Tobacco consumption and pancreatic cancer mortality: what can we conclude from historical data in Australia?

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Introduction

Trends in tobacco consumption during the 20th century have had a large impact on mortality levels from lung cancer and chronic obstructive pulmonary disease (COPD) in many countries. The historical relationship between tobacco consumption and other smoking-related causes of death is also of interest. One cause of death that is strongly influenced by tobacco consumption is pancreatic cancer. Numerous studies have demonstrated an increased risk of pancreatic cancer mortality for smokers, especially heavy and long-term smokers, and systematic analyses have estimated that 15–30% of pancreatic cancer mortality in high-income countries is attributable to smoking.

Pancreatic cancer is associated with a high case-fatality rate, partly because it is difficult to detect at early stages of the disease and is usually significantly advanced by the time it is diagnosed. Given this high case-fatality rate, trends in exposure to risk factors such as tobacco consumption are likely to strongly influence mortality rates.

Globally, over 200 000 people die each year from pancreatic cancer. It is estimated to be the fifth leading cause of cancer death in Australia and occupies a similar position in many other high-income countries. In many developed countries, such as the USA, Canada, New Zealand, Sweden, Norway, England and Wales, male mortality rates from pancreatic cancer rose during the mid-20th century to peak in the 1960s–80s period, before levelling off or declining over the past three decades. However, in countries that had relatively low rates 50 years ago, such as southern and eastern European countries, Japan and China, male mortality rates continued to rise in the 1990s, and in many of these countries, rates are continuing to increase. Female rates are generally much lower, but continued to rise in many Western countries up until the 1990s, beyond which they stabilized in Canada, the USA, Hong Kong, New Zealand and England and Wales. It has been postulated that long-term trends in pancreatic cancer mortality in the USA, and England and Wales are largely due to smoking. However, research in some European countries suggests other influences also have a role. None of these studies statistically analysed the relationship between pancreatic cancer and various risk factors.

There have been previous attempts to analyse temporal trends of pancreatic cancer mortality in Australia, which found that male mortality trends are similar to those of many Western countries, rising during the middle of the 20th century before falling from around the mid-1970s. The same studies found female rates rose over the same period, but at a slower rate than those of males, and stabilized from the late 1970s. These studies were primarily descriptive, and did not undertake detailed analysis of potential influences on these trends. Rohan and McMichael suggested an association between mortality and tobacco consumption trends; however, they did not conduct a formal statistical analysis of this relationship.

While tobacco consumption is an established cause of pancreatic cancer, other risk factors are less well identified. Studies have shown that fruit and vegetable intake lowers the risk of pancreatic cancer...
mortality, while saturated fat consumption may elevate this risk.\textsuperscript{17–19} Diabetes has been found to be positively associated with pancreatic cancer mortality.\textsuperscript{20} The evidence for obesity is less clear, although a number of studies demonstrate a positive relationship.\textsuperscript{20,21} Many studies have found no association between alcohol consumption and pancreatic cancer mortality; however, some have found heavy drinking has a positive relationship with pancreatic cancer mortality.\textsuperscript{20,22}

Although the literature has described long-term trends in pancreatic cancer mortality and identified certain risk factors, there are no studies that attempted to confirm this association using statistical methods at the population level. We have attempted to do so in this article using historical data for Australia covering 76 years on the long-term relationship that tobacco and fruit and vegetable consumption have with mortality from pancreatic cancer. Lessons from these historical observations should be useful for informing health policy and programmes in countries that are continuing to experience increasing mortality rates.

**Methods**

**Mortality and population data**

Pancreatic cancer mortality data were available from the Australian Bureau of Statistics (ABS) historical data files (1931–49) and the World Health Organization (WHO) mortality database (1950–2006).\textsuperscript{23–25} Pancreatic cancer has been reported as a cause of death in Australia since 1931. Population data for Australia were available by age, sex and year (L. Smith, personal communication).\textsuperscript{26} The pancreatic cancer mortality rates were standardized to the 2006 Australian population.

**Covariate data**

**Tobacco consumption**

We utilized data on tobacco sales, age and sex-specific self-reported cigarette consumption and tobacco smoking prevalence in Australia from the International Mortality and Smoking Statistics (IMASS) database and a paper by Walker (1984).\textsuperscript{27–29} The prevalence and consumption data in the IMASS database are estimates based on data from a number of tobacco consumption surveys in Australia.\textsuperscript{27} We estimated tobacco consumption by calendar year, age (15–19, 20–24, . . . . ≥85 years) and sex back to 1887 using back-extrapolation techniques (T. Adair et al., manuscript under review). Data on tobacco sales were used for aggregate consumption, because of reliability and availability.\textsuperscript{30} Age and sex-specific tobacco consumption data were derived from age and sex-specific data on self-reported cigarette consumption and tobacco smoking prevalence.

Tobacco consumption by age and sex were matched to tobacco sales using the following formula:

\[ C_{asy} = R_{asy} \times \frac{T_y}{\sum_{a=1}^{10} \sum_{s=1}^{5} R_{asy} P_{asy}} \]

where \( a \) is age, \( s \) is sex, \( y \) is year, \( C \) is final tobacco consumption per person, \( B \) is self-reported tobacco consumption per person, \( T \) is tobacco sales, \( P \) is population.

**Tar content**

The data on the tar content of cigarettes (milligram per cigarette) from 1920 to 1994 were obtained from the IMASS database, and estimated for other years. (T. Adair et al., manuscript under review). The IMASS data show that tar content fell from 35 mg in 1955 to 18.9 mg in 1970, 8.8 mg in 1990 and to an estimated level of 3.8 mg in 2004.

**Fruit and vegetable consumption**

Fruit and vegetable consumption data are available from the ABS.\textsuperscript{31} The data are provided as fresh fruit and vegetable equivalent consumption in kilograms per capita per year. The data are for a 3-year period in each decade, from 1936 to 39 until 1996 to 99. Data for intervening years are interpolated. Vegetable consumption data begin in 1946–49, so data for the previous decade are estimated by using the ratio of vegetable consumption for these two periods in the FAO Food Balance Sheets.\textsuperscript{32} Fruit and vegetable consumption data are not available by age and sex.

**Model of pancreatic cancer mortality**

For each sex, we used log-linear models, assuming the number of deaths have a Poisson distribution. The outcome variable is number of pancreatic cancer deaths, offset by population. The models were estimated separately for each sex.

\[ \ln(D_{ayz}) = \ln(P_{ay}) + \beta_0 + \beta_1 \text{Cohort}_z + \beta_2 \text{Age}_a + e_{ay} \]

\[ \ln(D_{ayz}) = \ln(P_{ay}) + \beta_0 + \beta_1 \text{CumulativeTobacco} \times \text{Tar}_{az} + \beta_2 \text{Fruit&Veg}_y + \beta_3 \text{Age}_a + e_{ay} \]

\[ \ln(D_{ayz}) = \ln(P_{ay}) + \beta_0 + \beta_1 \text{Tobacco} \times \text{Tar}_{ay} + \beta_2 \text{Fruit&Veg}_y + \beta_3 \text{Age}_a + \beta_4 \text{Cohort}_z + e_{ay} \]

where \( z \) is year of birth, \( D \) is deaths.

We first used an age-cohort model, to assess differences in birth cohort risk of pancreatic cancer mortality controlling for age. The next models included tobacco consumption measured as both cumulative, to represent consumption in each cohort’s life and time specific, which is number of years prior to death. In these models, the tobacco consumption variable was its product with tar content. We also conducted sensitivity analyses of the models with tar content not included. The appropriate number of years was determined by the goodness-of-fit of the model, as measured by the Akaike information criterion (AIC), whereby the fit is better where the AIC is lower.\textsuperscript{33} In each model, fruit and vegetable consumption was included to assess whether it has a protective effect against pancreatic cancer mortality. Pancreatic cancer mortality is rare at younger ages so only deaths at the age of 40 years and above were included in the model.

These models are an extension of age-period-cohort models, where we replaced period with fruit and vegetable consumption, and cohort with cumulative tobacco consumption data.\textsuperscript{3,34} The cohort variable in these models denotes a population group classified by age at birth, and represents the effect of exposures experienced by a cohort throughout their life on their risk of pancreatic cancer mortality.

We internally validated the models based on a sub-sample of years (i.e. years prior to 1991), applied the results to predict pancreatic mortality rates for the remaining years, and found the predicted findings closely tracked the observed data (data not shown but available from the authors upon request).

**Results**

Figure 1 shows the trends in age-standardized pancreatic cancer death rates for males and females. Male rates increased steadily during the middle decades of the 20th century, approximately doubling from 1931 to its peak in the early to mid-1970s. Thereafter, mortality rates declined steadily until 2006, although only negating less than half of the rise of the previous decades. Female pancreatic cancer mortality rose steadily and approximately doubled from 1931 to 2006. The male age-standardized death rate was almost double that of females in the 1970s; however, by 2006 they had converged considerably.

Historical trends in tobacco and fruit and vegetable consumption are presented in figure 2. Tobacco consumption increased steadily in the late 19th and early 20th centuries, declined briefly during the Depression in the 1930s, before rising in the decades thereafter. Male consumption rose sharply in the years following World War II, peaking in the 1950s before falling steadily from the 1970s. Female tobacco consumption also rose sharply after World War II, although from a much lower base, and peaked in the 1970s before declining. There was a strong convergence of male and female tobacco consumption by the 21st century. There has
been an overall trend of increased fruit and vegetable consumption since the early 1960s, although vegetable consumption had been higher in earlier years.

Figure 3 shows the risk of pancreatic cancer mortality by birth cohort, controlled for age in a regression model. The risk of male pancreatic cancer mortality was highest among those born in the early years of the 20th century. For females, the peak in mortality risk was approximately two decades later, in 1926, despite the period trend showing a continuing increase. There was not a substantial difference in risk between birth cohorts, with the peak cohort risk being <20% higher than the average.

Table 1 presents the results from the regression analyses for males and females from 1950 onwards, including fruit and vegetable data. This period was chosen because we sought to align the changes in tobacco consumption from World War II with mortality trends. For males, tobacco consumption and tar content, whether cumulative or with a lag of 15 years, is a significant predictor of pancreatic cancer mortality. This is consistent with the generally similar trends in pancreatic cancer mortality and tobacco consumption over the period of analysis. Model 2, with the measure of tobacco consumption lagged by 15 years, has a better goodness-of-fit measured by the AIC than Model 1, with cumulative tobacco consumption included. Fruit and vegetable consumption, lagged 10 years, had a negative and significant relationship in only one of the four models.

For females, cumulative tobacco consumption and tar content had a positive and significant relationship with pancreatic cancer mortality risk, and was a stronger predictor than for males. However, tobacco consumption and tar content with a lag of 25 years was non-significant; other lag years were utilized but were also non-significant (data not shown). The fruit and vegetable variable, with a lag of 10 years, was a significantly negative predictor of pancreatic cancer mortality in only one of the four models.

Discussion

Our results support the notion that tobacco consumption is a major cause of male pancreatic cancer in Australia. We found similar trends from World War II onwards between tobacco consumption in males and male pancreatic cancer mortality, with the regression results revealing tobacco consumption trends precede mortality by ~15 years. This is consistent with the studies that have demonstrated a reduction in the risk of pancreatic cancer a decade after smoking cessation.

We found a different scenario for women. While female tobacco consumption peaked in the 1970s, pancreatic cancer mortality among
women has continued to rise in recent years. Cohort tobacco consumption and mortality risk were associated, and cumulative tobacco consumption was a significant predictor of mortality; however, tobacco consumption with a lag of 25 years was non-significant in the regression models. This mortality trend is partly explained by the later peak in female tobacco consumption, and therefore declines in mortality in future are likely. However, it also suggests there may be other gender-specific environmental factors influencing pancreatic cancer mortality among women. The higher prevalence of obesity in women in some countries may be partially influencing this trend. Further research is needed to investigate this and other potentially important risk factors.

Our results provide evidence of a long-term population-level association between tobacco consumption and pancreatic cancer mortality in a high-income country, and support findings from case–control studies of this risk factor. Long-term male pancreatic mortality trends are similar to other English-speaking countries, although there was some difference in female mortality which flattened in these countries in the 1990s. Cohort mortality trends were broadly similar with those of Britain, as found by Fitzsimmons et al. The evidence from our analysis also supports other research findings that pancreatic cancer mortality has been influenced in part by tobacco consumption.

Our findings are also consistent with long-term trends of mortality from other tobacco-related illnesses, such as lung cancer and COPD, which for males exhibited a rise and then fall in the post-World War II period. The peak in pancreatic cancer mortality was later, and the increase was not as sharp, suggesting that smoking has a smaller influence on pancreatic mortality than on lung cancer and COPD. Nonetheless, the pattern of pancreatic cancer mortality in the second half of the 20th century was an important component of the epidemiological transition in Australia, where life expectancy stabilized following World War II. Continued declines in tobacco consumption should lead to further falls in male pancreatic cancer mortality in Australia in future, and a reversal of the long-term rise in female rates.

