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How many cancer cases and deaths are potentially preventable? Estimates for Australia in 2013

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Cancer is a leading cause of disease burden in Australia, particularly fatal burden, accounting for an estimated thirty percent of deaths. Many cancers develop because of exposure to lifestyle and environmental factors that are potentially modifiable. We aimed to quantify the proportions and numbers of cancer deaths and cases in Australia in 2013 attributable to 20 modifiable factors in eight broad groupings that are established causes of cancer, namely: tobacco smoke (smoking and second-hand), dietary factors (low intake of fruit, non-starchy vegetables and dietary fibre; and high intake of red and processed meat), overweight/obesity, alcohol, physical inactivity, solar ultraviolet radiation, infections (seven agents), and reproductive factors (lack of breastfeeding, menopausal hormone therapy use, combined oral contraceptive use). We estimated population attributable fractions (PAF) using standard formulae incorporating exposure prevalence and relative risk data. Of all cancer deaths in Australia in 2013, approximately 38% overall (males 41%, females 34%) could be attributed to the factors assessed; the corresponding PAF for cancer cases was 33% (males 34%, females 32%). Tobacco smoke was the leading cause of cancer deaths and cases, with PAFs of 23 and 13%, respectively, followed by dietary factors (5% deaths/5% cases), overweight/obesity (5%/4%) and infections (5%/3%). Cancer sites with the highest numbers of potentially preventable deaths/cases were lung ($n = 6{,}776/9{,}272$), colorectum ($n = 1{,}974/7{,}380$) and cutaneous melanoma ($n = 1{,}390/7{,}918$). We estimate that about 16,700 cancer deaths and 41,200 cancer cases could be prevented in Australia each year if people's exposures to 20 causal factors were aligned with levels recommended to minimise cancer risk.

Key words: neoplasms, population attributable fraction, risk factors, primary prevention, mortality

Abbreviations: BMI: body mass index; CI: confidence interval; CPS II: Cancer Prevention Study II; DALYs: disability adjusted life-years; EBV: Epstein–Barr virus; KSHV: Kaposi's sarcoma herpes virus; HIV: human immunodeficiency virus; HPV: human papillomarvirus; IARC: International Agency for Research on Cancer; OCP: oral contraceptive pill; PAF: population attributable fraction; RR: relative risk; SCC: squamous cell carcinoma; UV: ultraviolet; WCRF: World Cancer Research Fund

Additional Supporting Information may be found in the online version of this article.

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Cancer imposes the greatest total burden of disease in the Australian population due to a combination of high incidence, disability and premature mortality.[1] In the population of 24.5 million, nearly 48,000 people are expected to die from cancer in 2017 accounting for around 30% of registered Australian deaths.[2]

There is evidence that many cancers are caused by exposure to environmental and lifestyle factors.[3,4] It is therefore important to quantify the proportion of cancer incidence and mortality [using the population attributable fraction (PAF)] that might be avoided if exposure to those factors occurred at levels that minimise cancer risk.

Previously, we estimated that one in three of the 130,000 cancers newly diagnosed in Australia in 2010 were attributable to 20 discrete, potentially modifiable causes of cancer in eight broad groupings (33% of cancers in males and 31% in females).[5] Tobacco was the leading cause of incident cancer in 2010 (PAF all cancers: 13%), followed by solar ultraviolet (UV) radiation (6%), dietary factors (6% incorporating low intake of fruit, non-starchy vegetables and dietary fibre, and high intake of red and processed meat), overweight and obesity (3%), infections (seven agents) (3%), and alcohol (3%). Cancers with the highest counts of potentially preventable cancers were lung (8,569), colorectal (7,404), cutaneous melanoma (7,220) and breast (3,223).[5]

What's new?

Cancer is the leading cause of death in Australia. Yet many of these deaths could be prevented if known causes were avoided. In this study, the authors estimated the number and fraction of cancer deaths and cancer cases in Australia attributable to modifiable factors. They found that 38% of all cancer deaths and 33% of cancer cases could be attributed to 20 factors. Tobacco smoke was the leading cause of cancer death, followed by dietary factors, overweight/obesity, infections and solar ultraviolet radiation.

Because different types of cancer differ considerably in their case fatality rates, the preventable fraction of cancer deaths will differ from the preventable fraction of cancer cases diagnosed. Therefore, our present aim was to estimate the number and proportion of cancer deaths in Australia in 2013 that were attributable to modifiable causal factors. In doing so, we also updated our previous estimates of the attributable number and proportion of cancers diagnosed in Australia using 2013 incidence data and the most recent assessments of causality.

Methods

For most causal factors (hereafter referred to as "factors"), we calculated the PAF using relative risks and the prevalence of the factor in the population of interest. Factors for which the calculation method deviates from this approach [tobacco smoke, solar UV radiation, infections and use of the combined oral contraceptive pill (OCP)] are discussed below in Statistical Analyses.

We used the standard formula[6] to calculate the PAF by age and sex category:

$$\mathrm{PAF} = \frac{\sum (p_x \times \mathrm{ERR}_x)}{1 + \sum (p_x \times \mathrm{ERR}_x)}$$

Where p_x is the proportion of the population in factor level x and ERR_x the excess relative risk ($\mathrm{RR}_x - 1$) associated with factor level x.

The PAF is expressed as a percentage and is an estimate of the proportion of deaths/cases that would be prevented if exposure to the factor in the population were reduced to the level of the reference category (as described in Table 1).

We considered the same lifestyle and environmental factors as we included in our analyses of cancer incidence attributable to modifiable causes in Australia in 2010 (Australian PAF Incidence Study).[7] To be included, the factors had to meet the following three criteria: (*i*) evidence of a causal association between the factor and at least one cancer, as determined by either the World Cancer Research Fund (WCRF) or the International Agency for Research on Cancer (IARC); (*ii*) Australian prevalence data for the factor were available and (*iii*) exposure to the factor is potentially modifiable.[7] The factors that met these criteria are summarised in Table 1.

Both the WCRF and IARC continually reassess their causality assessments in light of new data.[5] Since our previous assessment in 2014, additional cancers have been newly determined as causally associated with body mass index (BMI; stomach—cardia,[8] liver,[9] advanced/fatal prostate,[10] thyroid,[11] multiple myeloma[11]), alcohol consumption (stomach[8]) and processed meat (stomach[8]). In contrast, the level of evidence has been revised downwards from "probable" to "limited" for associations between fruit and non-starchy vegetable intake and cancers of the oesophagus and stomach.[8,12] We therefore updated our estimates of the number and proportion of cancers diagnosed in Australia associated with these factors to enable comparison with our new estimates of PAF for mortality.

Cancer data

We sourced cancer incidence and mortality data from the Australian Institute of Health and Welfare.[13] For many cancers, the number of deaths in any one year is small and prone to fluctuate from year to year. We therefore averaged the number of deaths from 2012 to 2014 (latest available) to estimate the average number of deaths in 2013. Incidence data at the histology level (adenocarcinomas and squamous cell carcinomas (SCC) of the oesophagus) and sub-site level (cardia and non-cardia stomach cancers) were not available for 2013. To estimate the numbers of these cancers diagnosed in 2013 we applied the average age-, sex- and histology/subsite specific incidence rates between 2010 and 2012 (latest available) to the 2013 Australian estimated resident population. As cancer deaths are not coded at the histology level, we also applied the proportional distribution of histology-specific incidence to the number of oesophageal cancer deaths (by age and sex) to estimate the histology-specific mortality in 2013 (*i.e.*, assuming the distribution of deaths by histology for these sites is similar to the distribution of new diagnoses).

For cancers with only a small number of deaths (*viz.*, vulva, vagina, penis, lip, salivary glands and the pharyngeal cancers) data were only available on the total deaths in 2012[14] and 2014.[2] To estimate the number of deaths for each of these cancers by age and sex in 2013, we applied the distribution of the incident cancers by age and sex (averaged from 2011 to 2013) to the number of deaths (averaged for 2012 and 2014) for each cancer.

Table 1. Potentially modifiable causal factors assessed, reference levels of exposure and cancer outcomes included

Factor	Reference level of exposure	Cancers causally associated
Alcohol consumption	Nil consumption	Oral cavity and pharynx, oesophagus (squamous cell carcinoma), stomach[1], colorectum, liver, breast (pre- and post-menopausal)
Diet		
– Low intake of dietary fibre	> 30 g/day for adult males > 25 g/day for adult females	Colorectum
– Low intake of fruit	> 300 g/day (~ 2 serves/day)	Oral cavity and pharynx, larynx, lung[2]
– Low intake of non-starchy vegetables	> 260 g/day (~ 3.5 serves/day)	Oral cavity and pharynx, larynx[2]
– High intake of red and processed meat	Nil consumption	Colon, rectum[3]
Infections		
– Epstein-Barr virus (EBV)	No infection	Nasopharynx, Hodgkin's lymphoma, Burkitt's lymphoma
– Hepatitis B virus (HBV)	No infection	Liver
– Hepatitis C virus (HCV)	No infection	Liver, non-Hodgkin's lymphoma
– Human papillomavirus (HPV)	No infection	Oral cavity, oropharynx, anus, vulva, vagina, uterine cervix, penis
– *Helicobacter pylori*	No infection	Stomach (non-cardia), low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma
– Human immunodeficiency virus, type 1 (HIV-1)	No infection	Anus[4], Kaposi's sarcoma[4], uterine cervix[4], non-Hodgkin's lymphoma
–Kaposi's sarcoma herpes virus (KSHV)	No infection	Kaposi's sarcoma
Overweight and obesity	Body mass index of < 25 kg/m^2	Oesophagus (adenocarcinoma), stomach (cardia)[1], colorectum, liver[1], gallbladder, pancreas, breast (post-menopausal), endometrium, ovary, prostate (advanced/fatal)[1], kidney, thyroid[1], multiple myeloma[1]
Physical inactivity	≥ 300 minutes (5 hours – 30 MET-hours) of moderate activity per week	Colon, breast (post-menopausal), endometrium
Reproductive/hormonal		
– Breastfeeding (< 12 months amongst Parous women, termed "insufficient")	> 12 months total duration	Breast (pre- and post-menopausal)
– Menopausal hormone therapy (MHT)	Nil use	Breast, endometrium, ovary
– Combined oral contraceptives (OCP)	Nil use (for cancers with an increase in risk only)	Increases risk: breast, uterine cervix Decreases risk: endometrium, ovary
Solar ultraviolet (UV) radiation	Melanoma mortality in low ambient solar UV radiation population (England/Wales 1950–1952)	Melanoma of the skin
Tobacco smoke		
– Tobacco smoking	Never smoked	Oral cavity and pharynx, oesophagus, stomach, colorectum, liver, pancreas, larynx, lung, uterine cervix, ovary (mucinous), kidney, bladder, acute myeloid leukaemia
– Exposure to smoking by partner in home	No exposure	Lung

NOTES:
[1]Additional cancers not considered in 2010 Australian PAF Incidence Study – declared causally associated by IARC or WCRF since November 2014.
[2]The 2010 Australian PAF Incidence Study also included oesophagus (squamous cell carcinoma) and stomach cancer. WCRF no longer considers that there is strong evidence for an association between consumption of fruit and non-starchy vegetables and these cancers.
[3]WCRF declares strong evidence for association between processed meat and cancer of the stomach (non-cardia). Not included here as separate prevalence estimate for processed meat not available for Australian population.
[4]Numbers not calculated separately as HIV is not necessary or sufficient.

Relative risk estimates

For our primary analysis, we used summary relative risks obtained from recent high-quality meta-analyses of cancer incidence (see Supporting Information Tables S1–S9). We used relative risks for cancer incidence rather than cancer mortality because incidence data are far more complete and of higher quality. The one exception was the relative risk for overweight/obesity and prostate cancer, for which the causal association is restricted to advanced/fatal cancer, so we used the WCRF relative risks for prostate cancer mortality. Where possible we used relative risks reported in the most recent meta-analyses conducted by the WCRF that summarised prospective studies of incidence. For factors not summarised by the WCRF, we used recent high-quality meta-analyses or risk estimates from pooled or prospective studies of cancer incidence.

Exposure prevalence estimates

We used the same prevalence data as used in the Australian PAF Incidence Study (see Supporting Information Tables S10–S18).[7] The exceptions to this were prevalence estimates for human papillomarvirus (HPV; see below) and duration of combined OCP use (see Supporting Information Table S16). Where possible we used population-based prevalence data from the National Health and Nutrition Surveys conducted by the Australian Bureau of Statistics.[15–18] Prevalence of infectious agents such as viral hepatitis and the human immunodeficiency virus (HIV) were sourced from the "HIV, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report 2012."[19] For other factors, we used "best estimates" of population prevalence from representative state-based surveys, population-based case-control studies or large-scale cohort studies.

The selection of prevalence estimates requires assumptions to be made about the latent period between exposure to the factor and death from cancer/diagnosis of cancer. In this study, we used the latest cancer data available (average 2012–2014) combined with prevalence data from 1995 (dietary factors) or 2001. Hence, latent periods ranged from 12–18 years for most factors.

Statistical analysis

To obtain the number of cancer deaths/cases attributable to each factor, we summed the product of age-, sex- and cancer site-specific PAFs and the corresponding average number of observed (or estimated) deaths/cases in 2013.

A combined PAF across all factors for each cancer site and all cancer deaths/cases combined was also calculated using the following formula[20]:

$$\text{combined PAF} = 1 - \prod_{r=1}^{R} (1 - \text{PAF}_r)$$

Where PAF_r is the PAF of each individual factor.

For each cancer site, we present the combined PAF and number of deaths/cases for all ages (0–85+ years) and the combined PAF and number of deaths/cases that occurred prematurely, defined here as deaths before the age of 75 years. We present the total number of attributable cancer deaths (all sites combined) for the age groups 0–74 years and 75+ years for each factor; these numbers are also expressed as a percentage of the number of all cancer deaths in these two age groups. We also compare the number and proportion of cancer deaths in 2013 to the updated results for cancer incidence for each factor.

Tobacco smoke. To estimate the PAF for tobacco smoke, we used the approach developed by Peto *et al.*[21] This method assumes tobacco smoking is the overwhelming cause of lung cancer mortality and incidence. The number of lung cancer deaths/cases attributable to smoking is the difference between the number of lung cancer deaths/cases observed in the population and the number expected if the entire population experienced the same age- and sex-specific lung cancer mortality and incidence rates as never smokers (see Supporting Information Table S19). From these estimates, a "notional prevalence" of smoking in the Australian population was derived and used to calculate the PAF for tobacco smoking for cancers other than lung using relative risks and standard formulae (see Supporting Information Table S20). To estimate the PAF for partners' smoking, we used the standard formula incorporating the proportion of non-smoking Australians living with an ever-smoking partner and relative risks associated with partner smoking (see Supporting Information Tables S21 and S22).

Solar UV radiation. The PAF for solar UV radiation was calculated as the proportional difference between the mortality/incidence from melanoma in Australian residents (*i.e.*, "exposed" to high ambient UV radiation) and the expected number of melanoma deaths/cases assuming an ethnically similar population was "minimally exposed" to ambient UV radiation. We used the 1950–52 mortality data for England and Wales as the "minimally exposed" reference population, as this preceded the advent of mass tourism and solarium use[22] (see Supporting Information Table S23). For the updated PAF incidence estimates, we used melanoma incidence rates for the United Kingdom (2012–2014) as our "minimally exposed" population.

Infections. For cancers caused by infectious agents [such as HPV and Epstein-Barr virus (EBV)] for which no other causes are known, the PAF is assumed to equal the prevalence of viral DNA in tumour cells.[23] We used updated HPV prevalence estimates from international sources for cancers of the vulva,[24] vagina,[25] penis,[26] anus,[27] oral cavity[28] and oropharynx.[28] For oropharyngeal cancers, we used HPV prevalence estimates from a recently published Australian study (see Supporting information Table S24).[29] For the association between *Helicobacter pylori* and non-cardia stomach cancer,

we used updated relative risks that were based on improved assay procedures using immunoblot rather than ELISA[30] (see Supporting Information Table S25).

Combined oral contraceptive pill (OCP). The combined OCP reduces the risk of deaths from endometrial and ovarian cancer, but increases the risk of breast and cervical cancer mortality (Table 1). For endometrial and ovarian cancers, we calculated the prevented fraction (PF) using the following formula:[31]

$$PF = \sum P_y \left(1 - RR_y\right)$$

Where P_y is the proportion of the population in each age and "duration of combined OCP use" category y and RR_y is the relative risk for each "duration of combined OCP use" category y compared to never users.

To estimate the total number of endometrial and ovarian cancer deaths/cases that would have occurred, but were prevented through use of combined OCPs, the following formula was used:

$$\text{Est. number of deaths/cases prevented} = \sum \left(\frac{N_x}{1 - PF_x}\right) - N_x$$

Where N_x is the observed number of deaths/cases in each age category and PF_x is the prevented fraction in each age category.

Results

In 2013, cancer was the cause of 44,004 deaths in Australia. We estimated that approximately 38% ($n = 16{,}739$) of these deaths were attributable to 20 discrete, potentially modifiable causal factors across eight broad groupings [41% ($n = 10{,}232$) males and 34% ($n = 6{,}507$) females]. These percentages were higher when we considered only deaths in people aged 0–74 years: 43% of all deaths; 47% among males (5,746 deaths) and 38% among females (3,483 deaths; Table 2). Detailed results for each exposure are included in Supporting Information (Tables S26 to S38).

