The impact of smoking on future pancreatic cancer: A computer simulation

Department of Chronic Disease Epidemiology, National Institute of Public Health and the Environment, Bilthoven, The Netherlands

Summary

Background: We studied the impact of several smoking cessation-based scenarios on future pancreatic cancer incidence in the European Union by means of computer simulation.

Material and methods: Among other data, published data on pancreatic cancer incidence rate and smoking prevalence in ten member states of the European Union, and on the relative risk of smoking were entered into a simulation model. Four different scenarios were simulated: one reference scenario, one based on theoretically maximal smoking reduction and two feasible scenarios based on WHO's Health for All targets. In each scenario, pancreatic cancer incidence was computed from 1994 up to the year 2020. Results were extrapolated to the European Union as a whole.

Results: When the percentage of smokers remains unchanged, 627,000 and 588,000 newly diagnosed pancreatic cancer cases among males and females respectively will arise in the European Union up to 2020. Theoretically, if all smokers would give up smoking instantly, this number can be reduced by 133,000 cases among men and 43,000 cases among women. In more feasible scenarios up to 35,500 male and 32,500 female pancreatic cancer cases can be prevented.

Conclusion: Giving up smoking substantially reduces future burden of pancreatic cancer up to almost 68,000 patients in the European Union up to the year 2020.

Key words: computer simulation, European Union, pancreatic cancer incidence, public health, smoking

Introduction

In the European Union (EU), more than 30,000 new pancreatic cancer cases are diagnosed each year in the 1990s [1]. In northern Europe, the incidence rate is about twice as high as in most southern European countries [1, 2]. Cancer of the pancreas is one of the most rapidly fatal cancers, 85% of the cases dies within 1 year [3]. This makes pancreatic cancer the sixth leading cause of cancer mortality among both men and women in the EU [4].

Tobacco smoking is consistently reported as a risk factor for pancreatic cancer. Case-control as well as cohort studies have shown that the risk of pancreatic cancer among smokers is about 1.5-3 fold the risk among never smokers [5-18]. Giving up smoking reduces the risk of pancreatic cancer [11, 12]. It is estimated that within 10-15 years after smoking cessation the risk of pancreatic cancer is reduced to that of a never smoker [6, 8, 11].

Anti-smoking policy measures may thus be of great help to reduce the pancreatic cancer burden in the future. In the Health for All (HFA) policy document of 1998, the World Health Organisation (WHO) sets out targets for future public health policy in the European region. One of these targets is to reduce the percentage of smokers by encouraging smokers to quit; it is stated that there should be at least 80% non-smokers in all countries in over 15 year-olds by the year 2015 [19]. In the present study we simulated this target and other public health targets and examined their impact on future pancreatic cancer incidence in the European Union by means of a computer simulation model.

Methods

Simulation model

To simulate several smoking cessation-based public health targets and examine their effect on future pancreatic cancer incidence, we developed a simulation model [20] with the age- and sex-specific size of the population in ten member states of the European Union in 1994 as the base population [21] (Table 1). To describe the demographic changes over time, including birth, ageing, and mortality, we used the age- and sex-specific projections of the population in each member state for each calendar year until 2050, as calculated by the United Nations [21]. Data on the age- and sex-specific incidence rate of pancreatic cancer and smoking prevalence in each member state, and on the sex-specific relative risk of smoking were used to estimate the age- and sex-specific pancreatic cancer incidence rate in the first year of simulation (1994) among smokers and non-smokers separately. This incidence rate was kept constant in the subsequent years. Then, for several scenarios, each representing a different public health target based on smoking reduction, the incidence rate among smokers and non-smokers, the scenario-specific smoking prevalence and information on the lag-time of smoking cessation were used to compute the number of incident pancreatic cancer cases for men and women in the member states of the EU. Five member states of the EU, Belgium, Luxembourg, Portugal, Greece, and Ireland, were excluded from analyses, because sufficient information on the pancreatic cancer incidence rate or the age-specific percentage of smokers was not available.