The findings also have implications for programmes in countries such as Japan and China, where pancreatic cancer mortality rates continue to increase. Improved case detection and surveillance systems may in part explain some of these increases; however, there are also a number of other plausible explanations. In many of these countries, increasing tobacco consumption is likely resulting in an increase in mortality rates. In addition, most of these populations are undergoing epidemiological transition and the proportion of the population in the older age groups is increasing, resulting in a larger cohort of people who are at risk of pancreatic cancer. Other studies have suggested that Helicobacter pylori is casually related to pancreatic cancer, which is more prevalent in low and middle-income countries than high-income countries. Lifestyle and dietary changes, and the increasing prevalence of obesity and diabetes in many of these countries may also be influencing mortality rates of pancreatic cancer.

While we found that fruit and vegetable consumption at the population level had a mixed association with pancreatic cancer mortality, this does not suggest that at the individual level it does not reduce the risk of mortality. A limitation of our analysis is that we were not able to access population-level historical data on other potential risk factors for pancreatic cancer mortality. This information would have strengthened our regression model and the conclusions we were able to

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**Table 1** Results from Poisson regression analysis of pancreatic cancer mortality (coefficients and 95% confidence intervals), males and females, Australia, 1950–2006

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
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<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
</tr>
<tr>
<td>Males</td>
<td>Tobacco × tar (cumulative)</td>
<td>0.040* 0.031–0.050</td>
</tr>
<tr>
<td>Tobacco</td>
<td></td>
<td>0.001* 0.000–0.002</td>
</tr>
<tr>
<td>Fruit</td>
<td></td>
<td>0.002* 0.001–0.002</td>
</tr>
<tr>
<td>Vegetable</td>
<td></td>
<td>8.78</td>
</tr>
<tr>
<td>AIC</td>
<td></td>
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</tr>
<tr>
<td>Females</td>
<td>Tobacco × tar (cumulative)</td>
<td>0.071* 0.061–0.081</td>
</tr>
<tr>
<td>Tobacco</td>
<td></td>
<td>0.002* 0.001–0.002</td>
</tr>
<tr>
<td>Fruit</td>
<td></td>
<td>8.78</td>
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<tr>
<td>Vegetable</td>
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<td>AIC</td>
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In Model 1, results for age not shown and in Model 2, results for age and cohort not shown

a: Tobacco coefficient multiplied by 1000
b: Tobacco coefficient multiplied by 100

*Significant at $P<0.01$
draw from it. Further research is needed to investigate in greater detail other environmental factors linked to pancreatic cancer mortality.

Other limitations of our study include the potential for improved certification and diagnosis of pancreatic cancer to have influenced mortality trends over time. Improved clinical management of pancreatic cancer may have also influenced trends, although it is unlikely it would have fully explained them. Related to this, a study was undertaken in Sweden to investigate whether changes in reported mortality from pancreatic cancer over time were genuine or whether they were due to changes in diagnostic and management practices. The authors concluded that the observed changes were largely real, as they appear to be in Australia.35

Despite these limitations, there are a number of strengths to our study compared with previous studies of pancreatic cancer mortality trends in Australia. First, our study has analysed mortality data up until 2006, whereas previous studies only had data up until the 1970s.16,36 Second, we used extensive age–sex–specific data on tobacco consumption, as well as fruit and vegetable consumption as covariates. Third, whereas previous studies provided only a description of trends, we conducted statistical analyses that demonstrated that tobacco consumption has significantly predicted pancreatic cancer mortality trends in Australia since 1950.

Acknowledgements

We wish to thank the Australian Bureau of Statistics for lending the Demography Bulletins, the staff that entered the data from these Bulletins and Len Smith for providing Australian population data for certain years prior to 1921.

Conflicts of interest: None declared.

Key points

- Historical mortality data can yield valuable policy–relevant information for disease control.
- Such analyses confirm the population level effects of tobacco smoking on pancreatic cancer in Australian men, although the effects are less obvious in women.
- Our model of the temporal effects of smoking on pancreatic cancer provides further evidence for the urgent need to strengthen tobacco control programmes in populations throughout the developing world where tobacco smoking has become prevalent.

References