cessation strategies on lung cancer mortality and gain in life years have been estimated for the Dutch population.[60]

Chapters 4, 5 and 6 of this thesis give estimations of the effect of smoking cessation on future incidence of pancreatic cancer, which is one of the most lethal tobacco-related cancers, mortality from all known tobacco-related diseases and (non)fatal coronary heart disease, respectively, by means of computer simulation. It is estimated that, if the 'Health for All' target of the WHO concerning smoking cessation would be achieved, which implied that smoking prevalence was reduced to 20% in 2015 in all member states of the EU, the number of pancreatic cancer cases up to 2015 would decrease by about 4% (29,500 male and 9,500 female patients) (Chapter 4). Additionally, the number of total deaths up to 2015 would decrease by 2.5% (around 1.1 million deaths) among men and 0.8% (almost 350,000 deaths) among women (Chapter 5). Furthermore, it is estimated that in a Dutch population of smokers with a high CHD risk, complete smoking cessation would decrease the number of CHD cases by about 25% among men and 31% among women in 10 years. More realistic smoking cessation interventions, obviously, would result in a smaller decrease in incidence and mortality.

These results should not be seen as absolute predictions of future morbidity or mortality, but rather as indications of the magnitude of change. This is related to the obvious fact that it is impossible to model real life. For most related factors, reliable data are not available and therefore, our models must be seen as a simplified reflection of reality. Three examples of simplifications are discussed here.

First, we simplified smoking behaviour and public health effects of smoking and smoking cessation. For instance, we were not able to account for trends in smoking

behaviour, differences in relative risk according to duration and amount of smoking, and, in Chapter 5 and 6, differences in relative risk according to time since quitting. Comparable data on trends in smoking behaviour for the EU member states were lacking and risk estimates for the different tobacco-related diseases according to duration or amount of smoking or time since quitting were generally not available or would have been derived from different sources, which would have made them difficult to compare. In Chapter 6, the Framingham risk function was used, which does not take these factors into account.

After smoking cessation, the relative risk of quitters decreases with time since quitting.[61] This indicates that short-term quitters have a larger risk compared long-term quitters. In Chapter 4, we were able to include relative risk estimates according to time since quitting, since, for pancreatic cancer, incidence estimates of the time span in which the risk of a smoker returns towards the risk of a never smoker after smoking cessation were published. However, for some other tobacco-related diseases, especially several types of cancer, this time span is not clear. Therefore, in Chapter 5, we used average relative risk estimates for the total group of ex-smokers in our computer simulation model, which incorporates short-term as well as long-term quitters. It is expected that these average group estimates of relative risk will partly average out the differences in risk within ex-smokers according to time since quitting. In additional analyses, we compared the effects of the two types of risk estimates among ex-smokers for the impact of smoking cessation on future pancreatic cancer incidence. If we would have used the average group estimates of ex-smokers (RR 1.3 among men and 1.1 among women[62]) in the simulation model of Chapter 4, in stead of relative risk estimates according to time since quitting, the number of preventable pancreatic cancer cases in the Health for All scenario would have been 45% and 74% larger, among men and women respectively. This suggests that the use of average group estimates of ex-smokers would have overestimated the effect of smoking cessation on future pancreatic cancer incidence. Since it would take several years before the relative risk of a quitter reaches and eventually becomes lower than the level of the average group estimate of ex-smokers, in this time span of simulation, the lower risk of long-term quitters compared to the average group estimate would not compensate for the larger risk of short-term quitters.

This does not necessarily imply that the use of average group estimates of ex-smokers in Chapter 5 overestimated the effect of smoking cessation on future mortality. The difference in effect between group estimates and estimates according to time since quitting depends on several factors, including the difference between the relative risks of smokers and ex-smokers, the time span in which the risk after

smoking cessation returns towards the risk of never smokers, and the time span of simulation. For instance, the effect of smoking cessation on coronary heart disease can be seen within a few years already. This means that in a relatively short period of time, about 10-15 years after smoking cessation, the risk of an ex-smoker may return to the risk of a never smoker and the relative risk of ex-smokers would thus be close to 1 in stead of the average group estimate of 1.3-1.8 we used in Chapter 5. A simulation comprising 21 years using average group estimates, as we performed, would thus probably underestimate the effect of smoking cessation. Additionally, in our study on pancreatic cancer incidence in Chapter 4, if we would expand the simulation time large enough, the proportion of long-term quitters with a relative risk close to 1 would increase, which would compensate for the larger risk of short-term quitters compared to the average group estimate. This would result in an underestimation when group estimates were used. Thus, the impact of simplified average group estimates on the results in Chapter 5 depends on the tobacco-related disease.

The second example of simplification is that we were not able to account for the impact of other public health risk factors on the effect of smoking and smoking cessation in Chapter 4 and 5, and partly in Chapter 6. For instance, results from Chapter 2 suggested that the effect of smoking may differ between cultures, depending on the culture-specific saturated fatty acid intake, which suggests that one should use separate relative risks for each culture in public health modelling. However, as previously shown, the modifying effect of other risk factors on smoking or smoking cessation often remains unclear. Besides this, more practically, separate relative risks for the different countries in the European Union are not available. In our studies, we chose to use relative risks derived from three of the most well-known large cohort studies in Western world, which were performed in the United States. Furthermore, smoking cessation may induce changes in other public health risk factors, such as body weight or cholesterol level (Chapter 3). Since these data are mostly not available, we were not able to include these effects into our models. For the analyses reported in Chapter 6, although repeated measurements were performed for both the MORGEN project as the Rotterdam Study, in which we could have examined changes in weight and cholesterol level, the number of quitters between two examinations in the elderly (Rotterdam Study) was too small to detect changes. Although it is important to have insight in the impact of other public health risk factors on the effect of smoking, in order to judge on the reliability of the estimated reductions in future morbidity and mortality after smoking cessation, in practice of public health modelling, it appears difficult to account for these effects.