Sources of information

Incidence of pancreatic cancer

Information on the age- and sex-specific incidence rate of pancreatic cancer (ICD-9 157) in the ten member states of the EU was obtained from the International Agency for Research on Cancer (IARC) (Table 1). The method of data collection is described in detail elsewhere [22]. Data reflect all newly diagnosed pancreatic cancer cases per 100,000 person-years in 5-year age-classes, in periods centred on 1990. In Denmark, Finland, the Netherlands, and Sweden, information was derived from national cancer registries. In France, Italy, and Spain data were only available from 8, 13, and 9 regional cancer registries respectively, which were spread over the country. In Germany, pancreatic cancer incidence data were obtained from East Germany and from the region of Saarland, West Germany. For the United Kingdom, incidence rates were derived from England/Wales and...
Scotland. To approximate the national age- and sex-specific pancreatic cancer incidence rate in these countries, we averaged the incidence rate over the different regions, weighted by the size of the population in the specific regions. In Austria, information about pancreatic cancer incidence was only available from the region of Tyrol. The national pancreatic cancer incidence rate in this country was obtained by extrapolating the incidence rate of Tyrol to the population of the whole country.

The quality of the data from the different cancer registries has been evaluated by IARC, using several criteria, including the percentage of morphological verified cases (MV%) and the mortality/incidence ratio (M/I) [22]. Despite the fact that all cancer registries need to provide cancer incidence data with an overall adequate quality to be included in IARC evaluation by IARC, using several criteria, including the percentage of morphological verified cases (MV%) and the mortality/incidence ratio (M/I) [22]. Despite the fact that all cancer registries need to provide cancer incidence data with an overall adequate quality to be included in IARC evaluation, using several criteria, including the percentage of morphological verified cases (MV%) and the mortality/incidence ratio (M/I) [22].

In the study of Fuchs et al., data of two cohort studies were re-analysed. In this scenario the current age- and sex-specific smoking prevalences and pancreatic cancer incidence rates were used for all subsequent years.

For each country we used the following criteria: the relative risk should have been calculated with data from a large cohort study, a way that the pancreatic cancer incidence rate in 2020 was 15% less than the present incidence rate. To achieve this value, we simulated a decrease of the sex-specific smoking prevalence each year, proportionally over the successive years and over the age-classes. In some member states, the composition of smokers among women was already 20% or less at the beginning of the simulation. In this case the age-specific smoking prevalence among women remained unchanged in this scenario.

The lag-time of smoking cessation is reported to be 10-15 years [6, 8, 11]. We used the most conservative, upper value of 15 years in our model. We assumed that within 15 years after cessation, the relative risk among quitters decreases linearly from the relative risk of a smoker to 1.

### Scenarios

We simulated four different smoking cessation-based scenarios: one reference scenario and three alternative scenarios.

In the 'reference scenario' the smoking prevalence remained unchanged. In this scenario the current age- and sex-specific smoking prevalences and pancreatic cancer incidence rates were used for all subsequent years. In the 'maximum scenario' we simulated that all smokers in a country would quit smoking in the first year of simulation (1994). In this scenario the theoretical maximum number of preventable pancreatic cancer cases can be calculated.

The 'HFA-smoking scenario' is a reformulation of the Health for All target with respect to tobacco smoking, which implies that the prevalence of non-smokers should be at least 80% by the year 2015 [19]. In this scenario we simulated a reduction of the percentage of smokers (male and female) down to 20% in each country by the year 2015. This was achieved by reducing the sex-specific smoking prevalence each year, proportionally over the successive years and over the age-classes. In some member states, the percentage of smokers among women was already 20% or less at the beginning of the simulation. In this case the age-specific smoking prevalence among women remained unchanged in this scenario.

The 'HFA-cancer scenario' was based on the HFA target implying that the total cancer mortality should be reduced with 15% by the year 2020 [19]. We applied this reduction of 15% to pancreatic cancer incidence in such a way that the pancreatic cancer incidence rate in 2020 was 15% less than the present incidence rate. To achieve this value, we simulated a decrease of the sex-specific smoking prevalence each year, proportionally over the successive years and over the age-classes. This resulted in a reduction of the smoking prevalence to a range of 8.5% in Sweden to 29% in Denmark among men. Because of much lower smoking prevalence, among women this reduction of 15% by 2020 was not met in six member states (Austria, France, Germany, Italy, Spain, and Sweden), even though we simulated a reduction of the smoking prevalence to zero. In the other member states the smoking prevalence was reduced to a range of 2% in the United Kingdom to 19% in Denmark among women.

