Cancers prevented in Australia in 2010 through the consumption of aspirin

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Abstract

Objectives: To estimate the proportion and number of cancers in Australia in 2010 that may have been prevented from occurring due to daily use of aspirin in the population.

Methods: We calculated the Prevented Fraction (PF) of colorectal and oesophageal cancers using standard formulae. The PF is the proportion of the hypothetical total load of cancer in the population that was prevented by exposure to aspirin. The formula incorporates estimates of the prevalence of aspirin use in Australian adult populations, the relative risks associated with aspirin use and cancer incidence.

Results: An estimated 335 colorectal cancers, 22 oesophageal adenocarcinomas and 29 oesophageal squamous cell carcinomas (SCC) were potentially prevented due to daily aspirin use. These figures equate to 2.2%, 3.1% and 5.4% of all colorectal cancers, oesophageal adenocarcinomas and oesophageal SCCs, respectively, that would otherwise have occurred but were potentially avoided due to the daily use of aspirin pertaining in the Australian population.

Conclusions: At current levels of consumption, a small but measurable reduction in cancer incidence can be attributed to daily aspirin use.

Implications: Assuming the benefits outweigh the harms of known gastrointestinal toxicity and other hazards, aspirin use may be considered for some people to prevent the development of particular gastrointestinal cancers.

Key words: prevented fraction, cancer, aspirin, protective factor

An increasing body of observational[1,2] and trial[3] evidence suggests that frequent use of aspirin reduces the risk of cancer in several organs, particularly of the gastrointestinal tract. Currently, the evidence is strongest for colorectal cancer, with effect sizes from well-conducted prospective studies converging on about 20% lower incidence of cancer among daily users compared to non-users of aspirin. Frequent aspirin use is also associated with significantly lower risks of adenocarcinomas and squamous cell carcinomas of the oesophagus.[1]

The mechanisms through which aspirin may inhibit tumour development remain unclear, although there is widespread consensus that aspirin's inhibition of cyclo-oxygenase (COX) enzymes is likely to mediate some of the observed effects. COX enzymes (notably the inducible form of COX-2) are over-expressed in colorectal adenomatous polyps and in precursor lesions in other organs, and are known to play a role in carcinogenesis, apoptosis and angiogenesis.[4,5]

Thus, although regular aspirin use is not formally advocated by any agencies for the primary prevention of cancer, it remains of interest to determine the magnitude of potential benefit of daily aspirin consumption in terms of cancer incidence. We therefore estimated the number and fraction of colorectal cancers that may have been prevented from occurring in Australia in 2010 through prior daily aspirin use. Given the suggestive – but weaker – evidence that frequent aspirin use reduces the risks of oesophageal cancer, we also estimated the number and fraction of those cancers that may have been prevented.

Methods

Relative Risk estimates

For our primary analysis, we used the pooled adjusted relative risk for the association between frequent (daily) aspirin use and colorectal cancer derived from a systematic review and meta-analysis of 5 cohort studies (RR=0.80, 95%CI 0.73-0.88).[1] This risk estimate was selected as it was sourced from a meta-analysis of large, prospective studies featuring community samples with long follow-up. Algra and Rothwell[1] also published pooled results from 4 case-control studies (RR=0.49, 95%CI 0.40-0.60) and relative risks for frequent aspirin use and CRC mortality from 6 randomised control trials (OR=0.58, 95%CI 0.44-0.78). We used these alternative effect estimates in sensitivity analyses.

For oesophageal cancer, we sourced the relative risks from the same publication as was used for the colorectal cancer risks;[1] however, we used the pooled risk

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estimates derived from case-control studies (oesophageal adenocarcinoma OR=0.72; 95%CI 0.62-0.85; oesophageal squamous cell carcinoma OR=0.56; 95%CI 0.40-0.77), as only one cohort study provided data on the effects of maximum aspirin use and oesophageal cancer. In the same publication,[1] meta-analysis of 6 RCTs showed even greater reductions in total oesophageal cancer mortality (OR=0.47, 95%CI 0.27-0.81); we used these summary relative risks in sensitivity analyses.

Exposure prevalence estimates

There are very few age- and sex-specific prevalence estimates of aspirin use for the Australian population. While the most recent Australian Health Survey (2011-12) collected information about frequency of use of medications, including aspirin, the data were not available at the time of analysis. Moreover, while the latent period between use of aspirin and benefit conferred is unknown, prospective studies suggest that effects manifest only after several years. We therefore sourced prevalence estimates from the population-based control group of men and women who participated in the Australian Cancer Study between 2002 and 2005. Participants in that study were randomly selected from the Australian Electoral Roll and sampled within 5-year age groups and state of residence to match the distribution of cases.[6] Respondents (n=1,576 controls; 52% participation fraction) were asked how often they had taken aspirin (purchased over the counter) during the past five years. Table 1 presents the prevalence of aspirin use in the response categories on the questionnaire, by 10-year age group and sex. To account for population ageing with time since exposure, and to accommodate an assumed latent period of around 10 years, we used prevalence data for the age category that was 10 years younger than the corresponding cancer incidence category. For example, cancers prevented in the 50–59 years age group in 2010 were attributed to aspirin use in the 40–49 years age category in 2002–05.

Statistical analysis

In our primary analysis, we combined the proportion of controls who reported taking aspirin 4–7 times a week with those who reported taking aspirin twice or more daily to estimate the proportion of the population who were daily aspirin users. Because the Australian Cancer Study did not collect data for a single category of daily use of aspirin, we conducted sensitivity analyses using a more conservative measure that comprised all the respondents in the category of most frequent use (twice or more per day) and half the respondents in the category '4–7 times per week'.

We calculated the Prevented Fraction (PF_x) of colorectal and oesophageal cancers in each age and sex category using the formula:[7]

$$PF_x = p_x (1 - RR)$$

where p_x is the prevalence of daily aspirin use by age and sex category.

The prevented fraction is the proportion of the hypothetical 'total load' of each cancer that would have occurred in the population, but which was prevented because of the prevailing use of aspirin.[8]

To estimate the number of cancers that were prevented through daily aspirin use, the formula was:

$$Number\ of\ prevented\ cancers = \sum \frac{N_x}{1 - PF_x} - N_x$$

where N_x is the number of observed cancers in 2010[9] in each age and sex category and PF_x is the prevented fraction in that age and sex category.

Because histology-specific incidence data for oesophageal cancers were not available for 2010, we derived the number of oesophageal adenocarcinomas and squamous cell carcinomas separately from incidence data for 2006–2008. Average age- and sex-specific incidence over this three-year period was applied to the 2010 Australian estimated resident population (by age and sex) to estimate the number of incident oesophageal adenocarcinomas and SCCs in 2010. We then calculated the Prevented Fraction for the entire Australian population by summing the numbers of prevented cancers across age and sex categories, and then expressed this number as a percentage of the sum of prevented and observed cancers across all age and sex categories.

Table 1: Prevalence (%) of Aspirin Use, Australian Cancer Study Controls (2002-05).

Age Group	Never	Occasionally	<once a month	2-3 times a month	Once a week	2-3 times a week	4-7 times a week	Twice or more a day
Males								
<30 yrs	57.1	42.9	0.0	0.0	0.0	0.0	0.0	0.0
30-39 yrs	22.7	54.5	13.6	9.1	0.0	0.0	0.0	0.0
40-49 yrs	46.7	33.3	13.3	4.4	1.1	0.0	1.1	0.0
50-59 yrs	43.4	36.7	6.4	4.9	0.4	1.1	7.1	0.0
60-69 yrs	38.6	33.2	5.4	3.6	1.0	2.1	15.7	0.5
70+ yrs	34.6	35.4	1.1	1.5	1.5	2.3	23.2	0.4
Total	39.3	35.2	5.4	3.6	1.0	1.6	13.7	0.3
Females								
<30 yrs	61.1	16.7	11.1	11.1	0.0	0.0	0.0	0.0
30-39 yrs	61.8	26.5	5.9	5.9	0.0	0.0	0.0	0.0
40-49 yrs	60.0	27.3	1.8	5.5	0.0	1.8	3.6	0.0
50-59 yrs	47.1	41.4	5.0	2.9	0.0	0.7	2.1	0.7
60-69 yrs	53.1	29.3	5.4	0.0	0.0	2.0	8.2	2.0
70+ yrs	49.4	23.6	2.2	0.0	1.1	2.2	20.2	1.1
Total	53.2	30.5	4.3	2.6	0.2	1.5	6.9	0.9