Besides, compared to the substantial favourable effect of smoking cessation itself, it can be expected that these effects would be minor.

The third example of simplification in our studies is that we did not include changes in other public health risk factors not related to smoking. For instance, changes in other risk factors for pancreatic cancer incidence, such as dietary factors, history of diabetes mellitus and chronic pancreatitis,[63] may influence future incidence of pancreatic cancer. Similarly, an increase in physical activity or a favourable change in diet may decrease future mortality from CVD or several types of cancer.

Using the computer simulation model 'Prevent', Mooy and Gunning-Schepers[60] estimated the reduction in lung cancer mortality for several smoking cessation scenarios in the Netherlands. In their estimations, a 5% reduction in the number of smokers resulted in an absolute decrease in lung cancer mortality of maximally around 400 male and 100 female cases, about 30 years after the intervention took place. Our model and Prevent differ concerning the time span in which the decrease in smoking prevalence took place. In our model, the decrease in smoking prevalence started at the beginning of simulation and would be reached in 2015. In Prevent, the decrease would take place 1 year after the start of the intervention. Therefore, Prevent resulted in a larger decrease in mortality.

Although our data on public health modelling should not be seen as public health projections, as we mentioned, it is interesting to compare our results with empirical data, in order to get an indication of the effect of our simplifications. Unfortunately, recent empirical data are not yet available for the European Union, but the International Agency for Research on Cancer and the World Health Organization[64] recently estimated cancer incidence and mortality for the year 2000. For these estimations, they used the most recent available incidence and mortality rates for each country, generally data for the years 1995-1997, and country specific population sizes for the year 2000. When we compared these estimations with our results in Chapter 4 and 5 for the year 2000, it appeared that the differences between our estimated number of pancreatic cancer cases (Chapter 4) and the IARC/WHO estimations were less than 25% for most countries, among both men and women. In 5 countries among men and in 3 countries among women, the difference was larger than 25%, up to 34% and 38% among men and women, respectively, for Finland. The differences between our estimated number of tobacco-related cancer deaths in the EU as a whole (Chapter 5) and the IARC/WHO estimations were smaller, up to 3.5% and 4.5% among men and women, respectively, for lung cancer.

Earlier, in the 1990's, IARC/WHO predicted cancer incidence and mortality for the year 2000, based on demographic changes alone.[65,66] When we compared these IARC/WHO predictions for pancreatic cancer incidence with their own recently estimated incidence for the year 2000, it appeared that the differences between the predicted values and the recently estimated values for 2000 were less than 25% for 6 countries among men and for 8 countries among women. For the remaining EU member states, the differences were larger than 25%, up to 32% and 35% among men and women, respectively, in Portugal. Furthermore, IARC/WHO predictions of tobacco-related cancer deaths for the EU as a whole and their own recent estimations differed less than 5% for most causes of death, except for larynx (20%) and bladder (6%) cancer among men and lung cancer (9%) among women.

When we compared our estimated number of pancreatic cancer cases and the IARC/WHO predictions on the one side with IARC/WHO estimations on the other side, it appeared that our data were closer to the recent WHO/IARC estimations for pancreatic cancer incidence for 9 of the 15 countries, for both men and women. Furthermore, when tobacco-related cancer mortality is concerned, our data were closer to the IARC/WHO estimations in the EU as a whole for 6 and 3 of the 7 tobacco-related cancers, among men and women respectively. Thus, in general, our simulation model would reflect real life more closely than a model in which only demographic changes were included, at least in the short run.

For the effects of smoking and smoking cessation on cause specific deaths in Chapter 5, we included those tobacco-related diseases which were conclusively related to cigarette smoking, including coronary heart disease, stroke, COPD and cancer of the lung, oral cavity and pharynx, oesophagus, larynx, pancreas, kidney and bladder.[61] Besides these diseases, there is more and more evidence that cigarette smoking also increases the risk of several other diseases. For instance, smoking is now thought to be associated with stomach cancer.[67-69] A meta-analysis showed that smokers have a 1.5-1.6 times higher risk for stomach cancer than non-smokers.[67] There is also increasing evidence that smoking is associated with increased risk for liver cancer,[69,70] cervical cancer[69,71,72] and acute myeloid leukemia.[69,73] Furthermore, it is suggested that smoking is associated with colorectal cancer,[74,75] although this effect may be confounded.[69] Besides these tobacco-related cancers, smoking may also increase the risk for type 2 diabetes,[76-78] disorders of the eye, especially age-related maculopathy,[79,80] infertility of females,[81] miscarriage,[82] osteoporosis[83] and hip fracture,[83] among other diseases. Smoking cessation is suggested to decrease the risks of at least some of these disorders,[68,77] although more research on this issue needs to be performed. If indeed smoking

cessation also decreases the risk for these diseases, the favourable effect of smoking cessation on health would thus be larger than presented in this thesis.

Smoking cessation and life expectancy

Cigarette smoking obviously results in loss of life expectancy. Shaw et al.[84] roughly estimated that each cigarette would cost a smoker 11 minutes of life. Generally, smokers live about 8 years shorter than never smokers.[85] Smokers who were killed by tobacco-related diseases would loose on average about 13 to 16 life years compared to never smokers,[86,87] which was about 23 years for those who were killed by tobacco between ages 35 and 69 years and about 8 years for those died at older age.[86] Heavy smokers would loose more years of life than light smokers.[88] The impact of cigarette smoking on life expectancy can be illustrated by the situation in the Netherlands. In this country, life expectancy used to be one of the highest in Europe.[89] However, starting around the mid 1980's, the increase in life expectancy among men, but especially among women, has stagnated compared to other European countries. Now, life expectancy of Dutch women is positioned in the middle of the European Union member states. A major explanation for this trend is the high smoking prevalence in the Netherlands, which decreased in time, but not as strong as in other countries and remains one of the highest in Europe.

Since smoking cessation reduces mortality, it will lead to an increase in life expectancy. Using the data and methods described in Chapter 6, it is estimated that smoking cessation in the Netherlands would increase life expectancy by about 3.5 years among 40-59 year old men and 2.5 years among 60-74 year old men and women (results not presented in Chapter 6). Taylor et al.[90] recently reported that smokers in the United States who quit smoking at age 35 years, increased their life expectancy with about 7 to 8.5 years among men and 6 to 7.5 years among women. Quitters would gain more life years when cessation took place earlier in life. However, even smokers who quit at age 65 years would gain 1.5 to 2 years among men and 2.5 to 3.5 years among women. Our estimated gain in life expectancy for 40-59 year old men was slightly lower than the estimates of the US study, when we compared it with the results for men quitting at age 45 years (gain in life expectancy in US study 5.5 to 7 years) or 55 years (gain 3.5 to 5 years). On the other hand, our estimated gain in life expectancy for men at older age was slightly larger than the US estimate for men who quit at age 65 years. Among women, the estimations of the two studies were roughly comparable.

Smoking cessation not only increases the total number of years lived, it is also expected to increase the number of years lived in health and to decrease the

number of years lived with disability.[91] In chapter 6 of this thesis, it is estimated that the gain in healthy life expectancy after smoking cessation was 4 years among men who would quit at age 40-59 years and 3 years among men and women who would quit at age 60-74 years. Nusselder et al.[91] estimated that non-smokers would live on average 2.5 years and 1.8 years longer in health, among men and women respectively, than persons in a population of both smoking and non-smoking men and women. Furthermore, non-smokers would live on average 1 year shorter with disability. Comparing healthy life expectancy at age 20 between lifelong never, ex- and current smokers, Brønnum-Hansen et al.[92] estimated that never smokers lived about 12 years longer in health and ex-smokers lived about 8.5 years longer in health than heavy smokers. The healthy life expectancy at age 65 was 5 years larger among never smokers and 2.5 years larger among ex-smokers, compared with heavy smokers. Other estimations on the difference in healthy life expectancy after smoking cessation are scarce.

In the calculation of the healthy life expectancy, we used disability weights for each known tobacco-related disease, in order to adjust life expectancy for disability or quality of life loss caused by these diseases. The gain in healthy life expectancy after smoking cessation was thus based on an improved quality of life due to a decrease in tobacco-related diseases. In Chapter 7, however, we showed that even in subjects without having a disease, ex-smokers experienced a better health-related quality of life than smokers. This result was stronger for mental health than for physical health. In general, these results were in line with results found in other cross-sectional studies[93-95] or in trials.[96] A causal relationship between smoking and poor physical health has been suggested to be biologically plausible.[97-99] However, the causal relationship between smoking and mental health is debated,[100,101] although an improvement in mental health after cessation was reported in a Japanese cohort study.[102] Unfortunately, we were not able to draw conclusions on the causality of this association, from our cross-sectional study. If the association between smoking cessation and health-related quality of life would be causal, then smoking cessation may also improve quality of life directly, besides through a decrease in tobacco-related diseases. This implies that the gain in healthy life expectancy, in a broader sense than we used in Chapter 6, would be larger than we estimated in that chapter. Furthermore, in the estimation of the healthy life expectancy, we have not included tobacco-related diseases, which were recently established or suggested to be related to smoking. If smoking cessation would decrease the risk for these diseases as well, then the gain in healthy life expectancy, as estimated in Chapter 6, would also be underestimated.

Smoking cessation and health care costs

The main goal in public health policy is to reduce the burden of disease and to increase healthy life expectancy; in other words, to let people live in health as long as possible. Therefore, due to the substantial benefits on morbidity and mortality and consequently on healthy life expectancy, smoking cessation is one of the major topics in public health policy these days. Economic aspects are an important component of public health policy, because of the continuously increasing costs of health care. Health care costs play nowadays a central role in the political debate. Although the public health effects are the dominating factor, it is important to have insight in the economic impact of smoking cessation in order to adapt the health care system to changes in smoking behaviour trends.

Smoking has great impact on health care costs, due to the increased morbidity and mortality rates. Estimations from Germany showed that the annual smoking-related health care costs accounted for almost 50% of the total costs for the most important smoking-related diseases in 1996.[103] For the US[104] and England,[105] it has been reported that the medical costs of smoking corresponded to about 6-8% of the total health care costs in the 1990's. From these results, it seems to be logical to conclude that, when health care costs are concerned, non-smoking is cheaper than smoking and thus that smoking cessation reduces health care costs. However, several studies have indicated that the effect of smoking cessation on health care costs is more complex. The key factor in this context is that non-smokers live longer than smokers. They may, therefore, develop diseases at older ages, such as dementia, which are associated with high health care costs. Barendregt et al.[106] estimated that the health care costs of a population of non-smokers were 7% and 4% larger than those of a population of both smokers and non-smokers, among men and women respectively, although the health care costs per person were larger for smokers than for non-smokers, for each age category. This effect was mainly due to the larger costs of non-smokers for diseases other than tobacco-related diseases. Other investigators, however, criticised these results, and argued that these estimations were not accounted for extra health-related or non-health related costs of smoking, such as costs of recently established smoking-related diseases, passive smoking, fires or sickness absence at work.[107-109] Thus, although the public health benefits of smoking cessation are abundantly clear, which makes it an important topic in public health policy making, the discussion on the impact of smoking cessation on health care costs will continue.

Smoking cessation and other public health interventions

The results reported in this thesis support the well established fact that encouraging smokers to quit is one of the most important interventions for primary prevention in public health. Other public health interventions carried out in primary prevention include, among others, cholesterol lowering medication, antihypertensive treatment and dietary advice. Only few studies compared the public health effects of smoking cessation and other public health interventions in primary prevention.

