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Regular Aspirin Use and the Risk of Lethal Prostate Cancer in the Physicians' Health Study

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Abstract

Background: Regular aspirin use probably protects against some malignancies including prostate cancer (PC), but its impact on lethal PC is particularly unclear.
Objective: To investigate the association between regular aspirin and (1) the risk of lethal PC in a large prospective cohort and (2) survival after PC diagnosis.
Design, setting, and participants: In 1981/82, the Physicians' Health Study randomized 22 071 healthy male physicians to aspirin, β-carotene, both, or placebo. After the trial ended in 1988, annual questionnaires have obtained data on aspirin use, cancer diagnoses, and outcomes up to 2009 for the whole cohort, and to 2015 for PC patients.
Outcome measurements and statistical analysis: We evaluated the relationship between regular aspirin (>3 tablets/week) and lethal PC (metastases or PC death). Cox proportional-hazards models estimated hazard ratios (HRs) for the risk of lethal PC in the whole cohort and postdiagnosis survival among men initially diagnosed with nonlethal PC.
Results and limitations: Risk analysis revealed that 502 men developed lethal PC by 2009. Current and past regular aspirin was associated with a lower risk of lethal PC (current: HR 0.68, 95% confidence interval [CI] 0.52–0.89; past: HR 0.54, 95% CI 0.40–0.74) compared to never users. In the survival analysis, 407/3277 men diagnosed with nonlethal PC developed lethal disease by 2015. Current postdiagnostic aspirin was associated with lower risks of lethal PC (HR 0.68, 95% CI 0.52–0.90) and overall mortality (HR 0.72, 95% CI 0.61–0.9). We could not assess aspirin dose, and inconsistencies were observed in some sensitivity analyses.
Conclusions: Current regular aspirin use was associated with a lower risk of lethal PC among all participants. Current postdiagnostic use was associated with improved survival after diagnosis, consistent with a potential inhibitory effect of aspirin on PC progression. A randomized trial is warranted to confirm or refute these findings.
Patient summary: We examined the potential effect of regular aspirin use on lethal prostate cancer. We found that taking aspirin was associated with a lower risk of lethal prostate cancer, and taking it after diagnosis may help to prevent prostate cancer from becoming fatal.

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1. Introduction

Regular aspirin probably protects against some malignancies [1,2]. Meta-analyses [3,4] and a recent study [5] suggest modest decreases in overall and advanced prostate cancers (PCs), although some studies reported no benefit [6–9]. An international consensus concluded that the potential effects of aspirin on PC warrant further evaluation [9]. Evidence for lethal PC is particularly limited.

The chemopreventive effects of aspirin may result from antiplatelet or anti-inflammatory properties [10–12]. Aspirin inhibits cyclo-oxygenase enzymes, which are overexpressed in several malignancies and are implicated in cell proliferation, angiogenesis, and cancer progression [13–16]. Platelet-tumor signaling may play a key role in metastatic initiation, and platelet depletion decreases metastatic burden in animal models [17,18].

Most low-grade and early-stage PCs are indolent [19,20], so the significance of overall incidence as an outcome is questionable. Therefore, we investigated regular aspirin and lethal PC.

2. Participants and methods

The Physicians' Health Study began in 1981/82 as a randomized, placebo-controlled trial of aspirin and β-carotene for prevention of cardiovascular disease and cancer ($n = 22\ 071$) [11]. The participants were male physicians aged 40–84 yr without a history of cancer (except for non-melanoma skin cancer), myocardial infarction (MI), stroke, or transient ischemic attack. Participants were randomized using a 2×2 factorial design to aspirin 325 mg, β-carotene 50 mg, both, or double placebo (all taken every other day). The aspirin trial ended in 1988 because of a 44% reduction in first MI in the aspirin group. Thereafter, most participants elected to receive complimentary unblinded aspirin. The β-carotene component continued up to 1995; no associations with cancer were observed [21].

We conducted two related analyses. Our risk analysis investigated prediagnostic aspirin and the risk of lethal PC among all participants who provided sufficient aspirin information ($n = 22\ 037$). Our survival analysis investigated postdiagnostic aspirin and survival among participants initially diagnosed with nonmetastatic PC between enrolment and 2009 ($n = 3462$).

The primary exposure was regular aspirin (>3 d/wk for ≥1 yr), defined a priori according to the study design. Aspirin use was ascertained from baseline until 2009. Annual questionnaires asked how many days/year participants missed study pills, and days/year of personal aspirin use. After the aspirin trial ended in 1988, participants reported days/year of complimentary study and personal aspirin use. After diagnosis, PC patients reported regular aspirin use (yes/no) on PC follow-up questionnaires up to 2015.

The primary outcome was lethal PC (metastatic PC or death from PC), chosen a priori on the basis of clinical significance and our hypothesis that aspirin would be associated with lethal PC. Secondary risk analysis outcomes included overall mortality, overall PC, high-grade PC (Gleason 8–10), and advanced PC (TNM stage ≥T3b, N1, or M1 at diagnosis). Secondary survival analysis outcomes included PC mortality and overall mortality.

We recorded stage (81% complete), Gleason score (based on biopsy, 82% complete), prostate-specific antigen (PSA) at diagnosis, and treatment(s) from self-reports and medical records. We conducted national death index searches to confirm the date and cause of death for the whole cohort up to 2009 and for PC patients up to 2015. Cause of death was assigned by a three-physician endpoint committee after review of death certificates, medical records, and information from family. Follow-up is >96% complete for PC incidence and >99% for mortality.

2.1. Statistical analysis

2.1.1. Main analyses

Descriptive statistics characterized the study population. We used Cox proportional-hazards regression models to estimate age and multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).

We categorized aspirin use as current (within 1 yr), past, and never from baseline to PC diagnosis, death, or 2009 in the risk analysis, and from diagnosis to death or 2015 in the survival analysis. We examined duration among current users (1–4 vs ≥5 yr) and time since stopping among past users (≥10, 8–9, 6–7, 4–5, 2–3 yr). If missing, the most recent aspirin report was carried forward for one questionnaire cycle, and then set to missing.

Risk analysis follow-up was from 1981/82 baseline to event, death, or end of follow-up (2009, the last aspirin assessment for all participants). Aspirin was updated throughout follow-up for non-cases and until PC diagnosis for cases. We adjusted risk analysis models for baseline age (in years), race (white vs other), body mass index (BMI; in kg/m^2), height (in inches), smoking (current, former [quit ≤10 yr ago], never/remote [quit >10 yr ago]), hypertension (yes vs no), and type 2 diabetes (yes vs no).

Survival analysis follow-up time was from PC diagnosis until an event, death, or the end of follow-up (2015). Time-varying aspirin was updated approximately annually after diagnosis. We adjusted for at-diagnosis age, race, Charlson comorbidity index (0, 1–2, >2 comorbidities) [22], BMI, smoking (current, former, never/remote), hypertension (yes vs no), and type 2 diabetes (yes vs no), stage (T1–2, T3, T4/N1), PSA (none, <10, 10–20, >20 ng/ml), Gleason (≤6, 7, 8–10), and treatment (radical prostatectomy, radiation, other/none).

2.1.2. Secondary analyses

Aspirin may confer different effects at different stages of PC progression. Because cases were generally diagnosed later in disease progression before PSA screening, we stratified both analyses by year of diagnosis: pre-PSA era (<1992) and PSA-era (≥1992).

Cancer, even when undiagnosed, might influence aspirin use (reverse causation). Thus, in the risk analysis we lagged aspirin exposure by both 2 yr and 4 yr; for example, we applied 1986 aspirin use to the 1988 time period (2-yr lag) and the 1990 time period (4-yr lag), thus using a prior exposure uninfluenced by possible underlying disease. In the survival analysis, we stopped updating aspirin 3 yr after diagnosis; when PC progresses, 3.5 yr is the average time from treatment to biochemical recurrence, a precursor to lethality [23,24]. Stopping the updating prevents this progression from influencing exposure status. Finally, we performed an intention-to-treat (ITT) analysis based on original randomization.

The proportional hazards assumption held throughout. We used SAS version 9 (SAS Institute, Cary, NC, USA). Two-sided p values <0.05 defined statistical significance.

3. Results

3.1. Risk analysis

From 1981/82 to 2009, 502 participants developed lethal disease. Baseline characteristics were similar among regular aspirin users and nonusers (Table 1).

Compared to never use, past regular aspirin use was associated with a lower risk of lethal PC (HR 0.54, 95% CI

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