### Model outcome variables

For each time-step of one year the model computed the total number of incident cases of pancreatic cancer among men and women, for the ten member states and for each scenario separately from the first year of simulation (1994) up to the year 2020. The number of cancer cases was cumulated over time to obtain the total number of incident pancreatic cancer cases in this period. For each alternative scenario, we computed the absolute and relative reduction of the cumulated number of pancreatic cases as compared to the 'reference scenario'.

For each scenario, the number of pancreatic cancer cases in the EU as a whole was estimated by applying the age-, sex-, and scenario-specific pancreatic cancer incidence rates from adjacent countries to the population of the remaining EU member states. The incidence rate of the United Kingdom was applied to the population of Ireland, the rate of Spain to Portugal, and the average incidence rate from Germany and the Netherlands to the member states Belgium and Luxembourg. We applied
the average incidence rate over the ten member states to the population of Greece, because no adjacent countries of Greece were present in this study. Subsequently, the absolute reduction of the cumulated number of pancreatic cancer cases in the EU was estimated until the year 2050.

Results

The estimated number of pancreatic cancer cases cumulated up to the year 2020 in the ‘reference scenario’ ranged from 10,000 to more than 145,000 and 132,000 in men and women respectively in the EU member states (Table 2). In the European Union, around 627,000 and 588,000 new pancreatic cancer cases in men and women respectively was observed in the ‘HFA-cancer scenario’. The absolute number of preventable pancreatic cancer cases, as compared to the reference scenario, ranged from 105 to around 6,600 (Figure 1). The relative reduction of pancreatic cancer cases in this scenario ranged between 5.5% and 6.0%. Among women, the absolute reduction of pancreatic cancer cases in this scenario was lower than among men, mainly because of the lower percentage of smokers among women (Figure 1). The relative reduction of pancreatic cancer cases ranged from 3.5% in Spain to 21% in Denmark.

More feasible is the ‘HFA-smoking scenario’. In this scenario, the absolute number of preventable pancreatic cancer cases up to the year 2020 in men, as compared to the reference scenario, ranged from 105 to around 6,600 (Figure 1). The lowest relative reduction, 0.6% was again seen in Sweden, the highest, 11%, in Denmark. Because the percentage of smokers among women was already around 20% in most countries, in females the ‘HFA-smoking scenario’ did not lead to a reduction of pancreatic cancer cases, except for Sweden (0.5% reduction as compared to the reference scenario), the United Kingdom (1.3%), the Netherlands (1.8%), and Denmark (6.5%) (Figure 1).

The absolute number of preventable pancreatic cancer cases up to 2020 in the ‘HFA-cancer scenario’ ranged from 560 to 2,600 to over 29,000 male cases would be prevented until 2020 (Figure 1). The relative reduction of pancreatic cancer cases was highest in Denmark: the absolute reduction of 3,200 pancreatic cancer cases (Figure 1) corresponded to a relative reduction of almost 32%, as compared to the ‘reference scenario’. Sweden showed the lowest relative reduction (18%). Among women, the absolute reduction of pancreatic cancer cases in this scenario was lower than among men, mainly because of the lower percentage of smokers among women (Figure 1). The relative reduction of pancreatic cancer cases ranged from 3.5% in Spain to 21% in Denmark.

Table 2. Estimated number of pancreatic cancer cases cumulated up to the year 2020 in men and women in the ‘reference scenario’.

<table>
<thead>
<tr>
<th></th>
<th>men</th>
<th>women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark</td>
<td>10,014</td>
<td>10,555</td>
</tr>
<tr>
<td>Finland</td>
<td>11,685</td>
<td>13,004</td>
</tr>
<tr>
<td>Austria</td>
<td>13,047</td>
<td>18,299</td>
</tr>
<tr>
<td>Sweden</td>
<td>17,086</td>
<td>18,132</td>
</tr>
<tr>
<td>the Netherlands</td>
<td>25,660</td>
<td>22,643</td>
</tr>
<tr>
<td>Spain</td>
<td>53,759</td>
<td>47,081</td>
</tr>
<tr>
<td>France</td>
<td>68,099</td>
<td>51,935</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>107,518</td>
<td>106,149</td>
</tr>
<tr>
<td>Italy</td>
<td>131,736</td>
<td>121,679</td>
</tr>
<tr>
<td>Germany</td>
<td>145,477</td>
<td>132,386</td>
</tr>
<tr>
<td>European Union</td>
<td>627,325</td>
<td>588,460</td>
</tr>
</tbody>
</table>

