A REVIEW OF THE SAFETY AND EFFICACY OF ASPIRIN IN PROSTATE AND OTHER CANCERS: IS CURRENT EVIDENCE SUFFICIENT FOR PUBLIC HEALTH POLICY EVALUATION?

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Summary

Objective: To survey and review published literature on the safety and efficacy of aspirin (acetylsalicylic acid) in the prevention and / or adjuvant treatment of prostate and other cancers.

Methods: A series of 4 searches and a review of journal reports published between 1990 and 2013 were performed in July 2014 using the following databases: Academic Search Premier; Africa-Wide Information; CINAHL; E-Journals; MEDLINE; PubMed; Cochrane Library; and Clinicaltrials.com. Only publications referring to “aspirin” or “acetylsalicylic acid” and “cancer” and “prostate” were included in the narrative review by a reviewer.

Results: The articles in the final data set included meta-analyses of cancer outcomes from studies originally designed to investigate the effect of daily aspirin on cardiovascular outcomes. These studies demonstrated variable effect sizes, which consistently showed a protective effect by aspirin for most types and stages of neoplastic disease. Basic research studies elucidated the possible mechanism by which aspirin is thought to prevent incident cancer and also attenuate the progression of established cancer. The narrative review critiqued the current methodologies used to investigate this topic.

Conclusion: There is growing epidemiological evidence that daily aspirin has a role in the prevention and remission of some cancers, including prostate cancer. There is however currently very limited experimental evidence to withstand rigorous regulatory assessment,
and hence enable preventative and/or adjuvant public health recommendations in high risk populations in South Africa and elsewhere.

**Key words:** aspirin, neoplasms, prostate cancer, prevention, adjuvant treatment, experimental evidence.

**Introduction**

One in six South African men is at risk of developing cancer during their lifetime.  

The prevalence of certain cancers is further determined by age, race, and socio-economic status. In particular, prostate cancer is rated world-wide as the second most common cancer in men, with cases expected to double by the year 2030. A suggested reason for the higher rates recorded in some countries is the increased availability of screening for blood prostate-specific antigen (PSA) or less frequently, by digital rectal examination, in men without symptoms of the disease. The PSA test detects many prostate cancers which are small and/or would otherwise remain unrecognized, and which may or may not develop further into advanced stage disease. Consequently, the evidence from systematic reviews has not been clear on whether screening for prostate cancer ultimately decreases the risk of death, or that the benefits of screening outweigh the risks thereof.  

Prostate cancer incidence increases with age, and rates increase exponentially in men 50 years and older, from the very low baseline rates for men under 50 years. For instance, in 1996 the National Cancer Institute of the United Kingdom reported an age cohort in England and Wales that showed increases of prostate cancer rates from 8/1 000 population in men aged 50-56 years to 68/1 000 in men aged 60-64 years; and 260/1 000 in men aged 70-74 years. The rates peaked at 406/1 000 in men aged 75-79 years. In comparison, the background population death rates per thousand in 1992 in cohorts of men aged 50-54 years, 60-64 years, and 70-74 years were 4, 37, and 166, respectively. Also significantly,
rates stratified by race indicated that the incidence in Black males exceeded that in White males.\[^4\]

Coupled with general increases in life-expectancy and attendant life-time lifestyle risks of modern living, the incidence of all cancers will impact public and private healthcare spend adversely due to the high cost of current cancer treatments.

According to Rose et al.,\[^5\] there are strong indications from current experimental and observational studies that exposure to a range of aspirin doses, at variable frequencies and durations of exposure, before or after diagnosis of prostate cancer, improves outcomes. This occurs to varying extents by reducing the frequency of incident neoplasms and increases 5-year post-diagnosis survival rates through a postulated attenuation of distant metastasis. There is, however, currently no consensus on the clinical significance and size of the reduction in risk of incident cancer and improvements in post-diagnosis 5-year survival. There is also no consensus on the induction time of positive effect, even when stratified according to the exposure co-variables of dose, frequency, duration, and age.\[^5\] Rose et al. also highlight the lack of consensus on the appropriateness of the design of some of the pivotal meta-analytical studies by Rothwell et al.\[^6-9\] on aspirin and cancer. The studies derived favourable cancer outcomes with statistically significant combined effect sizes, from pooled studies originally designed to investigate the effect of daily aspirin on cardiovascular outcomes.

