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Effect of long term aspirin use on the incidence of prostate cancer: A systematic review and meta-analysis

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ABSTRACT

Background: Previous studies found divergent effects of aspirin use on prostate cancer incidence, potentially due to studies with short durations of aspirin use and insufficient adjustment for screening.
Methods: A systematic review on the association between aspirin use ≥3 years and incident prostate cancer was performed in accordance with the PRISMA and MOOSE criteria.
Results: In the cohort studies, aspirin use for at least 3 years was associated with a lower incidence rate of prostate cancer (Odds ratio (OR) 0.88, 95% CI 0.80-0.97). No protective association was established for the case-control studies (OR 0.92, 95% CI 0.68–1.23). Subgroup analysis of advanced and aggressive cancers showed a protective association (OR 0.82, 95% CI 0.71-0.94 and OR 0.75, 95% CI 0.61-0.97).
Conclusion: This synthesis of observational studies suggests a potential protective association between long term aspirin use and incident prostate cancer. The current literature is highly heterogenous and suffers from inconsistent aspirin dose definition and measurement.

1. Introduction

Prostate cancer is a major cause of morbidity and mortality in men. Worldwide an estimated 1.6 million men were newly diagnosed with prostate cancer, and 366,000 men died from prostate cancer in 2015 (Global, 2016). Prostate cancer accounts for 15% of the cancers diagnosed in men, is the fifth leading cause of cancer deaths, and results in 6.6% of total deaths in males (Siegel et al., 2017). Major risk factors for the incidence of overall prostate cancer include age, race, and family history (Gann, 2002). In addition, genetic epidemiology studies have now identified > 140 independent genetic risk loci (Pernar et al., 2018). Previous research established divergent effects of most risk factors on overall incident and advanced/ aggressive disease (Pernar et al., 2018; Giovannucci et al., 2007).

Extensive epidemiological research has been dedicated to examining the potential of chemoprevention of prostate cancer, in particular use of non-steroidal anti-inflammatory drugs (NSAIDs). NSAID use was first reported to be inversely associated with risk of malignancies in the 1980s, including prostate cancer (Paganini-Hill et al., 1989; Cuzick et al., 2014). These drugs primarily inhibit the activity of the cyclooxygenase (COX) enzymes affecting the synthesis of prostaglandin signaling molecules, which are involved in a wide range of physiological processes including inflammation (Ulrich et al., 2006). Over the years, several meta-analyses have been conducted to help clarify the impact of aspirin use on prostate cancer incidence (Liu et al., 2014; Wang et al., 2014; Qiao et al., 2018). In 2014, Liu et al. reported no adverse or positive effects of non-aspirin NSAIDs on prostate cancer development or prostate cancer specific mortality. However, the meta-analysis found a protective effect of aspirin use for risk of total prostate cancer (OR 0.92; 95% CI 0.87-0.97) and more so for advanced prostate cancer (OR 0.81; 95% CI 0.73-0.89) (Liu et al., 2014). Since that meta-analysis was published, the results of five new epidemiological studies have reported either a protective or no effect of aspirin use on overall prostate cancer incidence (Veitonmaki et al., 2014, 2015; Vidal et al., 2015; Skriver et al., 2016).

A major concern regarding the currently published literature on aspirin use and prostate cancer is that most studies have lacked information on dosage, frequency and duration of use. Furthermore, if the information was provided, there was considerable heterogeneity in exposure definition. Subsequently, study results are heterogenous and frequently contradictory, difficult to compare, and statistically difficult to pool. Of note, initiation of aspirin use immediately preceding

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diagnosis is likely due to reverse causation, whereby symptomatic patients start taking aspirin for symptom relief. Lastly, most studies solely report "anytime use" without specifying timeframes or do not report durations altogether. These limitations have prevented the ability to make clinical recommendations for the use of aspirin for prostate cancer chemoprevention. It is of considerable importance to assess the evidence for clinically meaningful doses and durations of aspirin use.

In colorectal cancer (CRC) chemoprevention with aspirin has been established to provide a protective effect only after approximately five to ten years of use (Rothwell et al., 2011; Cook et al., 2013). Since prostate cancer is a slow growing malignancy with tumorigenesis occurring over decades, it is biologically plausible that the putative protective effect of aspirin would only occur after years of usage.

We therefore conducted this meta-analysis with the intention to examine the effect of long term use of aspirin (a minimum of ≥3 years) on the incidence of prostate cancer. In addition, we conducted sensitivity analyses including duration of aspirin use of ≥5 years and ≥10 years.