In Chapter 6 of this thesis, the effect of smoking cessation on life expectancy and on the primary prevention of coronary heart disease was compared with the effects of cholesterol lowering medication (statins), among smokers with a high risk for CHD. It was estimated that smoking cessation would lead to a larger gain in (healthy) life expectancy than cholesterol lowering medication. Even if half of the smokers would quit, still they would gain a few months more than if they all had used statins. The same result was seen in a study in which smoking cessation was compared with a cholesterol lowering intervention through diet.[110] These results could be expected since smoking cessation is beneficial for far more diseases than cholesterol lowering medication is. However, results from merely secondary prevention studies suggest that statins also reduce the risk of stroke.[111] The effect of statins in primary prevention of stroke is not clear, but if statins would be preventive for stroke as well in primary prevention, then the gain in (healthy) life expectancy due to cholesterol lowering medication would have been underestimated in Chapter 6. But, since smoking cessation also reduces cancer risk, it can be expected that the gain in health life expectancy due to smoking cessation would still be larger than that due to cholesterol lowering medication.

When the effects of smoking cessation and cholesterol lowering therapy on primary prevention of CHD was examined in this population of smokers with high risk for CHD, it appeared that smoking cessation led to a less strong (men) or comparable (women) reduction in the expected number of CHD events than cholesterol lowering medication (Chapter 6). Yudkin[112] simulated the effect of smoking cessation and cholesterol lowering and blood pressure lowering medication on CHD mortality, using the MRFIT population as the baseline and assuming that smokers, subjects with a high total cholesterol level and subjects with high blood pressure took part in a corresponding intervention. In this study, smoking cessation would result in a larger reduction in CHD mortality than both cholesterol lowering and blood pressure lowering therapy. The reverse results of this study and of our study described in Chapter 6 may partly be explained by differences in the CHD risk reduction by cholesterol lowering treatment. The reduction in CHD risk due to cholesterol lowering medication in the study of Yudkin was probably based on the

effects of formerly used treatments, which may be less effective than the effects of currently available statins, on which we based our reduction in CHD risk. Furthermore, differences in study population and in the assumption of who would take part in the interventions are likely to account for the conflicting results. In our study, all subjects, who were all smokers, were assumed to give up smoking or to use cholesterol lowering medication. In the estimation of Yudkin, however, the population consisted of both smokers and non-smokers, and about one third (all smokers) were assumed to take part in the smoking cessation intervention compared to only one fifth (all subjects with high cholesterol level) in the cholesterol lowering intervention.

Based on this limited number of studies comparing the public health effects between smoking cessation and cholesterol lowering medication, it is thus suggested that in populations at high CHD risk, cholesterol lowering medication, at least the currently available statins, is more or comparably effective in the primary prevention of CHD than smoking cessation. Nevertheless, in a broader public health perspective, smokers would gain more healthy life years by quitting smoking than by using cholesterol lowering therapy.

In the decision making process on the implementation of and eligibility to public health interventions, besides the effectiveness, the costs of the intervention play a role. For instance, the costs of statins are high (about €225 million on material costs in the Netherlands in 2001[113]), and therefore statins are only indicated for high risk populations in the Netherlands.[114] A useful tool for public health policy makers in this decision making process is the cost-effectiveness, which reflects the costs necessary to save one year of life by the intervention. It was estimated that smoking cessation would be 17 times more cost effective than using cholesterol lowering medication.[115] Tengs et al.[116] reviewed the cost-effectiveness of over 500 public health interventions, including several smoking cessation interventions and cholesterol lowering and blood pressure lowering treatment. Generally, medical interventions in primary prevention were more cost-effective than medical interventions in secondary or tertiary prevention. The costs per life year saved for smoking cessation interventions ranged from money savings (the saved costs due to risk decrease exceed the costs of the intervention), for smoking cessation advice to hospitalised patients with myocardial infarction, to about €9,600 for nicotine gum together with smoking cessation advice for women. In general, cholesterol lowering treatment and blood pressure lowering medication were less cost-effective. The costs per life year saved for most interventions were in the range of about €9,600 to more than €380,000 for cholesterol lowering therapy and €3,800 to €86,000 for

blood pressure lowering medication. However, the completeness of this review is limited by the availability of cost-effectiveness studies in the literature and therefore, due to possible publication bias, not all interventions may be represented in this study.[116]

Conclusion

In conclusion, the results described in this thesis are one of the first to quantify the effects of smoking cessation on future morbidity and mortality. Since the overwhelming evidence that smoking cessation reduces the tobacco-related disease burden, a reduction of the smoking prevalence has been a major target worldwide in public health policy making and numerous smoking cessation interventions have been developed. The quantification of the future public health benefits of smoking cessation are useful to policy makers in order to adjust future health care to changes in smoking behaviour.

Furthermore, in this thesis, the impact of other public health risk factors on the effect of smoking and smoking cessation was examined. Although we have shown that lung cancer mortality among smokers was higher among cultures with high saturated fatty acid intake compared to cultures with low saturated fatty acid intake, there was not enough evidence to conclude whether saturated fatty acid intake, or other dietary factors, enhance the effect of smoking on lung cancer. Moreover, our results suggested that smoking cessation leads to a favourable increase in HDL cholesterol level, which may contribute to the beneficial effect of smoking cessation on CVD mortality, and to unfavourable changes in body weight and, consequently, in total cholesterol and blood pressure level. This implies that favourable effect of smoking cessation on CVD risk may partly be mediated by smoking cessation induced changes in other major CVD risk factors, such as cholesterol level and blood pressure.

Besides reducing the risk for morbidity and mortality, results in this thesis also suggested that smoking cessation improves health-related quality of life, especially mental health. Since the health-related quality of life has great impact on daily living, improved quality of life after smoking cessation may be important in encouraging smokers to quit, also because the beneficial effects may be seen readily after smoking cessation. However, since the causality of the effect of smoking cessation on health-related quality of life is not established yet, this topic needs to be further studied in cohort studies.

