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The Association between Aspirin Use and Risk of Hepatocellular Carcinoma: Results from Two Prospective U.S. Cohort Studies

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Abstract Text

Background:

Evidence suggests that aspirin may prevent incident hepatocellular carcinoma (HCC). However, the optimal dose and duration of aspirin for HCC prevention remain undefined. We examined the influence of aspirin use, dose and duration of use on incident HCC risk in two prospective cohort studies.

Methods:

We included 133,371 individuals from the Nurses' Health Study (NHS; n=87,507) and the Health Professionals Follow-up Study (HPFS; n=48,864), who have reported aspirin use, dosage and duration biennially since 1980 (NHS) and 1986 (HPFS), through 2012. Regular aspirin use was defined as ≥2 standard (325mg) aspirin tablets/week, and data were updated prospectively at each biennial follow-up. Cases of incident HCC were reported by participants, next-of-kin, or through death certifications, and subsequently confirmed by physician review of the medical records. Cox proportional hazards regression models were used to calculate age- and multivariable adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for incident HCC.

Results:

Over 4,232,188 person-years of follow-up, we documented 108 incident HCC cases (65 women, 43 men). Compared to non-regular use, regular aspirin use was associated with significantly lower HCC risk (multivariable HR 0.51, 95% CI 0.34-0.77). This relationship appeared dose-related: compared to non-use, the multivariable adjusted HR for HCC was 0.87 (95% CI 0.51-1.48) for ≤1.5 standard tablets/week, 0.51 (95% CI 0.30-0.86) for >1.5 to 5 tablets/week, and 0.49 (95% CI 0.28-0.96) for >5 tablets/week (P_{trend}=0.006). This inverse association also appeared duration-dependent (P_{trend}=0.03); moreover, among former aspirin users, increasing duration of time since discontinuation of aspirin was associated with progressively increased HCC risk (P_{trend}=0.006). In joint analyses of dose and duration, significant HCC risk reduction was observed with ≥1.5 standard aspirin tablets/week for ≥5 years, compared to non-use (multivariable HR 0.41, 95% CI 0.21-0.77). In contrast, non-aspirin NSAID use was not associated with HCC risk, compared to non-NSAID use (multivariable HR 1.09, 95% CI 0.78-1.51; P_{trend} for increasing duration of use=0.42).

Conclusion:

Regular aspirin use is associated with a dose-dependent reduction in HCC risk, apparent after at least 5 years of use. In contrast, non-aspirin NSAID use was not associated with incident HCC risk. Further research is needed to clarify whether aspirin use represents a feasible strategy for HCC primary prevention.

Figure 1A. Duration of Aspirin Use[1] and Hepatocellular Carcinoma Risk

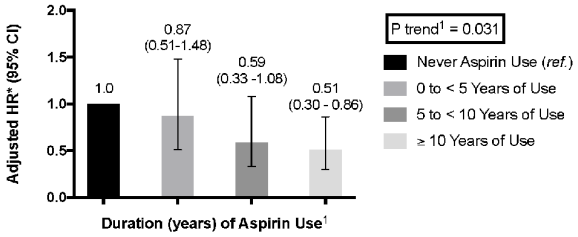
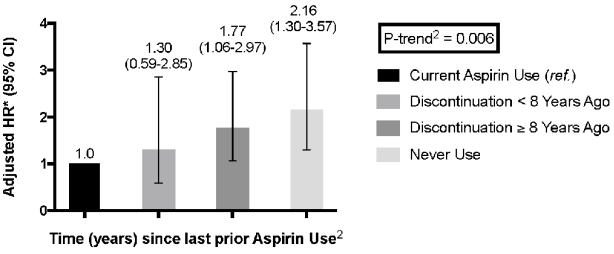


Figure 1B. Time Since Discontinuation of Aspirin[2] and Hepatocellular Carcinoma Risk



Abbreviations: HR, hazard ratio; CI, confidence interval; ref., reference.
*Multivariable-adjusted model was conditioned on age (continuous years), year of questionnaire return and sex/cohort, and was further adjusted for race (white vs. non-white), body mass index (continuous kg/m2), alcohol intake (0-4.9, 5-14.9, ≥15 g/day), smoking status (current vs. prior vs. never), physical activity (<3, 3 to 8.9, ≥ 9 MET-hours/week), diabetes (yes vs. no), hypertension (yes vs. no), dyslipidemia (yes vs. no), regular multivitamin use (≥2 multivitamin tablets per week vs. no), regular use of oral antidiabetic medications (yes vs. no) and regular use of statins (yes vs. no). All relevant covariates were updated over time.
[1] Categories of aspirin use duration were compared to individuals reporting never-use of aspirin (reference). The P-trend was calculated using continuous duration of use (months) among aspirin users, compared to the lowest reported duration of use.
[2] Current aspirin use (reference group) was defined as consumption of ≥2 standard (325 mg) aspirin tablets per week on the most recent questionnaire. Among prior aspirin users, time since discontinuation of regular use was defined as non-regular use on the most recent questionnaire but regular aspirin use <8 or ≥8 years in the past. P-trend was calculated using continuous elapsed time in months since last regular aspirin use, among prior aspirin users.

Disclosures

Charles Fuchs – Eli Lilly: Consulting; Entrinsic Health: Consulting; Genentech: Consulting; Merck: Consulting; Sanofi: Consulting; Five Prime Therapeutics: Consulting; Merrimack: Consulting; Bayer: Consulting; Agios: Consulting; Taiho: Consulting; Kew: Consulting; CytomX: Consulting; Bain Capital: Consulting; Unum: Consulting

Kathleen E. Corey – Novo Nordisk: Consulting

The following people have nothing to disclose: Tracey G Simon, Dawn Q Chong, Edward Giovannucci

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