Cancers of the uterine cervix and Kaposi's sarcoma had PAFs of 100% (227 and 2 deaths respectively at all ages), as the infectious agents [HPV and Kaposi's sarcoma herpes virus (KSHV), respectively] are considered necessary causal factors. Other cancer sites with very high mortality PAFs were cutaneous melanoma (90%), anus (86%), larynx (83%), lung (82%) and lip, oral cavity and pharynx (77%). The sites with the largest number of potentially preventable cancer deaths were lung ($n = 6{,}776$), colorectum ($n = 1{,}974$), cutaneous melanoma ($n = 1{,}390$), liver ($n = 1{,}052$) and stomach ($n = 898$; Table 2).

Tobacco smoke was the leading cause of cancer death in 2013 with a PAF of 23% (26% males and 18% females; 9,921 cancer deaths). This was followed by dietary factors (PAF = 5%, 2,329 cancer deaths), overweight/obesity (5%, 1,990) and infections (5%, 1,981; Fig. 1).

While only 15 cancer deaths in 2013 could be attributed to the use of combined OCPs, we estimated that 159 endometrial cancer deaths and 294 ovarian cancer deaths were prevented in 2013 because women had used the combined OCP (Table 3).

In the updated incidence analysis, the overall PAF (0–85+ years) was essentially unchanged from our previously reported overall estimate (33%; males 34% and females 32%),[5] despite some changes in relative risk estimates arising from newer data. The PAFs were similar in people age 0–74 years (Table 4). Cancer sites with the largest number of potentially preventable cancers were lung ($n = 9{,}272$), cutaneous melanoma ($n = 7{,}918$), colorectum ($n = 7{,}380$) and breast ($n = 3{,}609$; Table 4). Figure 1 shows the updated PAFs for incidence for each factor; the main changes were a decrease for diet (from 6.1% to 5.4%) and an increase in overweight/obesity (from 3.4% to 4.3%) due to changes in cancers included. There was an increase in the PAF for infections only for men (from 2.4 to 3.0%) due to the use of updated relative risks and prevalence data for cancers that are more common in men than women (oropharynx and stomach). Changes were also seen in the prevented fraction for oral contraceptive use and ovarian cancer because we updated our estimates of the prevalence of combined OCP use by duration in 2013. This resulted in an increase in the prevented fraction from 19 to 25%. A similar increase was not seen for endometrial cancer because we also updated the relative risk to that reported from a more recent pooled analysis of prospective studies[32] and this change offset the effect of changing the prevalence. For many factors, the cancer mortality PAFs were similar to those estimated for cancer incidence (Fig. 1). The main exceptions were tobacco smoke and solar UV radiation. For smoking, the PAF for cancer mortality was around two-thirds higher than for cancer incidence (23 *vs.* 13%); for solar UV radiation, the cancer mortality PAF was half that for incidence (3 *vs.* 6%).

When we stratified by age group (0–74 years *vs.* 75+ years), tobacco smoke accounted for the greatest proportion of cancer deaths in both younger (30% males and 20% females) and older persons (22% males, 17% females; Table 5). For males aged 0–74 years, dietary factors (7%), overweight/obesity (6%) and infections and alcohol (both 5%) were the next greatest contributors to premature cancer deaths, whereas dietary factors (5%), overweight/obesity (4%) and solar UV radiation (4%) were the next greatest contributors to avoidable cancer deaths among the older group (Table 4). Of note, markedly fewer cancer deaths in males were attributable to alcohol (<2%) among those aged 75+ years compared with those 0–74 years (5%; Table 5). For females, tobacco smoke was the leading cause of cancer death, followed by infectious agents, dietary factors, and overweight/obesity, although the rank order of these factors differed between younger and older women (Table 5).

Table 2. Estimated number and proportion (%) of cancer deaths in Australia in 2013 attributable to potentially modifiable factors[1]: all ages (0–85+ years) and 0–74 years