Discussion

The results of our simulation indicate that, theoretically, if all smokers would quit smoking instantly, more than 175,000 pancreatic cancer cases could be prevented in the European Union up to the year 2020. In more realistic scenarios, like the Health for All targets of the WHO, until the year 2020 the number of pancreatic cancer cases could be reduced substantially, up to almost 68,000 in the ‘HFA-cancer scenario’.

Obviously, our simulation model is a simplified reflection of real life. For instance, our base population did not contain a group of former smokers, because information about the percentage of former smokers in the member states of the European Union was insufficient. This will have influenced the absolute number of new pancreatic cancer cases in the alternative scenarios and, consequently, the reduction of pancreatic cancer cases as compared to the reference scenario. Also, we assumed the group of smokers to be homogeneous, whereas in real life risks vary according to the number of cigarettes smoked. Other simplifications of our model include the assumption of no time trend in the percentage of smokers and in the pancreatic cancer incidence rate. However, simplifications are inevitable in simulation modelling.

Some input variables of our model need further attention. First, although information about the smoking prevalence was derived from national surveys in all member states, each member state had its own method of data collection, which could influence the comparability of the data. For example, in France and the United Kingdom, sampling was done from among households, whereas in other countries a random sample was drawn from individuals. Besides, two different definitions of smoking were used in the member states. In Austria and the United Kingdom, smoking included cigarette smoking only, whereas in other member states smoking was defined as smoking all sorts of tobacco, including pipe and cigars. However, we do not expect that these differences between the member states are of great influence on our results.

Moreover, differences in quality of incidence will have influenced our findings. For instance, four of the cancer registries in France, which provided pancreatic cancer incidence data in our study, showed an unfavourably high mortality/incidence ratio (more than 200%) for pancreatic cancer. The pancreatic cancer incidence rates in these registries were among the lowest as compared to the other French cancer registries for which the M/I ratio was closer.
A value of 10 year, which is also mentioned in the literature, lag-time of smoking cessation, we used a value of 15 year. These values were lower among women. For the both the ‘HFA-smoking scenario’ and the ‘HFA-cancer scenario’. These values were lower among women. For the ‘HFA-smoking scenario’ and the ‘HFA-cancer scenario’, which were more feasible scenarios, a substantial reduction of the pancreatic cancer incidence can also be achieved. In these scenarios, around 34,000 and 67,000 pancreatic cancer cases respectively could be prevented in the EU, which is 19% and 38% respectively of the theoretical maximum. The lower percentage of smokers among women, their lower pancreatic cancer incidence rate and the lower relative risk as compared to men, explains the lower number of preventable pancreatic cancer cases among women than among men in all three alternative scenarios. Expressing our results in terms of number of life-years lost did not change the relative position of the member states in the range of the effect of the different scenarios.

Although several studies simulated the effect of smoking and smoking cessation on lung cancer [28-30], to our knowledge, no other studies were published in which the effect of smoking and smoking cessation on future pancreatic cancer was simulated. Parkin et al. [1] computed projections of the number of pancreatic cancer cases until 2020, which can be compared to our ‘reference scenario’. As one would expect, their values of the future number of pancreatic cancer cases in Denmark, Finland, the Netherlands, and Sweden were closely resembled to the values we computed in our ‘reference scenario’, since in both studies national incidence data were used for these countries. Because Parkin et al. [1] estimated the national pancreatic cancer incidence rate from national mortality data in the other member states of the EU, our results for these countries differed in the same direction as mentioned earlier for the pancreatic cancer incidence rate.

A reduction of the percentage of smokers, can be achieved by several policy measures, including anti-smoking campaigns and tax measures. Warner [31] estimated that the percentage of smokers in the United States in 1985 would have been more than 15 percentpoints higher in the absence of anti-smoking campaigns. Another study found a decrease in the smoking prevalence of around ten percentpoints among students in a school based anti-smoking program [32]. Furthermore, it is reported that a one percent increase in the price of cigarettes by tax measures, can decrease the smoking prevalence by around 0.08%-0.18% among males and around 0.09%-0.23% among females [33, 34]. Among youth, this decline is larger [35, 36]. A restriction of the tobacco advertising and a ban on smoking in public places are other policy measures to reduce the percentage of smokers.