**Methods**

A reviewer, assisted by the institutional librarian, searched for journal reports on “aspirin”, “cancer”, and “prostate” published between 1990 and 2013. All available publications were considered, as long as they referred to aspirin, cancer, and prostate.

**Search strategy No. 1:**

Search stage 1
EBSCO host Research Databases were searched on 30 June 2014 using the Boolean/phrase search modes and search terms “aspirin” AND “prostate cancer”. The following databases yielded 391 results: Academic Search Premier; Africa-Wide Information; CINAHL; E-Journals; and MEDLINE.

Search stage 2

In a subsequent search, the above search strategy was narrowed to scholarly (peer reviewed) journals, still using the Boolean/phrase search modes, and yielded 102 results, 17 of which were reasonably more relevant than the rest in terms of exposure to aspirin on its own and various cancer outcomes.

Search strategy No. 2:

The second search, using the search terms “aspirin” AND “prostatic neoplasms” AND “clinical trial” in MEDLINE, yielded 4 results.

Search strategy No. 3:

The third search, using the search terms “aspirin” AND “prostate” in PUBMED, yielded 16 results.

Search strategy No. 4:

The fourth search, using the search terms “aspirin” AND “prostate” AND “clinical trial” in Clinicaltrials.gov, yielded 4 results.

Results

Literature search

| 415 potentially relevant records identified through database searches |
| Exclusion criteria |
| Aspirin in both intervention and control groups |
| Any other additional interventions in cancer prevention/treatment |

| Titles and abstracts screened |

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The final stage of Search strategy No. 1 yielded 17 results comprising 6 cohort, 3 nested case-control, and 8 meta-analytical studies; 3 clinical trials, and 1 basic research study.

Search strategy No. 2 yielded 4 results comprising 4 clinical trials.

Search strategy No. 3 yielded 16 results comprising 3 cohort, 4 nested case-control, 2 review, and 1 quality of life studies; 1 systematic review, 1 meta-analysis, 3 clinical trials, and 1 basic research study.

Search strategy No. 4 yielded 4 results, of which only 2 of them were complete and published clinical trials, the other 2 were ongoing and/or recruiting. In both of the published trials, exposure to aspirin was common to both arms. One study had adjuvant celecoxib in the intervention arm, with prostatic biomarkers as the primary end-point. The other had 'deferred diethylstilbestrol' as the intervention, with several clinical and patient-preference outcomes.

Observational study outcomes were variable but consistently showed a protective effect for aspirin in most types of neoplastic disease. Basic research study outcomes elucidated the possible mechanism by which aspirin is thought to prevent and attenuate the progression of established cancer. Except for two studies reported by Jacobs et al.\textsuperscript{[10]} and Choe et al.,\textsuperscript{[11]} randomised controlled clinical trial outcomes had the limitation of multivariate medicinal class (several selected non-steroidal anti-inflammatory drugs) exposures, with aspirin as
just one of the exposure variables. In most such cases, an a priori subset analysis was either not planned, or possible.

Four pivotal meta-analytical studies by Rothwell et al.[6-9] on aspirin and cancer, which derived promising cancer outcomes from pooled studies, originally designed to investigate the effect of daily aspirin on cardiovascular outcomes, were also identified separately. Although the methodological limitations of pooling studies of the main outcome variable of interest (cardiovascular disease), to derive quantitative associations with a co-variable (neoplastic disease), have been highlighted by Rose et al. above, these studies form a large part of this review due to their ability to quantitatively relate all-cancer outcomes to aspirin only, a single exposure of interest for this review.