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Summary

In the 1960's, the harmful effect of cigarette smoking on lung cancer was definitely established in a report of the Surgeon General in the United States. Since then, numerous studies have conclusively shown that smoking not only causes lung cancer, but also cardiovascular diseases, other types of cancer and chronic obstructive pulmonary disease (COPD). Besides, smoking may lead to poor health-related quality of life. Smoking cessation has been largely established to decrease the risks for tobacco-related diseases, and it is furthermore suggested, although not conclusively shown, that smoking cessation may improve healthy-related quality of life. Despite the overwhelming evidence that smoking cessation decreases future morbidity and mortality, the magnitude of this effect is not clear yet. The aim of this thesis, therefore, is to quantify the future public health benefits of smoking cessation. Furthermore, this thesis aims to give more insight into the impact of smoking cessation on health-related quality of life.

In order to quantify future public health benefits of smoking cessation, it is important to have insight in the association between smoking or smoking cessation and other risk factors for tobacco-related diseases. Therefore, first, the associations between smoking or smoking cessation and the main risk factors for two of the most important tobacco-related diseases, lung cancer and cardiovascular diseases (CVD), were studied. In Chapter 2, the impact of dietary factors on the effect of smoking on lung cancer was examined. This study was performed using ecological data from the Seven Countries Study, a cohort study comprising 12,763 middle-aged men in 16 cohorts from Europe, the United States and Japan. In this study, 25-year lung cancer mortality varied greatly across cohorts with comparable smoking prevalence. Moreover, lung cancer mortality among smokers differed statistically significantly between cultural areas: the lung cancer mortality risk was higher in northern Europe, the United States and inland southern Europe than in Japan. When the impact of dietary intake on the effect of smoking on lung cancer was examined, it appeared that lung cancer mortality among smokers was positively associated with average dietary fat intake, especially for saturated fatty acids. However, since power to detect associations among never smokers was low, we were not able to conclude whether the effects of smoking and dietary saturated fatty acid intake on lung cancer mortality were independent or that effect modification played a role. Population average fruit and vegetable intake was not associated with lung cancer mortality rate among smokers.

We furthermore examined the impact of smoking cessation on the main risk factors for cardiovascular diseases: cholesterol level, blood pressure and body weight (Chapter 3), using longitudinal data, obtained from two examinations of the Doetinchem cohort study. The study population consisted of 20-59 year old Dutch men and women. We found that, compared to persistent smokers, smokers who quit between the first and second examination experienced a larger increase in body weight (excess gain 3.4-3.8 kg), HDL cholesterol level (0.07 mmol/L) and diastolic blood pressure (1.7 mmHg-2.8 mmHg) among both men and women and in total cholesterol level (excess gain 0.17 mmol/L) and systolic blood pressure (2.7 mmHg) among men. The weight gain was larger for heavy than for light smokers who quit. After further adjustment for postcessation weight gain, the difference in the increase in total cholesterol and blood pressure level between quitters and persistent smokers lost statistical significance. The results of this study imply that postcessation increase in HDL cholesterol level may contribute to the beneficial effect of smoking cessation on CVD.

Then, the effect of smoking cessation on future morbidity and mortality was estimated in three studies, by means of computer simulation modelling. The impact of smoking cessation on future pancreatic cancer incidence in the European Union was examined in Chapter 4. Pancreatic cancer is the most fatal tobacco-related type of cancer. For this study, we developed a computer simulation model, Markov multi-state type, using country-specific data on population sizes, smoking behaviour, pancreatic cancer incidence and total mortality rates, corresponding relative risks for ex- and current smokers and probabilities of starting and quitting smoking. This model comprised the simulation period 1994-2015. With this model, we simulated several smoking cessation based targets. It was estimated that if, theoretically, all smokers in the European Union would quit instantly, the number of new pancreatic cancer patients up to 2015 would be reduced by 15%, which corresponds to around 150,000 patients. More feasible was WHO's 'Health for All' target concerning smoking behaviour, which implies that smoking prevalence is reduced to 20% in 2015 in each member state of the EU. This target was expected to give a reduction in pancreatic cancer cases up to 2015 of 29,500 males (5.7%) and 9,500 females (2.0%).

The same model was used to examine the impact of smoking cessation on total mortality and mortality from the currently established tobacco-related diseases, which are coronary heart disease, stroke, several types of cancer and COPD (Chapter 5), using mortality rates stead of incidence rates. The WHO's Health for All target was expected to reduce the number of total deaths up to 2015 with 2.5%

(around 1.1 million deaths) among men and 0.8% (almost 350,000 deaths) among women. The largest effect of smoking cessation would be reached for lung cancer mortality, which was estimated to decline by around 11% among men and 8% among women. Mortality from COPD would increase slightly among men (0.8%). This may be explained by the small difference between the relative risks of smokers and ex-smokers for COPD, which makes the reduction in COPD mortality too small to counterbalance the increase in COPD through a higher number of people at risk. Among women, it was estimated that the number of deaths from COPD would decrease following smoking cessation. The expected declines in mortality in this Health for All target were about 30% (among women) to 50% (among men) of those in the situation that all smokers would quit instantly.

In Chapter 6, the impact of smoking cessation on coronary heart disease (CHD) and healthy life expectancy was compared with the impact of another public health intervention: cholesterol lowering medication. The study population for this study consisted of 40-74 year old smokers without hyperlipidemia, cardiovascular diseases and diabetes mellitus, who participated in the MORGEN study (for subjects aged 40-59 years, men only), which is a cross-sectional study among inhabitants of three Dutch towns, or in the baseline examination of the Rotterdam Study (for subjects aged 60-74 years), which is a longitudinal study in an urban district in Rotterdam, the Netherlands. For our study, we selected all smokers eligible for cholesterol lowering therapy for primary prevention, according to the Dutch Consensus Cholesterol. This Consensus is based on the absolute risk for coronary heart disease according to the Framingham risk function. Results were extrapolated to the total Dutch population with the characteristics mentioned. If all subjects, in our population of smokers with a high CVD risk, would give up smoking, the number of subjects eligible for cholesterol lowering medication in this group would decrease by about 75%. Among men, the estimated reduction in CHD events after smoking cessation was 11% (40-59 year old men) and 22% (60-74 year old men) less than that obtained through using cholesterol lowering medication. Among 60-74 year old women, the expected reduction in CHD events was comparable for smoking cessation and cholesterol lowering medication. However, smokers were expected to gain 2-2.5 healthy life years more by quitting smoking than by using cholesterol lowering medication, since smoking cessation is favourable for the primary prevention of much more diseases than CHD. Obviously, these effects of smoking cessation were less pronounced when less strong smoking cessation interventions were simulated.

Finally, the impact of smoking cessation on health-related quality of life was examined, using cross-sectional data from the MORGEN study (Chapter 7). For this study, subjects with history of tobacco-related diseases were excluded. Ex-smokers reported similar quality of life scores than never smokers, except for the dimension bodily pain, and reported statistically significantly higher quality of life scores than current smokers, also with the exception of the dimension bodily pain. The difference between the quality of life scores of ex- and current smokers was more pronounced for mental health than for physical health, especially for the mental health dimension role functioning limitations due to emotional problems, for which the difference was 6.5 points ($p<0.001$). Among current smokers, amount of smoking was inversely related to health-related quality of life scores for all the eight quality of life dimensions ($p<0.001$). Among ex-smokers, amount of smoking was inversely related and number of years since quitting was positively related to quality of life scores for some of the dimensions, but the associations were weak. Finally, when the impact of amount of smoking and time since quitting on the difference in quality of life between ex- and current smokers was examined, we showed that, generally, the higher the amount of smoking, the larger were the differences between the quality of life scores of ex- and current smokers (p for trend < 0.05 when ex-smokers had quit < 5 or ≥ 10 years ago). We observed no trend with time since quitting. Although no conclusions on the causality of these findings can be drawn from this cross-sectional study, these results suggest that smoking cessation may improve health-related quality of life, which may play a role in encouraging smokers to quit. However, more results from cohort studies are needed to fully explore this association.

In conclusion, results described in this thesis are one of the first to quantify the effects of smoking cessation on future morbidity and mortality. These results are useful to policymakers in order to adjust future health care to changes in smoking behaviour. Furthermore, this thesis provides evidence that smoking cessation leads to a favourable increase in HDL cholesterol level and to unfavourable changes in body weight and, consequently, in total cholesterol and blood pressure level. This implies that the favourable effect of smoking cessation on the risk for cardiovascular diseases may partly be mediated by smoking cessation induced changes in other classical CVD risk factors, such as cholesterol level and blood pressure. Finally, besides the favourable effect on morbidity and mortality, our results suggest that smoking cessation also may improve health-related quality of life, especially in the field of mental health, but this finding needs to be confirmed in cohort studies.

Samenvatting

Met het verschijnen van het eerste Surgeon General rapport in de Verenigde Staten over de gezondheidseffecten van roken, werd in de jaren ’60 definitief vastgesteld dat roken longkanker kan veroorzaken. Sindsdien hebben vele studies aangetoond dat roken niet alleen leidt tot longkanker, maar ook tot hart- en vaatziekten, andere vormen van kanker en COPD (chronic obstructive pulmonary disease). Daarnaast zijn er aanwijzingen dat roken kan leiden tot een verminderde aan gezondheid gerelateerde kwaliteit van leven. Stoppen met roken leidt tot een daling in het risico voor tabaksgerelateerde ziekten. Of stoppen met roken ook de kwaliteit van leven verbetert is nog onduidelijk, hoewel resultaten van enkele studies dit wel suggereren. Ondanks het overweldigende bewijs dat stoppen met roken de ziekte- en sterftelast in de toekomst vermindert, is de totale omvang van deze positieve effecten op de volksgezondheid nog niet bekend. Het doel van dit proefschrift is het kwantificeren van het effect van stoppen met roken op de ziekte- en sterftelast in de toekomst. Verder heeft dit proefschrift als doel meer inzicht te verschaffen in de impact van stoppen met roken op de aan gezondheid gerelateerde kwaliteit van leven.

Om het effect van stoppen met roken op ziekte en sterfte in de toekomst te kwantificeren, is het belangrijk om inzicht te hebben in de associatie tussen roken of stoppen met roken en andere risicofactoren voor tabaksgerelateerde ziekten. Daarom zijn eerst de associaties onderzocht tussen roken of stoppen met roken en de belangrijkste risicofactoren voor de twee voornaamste tabaksgerelateerde ziekten: longkanker en hart- en vaatziekten (HVZ). In Hoofdstuk 2 is de invloed van voeding op het effect van roken op longkankersterfte bestudeerd. In deze studie is gebruik gemaakt van ecologische gegevens van de Zeven Landen Studie, een multi-centrum studie onder 12.763 mannen van middelbare leeftijd in 16 cohorten uit Europa, de Verenigde Staten en Japan. De 25-jaars longkankersterfte varieerde in dit onderzoek sterk tussen cohorten met een vergelijkbaar percentage rokers. Verder verschilde de longkankersterfte onder rokers tussen de verschillende regio’s: het longkankersterfte risico was statistisch significant hoger in noord Europa, zuid Europa en de Verenigde Staten dan in Japan. Vervolgens werd de invloed van voeding op het effect van roken op de longkanker sterfte bestudeerd. Er kwam naar voren dat longkankersterfte onder rokers positief geassocieerd was met de gemiddelde vet inname, met name voor verzadigde vetzuren. Echter, door de lage power om associaties aan te tonen bij nooit rokers, konden we hier niet uit opmaken of de effecten van roken en de inname van verzadigde vetzuren op

longkankersterfte onafhankelijk van elkaar optraden of dat effect modificatie een rol speelde. Groente en fruit inname was niet geassocieerd met longkankersterfte onder rokers.