	Attributable cancer deaths 2013: 0–85+ years									Attributable cancer deaths 2013: 0–74 years								
	Males			Females			Persons			Males			Females			Persons		
Cancer Site (ICD-10 code)	Obs. deaths	Excess deaths	PAF %	Obs. deaths	Excess deaths	PAF %	Obs. deaths	Excess deaths	PAF %	Obs. deaths	Excess deaths	PAF %	Obs. deaths	Excess deaths	PAF %	Obs. deaths	Excess deaths	PAF %
Lip, Oral cavity and pharynx (C00-C14)	519	437	84.2	252	159	63.1	771	596	77.3	408	347	85.0	156	101	64.7	564	448	79.4
Oesophagus (C15)	882	608	68.9	344	228	66.3	1,226	836	68.2	547	386	70.6	121	84	69.4	668	470	70.4
Stomach (C16)	739	564	76.3	433	334	77.1	1,172	898	76.6	402	291	72.4	197	147	74.6	599	438	73.1
Colorectum (C18-C20)	2,259	1,233	54.6	1,829	741	40.5	4,088	1,974	48.3	1,185	682	57.6	754	314	41.6	1,939	996	51.4
Anus (C21)	37	30	81.1	44	40	90.9	81	70	86.4	26	21	80.8	27	25	92.6	53	46	86.8
Liver (C22)	1,054	731	69.4	559	321	57.4	1,613	1,052	65.2	675	481	71.3	285	168	58.9	960	649	67.6
Gall Bladder (C23)	52	7	13.5	115	15	13.0	167	22	13.2	25	3	12.0	47	6	12.8	72	9	12.5
Pancreas (C25)	1,317	384	29.2	1,232	347	28.2	2,549	731	28.7	752	227	30.2	548	168	30.7	1,300	395	30.4
Larynx (C32)	188	156	83.0	26	21	80.8	214	177	82.7	106	89	84.0	14	11	78.6	120	100	83.3
Lung (C34)	4,967	4,219	84.9	3,277	2,557	78.0	8,244	6,776	82.2	2,720	2,324	85.4	1,808	1,435	79.4	4,528	3,759	83.0
Melanoma of the skin (C43)	1,050	980	93.3	492	410	83.3	1,542	1,390	90.1	570	516	90.5	271	211	77.9	841	727	86.4
Kaposi's Sarcoma (C46)	2	2	100.0	0	0	0.0	2	2	100.0	1	1	100.0	0	0	0.0	1	1	100.0
Breast (C50)	–	–	–	2,833	627	22.1	2,833	627	22.1	–	–	–	1,722	412	23.9	1,722	412	23.9
Vulva (C51)	–	–	–	85	21	24.7	85	21	24.7	–	–	–	50	15	30.0	50	15	30.0
Vagina (C52)	–	–	–	24	18	75.0	24	18	75.0	–	–	–	15	11	73.3	15	11	73.3
Uterine Cervix (C53)	–	–	–	227	227	100.0	227	227	100.0	–	–	–	167	167	100.0	167	167	100.0
Endometrium (C54, C55)	–	–	–	453	147	32.5	453	147	32.5	–	–	–	240	82	34.2	240	82	34.2
Ovary (C56)	–	–	–	954	56	5.9	954	56	5.9	–	–	-	542	36	6.6	542	36	6.6
Penis (C60)	11	4	36.4	–	–	–	11	4	36.4	7	3	42.9	–	–	–	7	3	42.9
Prostate (C61)	3,119	221	7.1	–	–	–	3,119	221	7.1	772	65	8.4	–	–	–	772	65	8.4
Kidney (C64)	594	235	39.6	339	85	25.1	933	320	34.3	340	138	40.6	132	35	26.5	472	173	36.7
Bladder (C67)	732	233	31.8	305	78	25.6	1,037	311	30.0	224	76	33.9	75	22	29.3	299	98	32.8
Thyroid (C73)	61	7	11.5	72	2	2.8	133	9	6.8	34	4	11.8	32	1	3.1	66	5	7.6
Hodgkin's lymphoma (C81)	46	21	45.7	31	13	41.9	77	34	44.2	28	12	42.9	16	6	37.5	44	18	40.9
Non-Hodgkin's lymphoma (C82-C85, C96)	845	29	3.4	627	18	2.9	1,472	47	3.2	399	14	3.5	215	5	2.3	614	19	3.1
Multiple myeloma (C90)	474	48	10.1	373	24	6.4	847	72	8.5	217	24	11.1	150	11	7.3	367	35	9.5
Acute Myeloid Leukaemia (C92.0, C92.3–C92.5, C93.0, C94.0, C94.2, C94.4, C94.5)	491	83	16.9	371	18	4.9	862	101	11.7	249	42	16.9	184	10	5.4	433	52	12.0
All Cancer Deaths	24,796	10,232	41.3	19,208	6,507	33.9	44,004	16,739	38.0	12,211	5,746	47.1	9,266	3,483	37.6	21,477	9,229	43.0

ABBREVIATIONS: Obs. Deaths: observed deaths; Excess Deaths: estimated number of excess deaths attributable to potentially modifiable factors;.
PAF % = combined population attributable fraction (PAF) expressed as a percentage [calculated using the formula: $PAF_{Combined} = 1 - (1 - PAF_1)*(1 - PAF_2)*(1 - PAF_n)$ – see Methods in main text].
[1]Potentially modifiable factors considered: tobacco smoke (smoking and smoking by partner), alcohol consumption, overweight/obesity, dietary factors (low intake of fruit, non-starchy vegetables and dietary fibre, high intake of red and processed meat), insufficient physical activity, lack of breastfeeding, menopausal hormone therapy use, combined oral contraceptive use, infections (seven agents) and solar ultraviolet radiation.

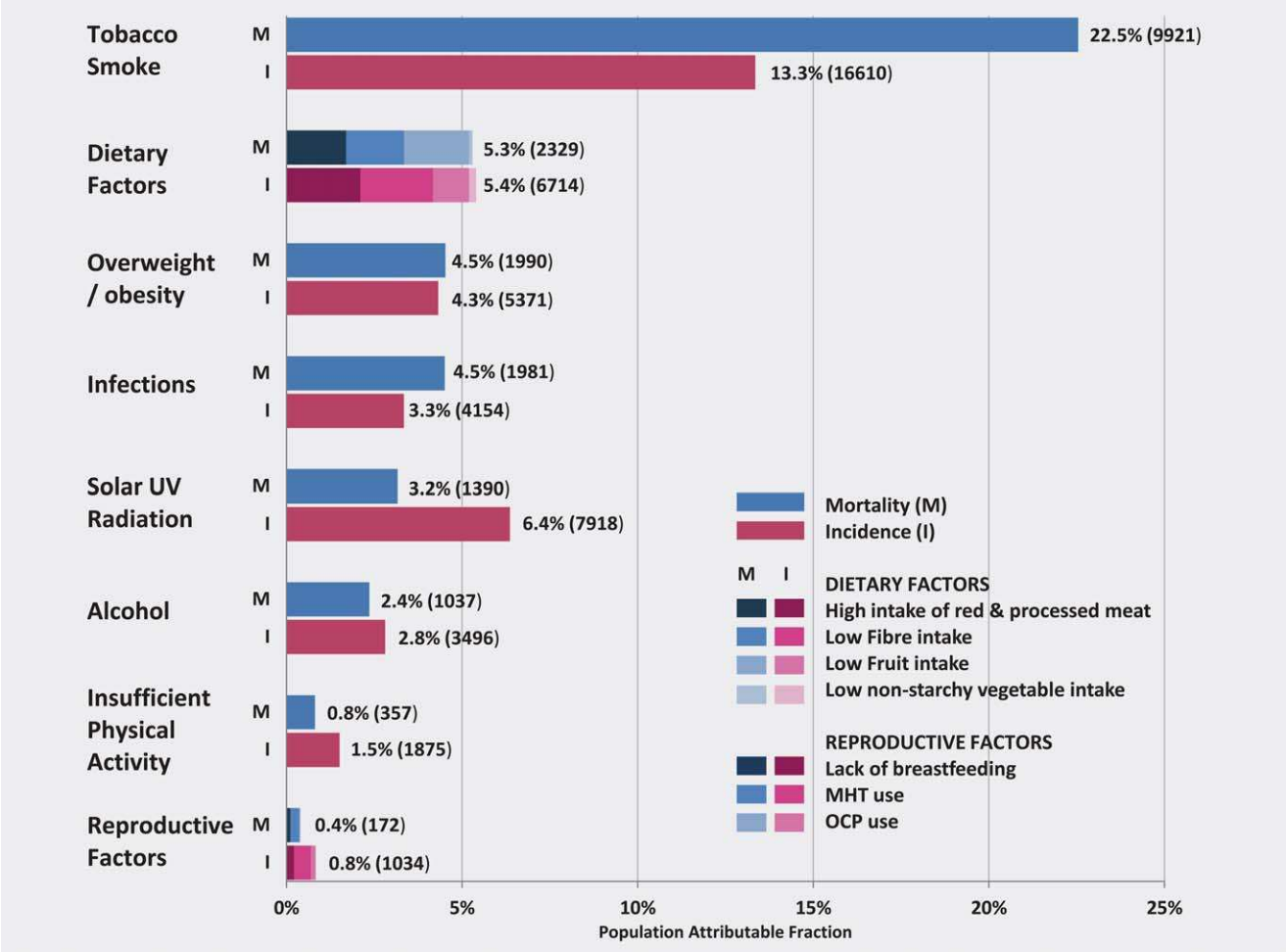

Figure 1. Percentage (and estimated numbers) of cancer deaths and cancer cases in Australia in 2013 attributable to potentially modifiable factors. Abbreviations: M: mortality; I: incidence; UV: ultraviolet; MHT: menopausal hormone therapy; OCP: combined oral contraceptive pills.

Table 3. Prevented fraction (PF) and estimated number of cancer deaths and cancers cases prevented in Australia in 2013 through the use of combined oral contraceptive pills (OCPs)

	Mortality			Incidence		
Cancer site (ICD-10 code)	Observed deaths	Cancer deaths prevented	PF%	Observed cancers diagnosed	Cancer cases prevented	PF%
Endometrium (C54, C55)	453	159	26.0	2,513	1,038	29.2
Ovarian (C56)	954	294	23.6	1,393	469	25.2

ABBREVIATIONS: PF = prevented fraction expressed as a percentage.

Discussion

An estimated 38% of cancer deaths and 33% of cancer cases (all ages) in Australia in 2013 were attributable to 20 discrete, modifiable causal factors across eight broad groupings. This proportion was higher for deaths occurring below the age of 75 years (persons 43%; males 47%; females 38%). The leading preventable cause of cancer death in Australia was tobacco smoke, accounting for around half of the estimated preventable deaths from cancer. Dietary factors, overweight/obesity, infections (seven agents) and solar UV radiation were also important contributors. Although arbitrary, we selected 75 years as the cut-off for "premature death" on the basis that the level of general frailty and presence of co-morbidities is higher in people over 75 years making it difficult to disentangle contributory causes of death.[33,34] The same cut-off has been used previously by studies of avoidable mortality in Australia[34] and the United Kingdom.[33]

PAF estimates for other national studies of cancer mortality range from 35% in France[35] to 60% in the United States[36] (see Supporting Information Table S39). Differences in the

Table 4. Estimated number and proportion (%) of cancer cases in Australia in 2013 attributable to potentially modifiable factors[1]: all ages (0–85+ years) and 0–74 years

	Attributable cancer cases 2013: 0–85+ years									Attributable cancer cases 2013: 0–74 years								
	Males			Females			Persons			Males			Females			Persons		
Cancer Site (ICD-10 code)	Obs. cases	Excess cases	PAF %	Obs. cases	Excess cases	PAF %	Obs. cases	Excess cases	PAF %	Obs. cases	Excess cases	PAF %	Obs. cases	Excess cases	PAF %	Obs. cases	Excess cases	PAF %
Lip, Oral cavity and pharynx (C00-C14)	2,560	2,079	81.2	1,083	676	62.4	3,643	2,755	75.6	2,095	1,716	81.9	761	485	63.7	2,856	2,201	77.1
Oesophagus (C15)	1,013	724	71.5	423	289	68.3	1,436	1,013	70.5	694	507	73.1	190	138	72.6	884	645	73.0
Stomach (C16)	1,418	909	64.1	699	476	68.1	2,117	1,385	65.4	902	556	61.6	398	265	66.6	1,300	821	63.2
Colorectum (C18–C20)	8,214	4,578	55.7	6,748	2,802	41.5	14,962	7,380	49.3	5,345	3,073	57.5	3,897	1,644	42.2	9,242	4,717	51.0
Anus (C21)	161	137	85.1	224	201	89.7	385	338	87.8	119	101	84.9	162	160	98.8	281	261	92.9
Liver (C22)	1,283	898	70.0	496	287	57.9	1,779	1,185	66.6	949	677	71.3	296	175	59.1	1,245	852	68.4
Gall Bladder (C23)	102	15	14.7	214	28	13.1	316	43	13.6	64	10	15.6	110	15	13.6	174	25	14.4
Pancreas (C25)	1,492	450	30.2	1,375	398	28.9	2,867	848	29.6	904	285	31.5	691	220	31.8	1,595	505	31.7
Larynx (C32)	512	431	84.2	79	62	78.5	591	493	83.4	377	321	85.1	52	41	78.8	429	362	84.4
Lung (C34)	6,626	5,682	85.8	4,547	3,590	79.0	11,173	9,272	83.0	3,967	3,436	86.6	2,830	2,282	80.6	6,797	5,718	84.1
Melanoma of the skin (C43)	7,510	5,113	68.1	5,231	2,805	53.6	12,741	7,918	62.1	5,461	3,712	68.0	3,995	2,072	51.9	9,456	5,784	61.2
Kaposi's Sarcoma (C46)	52	52	100.0	11	11	100.0	63	63	100.0	41	41	100.0	6	6	100.0	47	47	100.0
Breast (C50)	–	–	–	15,902	3,609	22.7	15,902	3,609	22.7	–	–	–	13,070	3,045	23.3	13,070	3,045	23.3
Vulva (C51)	–	–	–	339	84	24.8	339	84	24.8	–	–	–	201	62	30.8	201	62	30.8
Vagina (C52)	–	–	–	84	62	73.8	84	62	73.8	–	–	–	51	38	74.5	51	38	74.5
Uterine Cervix (C53)	–	–	–	814	814	100.0	814	814	100.0	–	–	–	726	726	100.0	726	726	100.0
Endometrium (C54, C55)	–	–	–	2,513	830	33.0	2,513	830	33.0	–	–	–	2,008	669	33.3	2,008	669	33.3
Ovary (C56)	–	–	–	1,393	78	5.6	1,393	78	5.6	–	–	–	1,012	59	5.8	1,012	59	5.8
Penis (C60)	105	35	33.3	–	–	–	105	35	33.3	63	21	33.3	–	–	–	63	21	33.3
Prostate (C61)	19,234	343	1.8	–	–	–	19,234	343	1.8	14,835	274	1.8	–	–	–	14,835	274	1.8
Kidney (C64)	1,986	798	40.2	1,071	277	25.9	3,057	1,075	35.2	1,563	635	40.6	776	201	25.9	2,339	836	35.7
Bladder (C67)	1,956	650	33.2	598	162	27.1	2,554	812	31.8	918	326	35.5	250	78	31.2	1,168	404	34.6
Thyroid (C73)	664	72	10.8	1,890	38	2.0	2,554	110	4.3	599	65	10.9	1,755	35	2.0	2,354	100	4.2
Hodgkin's lymphoma (C81)	338	117	34.6	274	90	32.8	612	207	33.8	304	100	32.9	247	77	31.2	551	177	32.1
Non-Hodgkin's lymphoma (C82–C85, C96)	2,813	110	3.9	2,164	66	3.0	4,977	176	3.5	2,001	82	4.1	1,434	42	2.9	3,435	124	3.6
Multiple myeloma (C90)	986	103	10.4	740	46	6.2	1,726	149	8.6	634	70	11.0	442	28	6.3	1,076	98	9.1
Acute Myeloid Leukaemia (C92.0, C92.3–C92.5, C93.0, C94.0, C94.2, C94.4, C94.5)	550	89	16.2	407	18	4.4	957	107	11.2	350	55	15.7	260	12	4.6	610	67	11.0
All Cancers	68,935	23,385	33.9	55,527	17,799	32.1	124,462	41,184	33.1	48,158	16,063	33.4	39,179	12,575	32.1	87,337	28,638	32.8

ABBREVIATIONS: Obs. cases: observed cases; Excess cases: estimated number of excess cases attributable to potentially modifiable factors.
PAF % = combined population attributable fraction (PAF) expressed as a percentage [calculated using the formula: $PAF_{Combined} = 1 - (1 - PAF_1)*(1 - PAF_2)*(1 - PAF_n)$ – see Methods in main text].
[1]Potentially modifiable factors considered: tobacco smoke (smoking and smoking by partner), alcohol consumption, overweight/obesity, dietary factors (low intake of fruit, non-starchy vegetables and dietary fibre, high intake of red and processed meat), insufficient physical activity, lack of breastfeeding, menopausal hormone therapy use, combined oral contraceptive use, infections (seven agents) and solar ultraviolet radiation.

Table 5. Number of cancer deaths and population attributable fraction (PAF%) ranked by exposure factor for males and females (0–74 years and 75+ years)

	MALES						FEMALES					
	0–74 years			75+ years			0–74 years			75+ years		
RANK	Exposure	Excess deaths	PAF%	Exposure	Excess deaths	PAF%	Exposure	Excess deaths	PAF%	Exposure	Excess deaths	PAF%
1	Tobacco smoke	3,625	29.7	Tobacco smoke	2,781	22.1	Tobacco smoke	1,874	20.2	Tobacco smoke	1,641	16.5
2	Dietary factors	801	6.6	Dietary factors	650	5.2	Infectious agents	497	5.4	Dietary factors	464	4.7
3	Overweight/obese	680	5.6	Overweight/obese	532	4.2	Dietary factors	414	4.5	Infectious agents	392	3.9
4	Infectious agents	654	5.4	Solar UV radiation	464	3.7	Overweight/obese	403	4.3	Overweight/obese	375	3.8
5	Alcohol	579	4.7	Infectious agents	438	3.5	Solar UV radiation	211	2.3	Solar UV radiation	199	2.0
6	Solar UV radiation	516	4.2	Alcohol	185	1.5	Alcohol	203	2.2	Physical inactivity	144	1.4
7	Physical inactivity	30	0.2	Physical inactivity	28	0.2	Physical inactivity	155	1.7	Alcohol	70	0.7
8	–	–	–	–	–	–	MHT use	87	0.9	MHT use	23	0.2
9	–	–	–	–	–	–	Lack of breastfeeding	28	0.3	Lack of breastfeeding	19	0.2
10	–	–	–	–	–	–	Combined OCP use	15	0.2	Combined OCP use	0	-

ABBREVIATIONS: PAF: population attributable fraction, expressed as a percentage; Excess deaths: estimated number of excess deaths attributable to potentially modifiable factors; MHT use: menopausal hormone therapy use; combined OCP use: combined oral contraceptive use.

PAFs for some of the factors can be explained by differences in exposure prevalence between countries. For example, the PAFs for cancer mortality associated with overweight/obesity are much lower for China (0.3%)[37] and Japan (1%)[38] than for Australia (5%)[39] and the United States (5–15%).[36] Conversely, the cancer mortality PAFs for infections are higher in the Asian countries (29% and 22% in China and Japan respectively, *vs*. 5% in Australia), where prevalence of hepatitis B and *Helicobacter pylori*, in particular, is high.[38] Differences in PAFs between countries are also due to inclusion of different sets of risk factors, the cancer sites considered causally associated with those risk factors, the choice of relative risks and differences in analytic methods.

Although different methods and outcomes are used, we note that the Australian Burden of Disease Study estimated that the joint effect of selected modifiable risk factors contributed 44% of the total cancer burden (fatal and non-fatal) in Australia in 2011.[40] Using Disability Adjusted Life-Years (DALYs) as the measure, tobacco contributed 22% of the total cancer burden, followed by high body mass (7%), dietary risk factors (7%), physical inactivity (6%) and sun exposure (5%).[40]

The proportion of cancer deaths attributable to potentially modifiable factors was higher than that for cancer diagnoses (38% compared to 33%). Other studies that have published PAFs for both mortality and incidence have also reported higher PAFs for mortality (Brazil: PAF mortality 42% *vs*. PAF incidence 34%[41]; Japan: 46 *vs*. 43%[38]). In our study, this difference appears to be mostly due to PAFs for tobacco smoke (23% for mortality *vs*. 13% for incidence). Smoking-related cancers generally have high mortality, in particular lung cancer remains the leading cause of cancer death in both males and females with a 5-year relative survival at diagnosis of only 16% (14% males and 19% females).[2] We estimated that two-thirds of the tobacco-attributable cancer deaths were deaths from lung cancer.

Our study has a number of strengths. We followed the most recent judgements on causality from IARC and the WCRF, international agencies that have a continuous process for systematically reviewing the evidence. For the majority of factors, we were able to use prevalence data from surveys with nationally representative samples and high response rates[15,17,18] or, where these were not available, population-based studies with large samples.[42]

For our calculations of PAF mortality, we used relative risks for cancer incidence in preference to relative risks for cancer mortality. We did this for several reasons. There are more studies with cancer incidence as an outcome, and large prospective cohorts generally have many incident cancer cases over a 5–10 year follow-up period making their estimates more precise; in contrast, cancer mortality studies require very long follow-up periods to record a sufficient number of cancer deaths for analysis. In addition, the quality of data is often better for cancer diagnosis than for cause of death, especially for registration of histological subtypes. Data

on cancer deaths relies on the specificity and completeness of the underlying causes of death listed on the death certificate. Notwithstanding the above, our approach assumes equivalence between the relative risks for incidence and mortality; that is, that the factor does not have an appreciable influence on survival after diagnosis. This assumption may not hold true for all of the factor-cancer couplets that were considered. To explore the potential impact of using relative risks for cancer incidence, we performed a sensitivity analysis using relative risks from prospective cohort studies (CPS II, CPS II Nutrition Cohort and Million Women Study) that had published effect estimates for both mortality and incidence for BMI-cancer associations[43–49](see Supporting Information Table S40). We found that this assumption held true for most, but not all, cancer sites. There was no clear explanation for the discrepancies between the relative risks for incidence and mortality, as these occurred in cancers with quite different patterns of incidence, survival and mortality (pancreas, colorectum and multiple myeloma; see Supporting Information Table S41).

We acknowledge some limitations of this study. Our list of causal factors was restricted due to the availability of appropriate prevalence data. For example, we could not consider other factors that have been associated with cancer risk including ionising radiation, air pollution, coffee intake (protective), glycaemic load and processed meat (separate to red meat). We also did not include occupational exposures because an estimate of the future cancer incidence burden of Australians of working age in 2012 has been recently published; the proportion estimated was 1.4%.[50]

The PAFs are sensitive to both the selection of prevalence data and the relative risks used in the calculations. We used the same prevalence estimates as used in the Australian PAF Incidence Study; the limitations of these data have been outlined in detail elsewhere.[5] In particular, nationally representative data on hormone use by type, duration of use and age group were not available, and there was only limited Australian data on exposure to infectious agents.[5]

The accuracy of data on cancer deaths relies on the specificity of information on the death certificate. In particular, the Australian Bureau of Statistics has noted there is a high likelihood that there may be under-counting of the number of colorectal cancer deaths due to the frequent use of the broader term "bowel cancer" on death certificates, and the consequent coding of these deaths to the International Classification of Diseases code C26.0 (Malignant neoplasm: Intestinal tract, part unspecified) in accordance with the World Health Organisation internationally agreed rule set.[51] As several factors considered in our analysis (tobacco, alcohol, overweight/obesity, low intake of dietary fibre, high intake of red and processed meat, physical inactivity) are causally associated with cancers of the colon and rectum, our overall PAF may have been underestimated. For deaths due to cancers of the cervix and endometrium, all deaths coded as "uterus – unspecified" (ICD-10 code C55) were considered endometrial cancer deaths, although a proportion of deaths allocated this code were likely to be caused by cervical rather than endometrial cancer.[52] This misallocation will not have affected the overall proportion of deaths attributable to causal factors, but sensitivity analysis suggested that we may have modestly underestimated the number of deaths from cervical cancer and conversely, modestly over-estimated the number of deaths from endometrial cancer.

PAFs are not static and should be recalculated at regular intervals to reflect both changing prevalence in exposures and the most up-to-date findings of cancer risk assessments and causal associations. For example, trends in the prevalence of exposure to tobacco smoke (declining) and obesity (increasing) in Australia, as well as the introduction of the HPV vaccine and new treatments for HIV and Hepatitis C, will all likely result in large changes in in future cancer incidence and mortality. Finally, we note that some modifiable causes of cancer act in synergy with other factors to markedly increase risks among people exposed. Such interactions were not explored in this analysis.

Conclusions

Cancers remain the leading cause of death in Australia, and we have shown that a large proportion of cancer cases in addition to deaths from cancer are, in theory, preventable. Tobacco smoke was the leading cause of avoidable cancer death, followed by dietary factors, overweight/obesity, infections and solar UV radiation. Even modest reductions in population exposure to known causes of cancer would likely translate to sizable reductions in premature deaths from cancer.

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