Results

Prevalence of aspirin use

In the Australian Cancer Study control group, 12% of the population were frequent users of aspirin (4+ times per week), with the proportion of men (14%) greater than that of women (8%). Use increased with increasing age, with the highest proportion of frequent users in the 70+ age category (24% of men and 21% of women), see Table 1.

Proportion of colorectal cancers prevented due to daily aspirin use

Assuming an effect size of 0.80 for daily aspirin use and assuming the prevalence of daily use in the Australian population described above, we estimated that 2.2% of colorectal cancers that would otherwise have occurred in 2010 were prevented through daily aspirin use in the population. Using 2010 cancer incidence data, this equates to the prevention of 335 colorectal cancer cases (198 in men and 137 in women), see Table 2. When we used the more conservative estimate for the prevalence of daily aspirin use (7.1% for men and 4.4% for women), our estimate for the prevented fraction of colorectal cancers was reduced to 1.2% (173 cases; 99 men and 74 women). In contrast, we found that 904 (PF=5.7%) or 732 (PF=4.7%) colorectal cancers would have been prevented when we used the more extreme effect sizes for daily aspirin use reported by Algra and colleagues[1] for case-control studies and RCTs (CRC mortality) respectively.

Proportion of oesophageal cancers prevented due to daily aspirin use

Assuming a protective effect of frequent aspirin use on cancers of the oesophagus, we estimated an additional 22 adenocarcinomas (3.1%) and 29 squamous cell carcinomas (5.4%) would have occurred in 2010 if no one in the population had taken aspirin on a daily basis (3.5% of all oesophageal cancers). The majority of cancers prevented (34 out of 51; 67%) would have occurred in men. When we used the more conservative estimate for the prevalence of daily aspirin use, our estimate for the prevented fraction of oesophageal cancers was reduced to 1.8% (26 cases; 17 men and 9 women). In contrast, when we used the more extreme effect sizes for maximum aspirin use for oesophageal cancer deaths in RCT follow-ups,[1] we found that 96 (PF=6.3%) oesophageal cancers would have been prevented.

Discussion

We estimated that at prevailing levels of aspirin use, the incidence of colorectal cancer in Australia in 2010 was potentially about 2% (or 335 cases) lower than would otherwise have been the case. Similarly, about 50 cases of oesophageal cancer were likely prevented through the use of aspirin, resulting in an incidence reduction of about 4%.

The analyses presented here assume that aspirin protects against the occurrence of cancers of the colorectum and oesophagus. The evidence for a beneficial effect on both cancers stems from a number of recent, well-conducted meta-analyses that have examined these associations in detail. As expected, the summary risk estimates from meta-analyses have varied somewhat depending upon their inclusion and exclusion criteria (e.g. trials vs. observational studies, dosage ranges, durations of follow-up), but there is an overall consistency of effect in the order of 20–40% risk reductions for cancers of the colorectum and oesophagus associated with daily aspirin use. For example, a recent analysis of pooled data from 14,033 participants in four randomised control trials who had taken low-dose aspirin (75–300 mg daily) for a median trial period of six years and were followed up for cancer incidence and mortality for a median 18.3 years.[3] That analysis reported significant reductions in colorectal cancer incidence (HR 0.75, 95%CI 0.56-0.97) and mortality (HR 0.61, 95%CI 0.43-0.87). We used a more conservative risk estimate from a meta-analysis of cohort studies in our primary analysis (RR 0.80, 95%CI 0.73-0.88),[1] and more extreme estimates from meta-analyses of case-control studies (OR 0.49, 0.40-0.60) and randomised control trials (OR=0.58, 95%CI 0.44-0.78) in our sensitivity analyses.[1] A further meta-analysis of nine cohort studies[2] (including four of the five cohort studies in the meta-analysis by Algra and colleagues[1]) reported a similar effect size associated with use of aspirin seven times per week (RR = 0.82, 95%CI 0.78-0.87).

