The burden of pancreatic cancer in Australia attributable to smoking

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The known The future pancreatic cancer burden attributable to tobacco smoking has not been estimated in Australia.

The new Nearly 22% of the future burden of pancreatic cancer is attributable to current and former smoking, 15% (5500 cases over the next 10 years) to current smoking alone. The smoking-related burden of pancreatic cancer is markedly higher for men and for people under 65.

The implications Reducing smoking rates among men and people under 65 would have the greatest impact on reducing the future burden of pancreatic cancer in Australia.

Abstract

Objective: To estimate the burden of pancreatic cancer in Australia attributable to modifiable exposures, particularly smoking.

Design: Prospective pooled cohort study.

Setting, participants: Seven prospective Australian study cohorts (total sample size, 365 084 adults); participant data linked to national registries to identify cases of pancreatic cancer and deaths.

Main outcome measures: Associations between exposures and incidence of pancreatic cancer, estimated in a proportional hazards model, adjusted for age, sex, study, and other exposures; future burden of pancreatic cancer avoidable by changes in exposure estimated as population attributable fractions (PAFs) for whole population and for specific population subgroups with a method accounting for competing risk of death.

Results: There were 604 incident cases of pancreatic cancer during the first 10 years of follow-up. Current and recent smoking explained 21.7% (95% CI, 13.8–28.9%) and current smoking alone explained 15.3% (95% CI, 8.6–22.6%) of future pancreatic cancer burden. This proportion of the burden would be avoidable over 25 years were current smokers to quit and there were no new smokers. The burden attributable to current smoking is greater for men (23.9%; 95% CI, 13.3–33.3%) than for women (7.2%; 95% CI, −0.4% to 14.2%; $P = 0.007$) and for those under 65 (19.0%; 95% CI, 8.1–28.6%) than for older people (6.6%; 95% CI, 1.9–11.1%; $P = 0.030$). There were no independent relationships between body mass index or alcohol consumption and pancreatic cancer.

Conclusions: Strategies that reduce the uptake of smoking and encourage current smokers to quit could substantially reduce the future incidence of pancreatic cancer in Australia, particularly among men.

Five-year survival for people with pancreatic cancer is lower than 10%; it is the fourth leading cause of cancer-related deaths of Australian men, and the fifth highest among women.[1] As this low survival rate is ascribed to the late onset of symptoms and the consequently advanced stage of disease at diagnosis, primary prevention is the best control strategy. The evidence that tobacco smoking and body fatness increase the risk of pancreatic cancer is strong, while data on the influence of alcohol, red and processed meats, and foods and beverages containing fructose and saturated fatty acids are suggestive.[2–4]

The cancer burden that could be prevented by modifying exposure to a risk factor is quantifiable as the population attributable fraction (PAF). As contemporary exposure prevalence data have not been analysed and the pancreatic cancer burden for population subgroups has not been compared in Australia or elsewhere, the preventable future burden has not been estimated. We therefore applied a comprehensive PAF method to estimate the future burden of Australian pancreatic cancer that could be avoided by modifying individual exposures, particularly smoking.

Methods

Data sources

We analysed individual-level data for the Australian cancer–PAF cohort consortium,[5] a total pooled study population of 365 084 adults (aged 18 years or more) from seven Australian prospective cohort studies (Box 1). We obtained the most recent sex-specific risk factor prevalence estimates from the Australian Bureau of Statistics 2014–15 National Health Survey (expanded confidentialised unit record file)[6] and the Australian Institute of Health and Welfare (AIHW) 2013 National Drug Strategy Household Survey[7] (Box 1).

Data collection and harmonisation

We analysed modifiable exposures for which there is convincing, probable, or suggestive evidence of causal association with pancreatic cancer[2–4] that were assessed in our cohort and in national health surveys: smoking, body mass index (BMI), and alcohol consumption.

We harmonised baseline data for these exposures across the cohort studies and health surveys (Supporting Information, table 1), both as continuous variables and classified according to Australian recommendations for healthy living.[5] For smoking, we examined status (never, former, current); for former and current smokers we further evaluated the pancreatic cancer risk by time since quitting (in years) and smoking intensity (cigarettes per day). We examined BMI categorised as underweight or healthy weight (< 25 kg/m^2), overweight (25.0–29.9 kg/m^2), and obesity (≥ 30 kg/m^2). For alcohol consumption, we compared the effect of drinking no more than

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1 Characteristics of the study cohorts included in the Australian cancer–PAF cohort consortium, of the pooled cohort, and of representative external data sources

	Baseline years	Number in cohort	Cases of pancreatic cancer*,†	Deaths*	State/territory	Age at baseline (years), mean (range)	Sex (women)
Cohort data							
Melbourne Collaborative Cohort Study	1990–1994	41 510	75	2274	Vic	55 (27–76)	59%
Blue Mountains Eye Study	1992–1993	3652	13	711	NSW	66 (45–97)	57%
Australian Longitudinal Study on Women's Health	1996	38 370	75	2727	All	45 (18–75)‡	100%
Australian Diabetes, Obesity and Lifestyle Study	1999–2000	11 198	16	827	All	51 (25–95)	55%
North West Adelaide Health Study	1999-2003	4037	7	298	SA	50 (18–90)	52%
Concord Health and Ageing in Men Project	2005–2007	1627	8	447	NSW	77 (70–97)	0
45 and Up Study	2006–2009	264 690	410	14 261	NSW	62 (45 to > 100)	53%
Pooled cohort	*1990–2009*	*365 084*	*604*	*21 545*	*All*	*59 (18 to > 100)*	*59%*
External prevalence data							
National Health Survey	2014–2015	14 560			All	46 (18–85)	51%
National Drug Strategy Household Survey	2013	22 696			All	46 (18–84)	51%

* During first 10 years of follow-up. † Incident cases of exocrine pancreatic cancer: ICD-O-3 morphology codes 8012, 8020, 8030, 8046, 8070, 8140, 8154, 8231, 8260, 8440, 8480, 8481, 8490, 8500, 8550, 8560, 8573, 8574, 8000, 8001, 8010. ‡ The age distribution for the ALSWH is not continuous (three age cohorts were recruited: 18–23, 45–50, 70–75 years).

two standard alcoholic drinks per day with drinking more than two (= 20 g alcohol/day).

We harmonised data for several non-modifiable exposures associated with pancreatic cancer risk (age, sex, height, diabetes mellitus) to allow adjustment of our analysis for potential confounding factors (Supporting Information, table 1).[4] We also harmonised data for country of birth, marital status, educational attainment, socio-economic status (Index of Relative Socio-economic Disadvantage [IRSD][8]), and residential location (major cities, inner regional, outer regional, or remote) for subgroup analyses.

Data linkage and ascertainment of outcomes

We probabilistically linked the pooled cohort data to the population-based Australian Cancer Database and National Death Index to 31 December 2012, providing 8–22 years' follow-up of individuals. We classified incident primary invasive pancreatic cancers by International Classification of Diseases for Oncology codes (ICD-O-3, C25). We included pancreatic cancers of exocrine and unspecified morphology, and censored cancers of the endocrine pancreas.

Statistical analysis

Follow-up time accrued from baseline to the date of pancreatic cancer diagnosis, death from any cause, or end of follow-up, whichever occurred first. We estimated the hazard ratios (HRs) for pancreatic cancer and death with a parametric piecewise constant exponential hazards model. We restricted follow-up to 10 years to allow comparable estimates across cohorts, and tested heterogeneity between cohorts with the asymptotic Q statistic of DerSimonian and Laird.[9]

We first modelled each exposure individually, adjusted for age, sex, and study. We then modelled all exposures, adjusted for other exposures, age, sex, and study, and exposures that were significantly associated with pancreatic cancer were retained in the final model. We computed the corresponding exposure prevalence estimates from the health surveys, and combined them with strength of association estimates, using our recently developed PAF method, which accounts for competing risk of death.[10,11] This method allows flexibility in the choice of risk and reference level for exposure modification. For smoking, for example, we evaluated the "attributable burden" in a scenario in which ever smokers (current and former smokers) had never smoked. We also examined "preventable burden" scenarios, in which current smokers had the same pancreatic cancer risk as never smokers (long term scenario) or recent former smokers (short term scenario), or in which heavier smokers had the same risk as never smokers or lighter smokers.

We tested for effect modification of PAFs by other behaviours, socio-demographic factors, and diabetes mellitus.[10,12,13] We assessed the potential for reverse causality by excluding the first 12 months' follow-up.[13]

We estimated the number of cases of pancreatic cancer that could be prevented in Australia by multiplying our PAF estimates by the projected numbers of cases during the subsequent 10 years (2017–2026) as calculated for our analysis by the AIHW with their standard methodology.[14]

Analyses were conducted in SAS 9.4 (SAS Institute) and with our publicly available PAF program.[12]

Ethics approval

The AIHW Ethics Committee approved our study (reference, EC2013/4/62).

Results

We followed participants for a total of 2 213 120 person-years, or a median 4.8 years (interquartile range, 4.3–9.9 years) per person. There were 604 incident primary invasive exocrine pancreatic cancers (294 in men, 310 in women) and 21 545 deaths (Box 1).

Non-modifiable pancreatic cancer risk factors

We found no evidence of heterogeneity in the study-specific HRs for non-modifiable factors (Supporting Information, table 2).

In the fully adjusted model for the pooled cohort, age (per year: HR, 1.08; 95% confidence interval [CI], 1.07–1.09), sex (men: HR, 1.26; 95% CI, 1.04–1.52), and history of diabetes mellitus (HR, 1.70; 95% CI, 1.34–2.16) were associated with pancreatic cancer risk, but height was not (per 5 cm: HR, 1.05; 95% CI, 0.99–1.11).

Modifiable pancreatic cancer risk factors

We found no evidence of heterogeneity in the study-specific HRs for modifiable factors (Supporting Information, table 2).

In the pooled cohort, current smoking was associated with an increased risk of pancreatic cancer (*v* never smoker: HR, 2.14; 95% CI, 1.62–2.83; Box 2); when assessed by number of cigarettes smoked, the difference in risk was significant only for those who smoked more than 10 cigarettes per day (Box 2, Supporting Information, table 3). The risk associated with current smoking was greater for men than for women (Box 2). Among current smokers, men smoked more cigarettes per day than women (median, 20 [IQR, 12–25] *v* 15 [IQR, 10–20]) and had smoked for longer (median duration, 38 [IQR, 32–46] *v* 32 [IQR, 18–39] years).

Former smokers who had quit less than 15 years ago were at higher risk of pancreatic cancer than never smokers (HR, 1.59; 95% CI, 1.23–2.06), but not those who had quit more than 15 years ago (HR, 0.85; 95% CI, 0.68–1.06; Box 2; Supporting Information, table 3).

After adjusting for smoking status, higher BMI was associated with greater pancreatic cancer risk (per 5 kg/m^2: HR, 1.10; 95% CI, 1.01–1.20; obesity *v* normal weight: HR 1.26; 95% CI, 1.01–1.59). However, the association between BMI and risk was not significant after adjusting for time since quitting smoking (Box 2, Supporting Information, table 4), smoking intensity (data not shown), or history of diabetes (data not shown).

Alcohol consumption was not associated with higher risk of pancreatic cancer, but few people in our cohorts were heavy drinkers (Supporting Information, table 5). The findings of sensitivity analyses that excluded the first year of follow-up were similar for all factors (data not shown).

Competing risk of death

Current and former smoking, and obesity were each associated with higher risk of death from any cause (Supporting Information, table 6).

Exposure prevalence

Current smoking (16%) was less common than former smoking (31%). More current smokers smoked 0–10 cigarettes/day (65%) than smoked more than 10 cigarettes/day (35%). More former smokers had quit at least 15 years ago (58%) than less than 15 years ago (42%). Sixty-three per cent of the cohort participants were overweight or obese (Box 2).

Future pancreatic cancer burden

The estimated future pancreatic cancer burden attributable to current and recent former smoking is 21.7% (95% CI, 13.8–28.9%) if the prevalence of smoking remains unchanged (Box 2). Most of this burden (PAF, 15.3%; 95% CI, 8.6–21.6%) is attributable to current smoking, equivalent to 5500 cases of exocrine pancreatic cancer during the next 10 years. As the risk for former smokers who quit less than 15 years ago is similar to that for current smokers, this figure corresponds to the burden avoidable over 25 years (long term scenario) if all current smokers were to quit. In the next 10 years (short term scenario), the expected reduction in the burden of pancreatic cancer were all current smokers to quit is 7.6% (95% CI, –1.0% to 15.4%). If the risks of recent and longer term former smokers are not differentiated in the PAF calculation ("smoking status" in Box 2), the overall pancreatic cancer burden attributable to smoking is underestimated (17.4% *v* 21.7%) and the short-term benefits of quitting smoking overestimated (15.2% *v* 7.6%). If those currently smoking more than ten cigarettes per day instead smoked no more than ten per day, 7.5% (95% CI, 1.4–13.2%) of pancreatic cancers are potentially avoidable (Box 2).

The prevalence of current smoking was higher among men than women. The burden of pancreatic cancer attributable to current smoking was correspondingly greater for men than women, both in the long term (23.9% [95% CI, 13.3–33.3%] *v* 7.2% [95% CI, –0.4% to 14.2%]; $P = 0.007$) and in the short term (16.4% [95% CI, 3.1–27.8%] *v* –0.3% [95% CI, –10.5% to 9.0%]; $P = 0.037$). These differences also reflect the fact that the hazard ratio for pancreatic cancer in current smokers was greater for men than for women (Box 2).

