The future burden of kidney and bladder cancers preventable by behaviour modification in Australia: a pooled cohort study

Running title: Preventable kidney and bladder cancer burden in Australia

Maarit A. Laaksonen[1], Robert J. MacInnis[2,3], Karen Canfell[4-6], Graham G. Giles[2,3], Peter Hull[1], Jonathan E. Shaw[7], Robert G. Cumming[5,8], Tiffany K. Gill[9], Emily Banks[10], Paul Mitchell[11], Julie E. Byles[12], Dianna J. Magliano[13], Vasant Hirani[5,14], David Connah[15], Claire M. Vajdic[1]

[1] Centre for Big Data Research in Health, University of New South Wales, Sydney, Australia

[2] Cancer Epidemiology and Intelligence Division, Cancer Council Victoria, Melbourne, Australia

[3] Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia

[4] Cancer Research Division, Cancer Council New South Wales, Sydney, Australia

[5] School of Public Health, University of Sydney, Sydney, Australia

[6] Prince of Wales Clinical School, University of New South Wales, Sydney, Australia

[7] Clinical Diabetes Laboratory, Baker Heart and Diabetes Institute, Melbourne, Australia

[8] ANZAC Research Institute, University of Sydney and Concord Hospital, Sydney, Australia

[9] Adelaide Medical School, University of Adelaide, Adelaide, Australia

[10]ANU College of Medicine, Biology and Environment, Australian National University, Canberra, Australia

[11] Centre for Vision Research, Westmead Institute for Medical research, University of Sydney, Sydney, Australia

[12] Research Centre for Generational Health and Ageing, University of Newcastle, Newcastle, Australia

[13] Diabetes and Population Health Laboratory, Baker Heart and Diabetes Institute, Melbourne, Australia

[14] School of Life and Environmental Sciences, Charles Perkins Centre, University of Sydney, Sydney, Australia

[15] Cancer Voices NSW, Sydney, Australia

Corresponding author: Maarit Laaksonen, Centre for Big Data Research in Health, University of New South Wales, Level 4 Lowy Cancer Research Centre, Sydney NSW 2052, Australia; Tel: +61 2 9385 1402; Email: m.laaksonen@unsw.edu.au, ORCID-ID: 0000-0002-3676-0787

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KEYWORDS

Kidney cancer, bladder cancer, risk factors, population attributable fraction, preventable burden

ABBREVIATIONS

AIHW	The Australian Institute of Health and Welfare
BMI	Body mass index
CI	Confidence interval
HR	Hazard ratio
ICD-O	International Classification of Diseases for Oncology
PAF	Population attributable fraction

NOVELTY AND IMPACT

We use contemporaneous exposure prevalence data to show that body fatness is overtaking smoking as the leading modifiable cause of the future kidney cancer burden in Australia. Overweight and obesity explain 29%, current and past smoking 16%, and these two exposures jointly 40% of the future kidney cancer burden. Current and past smoking explain 44% of future bladder cancers, with men, those under 65 years and those consuming excessive alcohol experiencing the highest modifiable burden.

ABSTRACT

Substantial changes in the prevalence of the principal kidney and bladder cancer risk factors, smoking (both cancers) and body fatness (kidney cancer), have occurred but the contemporary cancer burden attributable to these factors has not been evaluated. We quantified the kidney and bladder cancer burden attributable to individual and joint exposures, and assessed whether these burdens differ between population subgroups. We linked pooled data from seven Australian cohorts (N=367,058) to national cancer and death registries, and estimated the strength of the associations between exposures and cancer using adjusted proportional hazards models. We estimated exposure prevalence from representative contemporaneous health surveys. We combined these estimates to calculate Population Attributable Fractions (PAFs) with 95% confidence intervals (CIs), accounting for competing risk of death, and compared PAFs for population subgroups. During the first 10-years follow-up, 550 kidney and 530 bladder cancers were diagnosed and over 21,000 people died from any cause. Current levels of overweight and obesity explain 28.8% (CI=17.3-38.7%), current or past smoking 15.5% (CI=6.0-24.1%), and these exposures jointly 39.6% (CI=27.5-49.7%) of the kidney cancer burden. Current or past smoking explains 44.4% (CI=35.4-52.1%) of the bladder cancer burden, with 24.4% attributable to current smoking. Ever smoking explains more than half (53.4%) of the bladder cancer burden in men, and the burden potentially preventable by quitting smoking is highest in men (30.4%), those aged <65 years (28.0%) and those consuming >2 standard alcoholic drinks/day (41.2%). In conclusion, large fractions of kidney and bladder cancers in Australia are preventable by behaviour change.

KEYWORDS Kidney cancer, bladder cancer, risk factors, population attributable fraction, preventable burden

INTRODUCTION

Kidney and bladder cancers are among the ten most commonly diagnosed cancers in Australia.[1] Several potentially modifiable behavioural factors affect the risk of developing these cancers.[2-5] Smoking is an established risk factor for both cancers,[2] and there is convincing evidence that body fatness increases the risk of kidney cancer, especially renal cell carcinoma.[3,4] There is probable evidence that alcohol consumption decreases the risk of kidney cancer and suggestive evidence that the consumption of vegetables, fruit and tea decreases the risk of bladder cancer.[4,5]

Several studies have estimated population attributable fractions (PAFs) for the burden of kidney and bladder cancers attributable to behavioural exposures.[6-17] However, these estimates are based on non-contemporary exposure distributions, and thus do not represent the currently preventable burden and priorities for prevention. For example, the prevalence of smoking has continuously decreased over time, whilst body fatness has increased, both in Australia[15,18] and in other industrialised countries.[19] Moreover, although change in exposure distribution may affect both cancer incidence and death, no study has accounted for potential competing risk of death, which can bias PAF estimates.[20] Additionally, no study to our knowledge has statistically compared the burdens across population subgroups, potentially useful for targeted prevention strategies.

We quantified the future Australian burden of kidney and bladder cancer that could be prevented by modifying current behaviours, for the population as a whole and for subgroups, accounting for potential competing risk of death and risk factor interdependence.

METHODS

Cohort data

We pooled individual-level data, using a 1-step approach, from the Australian cancer-PAF cohort consortium,[21] which comprises seven well-established Australian prospective cohort studies (N =369,515). We excluded 2,457 men and women who enrolled in more than one cohort and 1,885 who did not consent to record linkage. The final study sample for kidney cancer comprised 364,423 men and women after further excluding 750 with a history of kidney cancer (**Table 1**). For bladder cancer, we studied 364,426 men and women after excluding 747 with a history of bladder cancer (**Table 1**).

The Australian Institute of Health and Welfare Ethics Committee approved the study (EC2013/4/62).

Prevalence data

We obtained the risk factor exposure prevalence estimates from the 2014-2015 National Health Survey[18] and 2013 National Drug Strategy Household Survey,[22] and used the most recent available prevalence estimate (**Table 1, Supplementary Table 1**).