Despite the apparent consistency of reported effects, the risk estimates summarised above must be interpreted with caution, as there remains considerable debate as to the dose and frequency of aspirin required for cancer prevention, with widely differing views as to the merits of daily intake versus other schedules.[10] For example, with respect to dose, meta-analyses suggest that risks of colorectal cancer decrease with increasing doses of aspirin up to 325 mg/day (with a reduced risk of 20% at this level) but that risks are not substantially lowered with higher doses.[2] The analysis by Ye and colleagues[2] also suggests a non-linear relationship between colorectal cancer risk and frequency of aspirin use, with approximately log-linear reductions in risk associated with intakes up to seven times per week, but no further risk reductions with more frequent aspirin intake.[2] Risks of colorectal cancer were also inversely associated with increasing duration of aspirin use.

It is also notable that randomised clinical trials have typically reported even greater effects on colon cancer than observational studies, with summary hazard ratios of 0.58 to 0.76 reported.[3] The discordance in the magnitude of effects of aspirin use reported by trials and observational studies defies simple explanation, despite considerable inquiry, although potential differences in participant selection, measurement, adherence, dose, frequency and duration of follow-up have all been implicated.[11] For our calculations, we elected to use the more conservative estimates

Table 2: Prevented fraction (PF) and estimated number of cancers prevented in Australia in 2010 attributable to daily use of aspirin.

Age at outcome[a]	Colorectal (C18-C20)[b]			Oesophagus (C15) – adenocarcinoma[b,c]			Oesophagus (C15) – squamous cell carcinoma[b,d]			Total Oesophagus (C15)[b]
	PF	Obs.	Prev.	PF	Obs.	Prev.	PF	Obs.	Prev.	Prev.
Males										
<40 yrs	0.0	138	0	0.0	6	0	0.0	1	0	0
40-49 yrs	0.0	410	0	0.0	34	0	0.0	14	0	0
50-59 yrs	0.2	1,264	3	0.3	107	0	0.5	45	0	0
60-69 yrs	1.4	2,425	35	2.0	154	3	3.1	84	3	6
70-79 yrs	3.2	2,432	81	4.5	157	7	7.1	77	6	13
80+ yrs	4.7	1,588	79	6.6	112	8	10.4	58	7	15
Total		8,257	198		570	18		279	16	34
PF_{aw}	2.3			3.1			5.4			PF_{aw}=3.3%[e]
Females										
<40 yrs	0.0	149	0	0.0	1	0	0.0	1	0	0
40-49 yrs	0.0	361	0	0.0	4	0	0.0	4	0	0
50-59 yrs	0.7	917	7	1.0	10	0	1.6	19	0	0
60-69 yrs	0.6	1,512	9	0.8	18	0	1.3	50	1	1
70-79 yrs	2.0	1,751	36	2.9	34	1	4.5	65	3	4
80+ yrs	4.3	1,911	85	6.0	48	3	9.4	92	9	12
Total		6,601	137		115	4		231	13	17
PF_{aw}	2.0			3.4			5.3			PF_{aw}=3.9%[e]
Persons										
<40 yrs		287	0		7	0		2	0	0
40-49 yrs		771	0		38	0		18	0	0
50-59 yrs		2,181	10		117	0		64	0	0
60-69 yrs		3,937	44		172	3		134	4	7
70-79 yrs		4,183	117		191	8		142	9	17
80+ yrs		3,499	164		160	11		150	16	27
Total		14,858	335		685	22		510	29	51
PF_{aw}	2.2			3.1			5.4			PF_{aw}=3.5%[e]

Abbreviations: Obs. = observed cancers in 2010; Prev. = cancers prevented in 2010 through use of aspirin; PF = prevented fraction (expressed as a percentage); PFaw = age-weighted prevented fraction (expressed as a percentage)

a: Prevalence data age groups are 10 years younger than cancer incidence age groups assuming a 10 year latent period between exposure and outcome (see text)

b: International Classification of Diseases Code (ICD-10)

c: Oesophageal cancer (adenocarcinoma) with histology codes 8140–8573;

d: Oesophageal cancer (squamous cell carcinoma) with histology codes 8050-8082

e: % of all oesophageal carcinoma

from observational studies, since they comprised participants who were unselected with respect to underlying morbidities (unlike the trials, which recruited patients at high risk for cardiovascular events) and thus would be expected to more closely approximate the general population. To explore the potential impact of protective effects of greater magnitude, however, we performed sensitivity analyses using the risk estimates derived from the trials and, as expected, observed somewhat higher prevented fractions.

A challenge for these analyses was the lack of high quality prevalence data for daily aspirin use by age and sex in the Australian population. Earlier iterations of the National Health Survey did not capture this information, and while the most recent survey (2011-12) did measure aspirin use, the data were not yet available at the time of analysis. We therefore used data from the control group of a national case-control study with a participation fraction of 52%. Measurement of aspirin use in that study was by self-report and was approximate with respect to daily use. Moreover, the question referred to over-the-counter medication, so prescription medicines were not included. For these reasons, our estimates of the fraction of cancers prevented by daily aspirin use cannot be considered robust. To mitigate these concerns, we performed sensitivity analyses in which we varied the prevalence of exposure and the magnitude of the risk estimates. Under a range of scenarios, the prevented fraction varied between 1.2% and 5.7% for colorectal cancer and 1.8% and 6.3% for oesophageal cancer.

It must also be emphasised that aspirin carries significant risks of adverse events, including gastrointestinal toxicity and haemorrhage.[4,12] Such adverse events are reasonably frequent and can be severe, even fatal. A number of systematic reviews have summarised the benefits and harms of aspirin use in the general population.[13-15] In general, the accumulated literature suggests that the frequency and severity of adverse events increases with dose, and the likelihood of severe haemorrhagic events is highest in the first few years of use and then declines over time. It is concluded by some, but not all, that the balance of benefits versus harms of daily aspirin use improves with duration of use when all outcomes are considered (i.e. cardiovascular, haemorrhagic, cancer, etc).[15]

Guidelines regarding the use of aspirin as a preventive agent are under review around the world. In Australia, the *Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer*[16] do not recommend aspirin or nonsteroidal anti-inflammatory drugs for prevention of colorectal cancer due to uncertainties about dose and side effects. However, they do suggest that aspirin should be considered as prophylaxis against further adenoma development in people who have had an adenoma removed.[16] Similarly, the United States Preventive Services Taskforce recommends against the routine use of aspirin and nonsteroidal anti-inflammatory drugs to prevent colorectal cancer in persons at average risk for colorectal cancer.[17] Both the Australian and US guidelines pre-date the extensive literature that has arisen on this subject in recent years, including the systematic reviews of benefits versus harms of daily aspirin for the prevention of cancer and cardiovascular disease. The US guidelines are currently under review, and will specifically include assessment of daily and alternate-day dosing of aspirin for all cancer outcomes.[18]

Notwithstanding the known hazards, these analyses suggest a modest benefit of aspirin use in terms of cancer prevention that may help to guide practice and policy in this area. These analyses should be repeated in the future when nationally representative aspirin prevalence data become available, and when more is known about the effects on cancers at other sites.

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PAF Project

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