In Hoofdstuk 3 is het effect beschreven van stoppen met roken op de belangrijkste risicofactoren voor hart- en vaatziekten: cholesterol en bloeddruk niveau en lichaamsgewicht. Hierbij hebben we gebruik gemaakt van longitudinale gegevens, welke afkomstig waren van twee meetpunten van het Doetinchem cohort. De studiepopulatie bestond uit 20-59 jarige Nederlandse mannen en vrouwen. In vergelijking met blijvende rokers, ondervonden rokers die stopten met roken tussen het eerste en tweede meetpunt een grotere stijging in lichaamsgewicht (extra stijging 3,4-3,8 kg), HDL cholesterolgehalte (0,07 mmol/L) en diastolische bloeddruk (1,7 mmHg-2,8 mmHg), bij zowel mannen als vrouwen, en in totaal cholesterolgehalte (extra stijging 0,17 mmol/L) en systolische bloeddruk (2,7 mmHg), bij alleen mannen. De stijging in lichaamsgewicht was groter voor zware dan voor lichte rokers die stopten. Na correctie voor gewichtstoename was het verschil in stijging in totaal cholesterolgehalte en bloeddruk tussen stoppers en blijvende rokers niet meer statistisch significant. Deze resultaten suggereren dat een stijging in HDL cholesterolgehalte na stoppen met roken bijdraagt tot het gunstige effect van stoppen met roken op risico voor hart- en vaatziekten.

Vervolgens is het effect van stoppen met roken op ziekte en sterfte in de toekomst geschat in drie onderzoeken, met behulp van computer simulatie modellen. De impact van stoppen met roken op pancreaskanker incidentie in de Europese Unie (EU) is gerapporteerd in Hoofdstuk 4. Pancreaskanker heeft van de aan tabak gerelateerde vormen van kanker de laagste overlevingskansen. Voor deze studie hebben we een computer simulatie model ontwikkeld, gebaseerd op het Markov multi-state model, waarbij landspecifieke gegevens over bevolkingsomvang, rookgedrag, pancreaskanker incidentie en totale sterfte cijfers, corresponderende relatieve risico's voor ex- en huidige rokers en kansen om te beginnen en te stoppen met roken zijn gebruikt. Dit model omvatte de periode 1994-2015. Met dit model hebben we verschillende op stoppen met roken gebaseerde strategieën gesimuleerd. We hebben geschat dat indien, in theorie, alle rokers in de EU direct zouden stoppen met roken, het aantal nieuwe pancreaskanker patiënten tot en met 2015 gereduceerd zou worden met 15%, wat zou neerkomen op een totaal van ongeveer 150.000 patiënten. Beter haalbaar was het doel van de WHO aangaande rookgedrag, dat beschreven is in de 'Health for All' strategie van de WHO. Hiervoor werd het percentage rokers gereduceerd tot 20% in 2015, in ieder land van de EU.

Dit Health for All doel gaf een verwachte reductie in het aantal pancreaskanker patiënten tot en met 2015 van 29.500 mannen (5,7%) en 9.500 vrouwen (2,0%).

Hetzelfde model is gebruikt om het effect te schatten van stoppen met roken op de totale sterfte en sterfte aan de op dit moment bekende aan tabak gerelateerde ziekten, zoals coronaire hartziekten, beroerte, verschillende vormen van kanker en COPD (Hoofdstuk 5), waarbij sterftecijfers in plaats van incidentiecijfers zijn gebruikt. In deze studie is geschat dat het Health for All doel van de WHO het totale aantal sterfgevallen tot en met 2015 reduceert met 2,5% (ongeveer 1,1 miljoen sterfgevallen) bij mannen en met 0,8% (bijna 350.000 sterfgevallen) bij vrouwen. Het grootste effect zou worden bereikt voor longkankersterfte, waarbij de geschatte daling ongeveer 11% bij mannen en 8% bij vrouwen was. Verder werd geschat dat de sterfte aan COPD bij mannen licht zou stijgen (0,8%). Dit kan verklaard worden door het kleine verschil tussen de relatieve risico's van rokers en ex-rokers voor COPD, waardoor de reductie in COPD sterfte te klein wordt om tegenwicht te bieden aan de stijging in COPD door een groter aantal personen at risk. Bij vrouwen zou het aantal sterfgevallen door COPD afnemen door stoppen met roken. De verwachte daling in sterfte in dit Health for All doel was ongeveer 30% (vrouwen) tot 50% (mannen) van de verwachte sterftedaling indien alle rokers direct zouden stoppen met roken.

In Hoofdstuk 6 is het effect van stoppen met roken op coronaire hartziekten (CHZ) en op gezonde levensverwachting vergeleken met de impact van een andere volksgezondheidsinterventie: cholesterol verlagende medicatie. De studiepopulatie voor dit onderzoek bestond uit 40-74 jarige rokers zonder hyperlipidemie, hart- en vaatziekten en diabetes mellitus, die deelgenomen hebben aan het MORGEN-project (voor 40-59 jarigen, alleen mannen), een cross-sectionele studie onder een aselecte steekproef van inwoners in Amsterdam, Doetinchem en Maastricht, of aan de baseline meting van het ERGO onderzoek (voor 60-74 jarigen), een longitudinale studie onder bewoners van de wijk Ommoord, Rotterdam. Voor ons onderzoek selecteerden we alle rokers die volgens de CBO Consensus Cholesterol in aanmerking komen voor cholesterolverlagende medicatie in het kader van primaire preventie. Deze consensus is gebaseerd op het 10-jaars absolute risico voor CHZ, volgens de Framingham risicofunctie. De resultaten zijn geëxtrapoleerd naar de totale Nederlandse bevolking met genoemde karakteristieken. Als alle personen, in deze groep van rokers met een hoog CHZ risico, zouden stoppen met roken, dan zou het aantal personen dat voor cholesterolverlagende medicatie in aanmerking komt, in deze groep, dalen met ongeveer 75%. De geschatte reductie in CHZ gevallen bij mannen was 11% (40-59 jaar) en 22% (60-74 jaar) lager na stoppen met roken dan na gebruik van cholesterolverlagende medicatie. Bij 60-74 jarige