Data collection and harmonisation

We examined potentially modifiable behavioural exposures with convincing, probable or suggestive evidence of a causal association with kidney or bladder cancer,[2-5] if they were measured in our cohort and there were available sources of prevalence data. These exposures were smoking, body fatness (approximated by body mass index, BMI), alcohol consumption, available in all cohorts, and fruit and vegetable consumption, available in four cohorts, ascertained at baseline. All cohort studies collected information on behavioural exposures through self-completed questionnaires and some also through interviews and medical

examinations (**Supplementary Table 1**). All exposures were either self-reported or measured across all cohorts except for BMI which was measured in four cohorts and self-reported in three.

We harmonised the exposures across the cohort studies and external prevalence data sources**(Supplementary Table 1**), both as continuous variables and classifying them in accordance with current evidence on dose-response relationships or current Australian recommendations for healthy living: not smoking, maintaining a healthy weight (BMI ≤ 25 kg/m^2), not drinking more than two standard alcoholic drinks per day, and eating at least two serves of fruit and five serves of vegetables per day.[21] However, as the probable protective effect of alcohol consumption on the risk of kidney cancer may be present at higher levels of consumption,[4] we used a more detailed categorisation (0, < 1, 1-2, >2-3, > 3 drinks/day).

We harmonised non-modifiable exposures associated with kidney or bladder cancer risk,[4,5] age, sex and height, available in all cohorts, to allow adjustment for potential confounders (**Supplementary Table 1**). We also harmonised systolic and diastolic blood pressure (BP) variables, available in three cohorts, and formed a high blood pressure variable (systolic BP > 140 or diastolic BP > 90), associated with kidney cancer,[4] to allow for further adjustment of potential confounding. We further harmonised country of birth, marital status, educational attainment, socio-economic status and residential location (rurality), available in all cohorts, for subgroup analyses.

Data linkage and ascertainment of outcomes

The Australian Institute of Health and Welfare (AIHW) linked the pooled cohort to the Australian Cancer Database and National Death Index using probabilistic matching. Each of the Australian jurisdictional cancer registries operates according to the conventions of the International Association of Cancer Registries, with reconciliation of information across

multiple sources, validation of data entry and periodic audits of coding accuracy. Cancer is a notifiable condition and Australian cancer registration is of high quality.[23] The records were matched probabilistically on the basis of full name, sex, date of birth, date of death and geographical variables using an established algorithm and manual clerical review of potential record pairs using explicit rules.[24] These records were available until 31st December 2012, providing a maximum of 8-22 years follow-up (**Table 1**).

We classified primary invasive kidney and bladder cancers of epithelial origin according to the International Classification of Diseases for Oncology (ICD-O-3; C64 and C67, respectively), separately identifying renal cell carcinomas (morphology 8050, 8140, 8260, 8270, 8280–8312, 8316–8320, 8340–8344).[23] Both non-fatal and fatal cancers were included.

Statistical methods

We performed separate analyses for kidney and bladder cancers. We defined follow-up as the time from baseline to the date of cancer diagnosis, death or end of follow-up, whichever occurred first. We estimated the strength of exposure-cancer and exposure-death associations using a parametric piecewise constant exponential hazards model, and expressed them as hazard ratios (HR) and their 95% confidence intervals (CI). We included the first 10-years of follow-up to generate comparable estimates across the cohorts, and tested heterogeneity between the cohort-specific HRs using the asymptotic DerSimonian and Laird Q statistic.

For each cancer, we first modelled each risk factor or confounding factor separately, adjusted for age, sex and study. We then modelled all risk factors and confounding factors together. Risk factors with suggestive evidence for causal association were retained in the final model if the association was supported by our data. We computed the corresponding age- and sex-specific exposure prevalence estimates from the health surveys, and combined them with the

strength of association estimates to calculate PAFs and their 95% CIs for the individual and joint contribution of the modifiable exposures to the cancer burden.[20,25] Our PAF method accounts for potential competing risk of death, i.e. censoring due to death, and risk factor interdependence, and allows a flexible choice of the risk and reference level for the hypothetical exposure modification (**Appendix 1**). We evaluated scenarios in which the exposure was either completely removed or reduced. We tested for potential differences in the distribution of the preventable cancer burden by other exposures and socio-demographic factors by including an interaction term between the risk factor and the potential effect modifying factor in the model and calculating the 95% CI for the difference in PAF estimates between the categories of the effect modifying factor (**Appendix 1**).[25] If this CI did not include zero, the PAF estimates were deemed to differ. We conducted sensitivity analysis adjusting for potential confounding factors only available for a subset of participants and excluding the first year of follow-up, to assess the potential effect of reverse causality.

We estimated the number of kidney and bladder cancers in Australia over the next 10 years that could be attributed to the current risk factors by multiplying the PAF estimates by the numbers of kidney and bladder cancers projected during 2017-2026 by the AIHW using their published method and data.[26]

We performed all analyses using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA) and our publicly available PAF program.[25]

RESULTS

During a median of 4.8 years (interquartile range 4.3-9.9) follow-up, we observed 550 incident kidney cancers (521 renal cell carcinomas) and 21,784 deaths from all causes. The corresponding figures for the bladder cancer analyses were 530 cancers and 21,675 deaths from all causes (**Table 1**).

Kidney and bladder cancer risk factors

We found no significant heterogeneity between the cohort-specific HRs for kidney or bladder cancer in relation to risk factors (**Supplementary Tables 2 and 3**).

Older age at baseline and male sex were associated with a higher risk of kidney (HR 1.58, 95% CI: 1.46-1.71 per 10 years and 1.80, 95% CI: 1.38-2.34, respectively) and bladder cancer (HR 2.64, 95% CI: 2.42-2.88 per 10 years and 3.78, 95% CI: 2.99-4.78, respectively). Greater height was also associated with a higher risk of kidney cancer (HR 1.10, 95% CI: 1.03-1.17 per 5 cm), as was a high blood pressure (HR 1.71, 95% CI: 1.11, 2.61).

In the multivariable model including risk factors and confounding factors, current smoking was associated with 1.4-fold risk of kidney cancer (**Table 2**) and 3.5-fold risk of bladder cancer (**Table 3**). Those smoking 20 or more cigarettes per day had a 1.8-fold risk of kidney cancer (**Table 2**) and 4.5-fold risk of bladder cancer (**Table 3**). The risk of bladder cancer associated with current smoking was more pronounced for men than women (P for interaction 0.02; **Table 3**). Men smoked more cigarettes per day on average (median 20 compared with 15 cigarettes/day, respectively; $P < 0.001$) and had smoked for longer than women (median 38 compared with 32 years, respectively; $P < 0.001$). Former smokers were also at an increased risk of both cancers; risk decreased over time since quitting (P for trend < 0.001) but remained elevated for up to 40 years since quitting (**Tables 2 and 3**).

Kidney cancer risk was 1.4-fold with overweight (BMI 25.0-29.9 kg/m^2) and 1.8-fold with obesity (BMI ≥ 30 kg/m^2) (**Table 2**). The results for the association between body fatness and renal cell carcinomas were very similar to those for all kidney cancers, but with overweight also significantly increasing risk in women (**Supplementary Table 4**). Regularly drinking more than three standard alcoholic drinks per day was associated with a decreased risk of kidney cancer (**Table 2**). Adjustment for a high blood pressure did not affect the strength of associations between smoking and alcohol consumption and kidney cancer but attenuated the strength of association between body fatness and kidney cancer (data not shown).