The burden of pancreatic cancer attributable to current smoking was greater for younger people (under 65 years of age) than for older people (65 years or older) in the long term (19.0% [95% CI, 8.1–28.6%] *v* 6.6% [95% CI, 1.9–11.1%]; $P = 0.030$) (Box 3). This difference may be related to the higher prevalence of current smoking among older people.

The burden attributable to current smoking was not significantly modified by level of alcohol consumption ($P = 0.20$) or BMI ($P = 0.08$), nor by country of birth, marital status, educational attainment, or remoteness of residence (Box 3). Effect modification by socio-economic status and history of diabetes mellitus could not be evaluated because data for these variables were insufficient for some smoking level strata.

The burden of pancreatic cancer attributable to being overweight or obese was not statistically significant (Box 2), and did not differ by population subgroups (data not shown).

Discussion

We found the future burden of pancreatic cancer in Australia could be substantially reduced were all current smokers to quit and the uptake of smoking prevented. We also identified marked sex- and age-related differences in the burden of pancreatic cancer attributable to current smoking.

We estimate that 21.7% of future pancreatic cancers in Australia are attributable to current and recent smoking. The preventable burden attributable to current smoking is 15.3% of all cases, or 5500 cases over the next 10 years; the corresponding figures for lung cancers are 53.7% (74 500 cases)[10] and for colorectal cancers 3.9% (7100 cases).[15] Further, the lag time in reducing the risk of pancreatic cancer for former smokers means that half the burden could be averted in the next 10 years. Our analysis found

2 Prevalence of risk factor exposure; hazard ratios for pancreatic cancer, by exposure; proportions of cases of pancreatic cancer avoidable over 10 years (population attributable fraction) by reducing exposure

	Prevalence*			Hazard ratio (95% confidence interval)†			Population attributable fraction (95% confidence interval)†			
Risk factor	**All**	**Men**	**Women**	**All**	**Men**	**Women**	**Change in exposure‡**	**All**	**Men**	**Women**
Smoking status										
1. Never smoker	53%	45%	60%	1	1	1	2–3 → 1§	17.4% (8.1–25.8%)	23.6% (8.5–36.3%)	12.6% (1.4–22.6%)
							2 → 1	2.1% (–3.2% to 7.2%)	–0.6% (–8.1% to 6.4%)	5.6% (–1.8% to 12.3%)
							3 → 1¶	15.3% (8.5–21.6%)	24.2% (13.3–33.7%)	7.0% (–0.6% to 13.9%)
2. Former smoker	31%	36%	27%	1.08 (0.90–1.30)	0.98 (0.75–1.27)	1.23 (0.96–1.59)	3 → 2	15.2% (7.2–20.7%)	**24.5% (13.8–33.9%)**	**4.2% (–3.9% to 11.7%)**
3. Current smoker	16%	19%	13%	2.14 (1.62–2.83)	2.70 (1.87–3.91)	1.62 (1.07–2.43)	—	—	—	—
Time since quitting smoking**										
1. Never smoker	53%	45%	60%	1	1	1	3–4 → 1§	21.7% (13.8–28.9%)	**30.0% (17.7–40.4%)**	**13.8% (4.1–22.6%)**
							3 → 1	6.4% (2.3–10.4%)	6.0% (0.3–11.4%)	6.6% (0.8–12.1%)
							4 → 1¶	15.3% (8.6–21.6%)	**23.9% (13.3–33.3%)**	**7.2% (–0.4% to 14.2%)**
Former smoker, who quit:										
2. ≥ 15 years ago	18%	21%	15%	0.85 (0.68–1.06)	0.81 (0.60–1.09)	0.95 (0.68–1.34)	—	—	—	—
3. < 15 years ago	13%	15%	12%	1.59 (1.23–2.06)	1.55 (1.08–2.24)	1.65 (1.14–2.38)	4 → 3††	7.6% (–1.0% to 15.4%)	**16.4% (3.1–27.8%)**	**–0.3% (–10.5% to 9.0%)**
4. Current smoker	16%	19%	13%	2.17 (1.64–2.87)	2.76 (1.91–3.99)	1.62 (1.06–2.49)	—	—	—	—
Smoking intensity‡‡										
1. Never smoker	56%	52%	61%	1	1	1	3 → 1§§	9.3% (5.3–13.1%)	12.7% (6.4–18.6%)	5.4% (0.8–9.8%)
Current smoker, who smokes:							—	—	—	—
2. 0–10 cigarettes/day	11%	13%	9%	1.33 (0.74–2.38)	1.91 (0.89–4.11)	0.93 (0.38–2.28)	3 → 2¶¶	7.5% (1.4–13.2%)	7.8% (–3.2% to 17.7%)	5.7% (–0.7% to 11.7%)
3. > 10 cigarettes/day	6%	7%	6%	2.73 (2.02–3.69)	3.36 (2.26–5.00)	2.10 (1.31–3.35)				

(Continues)

2 Continued

Risk factor	Prevalence*			Hazard ratio (95% confidence interval)†			Change in exposure‡	Population attributable fraction (95% confidence interval)†		
	All	Men	Women	All	Men	Women		All	Men	Women
Body mass index (BMI)										
1. < 25.0 kg/m^2***	37%	29%	43%	1	1	1	2–3 → 1	7.5% (−4.2% to 17.9%)	8.9% (−10.2% to 24.7%)	6.2% (−8.3% to 18.7%)
							2 → 1	2.1% (−4.7% to 8.5%)	2.4% (−9.0% to 12.7%)	1.8% (−5.9% to 8.9%)
							3 → 1	5.4% (−1.5% to 11.9%)	6.5% (−3.9% to 15.8%)	4.5% (−5.1% to 13.0%)
2. 25.0–29.9 kg/m^2	36%	42%	29%	1.06 (0.88–1.29)	1.06 (0.80–1.40)	1.07 (0.82–1.39)	3 → 2	3.8% (−3.2% to 10.4%)	4.9% (−5.2% to 14.0%)	2.6% (−7.4% to 11.7%)
3. ≥ 30.0 kg/m^2	28%	28%	27%	1.21 (0.96–1.53)	1.26 (0.89–1.77)	1.17 (0.85–1.60)	—	—	—	—

* Sources: National Health Survey (smoking status, time since quitting smoking, body mass index)[6] and National Drug Strategy Household Survey (current smoking frequency).[7] † Adjusted for age, sex, study; smoking models (smoking status, time since quitting smoking, smoking intensity) were also adjusted for BMI; the BMI model was also adjusted for time since quitting smoking. ‡ Modification of risk factor exposure level to target reference level. § Attributable burden scenario. ¶ Preventable burden (long term scenario: current smokers to never smokers). ** For 95% of former smokers who provided information on time since quitting. †† Preventable burden (short term scenario: current smokers to recent former smokers). ‡‡ For 93% of current smokers who provided information about smoking intensity. §§ Preventable burden (heavier smokers to never smokers scenario). ¶¶ Preventable burden (heavier smokers to lighter smokers scenario). *** As only 1% of the study population (eight people with pancreatic cancer) were underweight (BMI < 18.5 kg/m^2), this group could not be analysed separately. **Bold**: Burden in men differs from that in women (the 95% confidence interval for the difference in PAF estimates for men and women does not include zero).

that PAF estimates for pancreatic cancer that do not differentiate between the risks for recent and longer term former smokers lead to erroneous conclusions about the burden attributable to smoking. The long term pancreatic cancer burden attributable to smoking reinforces the need for preventing the uptake of smoking and encouraging smoking cessation.

When planning prevention strategies, understanding which population subgroups have the greatest burden of disease is crucial. We found that the preventable burden was greater for men than for women, both in the short and long term, and was also greater in the long term for those under 65 than for people aged 65 years or more. The sex difference may be related to the higher prevalence of current smoking among men and the larger hazard ratio for pancreatic cancer for male current smokers, the latter probably explained by men being heavier smokers and having smoked for longer than women. The sex- and age group-related differences in PAFs for pancreatic cancer identify broad population subgroups that could gain most from tobacco control initiatives.

Our finding that higher alcohol consumption does not significantly modify the burden associated with current smoking is consistent with other studies of the interaction between the effects of alcohol and smoking on the risk of pancreatic cancer.[16–20] As the statistical power of our study for examining this relationship was inadequate, and there is some evidence for overlap of carcinogenic pathways for tobacco and alcohol in pancreatic cancer,[21] further investigation is warranted.

Greater body weight is a recognised risk factor for pancreatic cancer; meta-estimates of the hazard ratio include 1.10 per 5 kg/m^2 increase in BMI (95% CI, 1.07–1.14; World Cancer Research Fund [WCRF] and American Institute of Cancer Research [AICR][4]) and 1.14 per 5 kg/m^2 increase (1.07–1.21; International Agency for Research on Cancer [IARC][3]). The WCRF/AICR did not report covariables, whereas the pooled analysis[22] of the IARC was adjusted for smoking status, pack-years of smoking, and history of diabetes. In our study, higher BMI was associated with greater risk after adjusting for smoking status only, but not after adjusting for time since quitting smoking or personal history of diabetes; our PAF estimates for overweight/obesity (7.5%) and obesity alone (5.4%) were therefore not statistically significant. An earlier study had reported a PAF point estimate of 7.8% for the pancreatic cancer burden attributable to overweight and obesity in Australia in 2010.[23]

It has been suggested that residual confounding may explain reports that PAFs for pancreatic cancer associated with greater body weight are larger for never or former smokers than for current smokers,[13,24] but the differences between such burden estimates have not been statistically assessed. We found no modification of the smoking-related burden of pancreatic cancer by BMI level.

There is suggestive evidence that excessive alcohol consumption increases the risk of pancreatic cancer.[4] In their latest update, the WCRF and AICR reported that consuming 30 or more alcoholic drinks (10–15 g ethanol/drink) per week (HR, 1.27; 95% CI, 1.16–1.39) or 20–30 alcoholic drinks per week (HR, 1.11; 95% CI, 1.03–1.20) significantly increased the risk of pancreatic cancer in cohorts of predominantly heavy drinkers.[4,25] The numbers of heavy drinkers and the follow-up time in our study may have been insufficient for detecting an association.

Strengths

This was a large prospective pooled cohort study with individual-level data, allowing harmonisation of risk factors,

3 Exposure prevalence, hazard ratios for pancreatic cancer, and fractions of pancreatic cancer attributable to current smoking, by level of effect-modifying factors

Effect modifier and smoking categories	Prevalence* and hazard ratio (95% CI)†					
	Level 1		Level 2		Level 3 (if applicable)	
Alcohol consumption	**≤ 2 drinks/day**		**> 2 drinks/day**			
1. Never smoker	58%	1	29%	1		
2. Former smoker who quit ≥ 15 years ago	17%	0.96 (0.76–1.22)	25%	0.44 (0.23–0.86)		
3. Former smoker who quit < 15 years ago	12%	1.39 (1.02–1.90)	17%	1.64 (0.91–2.97)		
4. Current smoker	13%	2.09 (1.52–2.87)	29%	2.22 (1.18–4.18)		
PAF (4 → 1)‡		12.3 (5.63–18.6)		26.2 (2.76–43.9)		
Body mass index	**< 25 kg/m²**		**≥ 25 kg/m²**			
1. Never smoker	59%	1	49%	1		
2. Former smoker who quit ≥ 15 years ago	13%	0.81 (0.56–1.17)	21%	0.87 (0.66–1.15)		
3. Former smoker who quit < 15 years ago	11%	1.61 (1.03–2.53)	14%	1.58 (1.16–2.17)		
4. Current smoker	17%	2.65 (1.80–3.90)	15%	1.80 (1.21–2.67)		
PAF (4 → 1)‡		22.1 (11.1–31.7)		10.5 (1.95–18.2)		
Age	**< 65 years**		**≥ 65 years**			
1. Never smoker	54%	1	49%	1		
2. Former smoker who quit ≥ 15 years ago	14%	0.91 (0.58–1.42)	36%	0.83 (0.65–1.08)		
3. Former smoker who quit < 15 years ago	14%	1.47 (0.95–2.25)	8%	1.67 (1.21–2.31)		
4. Current smoker	18%	2.34 (1.57–3.50)	7%	2.02 (1.37–2.97)		
PAF (4 → 1)‡	—	**19.0 (8.06–28.6)**	—	**6.6 (1.85–11.1)**		
Country of birth	**Australia**		**Other**			
1. Never smoker	50%	1	58%	1		
2. Former smoker who quit ≥ 15 years ago	18%	0.80 (0.61–1.05)	18%	0.99 (0.66–1.49)		
3. Former smoker who quit < 15 years ago	13%	1.44 (1.04–2.00)	13%	2.10 (1.35–3.26)		
4. Current smoker	18%	2.05 (1.45–2.91)	12%	2.37 (1.46–3.87)		
PAF (4 → 1)‡	—	15.6 (6.37–24.0)	—	12.9 (3.38–21.4)		
Marital status	**Not married**		**Married/de facto**			
1. Never smoker	52%	1	53%	1		
2. Former smoker who quit ≥ 15 years ago	13%	0.77 (0.51–1.16)	22%	0.88 (0.67–1.15)		
3. Former smoker who quit < 15 years ago	12%	1.25 (0.76–2.06)	14%	1.79 (1.32–2.42)		
4. Current smoker	22%	2.01 (1.29–3.13)	12%	2.14 (1.49–3.07)		
PAF (4 → 1)‡	—	18.5 (4.44–30.4)	—	11.2 (4.36–17.6)		
Educational attainment	**Low**		**Intermediate**		**High**	
1. Never smoker	49%	1	46%	1	67%	1
2. Former smoker who quit ≥ 15 years ago	18%	0.85 (0.63–1.15)	20%	0.95 (0.65–1.40)	15%	0.62 (0.32–1.18)
3. Former smoker who quit < 15 years ago	13%	1.43 (1.02–2.01)	35%	1.90 (1.19–3.04)	11%	1.31 (0.58–2.93)
4. Current smoker	20%	2.03 (1.43–2.87)	19%	1.80 (0.99–3.28)	7%	3.13 (1.52–6.47)
PAF (4 → 1)‡	—	17.0 (7.01–25.9)	—	11.6 (–2.92 to 24.2)		13.6 (0.39–25.0)
Residential location	**Major city**		**Regional or remote**			
1. Never smoker	55%	1	46%	1		
2. Former smoker who quit ≥ 15 years ago	17%	0.92 (0.69–1.23)	21%	0.77 (0.54–1.08)		
3. Former smoker who quit < 15 years ago	13%	1.68 (1.20–2.34)	13%	1.50 (1.00–2.26)		
4. Current smoker	15%	2.15 (1.50–3.10)	19%	2.15 (1.41–3.28)		
PAF (4 → 1)‡	—	13.8 (5.57–21.3)	—	18.3 (5.96–29.0)		

CI = confidence interval; PAF = population attributable fraction. Some percentages do not add to 100% because of rounding. * Source: National Health Survey.[6] † Adjusted for age, sex, study, and BMI. ‡ Modification of risk factor exposure level to target reference level. The PAF effect modification was evaluated by including an interaction between the smoking variable and the potential effect-modifying factor in the model, and calculating the 95% confidence interval for the difference in PAF estimates between the levels of the effect-modifying factor. **Bold**: Burden in younger people differs from that for older people (the 95% confidence interval for the difference in PAF estimates for the two groups does not include zero).

potential confounding factors, and effect modifiers across studies. Applying harmonised representative contemporary prevalence estimates maximised the accuracy and relevance of the PAF estimates; prevalence data from non-representative cohorts can reflect a healthy cohort effect and underestimate prevalence.[26]

Our PAF method accounts for competing risk of death — a potential explanation for subgroup differences[27] — and generates confidence intervals, further increasing the value of our PAF estimates by allowing their significance to be assessed. The flexible choice of risk and reference levels enabled realistic estimates of the burden avoidable by, for instance, reducing the risk of current smokers to that of recent former smokers. Another advantage is that PAFs for population subgroups can be estimated and compared, making it possible to identify groups with greater modifiable burdens.

Limitations

Data on dietary factors for which there is suggestive evidence of a causal association with pancreatic cancer[4] were not collected by recent national health surveys. Values for the factors assessed at baseline may have changed over time. As in earlier studies, our PAF estimates assume that a change in exposure will have an immediate effect on the risks of cancer and death, but the effect would be delayed in real life. To mitigate this limitation, we estimated PAFs for scenarios in which current smokers become recent former smokers.[10]

Conclusions

We found that further reducing the uptake and prevalence of smoking in Australia would substantially reduce the future burden of pancreatic cancer, especially among men. Applying sophisticated PAF methods to larger pooled cohorts may identify further subgroups with high burdens of disease that could benefit from targeted support for behavioural change.

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1 Australian Institute of Health and Welfare. Cancer in Australia 2017 (Cancer Series No. 101; Cat. No. CAN 100). Canberra: AIHW, 2017.

2 International Agency for Research on Cancer. A review of human carcinogens. Volume 100E: Personal habits and indoor combustions (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans). Lyon: IARC, 2012. http://monographs.iarc.fr/ENG/Monographs/vol100E/mono100E.pdf (viewed May 2018).

3 Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer: viewpoint of the IARC Working Group. *N Engl J Med* 2016; 375: 794–798.

4 World Cancer Research Fund; American Institute for Cancer Research. Diet, nutrition, physical activity and pancreatic cancer. 2012; revised 2018. https://wcrf.org/sites/default/files/Pancreatic-cancer-report.pdf (viewed May 2018).

5 Arriaga ME, Vajdic CM, Canfell K, et al. The burden of cancer attributable to modifiable risk factors: the Australian cancer–PAF cohort consortium. *BMJ Open* 2017; 7: e016178.