2. Methods

2.1. Search strategy and inclusion criteria

This study was conducted in accordance with the MOOSE criteria (Stroup et al., 2000). The study protocol was drafted *a priori* and registered on PROSPERO (registration number CRD42018095541). The search was performed by the author team and reviewed by an experienced librarian (CM), incorporating all studies published before 2/24/2018. A complete list of search terms used for searching PUBMED and EMBASE can be found in the appendix. Studies were included if they: 1) used a cohort, case cohort, case control, or randomized controlled trial design, 2) evaluated the relationship between aspirin exposure and incidence of prostate cancer 3) reported estimates of relative risk along with 95% Confidence Intervals (CIs) or standard errors. Commentaries, letter to the editors, case reports, abstracts, and reports that had not been peer reviewed were excluded. We excluded studies published in languages other than English, German, Dutch, Spanish, or French.

2.2. Data extraction

We used the online Covidence software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia) for the screening, selection, and data extraction. All records were independently evaluated by four members of the author team (CS, CEC, TS, GZ) through title and abstract screening. Disagreements regarding title and abstract eligibility were resolved by a discussion between two members as well as a fifth author (DM). Full text screening of selected papers was conducted by two members of the authors team (CS, TS). Disagreements regarding record eligibility were resolved by a discussion between both authors and if no consensus could be reached a third author (DM) cast a final vote. All studies meeting inclusion criteria were retained in the analysis. Access to all full texts could be obtained without having to contact corresponding authors.

For each included record, study characteristics were extracted by two independent members of the author team. Any discrepancies were resolved by discussion between the authors. These characteristics included study design, author and year of publication, name/source of database, number of participants with prostate cancer, duration of study and average follow up, the dose and duration of aspirin exposure when applicable, grade/severity of prostate cancer where applicable, characteristics on aspirin use (i.e. questionnaire vs prescription data), confounders adjusted for in final analysis, and the fully adjusted effect sizes (HR, OR, SIR, or RR) with corresponding 95% CIs, as well as number of participants. If possible, only the number of participants relevant for the presented effect estimates were extracted or calculated, i.e. omitting participants using other NSAIDs. In a final step, we restricted our findings to studies that reported at least three years of aspirin use. If studies used the same study population, studies with the largest study population were used. However, information on relevant subgroup analyses was used from smaller studies if they were not reported in the larger studies.

2.3. Quality of studies

The quality of randomized controlled trials was assessed using the Risk of Bias tool from the Cochrane Collaboration (Higgins et al., 2011) and the quality of observational studies was assessed using the Newcastle-Ottawa Scale (NOS) (Deeks et al., 2003). Case definition met the selection/outcome criteria if recorded in health-services/study databases as actual diagnoses and did not meet the NOS criteria if self-reported and/ or gathered by questionnaire. A similar approach was taken with ascertainment of aspirin use. This met relevant NOS criteria if recorded as prescriptions in health-services/study databases and did not meet NOS criteria if self-reported and/or gathered by an unvalidated questionnaire. Adjustment for age was deemed sufficient to meet the compatibility requirement. For loss-to follow up we considered any study with ≤10% loss-to follow up adequate. The remaining NOS criteria were followed routinely.

2.4. Statistical analysis

Due to earlier established clinical heterogeneity between the studies (Liu et al., 2014; Wang et al., 2014), we decided *a priori* to use a random effects model (DerSimonian and Laird, 1986) for all analyses. Testing for heterogeneity between the studies was performed using Cochran's Q test (Cochran, 1950) and the I^2 test (Higgins et al., 2003). A p-value < 0.05 or an I^2 higher than 50% were considered significant evidence for heterogeneity.

Prostate cancer incidence is relatively low and, relying on the rare-disease-assumption (Greenland and Thomas, 1982), we therefore deemed it appropriate to pool odds ratios (OR) and incident rate ratios (IRR) for the analyses. While hazard ratios refer to relative rates due to their time-dependent nature, in a setting where few individuals experience the event, the hazard ratio (HR) is an acceptable approximation of the odds/risk ratios (Sutradhar and Austin, 2018). To preserve precision and prevent false negative results, we therefore pooled OR, HR, and RR in our analyses. Sensitivity analyses were performed to assure that pooling the different measures of association did not bias the results.

Considering that the protective effect of aspirin probably only occurs after years of usage, we focused our meta-analysis on examining the effect of long-term use of aspirin. To capture potential effects over shorter periods, we artificially chose a 3-year minimum duration of use and conducted sensitivity analyses including duration of aspirin use of ≥5 years and ≥10 years. The choice of thresholds was limited by how studies had reported long-term risk estimates.

Subgroup analyses were performed to determine whether intake of aspirin differentially affected the risk of advanced (defined as either stage ≥ T3b, N1 or M1 at diagnosis as well as fatal disease) or high-grade (Gleason grade 4 + 3 or ≥8) disease. Furthermore, low dose (< 100 mg) and high dose (≥100 mg) aspirin use were contrasted to research a possible dose-dependent effect.

Visual assessment for potential publication bias was performed using Funnel and Egger's plots. The assumption that no publication bias is present was tested using Egger's test (Egger et al., 1997) and Begg's correlation test (Begg and Mazumdar, 1994) using a significance cut-off of $p \leq 0.05$.

All statistical analyses were performed using STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC)