Cancers in Australia in 2010 attributable to modifiable factors: introduction and overview

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Cancer is now the leading cause of death in Australia. In 2014, it is estimated that more than 45,500 people died from cancer in Australia and more than 123,500 new cancers were diagnosed,[1] with the number of new cases expected to rise to 150,000 by 2020[2] (not including keratinocyte cancers – basal cell carcinomas [BCC] and squamous cell carcinomas [SCC] of the skin). Apart from the extensive morbidity and mortality, cancer expenditure totals more than $4.5 billion[3] in direct health system expenditure each year. In addition, about 374,000 Australians each year are estimated to develop BCC or SCC of the skin,[4] and the costs of treating these cancers are higher than for any other cancer in Australia.[5,6] Many cancers are caused by exposure to environmental and lifestyle factors, offering opportunities to diminish the burden of cancer if these exposures can be minimised.

This series of reports was commissioned by Cancer Council Australia with the aim of estimating the burden of cancer arising in Australia that may be preventable. This work is similar in aims and scope to the recent analyses performed for Cancer Research UK by Professor Max Parkin.[7] For each factor considered, we estimated the proportion of cancers arising in the Australian population that could be attributed to it – the population attributable fraction (PAF). The calculation requires an estimate of the strength of association (usually a relative risk) between a given cause and a particular cancer and the prevalence of the causal factor in the population.

Abstract

Objective: To describe the approach underpinning a national project to estimate the numbers and proportions of cancers occurring in Australia in 2010 that are attributable to modifiable causal factors.

Methods: We estimated the population attributable fraction (PAF) (or prevented fraction) of cancers associated with exposure to causal (or preventive) factors using standard formulae. Where possible, we also estimated the potential impact on cancer incidence resulting from changes in prevalence of exposure. Analyses were restricted to factors declared causal by international agencies: tobacco smoke; alcohol; solar radiation; infectious agents; obesity; insufficient physical activity; insufficient intakes of fruits, vegetables and fibre; red and processed meat; menopausal hormone therapy (MHT); oral contraceptive pill (OCP); and insufficient breast feeding. Separately, we estimated numbers of cancers prevented by: aspirin; sunscreen; MHT; and OCP use. We discuss assumptions pertaining to latent periods between exposure and cancer onset, choices of prevalence data and risk estimates, and approaches to sensitivity analyses.

Results: Numbers and population attributable fractions of cancer are presented in accompanying papers.

Conclusions: This is the first systematic assessment of population attributable fractions of cancer in Australia.

Key words: population attributable fraction, cancer, risk factor, potential impact fraction

Selection of risk factors

To be selected as a potentially modifiable factor for this report, we required three conditions to be met:

1. There is evidence of a causal association between the factor and at least one cancer.

2. Australian exposure prevalence data for the factor were available.

3. The population's exposure to the cause could be modified favourably.

The third criterion is somewhat arbitrary, but distinguishes those causes for which policies or activities can be developed to change behaviour or modify risk (e.g. diet, physical activity, exposure to sunlight, smoking) from factors that are causal but would never be subject to policy recommendations in Australia (e.g. parity, age at menarche). For the majority of factors, we followed the judgements on causality of the two international agencies that have systematically reviewed the evidence for each factor, the International Agency for Research on Cancer (IARC) and the World Cancer Research Fund (WCRF). We restricted our primary analyses to those factors that IARC had declared as Group 1 (carcinogenic to humans) factors or by WCRF as having 'convincing' or 'probable' evidence of causality for at least one cancer. (For full description of the IARC and WCRF classifications, see supplementary file: Table S1, available with the online version of this article.)

In addition, several other factors not assessed by these agencies (e.g. aspirin and sunscreen) were included in this report on the basis of recent evidence from primary studies, systematic reviews and meta-analyses. A summary of such evidence is included in the relevant articles. Also, for some factors (obesity, insufficient breast-feeding, menopausal hormone therapy) declared by IARC or WCRF as causing cancer at specific sites, we have calculated PAFs for additional cancer sites where the association has not yet been declared 'causal' by those agencies. We have done this only where there has been substantial new evidence since the last report from IARC or WCRF. The arguments in support of those causal assessments are made in the respective articles.

Many other environmental or lifestyle factors were considered, but were excluded from this report because they failed to meet one or more of our criteria, and therefore have at least one of the following:

1. Inconclusive evidence for causality (e.g. vitamin D deficiency).

2. Lack of credible or useable prevalence data for the Australian population (e.g. salt; medical ionising radiation; historic occupational exposure data).

3. Factors for which modification is not ethical or practical (e.g. parity, age at menarche).

Finally, some factors identified in other reports as contributing to the international burden of cancer (e.g. chewing of betel quid, air pollution, infections other than those listed) were not considered further as they are likely to contribute only marginally to the cancer burden in Australia. The final list of factors included, together with the sources of exposure prevalence and the cancers assessed, is reported in Table 1.

PAF calculations

We used the standard formula to calculate PAF for most factors in the reports that follow. Using this approach, we estimated the numbers of cancers at each site that could be attributed to each causal factor. We used the most recent Australian national cancer incidence data available (2010). Wherever possible, PAFs were calculated by categories of age and sex to derive an overall estimate of the numbers of cancers attributable to each causal factor. PAFs were calculated for adult exposures and adult-onset cancers only; the definition of adult varied according to the availability of exposure prevalence data, but was typically >25 years.

The usual formula for calculating the PAF for any factor is:

$$ \mathrm{PAF} = \frac{\Sigma(p_x \; \mathrm{x} \; \mathrm{ERR}_x)}{1 + \Sigma(p_x \; \mathrm{x} \; \mathrm{ERR}_x)} $$

where p_x is the proportion of the population in exposure/consumption level x and ERR_x the excess relative risk (RR_x – 1) associated with exposure/consumption level x.

The PAF is typically expressed as a percentage and is interpreted as the proportion of cases that would be prevented if exposure to the causal factor in the entire population was reduced to the level of the reference category.

For all causal factors considered in this project except infection,[8] smoking[9] and ultraviolet radiation (UVR),[10] this formula provides a suitable method for estimating the population attributable fraction. The calculation makes the following assumptions. First, that the association between the factor and cancer is causal. Second, that the effect of the factor is independent of other causal factors (or that the influence of other causal factors is the same for persons exposed and unexposed to the causal factor under study). Thus, this method does not permit

estimation of the fractions of cancers arising through synergistic effects of causal factors (for example, through the combined effects of tobacco smoking and alcohol consumption for cancers of the upper aero-digestive tract), unless investigators have access to prevalence data and relative risk estimates across all strata of combined exposures. These data are seldom available in practice. Finally, it requires an assumption about the latent period between exposure to the factor and onset of cancer when selecting appropriate values for the prevalence and relative risk estimates to be used.

This last assumption is often implicit, but in the context of this project it is desirable to specify a reasonable latent period for each factor since the prevalence estimates should pertain, as near as possible, to the time at which exposure to the factor is considered to have caused the cancers being analysed. For most of the exposures considered in this report, a latent period of about 10 years was assumed based on typical durations of follow-up for the cohort studies that underpin the evidence base; deviations from this assumption are described explicitly in the relevant sections.[11]

For certain cancers caused by infectious agents (such as human papillomavirus and Epstein Barr virus) for which no other causes are known, the PAF is taken to equal the prevalence of the infectious agent among cancer cases. This approach can be used when mechanistic knowledge strongly suggests that the presence of infection in a cancer is sufficient to infer that the infection caused the cancer.[12]

To estimate a PAF for a number of ubiquitous factors that protect against cancer at higher levels of exposure (such as physical activity and consumption of fruit and vegetables), we modelled the effect of an *insufficient* level of these factors against a recommended threshold level, usually as suggested by National Guidelines. For another class of protective factors used specifically for health-related purposes (e.g. aspirin[13] and sunscreens[10]), exposure is deliberate and the natural state is to be 'unexposed'; for those factors we calculated a metric comparable to the PAF called the 'prevented fraction', which estimates the number of cancers that did not occur (i.e. were prevented) due to exposure to the protective factor. The formula for calculating the prevented fraction (PF) is:

$$ PF = p_x \, (1 - RR) $$

where p_x is the prevalence of exposure in the population to the protective factor.

As measures of prevalence, risk and attributable fractions necessarily have error, and as the latent periods are unknown, our estimates of the numbers and proportions of cancer attributable to modifiable factors are indicative only of the size of the burden and cannot be considered definitive. In addition, some factors under intense research scrutiny (e.g. body mass index) have been causally associated with additional cancers since the last round of WCRF/IARC reports.[14,15] The contribution of these exposures to the overall cancer burden may thus be greater than estimated in our primary analyses. Finally, for some factors, guidelines on optimum exposure in the Australian population have been developed, yet the potential impact on cancer burden of perfect adherence to such guidelines is not known. To explore issues

of uncertainty, additional causal association and 'optimum' exposure levels, we therefore performed additional analyses defined as:

- Sensitivity analyses: to calculate PAF using estimates of prevalence or relative risks from additional sources so as to explore the possible range within which the true effects probably lie.

- Supplementary analyses: based on likely causal associations identified in recent systematic reviews, we performed supplementary analyses to estimate the proportion of cancers at additional sites (i.e. not considered causal by WCRF/IARC) attributable to those causal factors.

- Potential impact of changing exposure prevalence: to provide an estimate of the burden of cancer attributable to levels of exposure outside those recommended by national guidelines (e.g. alcohol,[16] insufficient physical activity[17]).

Exposure prevalence estimates

For each exposure factor, where possible, we used population-based prevalence data from National Health Surveys (e.g. alcohol, body mass index, physical activity) conducted by the Australian Bureau of Statistics. These surveys are characterised by nationally representative samples and high response rates.[18,19] We obtained age- and sex-specific prevalence estimates so as to calculate, separately, the numbers of excess cases of cancer by age and sex in the national cancer incidence data. Typically, the questions used to elicit information on exposure to specific factors in the National Health Surveys differed markedly from those used to generate summary relative risk estimates, requiring one or more harmonisation procedures to align the data. These steps are described in detail in the respective articles.

Table 1: Factors assessed, sources of prevalence data and cancer outcomes.		
Exposure	**Sources of Australian prevalence data**	**Cancer outcomes**
Tobacco smoke	Estimated from lung cancer incidence rates using Peto method[22]	Oral cavity and pharynx, oesophagus (SCC and adenocarcinoma), stomach, colon, rectum, liver, pancreas, larynx, lung, uterine cervix, ovary (mucinous), urinary bladder, kidney and renal pelvis, acute myeloid leukaemia
Alcohol	National Health Survey 2001 Confidentialised Unit Record Files (CURF)[25]	Oral cavity and pharynx, oesophagus (SCC only), colon, rectum, liver, larynx, female breast,
UV radiation	Estimated from comparison of incidence rates for melanoma and keratinocyte cancers in Europe (United Kingdom and Nordic countries) vs Australia	Melanoma and keratinocyte cancers
Sunscreen	2010 New South Wales Population Health Survey[21]	Protective: Melanoma and keratinocyte cancers
Infection: Epstein-Barr virus (EBV)	Corry et al,[26] Armstrong et al,[27] Flavell et al,[28] Jarrett et al,[29] Glaser et al,[30] Thompson et al[31]	Nasopharynx, Hodgkin's lymphoma, Burkitt's lymphoma
Infection: Hepatitis B virus (HBV) and hepatitis C virus (HCV)	The Kirby Institute[20]	Liver, non-Hodgkin's lymphoma (Hepatitis C only)
Infection: Human papillomavirus (HPV)	Kreimer et al,[32] Hammarstedt et al,[33] De Vuyst et al,[34] Walboomers et al,[35] Backes et al,[36]	Oral cavity and pharynx, tonsil, anus, vulva, vagina, uterine cervix, penis
Infection: *Helicobacter pylori*	Moujaber et al,[37] Pandeya et al,[38] Newton et al[39]	Stomach (non-cardia), low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma
Infection: Human immunodeficiency virus, type 1 (HIV-1) and Kaposi's sarcoma herpes virus (KSHV)	The Kirby Institute[20]	Kaposi's sarcoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma
Overweight and obesity	National Health Survey 2001[40]	Oesophagus (adenocarcinoma only), gall bladder, pancreas, colon, rectum, breast (post-menopausal), endometrium, ovary, kidney
		Supplementary: Malignant melanoma, thyroid, non-Hodgkin lymphoma, multiple myeloma, leukaemia
Insufficient physical activity	National Health Survey 2001 (CURF)[25]	Colon, breast (post-menopausal), endometrium
Diet: Insufficient fibre	National Nutrition Survey 1995[41]	Colon, rectum
Diet: Insufficient fruit & vegetables	National Nutrition Survey 1995[42]	Oral cavity and pharynx, oesophagus (SCC only), stomach, larynx, lung (fruit only)
Diet: Red and processed meat	National Nutrition Survey 1995[41,42]	Colon, rectum
Hormones: Menopausal Hormone Therapy (MHT)	National Health Survey 2004-05 (CURF)[43]	Breast, endometrium, ovary
		Protective: Colon, rectum, breast, cervix
Hormones: Oral Contraceptives	National Health Survey 2001 (CURF)[25]	Protective: Colon, rectum, endometrium, ovary
	Australian Ovarian Cancer Study controls (2002-05)[44]	
Reproductive factors: Insufficient breastfeeding	National Health Survey 2001 (CURF)[25]	Protective: Breast
		Supplementary: Ovary
Aspirin	Australian Cancer Study Controls (2002-05)[45]	Protective: Colon, rectum, oesophagus

Many causal factors (e.g. infections, sunscreen use) were not captured in those surveys or were measured incompletely. Their prevalence estimates were sourced from other surveys such as the human immunodeficiency virus (HIV), viral hepatitis and sexually transmissible infection in the Australia Annual Surveillance Report[20] and the 2010 NSW Population Health Survey.[21] For factors not covered by such surveys, we used 'best estimates' of population prevalence from representative state-based surveys, population-based case-control studies or large-scale cohort studies conducted in Australia. While using estimates from individual or region-specific studies carries risks of bias (e.g. low response; non-representative samples) and less precision, the alternatives (e.g. using international prevalence estimates; excluding the factor from further consideration) were considered even less appropriate.

Regardless of the data source, we performed sensitivity analyses for the majority of factors using higher or lower prevalence estimates to establish the range of PAFs that might plausibly be expected. In addition, such 'alternative prevalence scenarios' provide insights into the likely effect of changing prevalence distributions.

As noted above, choosing a source of exposure prevalence data for any given factor requires an assumption about the latent period between exposure and cancer diagnosis. Often, the latent period is unknown, and investigators must make pragmatic judgements about the quality and availability of prevalence data balanced against the typical intervals between exposure and cancer onset in the cohort studies from which the effect sizes were estimated. Typically, for most exposures, we have followed precedent and assumed approximately 10-year latent periods. Again, deviations from this assumption (e.g. menopausal hormone therapy and breast cancer) are identified in the respective articles.

To estimate the PAF for smoking, we used the approach developed by Peto and colleagues[22] and also used for the UK analyses.[7] This approach was developed to overcome the complexities of estimating the prevalences of former and current smoking when the latent periods are unknown, and when the strengths of associations differ depending on the duration and intensity of past smoking. This method assumes that smoking is the major cause of lung cancer. The number of cases attributable to smoking is then the difference between the number of lung cancer cases observed in the population and the number expected if the entire population developed lung cancer at the same age- and sex-specific rates as never smokers.

Aetiological effect sizes

The recent IARC Monographs have not published pooled effect sizes, so we used aetiological effect sizes (relative risks) reported in meta-analyses conducted by WCRF (including continuous updates, where applicable) for most primary analyses. For factors not summarised by WCRF, we used recent high-quality meta-analyses or risk estimates from large-scale prospective studies; deviations from this approach are highlighted in the relevant articles (e.g. solar radiation[10]).

A key consideration for the PAF calculation is to define the exposure level (or range) of the factor in the population that is optimal for human health. Quite often, the aetiological effect sizes published in research articles compare those in the 'highest' category of exposure to those in the 'lowest' category. Using such relative risk estimates will derive a PAF that represents the maximum proportion of cases that could theoretically be eliminated by shifting the entire population to the lowest exposure category. Such analyses can result in over-optimistic estimates of the proportion of cancers that could be prevented, since such a shift is unlikely to be achieved for most exposures.[23] For the reports that follow, we assessed the optimum level of exposure that might reasonably be attained for each factor separately and used corresponding effect sizes wherever possible. We sourced exposure–response relative risks for those factors that appear to confer log-linear increases in risk (e.g. alcohol, physical activity, consumption of red and processed meat), allowing more detailed estimates of PAF across a continuum of exposure than is possible through simpler categorical analyses. Finally, we performed sensitivity analyses around these estimates to provide a credible range of PAFs.

Conclusions

The following papers are arranged by causal factor and present the estimates of PAF across the cancer sites causally associated with each factor. The articles follow a consistent format. The Introduction summarises the cancers causally associated with each factor and briefly describes the presumed causal mechanism. The Methods section displays the precise formula used for calculating PAF, highlighting any deviations from the standard calculation and any assumptions that were required to perform the analyses. Sources of prevalence data and aetiological effect sizes, including those used for sensitivity, supplementary and 'alternative prevalence scenario' analyses, are also described in the Methods section. The Results section tabulates separately the prevalence distributions used for the PAF calculations and the numbers and proportions of cancers attributed to exposure. The findings from additional analyses are also reported here. Finally, the Discussion section identifies pertinent issues relating to the sources of prevalence data or effect sizes, and explores the impact of any assumptions that were made to complete the analyses. Where relevant, these Australian analyses are compared with relevant international studies and any differences explored. In summary, this is the first attempt to systematically estimate the fraction of cancer in Australia attributable to modifiable factors using a standard methodology across all factors. Summary estimates of the 'preventable' burden of cancer are described in the final report.[24]

Acknowledgements

PAF Project

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References

1. Australian Institute of Health and Welfare. *Cancer in Australia: An Overview 2014.* Cancer Series No.: 90. Canberra (AUST): AIHW; 2014.
2. Australian Institute of Health and Welfare. *Cancer Incidence Projections: Australia, 2011 to 2020.* Cancer Series No.: 66. Canberra (AUST): AIHW; 2012.
3. Australian Institute of Health and Welfare. *Health System Expenditure on Cancer and Other Neoplasms in Australia: 2008-09.* Cancer Series No.: 81. Canberra (AUST): AIHW; 2013.
4. Staples MP, Elwood M, Burton RC, Williams JL, Marks R, Giles GG. Non-melanoma skin cancer in Australia: The 2002 national survey and trends since 1985. *Med J Aust.* 2006;184(1):6-10.
5. Australian Institute of Health and Welfare. *Health System Expenditures on Cancer and Other Neoplasms in Australia, 2000-01.* Health and Welfare Expenditure Series No.: 22. Canberra (AUST): AIHW; 2005.
6. Fransen M, Karahalios A, Sharma N, English DR, Giles GG, Sinclair RD. Non-melanoma skin cancer in Australia. *Med J Aust.* 2012;197(10):565-8.
7. Parkin DM. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. *Br J Cancer.* 2011;105 Suppl 2:2-5.
8. Antonsson A, Wilson LF, Kendall BJ, Bain CJ, Whiteman DC, Neale RE. Cancers in Australia in 2010 attributable to infectious agents. *Aust NZ J Public Health.* 2015; 39:446-51.
9. Pandeya N, Wilson LF, Bain CJ, Martin KL, Webb PM, Whiteman DC. Cancers in Australia in 2010 attributable to tobacco smoke. *Aust NZ J Public Health.* 2015; 39:464-70.
10. Olsen CM, Wilson LF, Green AC, Bain CJ, Fritschi L, Neale RE et al. Cancers in Australia attributable to exposure to solar ultraviolet radiation and prevented by regular sunscreen use. *Aust NZ J Public Health.* 2015; 39:471-6.
11. Jordan SJ, Wilson LF, Nagle CM, Green AC, Olsen CM, Bain CJ et al. Cancers in Australia in 2010 attributable to and prevented by the use of menopausal hormone therapy. *Aust NZ J Public Health.* 2015; 39:434-40.
12. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: A review and synthetic analysis. *Lancet Oncol.* 2012;13(6):607-15.
13. Wilson LF, Green AC, Kendall BJ, Jordan SJ, Nagle CM, Bain CJ et al. Cancers prevented in Australia in 2010 through the consumption of aspirin. *Aust NZ J Public Health.* 2015; 39:414-7.
14. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: A systematic review and meta-analysis of prospective observational studies. *Lancet.* 2008;371(9612):569-78.
15. World Cancer Research Fund International. *Continuous Update Project Report: Diet, Nutrition, Physical Activity and Prostate Cancer.* London (UK): WCRF; 2014.
16. Pandeya N, Wilson LF, Webb PM, Neale RE, Bain CJ, Whiteman DC. Cancers in Australia in 2010 attributable to the consumption of alcohol. *Aust NZ J Public Health.* 2015; 39:408-13.

17. Olsen CM, Wilson LF, Nagle CM, Kendall BJ, Bain CJ, Pandeya N et al. Cancers in Australia in 2010 attributable to insufficient physical activity. *Aust NZ J Public Health.* 2015; 39:458-63.
18. Australian Bureau of Statistics. *4363.0.55.001 – National Health Survey: User's Guide 2001* [Internet]. Canberra (AUST): ABS; 2003 [cited 2013 Feb 2]. Available from: http://www.abs.gov.au/Ausstats/abs@.nsf/Previouspr oducts/4363.0.55.001Contents12001?opendocumen t&tabname=Summary&prodno=4363.0.55.001&issu e=2001&num=&view=
19. Australian Bureau of Statistics. *4363.0.55.001 – 2004-05 National Health Survey: User's Guide – Electronic Publication.* Canberra (AUST): ABS; 2006.
20. The Kirby Institute. *HIV, Viral Hepatitis and Sexually Transmissible Infections in Australia Annual Surveillance Report 2012.* Sydney (AUST): University of New South Wales The Kirby Institute; 2012.
21. Centre for Epidemiology and Research. *2010 Report on Adult Health from the New South Wales Population Health Survey.* Sydney (AUST): New South Wales Department of Health; 2011.
22. Peto R, Lopez AD, Boreham J, Thun M, Heath C. Mortality from tobacco in developed countries: Indirect estimation from national vital statistics. *Lancet.* 1992;339:1268-78.
23. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable disease worldwide: An analysis of burden of disease and life expectancy. *Lancet.* 2012;380(9838):219-29.
24. Whiteman DC, Webb PM, Green AC, Neale RE, Fritschi L, Bain CJ. Cancers in Australia in 2010 attributable to modifiable factors: summary and conclusions. *Aust NZ J Public Health.* 2015; 39:477-83.
25. Australian Bureau of Statistics. *2001 National Health Survey Expanded CURF, RADL. Findings Based on Use of ABS CURF Data.* Canberra (AUST): ABS; 2001.
26. Corry J, Fisher R, Rischin D, Peters LJ. Relapse patterns in WHO 2/3 nasopharyngeal cancer: Is there a difference between ethnic Asian vs. non-Asian patients? *Int J Radiat Oncol Biol Phys.* 2006;64(1):63-71.
27. Armstrong AA, Alexander FE, Cartwright R, Angus B, Krajewski AS, Wright DH, et al. Epstein-Barr virus and Hodgkin's disease: Further evidence for the three disease hypothesis. *Leukemia.* 1998;12(8):1272-6.
28. Flavell KJ, Biddulph JP, Constandinou CM, Lowe D, Scott K, Crocker J, et al. Variation in the frequency of Epstein-Barr virus-associated Hodgkin's disease with age. *Leukemia.* 2000;14(4):748-53.
29. Jarrett RF, Krajewski AS, Angus B, Freeland J, Taylor PR, Taylor GM, et al. The Scotland and Newcastle epidemiological study of Hodgkin's disease: Impact of histopathological review and EBV status on incidence estimates. *J Clin Pathol.* 2003;56(11):811-6.
30. Glaser SL, Gulley ML, Clarke CA, Keegan TH, Chang ET, Shema SJ, et al. Racial/ethnic variation in EBV-positive classical Hodgkin lymphoma in California populations. *Int J Cancer.* 2008;123(7):1499-507.
31. Thompson MP, Kurzrock R. Epstein-Barr virus and cancer. *Clin Cancer Res.* 2004;10(3):803-21.
32. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: A systematic review. *Cancer Epidemiol Biomarkers Prev.* 2005;14(2):467-75.

33. Hammarstedt L, Lindquist D, Dahlstrand H, Romanitan M, Dahlgren LO, Joneberg J, et al. Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer. *Int J Cancer.* 2006;119(11):2620-3.
34. De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: A meta-analysis. *Int J Cancer.* 2009;124(7):1626-36.
35. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol.* 1999;189(1):12-9.
36. Backes DM, Kurman RJ, Pimenta JM, Smith JS. Systematic review of human papillomavirus prevalence in invasive penile cancer. *Cancer Causes Control.* 2009;20(4):449-57.
37. Moujaber T, MacIntyre CR, Backhouse J, Gidding H, Quinn H, Gilbert GL. The seroepidemiology of Helicobacter pylori infection in Australia. *Int J Infect Dis.* 2008;12(5):500-4.
38. Pandeya N, Whiteman DC, Australian Cancer S. Prevalence and determinants of Helicobacter pylori sero-positivity in the Australian adult community. *J Gastroenterol Hepatol.* 2011;26(8):1283-9.
39. Newton R, Ferlay J, Beral V, Devesa SS. The epidemiology of non-Hodgkin's lymphoma: Comparison of nodal and extra-nodal sites. *Int J Cancer.* 1997;72(6):923-30.
40. Australian Bureau of Statistics. *4812.0. – Health Risk Factors Australia 2001.* Canberra (AUST): ABS; 2001.
41. McLennan WP, Podger A. *National Nutrition Survey. Nutrient Intakes and Physical Measurements Australia 1995.* Canberra (AUST): Australian Bureau of Statistics; 1998.
42. McLennan WP, Podger A. *National Nutrition Survey. Foods Eaten Australia 1995.* Canberra (AUST): Australian Bureau of Statistics; 1999.
43. Australian Bureau of Statistics. *2004-2005 National Health Survey Expanded CURF, RADL. Findings Based on Use of ABS CURF Data.* Canberra (AUST): ABS; 2005.
44. Olsen CM, Bain CJ, Jordan SJ, Nagle CM, Green AC, Whiteman DC, et al. Recreational physical activity and epithelial ovarian cancer: A case-control study, systematic review, and meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2007;16(11):2321-30.
45. Whiteman DC, Sadeghi S, Pandeya N, Smithers BM, Gotley DC, Bain CJ, et al. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. *Gut.* 2008;57(2):173-80.

Supporting Information

Additional supporting information may be found in the online version of this article:

Supplementary Table 1: International Agency for Research on Cancer (IARC) and World Cancer Research Fund (WCRF) classifications.