vrouwen was de verwachte reductie in CHZ gevallen vergelijkbaar tussen stoppen met roken en cholesterolverlagende medicatie. Echter, rokers zouden 2-2,5 gezonde levensjaren meer winnen door te stoppen met roken dan door cholesterolverlagende medicatie te gebruiken, doordat stoppen met roken gunstig is voor primaire preventie van meer ziekten dan CHZ. Uiteraard was het effect van stoppen met roken minder sterk bij minder krachtige stoppen met roken interventies.

Tot slot is de impact van stoppen met roken op aan gezondheid gerelateerde kwaliteit van leven bestudeerd, met behulp van cross-sectionele gegevens uit het MORGEN-project (Hoofdstuk 7). Voor dit onderzoek zijn personen met een geschiedenis van aan tabak gerelateerde ziekten uitgesloten. Ex-rokers rapporteerden vergelijkbare scores voor kwaliteit van leven als nooit rokers, met uitzondering van de dimensie ‘pijn’, en rapporteerden statistisch significant hogere scores voor kwaliteit van leven dan huidige rokers, eveneens met uitzondering van de dimensie ‘pijn’. Het verschil tussen de scores voor kwaliteit van leven van ex- en huidige rokers was groter voor mentale dan voor lichamelijke gezondheid. Dit gold vooral voor de mentale gezondheidsdimensie ‘rolbeperkingen door emotionele problemen’, waarbij het verschil 6,5 punt ($p<0,001$) bedroeg. Binnen de huidige rokers was het aantal gerookte sigaretten per dag omgekeerd evenredig gerelateerd aan scores voor gezondheidsgerelateerde kwaliteit van leven voor alle acht dimensies van kwaliteit van leven ($p<0,001$). Binnen de ex-rokers was het aantal gerookte sigaretten per dag omgekeerd evenredig en het aantal jaar gestopt positief gerelateerd aan scores voor kwaliteit van leven voor enkele dimensies, maar deze associaties waren zwak. Tenslotte werd het effect van het aantal gerookte sigaretten per dag en het aantal jaar gestopt op het verschil in kwaliteit van leven tussen ex- en huidige rokers bestudeerd. Hierbij kwam naar voren dat, over het algemeen, hoe meer sigaretten per dag gerookt werden, hoe groter de verschillen waren in kwaliteit van leven tussen ex- en huidige rokers (p trend < 0,05 als ex-rokers < 5 of $\geq$ 10 jaar geleden zijn gestopt). We hebben geen trend gevonden voor aantal jaren gestopt. Hoewel geen conclusies over de causaliteit van deze bevindingen getrokken kunnen worden uit deze cross-sectionele gegevens, suggereren de resultaten dat stoppen met roken de kwaliteit van leven kan verbeteren. Dit zou rokers mede kunnen aanmoedigen te stoppen met roken. Er zijn echter meer gegevens nodig uit cohort studies om deze associaties te verhelderen.

De resultaten die beschreven zijn in dit proefschrift zijn een van de eerste die het effect van stoppen met roken op de ziekte- en sterftelast in de toekomst kwantificeren. Deze informatie is voor beleidsmakers van groot belang om de

toekomstige gezondheidszorg aan te kunnen passen aan veranderingen in rookgedrag. Verder toont dit proefschrift aan dat stoppen met roken leidt tot een gunstige stijging in het HDL cholesterolgehalte en tot ongunstige veranderingen in lichaamsgewicht en, daaruit voortkomend, in totaal cholesterolgehalte en bloeddruk. Dit suggereert dat het gunstige effect van stoppen met roken op het risico voor hart- en vaatziekten deels wordt beïnvloed via door stoppen met roken geïnduceerde veranderingen in andere belangrijke risicofactoren voor HVZ, zoals cholesterolgehalte en bloeddruk. Tot slot geven onze resultaten aanwijzingen dat stoppen met roken, naast een gunstig effect op ziekte en sterfte, ook de kwaliteit van leven zou kunnen verbeteren, vooral op het gebied van mentale gezondheid, maar deze bevinding zal bevestigd moeten worden in cohort studies.

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About the author

Ina Mulder was born on 7 October 1972 in ‘t Harde, the Netherlands. She completed secondary school (VWO) at the ‘RSG de Springborn’ in Epe in 1990. During 1990 through 1996, she studied Human Nutrition at Wageningen University. As a part of this study, she conducted research projects in the fields of human nutrition, epidemiology and health education. Furthermore, she had a practical training at the Cardiovascular Research Unit of the University of Edinburgh, Scotland. She received her MSc degree in August 1996. At the beginning of 1997, she started her PhD project on the public health impact of smoking and smoking cessation at the Centre for Prevention and Health Services Research of the National Institute of Public Health and the Environment, Bilthoven. The results of this PhD project are described in this thesis. In 1999, she obtained her MSc in Epidemiology at the Netherlands Institute for Health Sciences in Rotterdam. During her PhD project, she spent three months at the Institute for Global Tobacco Control, Johns Hopkins School of Public Health, Baltimore, USA, in 2000. Since May 2001, she works as an epidemiologist at the Comprehensive Cancer Centre Amsterdam and the National Cancer Institute in Amsterdam.

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