6 Australian Bureau of Statistics. 4324.0.55.001. Microdata: National Health Survey, 2014–15. May 2016. http://www.abs.gov.au/ausstats/abs@.nsf/Latestproducts/4324.0.55.001Main%20Features12014-15?opendocument&tabname=Summary&prodno=4324.0.55.001&issue=2014-15&num=&view= (viewed Nov 2018).

7 Australian Institute of Health and Welfare. National Drug Strategy Household Survey, 2013 [computer file]. Australian Data Archive Dataverse 2015; https://doi.org/10.4225/87/usgeqs (viewed Nov 2018).

8 Australian Bureau of Statistics. 2033.0.55.001. Census of population and housing: Socio-Economic Indexes for Areas (SEIFA), Australia, 2011. IRSD. Mar 2013. http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/2033.0.55.001main+features100052011 (viewed Nov 2018).

9 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7: 177–188.

10 Laaksonen MA, Canfell K, MacInnis R, et al. The future burden of lung cancer attributable to current modifiable behaviours: a pooled study of seven Australian cohorts. *Int J Epidemiol* 2018; 47: 1772–1783.

11 Laaksonen MA, Härkänen T, Knekt P, et al. Estimation of population attributable fraction (PAF) for disease occurrence in a cohort study design. *Stat Med* 2010; 29: 860–874.

12 Laaksonen MA, Virtala E, Knekt P, et al. SAS macros for calculation of population attributable fraction in a cohort study design. *J Stat Software* 2011; 43: 1–25.

13 Stolzenberg-Solomon R, Schairer C, Moore S, et al. Lifetime adiposity and risk of pancreatic cancer in the NIH-AARP Diet and Health Study cohort. *Am J Clin Nutr* 2013; 98: 1057–1065.

14 Australian Institute of Health and Welfare. Cancer incidence projections: Australia, 2011 to 2020 (Cancer Series No. 66; Cat. No. CAN 62). Canberra: AIHW, 2012.

15 Vajdic CM, MacInnis R, Canfell K, et al. The future colorectal cancer burden attributable to modifiable behaviours: a pooled cohort study. *JNCI Cancer Spectrum* 2018; 2: pky033.

16 Bosetti C, Lucenteforte E, Silverman DT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). *Ann Oncol* 2012; 23: 1880–1888.

17 Genkinger JM, Spiegelman D, Anderson KE, et al. Alcohol intake and pancreatic cancer risk: a pooled analysis of fourteen cohort studies. *Cancer Epidemiol Biomarkers Prev* 2009; 18: 765–776.

18 Gupta S, Wang F, Holly EA, et al. Risk of pancreatic cancer by alcohol dose, duration, and pattern of consumption, including binge drinking: a population-based study. *Cancer Causes Control* 2010; 21: 1047–1059.

19 Michaud DS, Vrieling A, Jiao L, et al. Alcohol intake and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium (PanScan). *Cancer Causes Control* 2010; 21: 1213–1225.

20 Naudin S, Li K, Jaouen T, et al. Lifetime and baseline alcohol intakes and risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition study. *Int J Cancer* 2018; 143: 801–812.

21 Duell EJ. Epidemiology and potential mechanisms of tobacco smoking and heavy alcohol consumption in pancreatic cancer. *Mol Carcinog* 2012; 51: 40–52.

22 Genkinger JM, Spiegelman D, Anderson KE, et al. A pooled analysis of 14 cohort studies of anthropometric factors and pancreatic cancer risk. *Int J Cancer* 2011; 129: 1708–1717.

23 Kendall BJ, Wilson LF, Olsen CM, et al. Cancers in Australia in 2010 attributable to overweight and obesity. *Aust N Z J Public Health* 2015; 39: 452–457.

24 Arnold M, Pandeya N, Byrnes G, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. *Lancet Oncol* 2015; 16: 36–46.

25 Imperial College London Continuous Update Project Team Members. The associations between food, nutrition and physical activity and the risk of pancreatic cancer (WCRF/AICR systematic

literature review: Continuous Update Project report). Oct 2011. https://www.wcrf.org/sites/default/files/pancreatic-cancer-slr.pdf (viewed Nov 2018).

26 Sedgwick P. Bias in observational study designs: prospective cohort studies. *BMJ Open* 2014; 349: g7731.

27 Renehan AG, Soerjomataram I, Leitzmann MF. Interpreting the epidemiological evidence linking obesity and cancer: A framework for population-attributable risk estimations in Europe. *Eur J Cancer* 2010; 46: 2581–2592. ■

Supporting Information

Additional Supporting Information is included with the online version of this article.