**Current research on prophylactic aspirin for cancer**

A meta-analytic study by Rothwell et al.[6] investigated the short-term effects of exposure to aspirin in the primary prevention of some cancers. The primary objective of the study was to assess cancer mortality in all eligible controlled trials of daily aspirin versus control in primary prevention of cardiovascular events, the time course of effects of low-dose aspirin on cancer incidence and mortality, as well as non-vascular, vascular, and all-cause mortality outcomes. The secondary study objective was to assess the time course of effects of low-dose aspirin on incident cancer, as well as the safety indicators of major vascular events and major extra-cranial bleeds, stratified by age, gender, and smoking status. In 34 trials (n=69 224) exposure to aspirin was observed to reduce incident cancer deaths by between 4 and 24% (OR 0.85, 95% CI 0.76 – 0.96), more so by a reduction of 18 to 51% from 5 years prospectively (OR 0.63, 95% CI 0.49 – 0.82). As a result, there were fewer non-vascular deaths overall (OR 0.88, 95% CI 0.78 – 0.96) in 51 trials (n=77 549). In six trials (n=35 535) of daily low-dose aspirin (75 mg) for prevention of vascular events, cancer incidence from 3 years prospective follow-up was reduced by 12 to 34% in women (OR 0.76, 95% CI 0.66 – 0.88), and 7 to 37% in men (OR 0.77, 95% CI 0.63 – 0.93).
Although the effects of aspirin on both the safety outcomes of major bleeding and major vascular events diminished with increasing follow-up, the frequency of events of major bleeding initially negated the reduced risk of major vascular events. Furthermore, the risk of cancer remained reduced (ARR 3.13 per 1 000 patients per year, 95% CI 1.44 – 4.82) from 3 years onwards. Unexpectedly, case-fatality rates from major extra-cranial bleeds were significantly lower on aspirin (8 cases in 203 patients on low-dose aspirin) than on control treatment (15 cases in 132 patients on control treatment), OR 0.32 (95% CI 0.12 – 0.83).

The authors concluded that the short-term reduction in cancer incidence and mortality, and the concomitant decrease in risk and case-fatality of major extra-cranial bleeds with extended use, further strengthen the case of daily aspirin in the prevention of some cancers.\(^6\)

**Current research on adjuvant aspirin for cancer**

The effects of aspirin on colorectal cancer incidence and mortality in relation to dose, duration of treatment, and site of tumour were assessed in only one follow-up study of four randomized controlled trials on the efficacy of aspirin versus control treatment in primary and secondary prevention of cardiovascular events (n=14033).\(^7\) Pooled individual patient data of over 20 years, during and after the trials, were meta-analysed and allocation to the aspirin group, with mean duration of exposure of 6 years, was found to reduce the 20-year risk of colon cancer by a statistically significant 24% (HR 0.76, 95% CI 0.6 – 0.96), in a median follow-up period of 18.3 years. Although there was no observed overall benefit in rectal cancer (HR 0.9, 95% CI 0.63 – 1.30), benefits stratified by duration of treatment indicated that treatment of 5 years or more, reduced risk by more than 40% (HR 0.58, 95% CI 0.36 – 0.92). There was a modest increase in the benefit observed at daily doses higher than 75 mg for 5 years (ARR = 1.76%, 95% CI 0.61 – 2.91), although in one small trial the risk of fatal colorectal cancer was found to be non-significantly higher with 30 mg versus 283 mg daily aspirin on long-term follow-up (OR 2.02, 95% CI 0.70 – 6.05). The authors concluded that daily aspirin doses of at least 75 mg, taken for at least 5 years,
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conferred some protection against long-term incidence and mortality due to colorectal cancer.

A follow-up meta-analysis of eight UK trials[^8], with 25 570 patients randomized to aspirin and control for prevention of cardiovascular events, found evidence that aspirin reduced long-term all-cancers mortality by more than 20% (Pooled OR 0.79, 95% CI 0.68 – 0.92). This study confirmed earlier findings of the long-term protective effects of aspirin in some gastrointestinal and non-gastrointestinal cancers. In a further analysis of available individual patient data (n=23 535), statistically significant benefit was observed only after 5 years for all cancers (HR 0.66, 95% CI 0.5 – 0.87) and gastrointestinal cancers (HR 0.46, 95% CI 0.27 – 0.77). In three trials there were 1 634 deaths in 12 659 patients (13%), and the 20-year risk of cancer mortality was lower in the aspirin groups than in the control groups. In all solid cancers follow-up time-dependent mortality was reduced by 20% (HR 0.80, 95% CI 0.72 – 0.88), and in gastrointestinal cancers by 35% (HR 0.65, 95% CI 0.54 – 0.78). A significant interaction between duration of treatment of at least 7.5 years and all solid cancers (p=0.003), was observed to reduce mortality by more than 30% (HR 0.69, 95% CI 0.54 – 0.88), and gastrointestinal cancers by almost 60% (HR 0.41, 95% CI 0.26 – 0.66). Deaths related to oesophageal, pancreatic, brain, and lung cancer occurred after 5 years. By contrast, the incidence of cancer-related mortality occurred much later than 5 years for stomach, colorectal, and prostate cancers.