A decrease in the smoking prevalence is an important factor in the reduction of the pancreatic cancer incidence rate. However, although smoking is the most consistently reported risk factor for pancreatic cancer, it is not the only factor which is related to this cancer site. A number of dietary factors are reported to be associated with pancreatic cancer, including an increased intake of carbohydrate, cholesterol, and meat, and a decreased intake of fruit and vegetables, dietary fibre, and vitamin C [37]. This indicates to 100%, which suggests that the incidence registration in these four registries may be incomplete. Exclusion of these registries resulted in an increase of the number of preventable cancer cases of around 19% for both men and women in France.

Furthermore, for the EU member states without national cancer registries, we approximated the national pancreatic cancer incidence rate from regional incidence data. This may lead to an over- or underestimation of the national pancreatic cancer incidence rate in these countries, if the regional data were not representative for the whole country. This concerns mainly Austria, for which the national incidence rate was estimated from data of only one cancer registry, and Germany, for which just one cancer registry in western Germany was available. In other studies, the national incidence rates in EU member states without national cancer registries were estimated from national mortality data, which are available for much more countries [1, 27]. With this method, higher pancreatic cancer incidence rates were found in Austria and among males in France, and slightly lower incidence rates in Germany, Italy and Spain [1, 27]. Implementation of these estimations in our model resulted in a number of preventable cases up to 60,000 in the ‘HFA-cancer scenario’ in the EU up to 2020, compared to almost 68,000 preventable cases calculated with our method. However, mortality data on pancreatic cancer are considered to be less accurate than incidence data, which indicates that approximation of the national incidence data based on mortality data may also lead to an estimation error in the national pancreatic cancer incidence rate.

Finally, from the range of published relative risks for smoking on pancreatic cancer we chose the values presented in the study of Fuchs et al. [11] for the reasons mentioned. Additional sensitivity analysis with respect to the relative risk showed that even a 50% change in the relative risk (for example from 3 to 4.5 in men) did not greatly influence the cumulated number of cases in the EU. Among men, the cumulated number of cases would change with 2%-4% in both the ‘HFA-smoking scenario’ and the ‘HFA-cancer scenario’. These values were lower among women. For the lag-time of smoking cessation, we used a value of 15 year. A value of 10 year, which is also mentioned in the literature, would decrease the number of cumulated cases with maximally 2% among men and 1% among women in the Health for All based scenarios.

Figure 1. Absolute reduction of the estimated number of pancreatic cancer cases cumulated up to the year 2020 in three alternative scenarios as compared to the reference scenario, among men and women.

---
that a reduction of the pancreatic cancer incidence rate, as we simulated in the ‘HPA-cancer scenario’, may also be achieved by a change in dietary habits. Several studies investigated the relation between pancreatic cancer and alcohol and coffee consumption [8, 9, 15, 17, 18]. However, results were inconclusive and review studies concluded that there was little evidence for this relation [38, 39]. Other factors which are thought to be associated with pancreatic cancer are a history of diabetes mellitus and chronic pancreatitis [37].

In this study we focused solely on the effect of smoking on pancreatic cancer. Since smoking is also a risk factor for several other smoking-related diseases, including lung cancer and coronary heart disease, which generally have a much greater contribution to the total disease burden than pancreatic cancer, the effect of the smoking cessation-based scenarios on the total burden of morbidity and mortality would be much larger. Peto et al. [40] estimated that 24% of all deaths in the European Union could be attributed to smoking, which corresponds to a total of more than 440,000 deaths each year.

We conclude that quitting smoking substantially reduces future burden of pancreatic cancer by around 68,000 patients in the European Union up to 2020. This underlines the importance of anti-smoking policies in the European Union to reduce the tobacco related burden of disease.

References
15. WHO. Health 21-the health for all policy for the WHO European Region- 21 targets for the 21st century. WHO; 1998.

Figure 2. Absolute reduction of the estimated number of pancreatic cancer cases cumulated over time up to 2050 in three alternative scenarios as compared to the reference scenario, among men and women, in the European Union.