Combined consumption of fruit and vegetables was not associated with bladder cancer risk (**Table 3**).

The smoking-cancer associations became stronger after excluding the first year of follow-up whereas the other exposure-cancer associations did not change materially (data not shown).

Competing risk of death

Smoking was more strongly associated with risk of death from other causes than of kidney cancer. No other exposure, except for age, was associated with a greater risk of death than risk of kidney or bladder cancer (data not shown).

Risk factor exposure prevalence

In Australia, 47% of the population are current or former smokers and 63% are overweight or obese (**Tables 2 and 3**; data from 2014-2015). Seventy-nine percent have at least one of these two risk factors and 32% both of them.

Kidney and bladder cancer burden

Individual and joint behaviours

15.5% and 44.4% of the future kidney and bladder cancer burden in Australia, respectively, are attributable to ever smoking (**Tables 2 and 3**). These PAFs correspond to 6,100 kidney and 15,200 bladder cancers over the next 10 years. The majority of the smoking-related kidney cancer burden (65%) is attributable to former smoking and of bladder cancer burden (55%) to current smoking. If all current smokers were to quit and become former smokers, a significant reduction in the bladder cancer burden could be seen after ten years. There would be little impact on the burden of kidney cancer or bladder cancer if current smokers of 20 or more cigarettes per day reduced their smoking to less than 20 cigarettes per day.

Current levels of overweight and obesity contribute 28.8% or 11,400 of the future kidney cancers, with obesity explaining 17.0% (**Table 2**). If all those currently obese were instead overweight, 7.9% of the kidney cancer burden could be prevented.

Combined, smoking and body fatness are responsible for 39.6% or 15,600 of the future kidney cancers, with modifiable current smoking and body fatness explaining 32.8% or 12,900 cancers (**Table 2**).

Population subgroups

There were no notable differences in the distribution of kidney cancer burden by population subgroups.

Men experience a higher smoking-attributable bladder cancer burden than women (53.4% compared with 18.9%, P-difference < 0.001), largely due to a higher burden attributable to current smoking in men than in women (30.4% compared with 8.2%, P-difference = 0.002) (**Table 3**). Men had a higher smoking-related risk and were also more likely to smoke than women (prevalence 19% compared with 13%, respectively). The relative burden attributable

to current smoking is also higher for those under 65 years compared with those 65 years or older (28.0% compared with 11.3%, P-difference = 0.01) and those who are consuming more than two standard alcoholic drinks per day compared with those consuming two or less standard alcoholic drinks per day (41.2% compared with 19.8%, P-difference = 0.02). The current smoking prevalence was more than double among those under 65 years compared with those 65 years or older (18% compared with 7%, respectively) and among those exceeding compared with those complying with the Australian recommendations for alcohol consumption (29% compared with 13%, respectively).

DISCUSSION

We found that body fatness is the leading preventable cause of the kidney cancer burden and smoking of the bladder cancer burden in Australia. Body fatness has overtaken smoking as the leading cause of kidney cancer burden,[15] currently explaining double the burden compared with ever smoking (29% compared with 16%). Jointly, body fatness and ever smoking are responsible for nearly 40% of kidney cancers, translating to 15,600 cancers over the next 10 years. Ever smoking is responsible for 44% of bladder cancers, or 15,200 cancers over 10 years, with the modifiable current smoking responsible for 24%. The bladder cancer burden preventable by smoking cessation is highest in men, due to both higher risk and prevalence of current smoking, as well as in those under 65 years of age and those consuming more than two alcoholic drinks per day, mainly due to higher current smoking prevalence.

In 2001, 52% of men and 37% of women in Australia were overweight or obese, explaining 16% of kidney cancers in 2010.[15] As the prevalence of overweight and obesity has since increased to 70% in men and 56% in women,[18] with the prevalence of obesity alone doubling (14% in men and 15% in women in 2001 compared with 28% and 27% in 2014-2015),[15,18] the body fatness–attributable kidney cancer burden has accordingly almost doubled to 29%. As the worldwide prevalence of overweight and obesity has increased,[19] all prior PAF estimates based on past prevalences[7,10-12,16] are likely under-estimates. Obesity alone explains 17% of the kidney cancer burden, and this burden could be significantly reduced by 8% if all those currently obese were instead overweight.

All prior PAF estimates for the smoking-attributable kidney and bladder cancer burden are also based on past prevalences;[6,8-10,13-15,17] therefore, it is likely they overestimate the burden currently preventable by smoking cessation due to decreases in smoking rates.[19] However,

ever smoking continues to explain a significant proportion of the kidney (16%) and bladder cancer burden (44%), with current smoking responsible for 24% of the bladder cancer burden. These findings support the continued investment in smoking cessation policies and public health measures, especially as we found that reduced smoking intensity does not appear to significantly reduce the burden and cancer risk remains elevated for up to 40 years since quitting smoking.

Our results support the probable protective effect of high alcohol consumption on kidney cancer risk but do not support the suggestive protective effect of combined fruit and vegetable consumption on bladder cancer risk.[4,5] Nevertheless, high levels of alcohol consumption increase the risk and burden of many other cancers and health conditions and thus its net effect is harmful.[10,15]

We are the first to quantify the joint effect of body fatness and smoking on the kidney cancer burden, and to evaluate differences in the preventable kidney and bladder cancer burden between population subgroups. If confirmed, our findings on the subgroups with the highest smoking-attributable bladder cancer burden may support targeted, in addition to population-wide, tobacco control strategies.

Strengths and limitations

This is a large pooled study with harmonised individual-level cohort data and representative contemporaneous prevalence data.[21] The advanced PAF method allowed us to assess the cancer burden preventable by individual and joint behaviour modifications, accounting for their interdependence, competing risk of death, and effect modification by population subgroups.[20,21,25]

We examined all modifiable and non-modifiable exposures with convincing, probable or suggestive evidence of causality, except for consumption of tea or arsenic in drinking water.[2-5] Some risk factors varied in how well they could be harmonised across the cohorts due to different measurement methods (e.g. self-reported versus measured BMI) but we did not observe any between-cohort heterogeneity. Sensitivity analyses indicated that part of the impact of body fatness on kidney cancer may be mediated through high blood pressure but did not indicate reverse causality. However, the possibility of residual confounding due to unmeasured factors or changes during follow-up in factors measured at baseline cannot be excluded, but there is a latency period between exposure and cancer diagnosis. Our analyses included a maximum 10-year follow-up and latency period; the relatively short follow-up may have attenuated some of the associations although behavioural exposures are often rather stable. Despite the large cohort, our power, especially in subgroup analyses, may have been inadequate. Finally, PAF estimation assumes immediate risk reduction following the hypothetical behavior modification, while with actual behavior modification there is a lag in risk and burden reduction, as demonstrated for smoking.

Conclusions

We show that large fractions of kidney and bladder cancers are preventable by behaviour change. The fraction of kidney cancers attributable to obesity and overweight is increasing, adding to the pressing need to halt and reverse the current trend in weight gain. Public health policies and practices that promote and support healthy choices of eating, drinking and exercise can help achieve that. Continued efforts to prevent smoking uptake and achieve smoking cessation are also needed to further reduce the notable bladder and kidney cancer burden attributable to smoking.

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DECLARATION OF INTERESTS

Prof Canfell is a co-PI of an unrelated investigator-initiated trial of cytology and primary HPV screening in Australia ("Compass"), which is conducted and funded by the Victorian

Cytology Service (VCS), a government-funded health promotion charity. The VCS have received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana Inc USA. However, neither Prof Canfell or her institution on her behalf (Cancer Council NSW) receives direct funding from industry for this trial or any other project.

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Table 1. Characteristics of the individual and pooled cohort and external data sources

Characteristic	Cohort data								Prevalence data	
	MCCS	**BMES**	**ALSWH**	**AusDiab**	**NWAHS**	**CHAMP**	**45&Up**	**Pooled**	**NHS[1]**	**NDSHS[1]**
Baseline year(s)	1990-1994	1992-1993	1996	1999-2000	1999-2003	2005-2007	2006-2009	1990-2009	2014-2015	2013
State/Territory	VIC	NSW	All	All	SA	NSW	NSW	All	All	All
Kidney cancer analysis										
Population (n)	41,487	3,647	38,351	11,191	4,032	1,614	264,101	364,423	14,560	22,696
Incident cancer cases (n)[2]	74	10	55	19	12	4	376	550	-	-
Deaths (n)[2]	2,305	719	2,760	837	298	446	14,419	21,784	-	-
Age in years at baseline, mean (range)	55 (27-76)	66 (45-97)	45[3] (18-75)	51 (25-95)	50 (18-90)	77 (70-97)	62 (45->100)	59 (18->100)	46 (18-85)	46 (18-84)
Women (%)	59	57	100	55	52	0	53	59	51	51
Bladder cancer analysis										
Population (n)	41,471	3,645	38,347	11,188	4,031	1,613	264,131	364,426	14,560	22,696
Incident cancer cases (n)[2]	71	12	35	22	9	16	365	530	-	-
Deaths (n)[2]	2,306	716	2,771	827	296	437	14,322	21,675	-	-
Age in years at baseline, mean (range)	55 (27-76)	66 (45-97)	45[3] (18-75)	51 (25-95)	50 (18-90)	77 (70-97)	62 (45->100)	59 (18->100)	46 (18-85)	46 (18-84)
Women (%)	59	57	100	55	52	0	53	59	51	51

45&Up (45 and Up Study); ALSWH (Australian Longitudinal Study on Women's Health); AusDiab (Australian Diabetes, Obesity and Lifestyle Study); BMES (Blue Mountains Eye Study); CHAMP (Concord Health and Ageing in Men Project); MCCS (Melbourne Collaborative Cohort Study); NDSHS (National Drug Strategy Household Survey); NHS (National Health Survey); NSW (New South Wales); NWAHS (North West Adelaide Health Study); SA (South Australia); VIC (Victoria)

[1] The NHS is the primary source of exposure prevalence for body fatness, smoking status and time since quitting and NDSHS for smoking intensity

[2] During the first 10-years follow-up.

[3] The ALSWH recruited three cohorts aged 18-23, 45-50 and 70-75 so the age distribution is not continuous.

Table 2. Risk factor frequencies, population exposure prevalences, hazard ratios and fractions of kidney cancers avoidable by change in exposure to behavioural risk factors over 10-years follow-up

	Cohort n/N (%)[1]			Population prevalence[2]			HR (95% CI)[3]		
Behavioural risk factor	**All**	**Men**	**Women**	**All**	**Men**	**Women**	**All**	**Men**	**Women**
Smoking status									
1. Never smoker	232/187,146 (56%)	118/65,505 (47%)	114/121,641 (63%)	53%	45%	60%	1	1	1
2. Former smoker	233/114,231 (34%)	171/61,567 (44%)	62/52,664 (27%)	31%	36%	27%	1.36 (1.12, 1.64)	1.40 (1.10, 1.78)	1.32 (0.96, 1.81)
3. Current smoker	45/31,430 (9%)	31/12,653 (9%)	14/18,777 (10%)	16%	19%	13%	1.41 (1.02, 1.96)	1.68 (1.12, 2.51)	1.05 (0.60, 1.85)
PAF (2-3 → 1)[4]							15.5 (6.0, 24.1)	20.9 (7.6, 32.3)	8.7 (-5.0, 20.6)
PAF (2 → 1)[4]							10.0 (3.5, 16.1)	11.6 (3.0, 19.5)	8.0 (-2.1, 17.1)
PAF (3 → 1)[4]							5.5 (-0.4, 11.1)	9.3 (0.8, 17.0)	0.7 (-6.8, 7.6)
Time since quitting smoking[5]									
1. Never smoker	232/187,146 (57%)	118/65,505 (48%)	114/121,641 (64%)	53%	45%	60%	1	1	1
Former smoker, who quit									
2. ≥40 years ago	29/8,944 (3%)	22/6,350 (5%)	7/2,594 (1%)	5%	6%	3%	1.36 (0.91, 2.03)	1.26 (0.79, 2.00)	1.92 (0.89, 4.14)
3. 30-39 years ago	55/17,874 (5%)	44/10,854 (8%)	11/7,020 (4%)	5%	6%	4%	1.79 (1.33, 2.42)	1.88 (1.32, 2.66)	1.62 (0.87, 3.02)
4. 20-29 years ago	46/29,752 (9%)	36/15,767 (12%)	10/13,985 (7%)	6%	6%	5%	1.09 (0.79, 1.50)	1.20 (0.82, 1.75)	0.86 (0.45, 1.65)
5. 10-19 years ago	52/26,810 (8%)	31/13,822 (10%)	21/12,988 (7%)	6%	7%	6%	1.38 (1.02, 1.87)	1.22 (0.82, 1.82)	1.79 (1.12, 2.87)
6. 0-9 years ago	41/25,767 (8%)	29/12,144 (9%)	12/13,623 (7%)	10%	11%	9%	1.29 (0.92, 1.81)	1.43 (0.95, 2.16)	1.08 (0.59, 1.97)
7. Current smoker	45/31,430 (10%)	31/12,653 (9%)	14/18,777 (10%)	16%	19%	13%	1.40 (1.01, 1.95)	1.66 (1.11, 2.49)	1.04 (0.59, 1.84)
PAF (7 → 2)[4]							0.6 (-9.3, 9.8)	6.0 (-6.6, 17.2)	-10.5 (-30.5, 6.5)
PAF (7 → 3)[4]							-5.5 (-15.3, 3.4)	-3.1 (-16.4, 8.6)	-6.9 (-21.1, 5.8)
PAF (7 → 4)[4]							4.4 (-3.2, 11.5)	6.9 (-3.9, 16.7)	2.1 (-7.4, 11.0)
PAF (7 → 5)[4]							0.3 (-7.9, 8.0)	6.6 (-4.5, 16.6)	-9.0 (-21.0, 1.9)
PAF (7 → 6)[4]							1.6 (-6.8, 9.3)	3.5 (-8.8, 14.4)	-0.4 (-10.8, 9.0)
Smoking intensity[6]									
1. Never smoker	232/187,146 (57%)	118/65,505 (48%)	114/121,641 (64%)	56%	52%	61%	1	1	1
Former smoker, who quit									
2. ≥40 years ago	29/8,944 (3%)	22/6,350 (5%)	7/2,594 (1%)	2%	3%	1%	1.36 (0.91, 2.03)	1.26 (0.79, 2.01)	1.92 (0.89, 4.15)
3. 30-39 years ago	55/17,874 (5%)	44/10,854 (8%)	11/7,020 (4%)	3%	4%	3%	1.80 (1.33, 2.43)	1.88 (1.32, 2.67)	1.62 (0.87, 3.03)
4. 20-29 years ago	46/29,752 (9%)	36/15,767 (12%)	10/13,985 (7%)	5%	5%	5%	1.09 (0.79, 1.51)	1.20 (0.82, 1.75)	0.87 (0.45, 1.67)
5. 10-19 years ago	52/26,810 (8%)	31/13,822 (10%)	21/12,988 (7%)	6%	6%	6%	1.38 (1.02, 1.88)	1.22 (0.82, 1.82)	1.81 (1.13, 2.90)
6. 0-9 years ago	41/25,767 (8%)	29/12,144 (9%)	12/13,623 (7%)	10%	10%	10%	1.30 (0.92, 1.81)	1.43 (0.95, 2.16)	1.09 (0.60, 1.99)
Current smoker									

7. 0-19 cigarettes/day	15/15,027	(4%)	31/13,822 (10%)	4/9,896	(5%)	14%	16%	11%	1.03 (0.61, 1.74)	1.43 (0.77, 2.67)	0.58 (0.21, 1.58)
8. ≥20 cigarettes/day	28/14,317	(4%)	29/12,144 (9%)	9/7,488	(4%)	4%	5%	4%	1.80 (1.20, 2.68)	1.94 (1.19, 3.18)	1.58 (0.79, 3.14)
PAF (8 → 7)[4]									2.9 (-0.4, 6.1)	2.0 (-3.0, 6.6)	3.3 (-0.8, 7.2)
Body fatness (BMI; kg/m^2)											
1. <25.0	145/133,298 (40%)		77/43,084 (31%)	68/90,214 (47%)		37%	29%	43%	1	1	1
2. 25.0-29.9	230/128,881 (39%)		167/66,972 (48%)	63/61,909 (32%)		36%	42%	29%	1.44 (1.17, 1.78)	1.51 (1.15, 1.98)	1.30 (0.92, 1.83)
3. ≥30.0	135/70,628 (21%)		76/29,669 (21%)	59/40,959 (21%)		28%	28%	27%	1.83 (1.44, 2.33)	1.70 (1.23, 2.34)	2.03 (1.42, 2.90)
PAF (2-3 → 1)[4]									28.8 (17.3, 38.7)	29.3 (13.0, 42.6)	27.2 (10.3, 41.0)
PAF (2 → 1)[4]									11.8 (4.9, 18.2)	15.2 (5.2, 24.1)	6.3 (-2.6, 14.4)
PAF (3 → 1)[4]									17.0(9.9, 23.4)	14.2 (5.1, 22.3)	20.9 (9.4, 31.0)
PAF (3 → 2)[4]									7.9 (0.4, 14.9)	3.8 (-5.6, 12.4)	14.9 (2.1, 26.0)
Alcohol consumption											
0 drinks/day	197/127,184 (38%)		88/34,819 (25%)	109/92,365 (48%)		42%	34%	50%	1	1	1
<1 drink/day	128/89,393	(27%)	90/36,665 (26%)	38/52,728 (27%)		28%	26%	29%	0.92 (0.73, 1.16)	1.04 (0.78, 1.40)	0.76 (0.52, 1.11)
1-2 drinks/day	109/70,089	(21%)	77/34,134 (24%)	32/35,955 (19%)		13%	15%	11%	0.87 (0.68, 1.11)	0.90 (0.66, 1.22)	0.88 (0.59, 1.33)
>2-3 drinks/day	43/24,644	(7%)	36/16,535 (12%)	7/8,109	(4%)	7%	9%	5%	0.86 (0.61, 1.21)	0.87 (0.59, 1.29)	0.97 (0.44, 2.10)
>3 drinks/day	33/21,497	(6%)	29/17,572 (13%)	4/3,925	(2%)	10%	16%	4%	0.63 (0.43, 0.93)	0.63 (0.41, 0.96)	0.89 (0.32, 2.42)
Joint behaviours											
Current and former smokers to never smokers, BMI ≥ 25 kg/m^2 to < 25kg/m^2									39.6 (27.5, 49.7)	44.0 (27.7, 56.6)	33.3 (14.4, 48.1)
Current smokers to never smokers, BMI ≥ 25 kg/m^2 to < 25kg/m^2									32.8 (20.8, 42.9)	36.1 (19.6, 49.1)	27.7 (9.6, 42.2)

BMI (body mass index); CI (confidence interval); HR (hazard ratio); PAF (population attributable fraction);
[1] Number of cancer cases / total N (%) per risk factor category
[2] Population exposure prevalence from the National Health Survey 2014-2015 (smoking status, body fatness, alcohol consumption) or the National Drug Strategy Household Survey 2013 (smoking intensity)
[3] Adjusted for age, sex, study, smoking, BMI, alcohol consumption, and height
[4] Modification of risk factor exposure level → target reference level
[5] Evaluated in the subset of former smokers (95%) who provided information on time since quitting
[6] Evaluated in the subset of current smokers (93%) who provided information on smoking intensity
Note: some percentages do not add up to 100 because of rounding

Table 3. Risk factor frequencies, population exposure prevalences, hazard ratios and fractions of bladder cancers avoidable by change in exposure to behavioural risk factors over 10-years follow-up

	Cohort n/N (%)[1]			Population prevalence[2]			HR (95% CI)[3]		
Behavioural risk factor	**All**	**Men**	**Women**	**All**	**Men**	**Women**	**All**	**Men**	**Women**
Smoking status									
1. Never smoker	167/204,381 (57%)	95/70,445 (47%)	72/133,936 (63%)	53%	45%	60%	1	1	1
2. Former smoker	293/122,798 (34%)	254/65,610 (44%)	39/57,188 (27%)	31%	36%	27%	2.06 (1.69, 2.50)	2.38 (1.88, 3.01)	1.48 (1.00, 2.19)
3. Current smoker	63/34,288 (9%)	53/13,433 (9%)	10/20,855 (10%)	16%	19%	13%	3.49 (2.59, 4.70)	4.46 (3.16, 6.28)	1.76 (0.91, 3.44)
PAF (2-3 → 1)[4]							44.4 (35.4, 52.1)	53.4 (43.1, 61.8)*	18.9 (1.1, 33.4)
PAF (2 → 1)[4]							20.0 (14.3, 25.3)	23.0 (16.5, 29.0)	10.6 (-1.3, 21.1)
PAF (3 → 1)[4]							24.4 (16.9, 31.2)	30.4 (21.6, 38.2)*	8.2 (-4.0, 19.0)
Time since quitting smoking[5]									
1. Never smoker	167/204,381 (58%)	95/70,445 (48%)	72/133,936 (64%)	53%	45%	60%	1	1	1
Former smoker, who quit									
2. ≥40 years ago	38/9,741 (3%)	34/6,872 (5%)	4/2,869 (1%)	5%	6%	3%	1.24 (0.86, 1.77)	1.39 (0.93, 2.06)	1.14 (0.42, 3.12)
3. 30-39 years ago	55/19,172 (5%)	51/11,558 (8%)	4/7,614 (4%)	5%	6%	4%	1.93 (1.42, 2.63)	2.32 (1.65, 3.26)	0.92 (0.34, 2.51)
4. 20-29 years ago	71/31,751 (9%)	59/16,687 (11%)	12/15,064 (7%)	6%	6%	5%	2.21 (1.67, 2.93)	2.47 (1.78, 3.42)	1.98 (1.07, 3.65)
5. 10-19 years ago	63/28,498 (8%)	53/14,608 (10%)	10/13,890 (7%)	6%	7%	6%	2.44 (1.82, 3.27)	2.85 (2.03, 4.00)	1.73 (0.89, 3.37)
6. 0-9 years ago	49/27,629 (8%)	42/12,793 (9%)	7/14,836 (7%)	10%	11%	9%	2.71 (1.95, 3.75)	3.36 (2.32, 4.86)	1.47 (0.67, 3.20)
7. Current smoker	63/34,288 (10%)	53/13,433 (9%)	10/20,855 (10%)	16%	19%	13%	3.62 (2.68, 4.88)	4.64 (3.29, 6.55)	1.84 (0.94, 3.58)
PAF (7 → 2)[4]							22.4 (13.9, 30.1)	27.1 (17.3, 35.7)	7.5 (-10.8, 22.7)
PAF (7 → 3)[4]							15.9 (6.4, 24.4)	19.3 (8.2, 29.1)	9.8 (-6.4, 23.5)
PAF (7 → 4)[4]							13.2 (3.6, 21.9)	18.1 (7.0, 27.9)	-1.5 (-20.1, 14.3)
PAF (7 → 5)[4]							11.1 (0.9, 20.2)	14.9 (2.9, 25.4)	1.1 (-17.0, 16.4)
PAF (7 → 6)[4]							8.6 (-2.8, 18.8)	10.7 (-3.3, 22.7)	4.0 (-14.2, 19.3)
Smoking intensity[6]									
1. Never smoker	167/204,381 (58%)	95/70,445 (48%)	72/133,936 (64%)	56%	52%	61%	1	1	1
Former smoker, who quit									
2. ≥40 years ago	38/9,741 (3%)	34/6,872 (5%)	4/2,869 (1%)	2%	3%	1%	1.23 (0.86, 1.77)	1.38 (0.93, 2.05)	1.13 (0.41, 3.10)
3. 30-39 years ago	55/19,172 (5%)	51/11,558 (8%)	4/7,614 (4%)	3%	4%	3%	1.93 (1.42, 2.63)	2.32 (1.65, 3.26)	0.92 (0.34, 2.51)
4. 20-29 years ago	71/31,751 (9%)	59/16,687 (11%)	12/15,064 (7%)	5%	5%	5%	2.22 (1.68, 2.94)	2.47 (1.78, 3.42)	1.98 (1.07, 3.66)
5. 10-19 years ago	63/28,498 (8%)	53/14,608 (10%)	10/13,890 (7%)	6%	6%	6%	2.45 (1.83, 3.29)	2.86 (2.04, 4.01)	1.74 (0.89, 3.38)
6. 0-9 years ago	49/27,629 (8%)	42/12,793 (9%)	7/14,836 (7%)	10%	10%	10%	2.73 (1.97, 3.78)	3.39 (2.34, 4.90)	1.47 (0.68, 3.21)
Current smoker									

7. 0-19 cigarettes/day	24/16,416	(5%)	18/5,438	(4%)	6/10,978	(5%)	14%	16%	11%	2.91 (1.89, 4.49)	3.57 (2.15, 5.93)	1.95 (0.84, 4.50)
8. ≥20 cigarettes/day	36/15,495	(4%)	32/7,243	(5%)	4/8,252	(4%)	4%	5%	4%	4.55 (3.14, 6.60)	5.90 (3.92, 8.90)	1.86 (0.67, 5.11)
PAF (8 → 7)[4]										4.0 (-0.9, 8.7)	(-1.1, 11.1)	-0.3 (-7.1, 6.1)
Fruit and vegetable consumption[7]												
Per serve	463/314,687		375/143,986		88/170,701					0.99 (0.97, 1.02)	1.00 (0.97, 1.03)	0.97 (0.91, 1.02)
1. Recommendation unmet	354/224,542	(73%)	297/112,943	(81%)	57/111,599	(67%)	94%	95%	93%	1	1	1
2. Recommendation met	96/82,592	(27%)	66/26,601	(19%)	30/55,991	(33%)	6%	5%	7%	0.89 (0.70, 1.12)	0.85 (0.65, 1.12)	0.99 (0.63, 1.54)

***** Burden in men differs from burden in women , i.e. the 95% confidence interval of the difference of the PAF estimates for men and women does not include zero. CI (confidence interval); HR (hazard ratio); PAF (population attributable fraction)

[1] Number of cancer cases / total N (%) per risk factor category

[2] Population exposure prevalence from the National Health Survey 2014-2015 (smoking status, time since quitting smoking, fruit and vegetable consumption) or the National Drug Strategy Household Survey 2013 (smoking intensity)

[3] Adjusted for age, sex, study, and smoking

[3] Modification of risk factor exposure level → target reference level

[5] Evaluated in the subset of former smokers (95%) who provided information on time since quitting

[6] Evaluated in the subset of current smokers (93%) who provided information on smoking intensity

[7] Australian recommendation: At least 2 serves of fruits and 5 serves of vegetables per day

Note: some percentages do not add up to 100 because of rounding

Supplementary Table 1. List of main harmonised baseline risk factors for cohort studies and external prevalence data sources

	Cohort data							External data	
Risk factors	**MCCS**	**BMES**	**ALSWH**	**AusDiab**	**NWAHS**	**CHAMP**	**45&Up**	**NHS**	**NDSHS**
Modifiable factors									
Smoking[1]									
Status (never, former, current)	√	√	√	√	√	√	√	√	√
Time since quitting (years)	√	√	√	√	√	√	√	√	√
Cigarettes/day	√	√	√	√	√	√	√	-	√
Duration (years)	√	√	√	√	√	√	√	√	√
Body fatness (BMI, kg/m^2)[2]	√	√	√	√	√	√	√	√	-
Alcohol consumption (drinks/day)[1]	√	√	√	√	√	√	√	√	√
Diet[1]									
Fruit consumption (serves/day)	√	√	-	√	-	-	√	√	-
Vegetable consumption (serves/day)	√	√	-	√	-	-	√	√	-
Blood pressure (systolic, diastolic)[3]	√	-	-	√	√	-	-	√	-
Non-modifiable factors									
Age	√	√	√	√	√	√	√	√	√
Sex	√	√	√	√	√	√	√	√	√
Height (cm)[2]	√	√	√	√	√	√	√	√	√
Country of birth (Australia, other)	√	√	√	√	√	√	√	√	√
Marital status (married/de facto, other)	√	√	√	√	√	√	√	√	√
Educational attainment (basic, intermediate, high)	√	√	√	√	√	√	√	√	√
Socioeconomic status (SEIFA)	√	√	√	√	√	√	√	√	√
Residential location (ARIA)	√	√	√	√	√	√	√	√	√

√ (available); - (not available); 45&Up (45 and Up Study); ALSWH (Australian Longitudinal Study on Women's Health); ARIA (Accessibility/Remoteness Index of Australia); AusDiab (Australian Diabetes, Obesity and Lifestyle Study); BMES (Blue Mountains Eye Study); CHAMP (Concord Health and Ageing in Men Project); MCCS (Melbourne Collaborative Cohort Study); NDSHS (National Drug Strategy Household Survey 2013); NHS (National Health Survey 2014-2015); NWAHS (North West Adelaide Health Study); SEIFA (Socio-Economic Indexes for Areas)

[1] Self-reported via questionnaires or interviews

[2] Measured weight and height (MCCS, AusDiab, NWAHS, CHAMP, NHS); self-reported weight and height (BMES, ALSWH, 45&Up)

[3] Average of 2 or 3 measurements

Supplementary table 2. Cohort-specific hazard ratios for kidney cancer incidence by exposure level over 10-years follow-up

	HR (95% CI)[1]							P[2]
Risk factors	**MCCS**	**BMES**	**ALSWH**	**AusDiab**	**NWAHS**	**CHAMP**	**45&Up**	
Incident kidney cancers (n)	74	10	55	19	12	4	376	
Non-modifiable risk factors								
Sex								
Male	1	1		1	1		1	
Female	0.34 (0.21, 0.55)	0.47 (0.13, 1.68)		0.29 (0.11, 0.82)	0.91 (0.29, 2.81)		0.44 (0.36, 0.55)	0.52
Height (per 5 cm)	1.05 (0.89, 1.24)	1.29 (0.81, 2.05)	1.11 (0.90, 1.36)	1.01 (0.72, 1.42)	0.75 (0.49, 1.15)	0.55 (0.27, 1.15)	1.10 (1.58, 1.18)	0.31
Modifiable risk factors								
Smoking								
Never smoker	1	1	1	1	1	1	1	
Former smoker	1.13 (0.68, 1.89)	3.15 (0.58, 7.30)	1.33 (0.72, 2.44)	2.78 (0.96, 8.00)	0.73 (0.17, 3.12)	1.34 (0.12, 4.77)	1.36 (1.10, 1.69)	0.69
Current smoker	1.26 (0.62, 2.59)	3.89 (0.52, 8.96)	1.74 (0.77, 3.90)	0.65 (0.08, 5.71)	2.15 (0.54, 8.49)	7.14 (0.44, 16.5)	1.04 (0.65, 1.65)	0.56
Body mass index (BMI; kg/m^2)								
<25.0	1	1	1	1	1	NA[3]	1	
25.0-29.9	1.31 (0.74, 2.32)	2.09 (0.38, 1.52)	1.49 (0.79, 2.81)	1.33 (0.40, 4.46)	2.19 (0.43, 11.1)		1.36 (1.06, 1.75)	0.99
≥30.0	1.60 (0.84, 3.06)	5.58 (1.00, 1.06)	1.79 (0.84, 3.81)	2.55 (0.75, 8.73)	2.07 (0.38, 11.3)		1.69 (1.27, 2.24)	0.81
Alcohol consumption								
0 drinks/day	1	1	1	1	1	1	1	
<1 drinks/day	1.06 (0.61, 1.84)	0.40 (0.05, 3.25)	0.23 (0.06, 0.96)	0.54 (0.11, 2.56)	0.89 (0.18, 4.45)	1.49 (0.09, 3.80)	0.99 (0.76, 1.29)	0.51
1-2 drinks/day	0.51 (0.22, 1.16)	0.29 (0.04, 2.32)	0.66 (0.26, 1.67)	0.74 (0.19, 2.84)	1.38 (0.27, 7.02)	2.07 (0.19, 2.90)	0.95 (0.72, 1.25)	0.64
>2-3 drinks/day	0.83 (0.36, 1.90)	-	3.86 (0.91, 16.39)	1.86 (0.48, 7.29)	3.37 (0.38, 29.8)	-	0.98 (0.67, 1.44)	0.26
>3 drinks/day	0.43 (0.17, 1.13)	-	2.30 (0.82, 6.43)	1.58 (0.39, 6.41)	1.25 (0.14, 11.2)	-	0.70 (0.43, 1.12)	0.14

45&Up (45 and Up Study); ALSWH (Australian Longitudinal Study on Women's Health); AusDiab (Australian Diabetes, Obesity and Lifestyle Study); BMES (Blue Mountains Eye Study); CHAMP (Concord Health and Ageing in Men Project); CI (Confidence interval); HR (Hazard ratio); MCCS (Melbourne Collaborative Cohort Study); NWAHS (North West Adelaide Health Study)

[1] Adjusted for age and sex

[2] P value for heterogeneity between the study-specific HRs tested using the asymptotic DerSimonian and Laird Q statistic

[3] HRs for BMI in CHAMP could not be calculated due to lack of cases in the reference category

Supplementary table 3. Cohort-specific hazard ratios for bladder cancer incidence by exposure level over 10-years follow-up

	HR (95% CI)[1]							P[2]
Risk factors	**MCCS**	**BMES**	**ALSWH**	**AusDiab**	**NWAHS**	**CHAMP**	**45&Up**	
Incident bladder cancers (n)	71	12	35	22	9	16	365	
Non-modifiable risk factors								
Sex								
Male	1	1		1	1		1	
Female	0.14 (0.07, 0.26)	0.13 (0.03, 0.60)		0.38 (0.16, 0.94)	0.27 (0.06, 1.29)		0.23 (0.17, 0.30)	0.40
Modifiable risk factors								
Smoking status								
Never smoker	1	NA[3]	1	1	1	1	1	
Former smoker	2.12 (1.15, 3.90)		1.18 (0.55, 2.56)	3.26 (1.14, 9.33)	2.04 (0.37, 11.36)	2.50 (0.70, 8.95)	2.00 (1.60, 2.52)	0.74
Current smoker	4.71 (2.37, 9.37)		1.39 (0.41, 4.76)	2.28 (0.43, 12.09)	4.51 (0.59, 34.33)	2.53 (0.26, 24.51)	3.62 (2.47, 5.32)	0.65
Fruit and vegetable consumption[4]								
Recommendation unmet	1	1		1			1	
Recommendation met	0.80 (0.50, 1.29)	1.09 (0.32, 3.71)		0.99 (0.23, 4.26)			0.84 (0.63, 1.11)	0.97

45&Up (45 and Up Study); ALSWH (Australian Longitudinal Study on Women's Health); AusDiab (Australian Diabetes, Obesity and Lifestyle Study); BMES (Blue Mountains Eye Study); CHAMP (Concord Health and Ageing in Men Project); CI (Confidence interval); HR (Hazard ratio); MCCS (Melbourne Collaborative Cohort Study); NWAHS (North West Adelaide Health Study)

[1] Adjusted for age and sex

[2] P value for heterogeneity between the study-specific HRs tested using the asymptotic DerSimonian and Laird Q statistic

[3] HRs could not be calculated due to lack of cases in the reference category

[4] Australian recommendation: At least 2 serves of fruits and 5 serves of vegetables per day

Supplementary Table 4. Risk factor exposure prevalence, hazard ratios and fractions of renal cell kidney cancers avoidable by change in exposure to body fatness over 10-years follow-up

Behavioural risk factor	Cohort n/N (%)[1]			Population prevalence[2]			HR (95% CI)[3]		
	All	Men	Women	All	Men	Women	All	Men	Women
Body fatness (BMI; kg/m^2)									
1. <25.0	132/133,298 (40%)	76/43,084 (31%)	56/90,214 (47%)	37%	29%	43%	1	1	1
2. 25.0-29.9	221/128,881 (39%)	160/66,972 (48%)	61/61,909 (32%)	36%	42%	29%	1.49 (1.20, 1.86)	1.44 (1.10, 1.90)	1.53 (1.06, 2.20)
3. ≥30.0	130/70,628 (21%)	75/29,669 (21%)	55/40,959 (21%)	28%	28%	27%	1.90 (1.49, 2.44)	1.66 (1.20, 2.30)	2.29 (1.56, 3.34)
PAF (2-3→ 1)[4]							30.6 (18.9, 40.7)	27.4 (10.6, 41.0)	33.8 (16.4, 47.6)
PAF (2 → 1)[4]							12.8 (5.8, 19.3)	13.6 (3.4, 22.8)	10.1 (0.8, 18.6)
PAF (3 → 1)[4]							17.8 (10.6, 24.4)	13.8 (4.6, 22.1)	23.7 (11.8, 34.0)
PAF (3 → 2)[4]							8.1 (0.3, 15.2)	4.5 (-4.9, 13.2)	14.0 (0.3, 25.8)

BMI (body mass index); CI (confidence interval); HR (hazard ratio); PAF (population attributable fraction);
[1] Number of cancer cases / total N (%) per risk factor category
[2] Population exposure prevalence from the National Health Survey 2014-2015
[3] Adjusted for age, sex, study, smoking, BMI, alcohol consumption, and height
[4] Modification of risk factor exposure level → target reference level
Note: some percentages do not add up to 100 because of rounding

Appendix 1. Calculation of PAF

We followed a population of $i = 1, \dots, n$ individuals with risk factor values $X_i = (x_{i1}, \dots, x_{im})^T$ from baseline (t = 0) to the date of diagnosis of cancer (T_i^D), death (T_i^M) or end of follow-up (t), whichever occurred first. PAF estimates the proportion of cancer cases that could hypothetically be avoided during the follow-up, if it was possible to modify some risk factor values, $X_i = (x_{i1}, \dots, x_{im})^T \rightarrow X_i^* = (x_{i1}^*, \dots, x_{im}^*)^T$. Death before cancer incidence causes censoring in the population during follow-up. If the risk factors for cancer incidence are also related to death, then their modification affects both the risk of cancer and the risk of death. Therefore, we take censoring due to death into account and calculate PAF for cancer incidence before death:

$$PAF(T^D \leq \min(T^M, t)) = 1 - \frac{\sum_{i=1}^{n} P\{T_i^D \leq \min(T_i^M, t) | X_i^*\}}{\sum_{i=1}^{n} P\{T_i^D \leq \min(T_i^M, t) | X_i\}},$$

where $P\{T_i^D \leq \min(T_i^M, t) \,|X_i\}$ is the probability of the cancer incidence up to time t, given the risk factors X_i, which can be either categorical, continuous or their interactions.

In the calculation of PAF, the survival times T^D and T^M are assumed to follow a parametric piecewise constant hazards model. This model was chosen due to its flexibility in accommodating to the shape of the underlying survival curve and ease of computation. In a parametric piecewise constant hazards model, the follow-up time is partitioned into *J-1* intervals $(0 = a_1, a_2], (a_2, a_3], \dots, \left(a_{j-1}, a_j\right], \dots, \left(a_{J-1}, a_J = t\right]$, where $a_{j-1} < a_j$ for all j and the hazard for the ith individual

$$h(t; X_i) = \sum_{j=1}^{J} 1\{a_{j-1} < t \leq a_j\} \lambda_{0j} \exp(X_i^T \beta) = \sum_{j=1}^{J} 1\{a_{j-1} < t \leq a_j\} \lambda_{ij}$$

is allowed to depend on time by letting the value of the baseline hazard λ_{0j} change at times a_j.

Thus, the PAF during the follow-up time interval $[0, t]$ can be calculated as

$$PAF(T^D \leq \min(T^M, t)) = 1 - \frac{\sum_{i=1}^{n} \sum_{j=1}^{J} \frac{\lambda_{ij}^{*D}}{\lambda_{ij}^{*D} + \lambda_{ij}^{*M}} \left(S_{i,j-1}^* - S_{ij}^*\right)}{\sum_{i=1}^{n} \sum_{j=1}^{J} \frac{\lambda_{ij}^{D}}{\lambda_{ij}^{D} + \lambda_{ij}^{M}} \left(S_{i,j-1} - S_{ij}\right)},$$

where $S_{iJ} = S_{ij}^D S_{ij}^M = \exp\left[-\sum_{j=1}^{J} \left(\lambda_{ij}^D + \lambda_{ij}^M\right)\left(a_{j-1} - a_j\right)\right]$ is the disease-free survival up to time t.

Maximum likelihood estimation with iterative methods was used to obtain the parameter estimates β^D and β^M and their estimated covariance matrices. Asymptotic variance estimate of PAF was obtained using the delta method and two-sided 95% confidence intervals for the PAFs were calculated by applying a symmetrising complementary logarithmic transformation of PAF.

In the calculation of PAF, we may want to consider the potential effect modification, i.e. whether the relationship between the risk factor and the cancer, and thus potentially also PAF, varies according to the values of a potential effect modifying factor. To analyse the impact of the potential effect modifying factor, an interaction term between the risk factor and the potential effect modifying factor is included in the model giving separate parameter estimates for the risk factor in the different categories of the potential effect modifying factor. Separate PAF estimates are then calculated in the subpopulations defined by the categories of the potential effect modifying factor. The statistical significance of effect modification can be determined by calculating the 95% confidence intervals for the differences between these PAF estimates and by comparing whether they cover zero.

In case of an effect modifying factor with two categories, for example, we calculate two separate PAF estimates $\widehat{PAF_1}$ and $\widehat{PAF_2}$ and estimate the PAF difference $\widehat{PAF_1} - \widehat{PAF_2}$ and its 95% confidence interval

$$\widehat{PAF_1} - \widehat{PAF_2} \pm 1.96 \times \sqrt{\hat{\delta}^2_{(PAF_1 - PAF_2)}}$$

The variance of PAF difference $\hat{\delta}^2_{(PAF_1 - PAF_2)}$ is obtained using the delta method.