For lung cancer, benefit on 20-year risk of cancer-related mortality was confined to adenocarcinomas (HR 0.66, 95% CI 0.56 – 0.77), and was unrelated to aspirin doses of 75 mg and higher, gender, or smoking. However, benefit increased with age, such that at age 65 years and older, the absolute reduction in 20-year risk of cancer death reached 7.08% (95% CI 2.42 – 11.74). Meaning that in the sub-group of patients aged 65 years and older, and followed-up over 20 years, 1 death due to cancer was prevented for every 14 patients exposed to at least 75 mg daily aspirin, for at least 5 years. The authors concluded that daily aspirin reduced deaths due to common gastrointestinal and non-gastrointestinal
cancers, during and after trials of aspirin versus control treatment in the prevention of vascular events in patients.\textsuperscript{[8]}

A study on the effect of aspirin on metastases, as a possible explanation for the appearance (only after a few years) of effects on mortality due to some cancers, was conducted on five large randomised trials of daily aspirin at doses of at least 75 mg versus control for the prevention of cardiovascular events in the UK.\textsuperscript{[9]} The primary objective of the study was to establish the frequency of distant metastasis in patients (n=17 285) who developed cancer during trials. Electronic and paper records of all incident cancer cases were reviewed, and the effect of aspirin on the risk of metastasis at presentation or on follow-up was stratified by tumour histology of adenocarcinoma versus other solid cancers and clinical characteristics. During a mean in-trial follow-up of 6.5±2 years, 987 (5.7\%) new solid cancer cases were diagnosed. Patients allocated to the daily aspirin arm had an observed 36\% reduced risk of distant metastasis for all cancers (HR 0.64, 95\% CI 0.48 - 0.84), a 46\% reduction for adenocarcinoma (HR 0.54, 95\% CI 0.38 - 0.77), and a statistically non-significant 18\% reduction in risk of distant metastasis for other solid cancers (HR 0.82, 95\% CI 0.53 - 1.25). An odds ratio of 0.52 (95\% CI 0.35 - 0.75) was observed for daily aspirin in the reduction of the proportion of adenocarcinomas that had metastatic versus local disease. Meaning that exposure to at least 75 mg daily aspirin reduced the proportion of metastatic, compared to localised, adenocarcinomas by 48\% in the patient population observed.

In patients with colorectal cancer, exposure to long-term aspirin reduced risk of adenocarcinoma with metastasis at initial diagnosis by 74\% (HR 0.26, 95\% CI 0.11 - 0.57). Also, patients who remained on trial treatment up to and after diagnosis had an almost 70\% reduction in risk (HR 0.31, 95\% CI 0.15 - 0.62). The study also found that while there was a reduced risk of fatal adenocarcinoma in the aspirin group (HR 0.65, 95\% CI 0.53 - 0.82), the risk modification in other fatal cancers was not significantly different from control treatment (HR 1.06, 95\% CI 0.84 - 1.32). The aspirin effects were independent of age and gender, but there was a greater absolute benefit in smokers. Importantly, a low-dose, slow-
release formulation of aspirin for inhibition of platelet adhesion, with little systemic bioavailability, was as effective as higher doses.

The authors concluded that early reduction in cancer deaths in trials of daily aspirin versus control treatment could be accounted for by findings that aspirin prevents distant metastases, suggesting that aspirin may have a role in the treatment of some cancers. The authors further suggest that this finding may provide proof of principle for pharmacological intervention specifically to prevent distant metastases.\cite{9} Other studies have corroborated these findings, and go further to extend the possibility to other newer cyclo-oxygenase-inhibitors (specifically COX-2 inhibitors) in the risk reduction of the incidence and mortality of some cancers.\cite{12,13}

Jacobs et al.\cite{10} studied the effects of anticoagulant therapy on high-risk prostate cancer in 74 eligible patients treated with radiotherapy from 2005 to 2008. Forty-three (43) of these patients were on anticoagulation therapy in the form of aspirin (41 patients or 95.6%), clopidogrel (8 patients or 17.5%), warfarin (9 patients or 20%), and a combination of anticoagulants (13 patients or 31.1%). On the hypothesis that any anticoagulation therapy attenuates biochemical failure and improves overall survival in conjunction with radiotherapy in high-risk prostate cancer patients, patients were followed-up for a median of 56.6 months post randomization and associations between anticoagulant use and freedom from biochemical failure (FFBF), overall survival (OS), distant metastasis, and toxicity, were analyzed. For aspirin, biochemical failure was attenuated by 84% versus 65% for those who were not on anticoagulation therapy (p=0.008). Rates of distant metastases at 5 years were reduced compared to the control group (12.2% vs. 26.7% cases, p=0.039). Five-year overall survival in patients with Gleason score 9-10 histology was improved by 88% versus 37% for the control group (p=0.032). Also, the 5-year survival rate remained statistically significant on multivariable analysis (p<0.05). The authors concluded that the results from this study represented an opportunity for anticoagulation therapy to augment current standards of care in prostate cancer.
Choe et al.\textsuperscript{[11]} adapted the Jacobs et al. study to investigate the risk of prostate cancer-specific mortality (PCSM), as compared between the anticoagulation and non-anticoagulation therapy groups. The study population consisted of 5,955 patients with localized adenocarcinoma of the prostate and treated with radical prostatectomy (RP) or radiotherapy (RT), 2,175 (37\%) of whom were receiving warfarin, clopidogrel, enoxaparin, and/or aspirin. Patients were followed-up for a median of 70 months, and the overall 10-year absolute risk reduction of PCSM was a statistically significant 5\% in the anticoagulation therapy group compared to the control group (3\% vs. 8\%; \(p<0.01\)). Sub-group analysis by clinical risk category demonstrated the most prominent 10-year reduction in PCSM risk in patients with high-risk disease (4\% vs. 19\%; \(p<0.01\)), and benefit was present in both RT and RP treatment groups. Analysis by type of adjuvant medication suggested that the PCSM reduction was primarily associated with aspirin. Also, multivariable analysis indicated that aspirin use was an independent predictor of a lower risk of PCSM (HR\textsubscript{adjusted} 0.43, 95\% CI 0.21 to 0.87, \(p=0.02\)).

**Discussion**

Apart from a few well-designed randomized controlled trials assessing the association between aspirin exposure and cancer outcomes, several challenges become apparent when population-based recommendations for aspirin, in the prevention and treatment of some cancers, are posited based on current evidence. Firstly, as pointed out by Rose et al.,\textsuperscript{[5]} the first of one of a series of meta-analyses reports by Rothwell et al.,\textsuperscript{[6-9]} to posit impressive potential benefits of aspirin in some types of cancer, had methodological challenges with respect to the types of studies combined, as well as the type of data analysed. For instance, out of the 8 trials analysed, only 3 provided data for follow-up, and one did not provide data for individual patients. Secondly, cancer was not the outcome of interest in these trials, and all-cause mortality was attenuated at 15 years of follow-up in the combined studies for which there was follow-up data, but the effect was not significant after 20 years of follow-up.
Consequently, Rose et al. have cautioned against promoting the evidence cited above out of context. Furthermore, the authors advise that factors that favour the potential population-based use of aspirin in cancer include the coherent pathophysiologic antiplatelet adhesion and anti-inflammatory mechanisms of aspirin in cancer and cardiovascular disease, by which aspirin would be expected to affect the incidence of disease. This stance is supported by epidemiological evidence of the benefits (and risks) of aspirin in cancer and cardiovascular disease cited above.

Conversely, the paucity of sufficient randomised controlled trials, specifically looking at exposure to aspirin and associated cancer outcomes, also lacking at the time of publication of the 2011 Rose et al. paper, was deemed to militate against recommending wide-spread use of aspirin in primary prevention of cancer and cardiovascular disease.

**Conclusion**

Although there is growing evidence from observational epidemiologic studies that daily aspirin has a role in the prevention and adjuvant therapy of some cancers, the literature search and study selection for this review were performed by one reviewer. This may have introduced some bias in the conclusions, and is acknowledged as a methodological weakness of the current narrative review.

There is still not sufficient randomized controlled evidence, however, to confirm the dose, duration, and induction time of positive effect for different types of cancers, particularly for those cancers manifesting outside the gastrointestinal system. There is also no consensus currently with regard to the magnitude of observed benefit of a daily aspirin intake of 75 mg and more in cancer. Furthermore, stratified analyses are needed to establish the sub-groups of patients most likely to benefit from daily aspirin intake,[14] to prevent unnecessary
exposure of low-risk patients to the safety outcomes of major vascular events and possible extra-cranial bleeding due to aspirin.

Therefore, without sufficient and robust randomized controlled data for regulatory evaluation, it is probably still premature for aspirin to be considered for a role in public health cancer programmes.

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**Competing interests**

None declared.

**Authors’ contributions**

T. Sehloho designed the study, conducted research for the review, and wrote the draft manuscript.

N. Ledibane guided the conception and design of the study/review, appraised and edited the draft manuscript.

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