Supplementary Online Content

Simon TG, Ma Y, Ludvigsson JF, et al. Association between aspirin use and risk of hepatocellular carcinoma. *JAMA Oncol*. Published online October 4, 2018. doi:10.1001/jamaoncol.2018.4154

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Ascertainment of Covariates in the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS) and Construction of Multivariable Models

Ascertainment of covariates

In both the NHS and HPFS cohorts, information on age, height, weight, smoking status, alcohol intake, personal and family medical history was collected at baseline and updated biennially. A validated semi-quantitative food frequency questionnaire (SFFQ) was added beginning in 1980, to assess the intake of foods and specific nutrients, as previously described in detail[1-3]. Self-reported diabetes prompted the mailing of a supplementary questionnaire that queried diagnosis date, diagnostic testing and symptoms, and the validity of this supplementary questionnaire has been previously confirmed in both cohorts, with accuracy exceeding 97% [4, 5]. Diabetes diagnosed before 1988 was defined according to the National Diabetes Data Group criteria [6], and using the American Diabetes Association criteria for cases identified after 1998 [7]. Body mass index (BMI) was computed from each questionnaire using weight in kilograms divided by height in square meters. Leisure time physical activity was first assessed in 1986 and was updated biennially, expressed as the average number of metabolic equivalent-hours (MET-hours) expended per week. Information regarding physician-diagnosed hypercholesterolemia and hypertension was collected at baseline and updated on each biennial questionnaire.

Construction of Multivariable Models

Consistent with our prior publication from the NHS and HPFS cohorts[8], our fully-adjusted multivariable model included covariates selected a priori for their established or putative associations with aspirin use and HCC risk[9-15]. Our main multivariable model (model 2) was adjusted for sex (in the pooled cohort), race (white, non-white), type 2 diabetes (yes, no), regular use of oral antidiabetic medication (yes, no), dyslipidemia (yes, no), hypertension (yes, no), smoking status (current, former, never), body mass index (BMI; continuous kg/m^2), alcohol intake (none, 1-14g/day, ≥15g/day), physical activity (continuous metabolic equivalent [MET]-hours/week), regular use of multivitamins (yes, no) and statins (yes, no). A third model (model 3) further accounted for regular nonaspirin NSAID use (yes, no). Because dietary factors related to a healthy lifestyle may be associated with both aspirin use and HCC risk, we constructed a fourth multivariable model that further adjusted for diet quality (continuous Alternative Healthy Eating Index [AHEI] 2010[3], excluding alcohol) as well as cumulative average consumption of coffee[16].

All covariates were updated biennially and included as time-varying covariates, as appropriate. Dietary factors were ascertained from validated semi-quantitative food frequency questionnaires (SFFQ), as previously described in detail[1-3]. Consistent with prior analyses of these cohorts[3, 17], we used cumulative average values for dietary factors, physical activity and alcohol, to minimize variance and to better reflect long-term patterns.

Statistical power for analysis of acetaminophen:

Based on the sample size of 133,371 participants in the NHS and HPFS populations in 1996 (the mid-point of study follow-up), among whom 38,521 were acetaminophen users, as well as the number of cases of incident HCC over study follow-up, we had greater than 80% power to detect a hazard ratio (HR) of 0.65 comparing acetaminophen users with non-users[18].

eTable 1. Age-Standardized Characteristics of Study Participants from NHS and HPFS Cohorts in 1996 (n=133,371)

Characteristics[1]	Non-Regular Use[2] (N=74,516)	Regular Aspirin Use[2] (N=58,855)
Women, %	68	62
Age, years, SD	62 (8)	64 (8)
White race, %	97	98
Body mass index (BMI), kg/m^2, SD	24.4 (4.4)	24.9 (4.2)
Obesity‡, %	10	10
Hypertension, %	26	37
Dyslipidemia, %	33	44
Type 2 diabetes, %	6	8
Smoking status, % • Current • Former • Never	 12 42 47	 11 45 44
Physical activity, MET-hours/week, median [IQR]	12 [22]	13 [25]
Alcohol intake, grams/day, median [IQR]	2 [6]	2 [9]
Oral antidiabetic medication use[3], %	6	6
Statin medication use[4], %	6	12
Multivitamin use[4], %	44	54
Non-aspirin NSAID use[4], %	22	19
Acetaminophen use[4], %	28	30

Abbreviations: BMI, body mass index; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalents; IQR, interquartile range; SD, standard deviation; NSAID, non-steroidal anti-inflammatory drug

[1] All data reported as percentage (%) or mean±standard deviation (SD), unless noted otherwise. Except for mean of age, all data were age-standardized to the age distribution of participants.

[2] Regular use of aspirin was defined as consumption of at least 2 or more standard tablets per week of that medication, and modeled as a time-varying covariate. Non-regular use was defined as consumption of <2 standard tablets/week.

[3] Oral antidiabetic medication use included any hypoglycemic medications taken by mouth, and did not distinguish by individual medication type.

[4] Regular use of multivitamins, NSAIDs, acetaminophen and statins was defined as consumption of at least 2 or more tablets of the medication of interest per week (vs. non-regular use).

‡Obesity defined as BMI ≥30kg/m^2.

eTable 2. Stratified Analyses: Regular Aspirin Use* and Risk of Hepatocellular Carcinoma in the Pooled Study Population (n=133,371)

Variable	No. of HCC Cases[1]	Multivariable-adjusted HR (95% CI)		P-interaction
		Regular aspirin use*		
		No (Ref.)	*Yes*	
Age, years				
• ≤ 65	20	1	0.61 (0.22-1.71)	0.29
• > 65	88	1	0.50 (0.32-0.78)	
Cohort				
• HPFS	43	1	0.54 (0.29-1.03)	0.92
• NHS	65	1	0.51 (0.30-0.87)	
Obesity (BMI > 25 kg/m^2)				
• No	67	1	0.39 (0.22-0.69)	0.39
• Yes	41	1	0.74 (0.39-1.42)	
Smoking status				
• Never	36	1	0.40 (0.19-0.86)	0.15
• Ever	72	1	0.58 (0.36-0.96)	
Alcohol intake, grams / day				
• < 2 grams	73	1	0.48 (0.29-0.80)	0.25
• ≥ 2 grams	35	1	0.62 (0.30-1.26)	
Type 2 diabetes				
• No	72	1	0.48 (0.28-0.80)	0.45
• Yes	36	1	0.56 (0.28-1.12)	
Hypertension				
• No	57	1	0.44 (0.24-0.82)	0.33
• Yes	51	1	0.61 (0.34-1.07)	
Dyslipidemia				
• No	69	1	0.47 (0.27-0.81)	0.38
• Yes	39	1	0.64 (0.33-1.21)	

Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; HPFS, Health Professionals' Follow-up Study; NHS, Nurses' Health Study; BMI, body mass index; Ref., reference

[1]Number of cases of hepatocellular carcinoma (HCC), recorded in each strata

*Regular aspirin use defined as self-reported use of aspirin at least 2 or more times per week, updated with each biennial questionnaire (vs. non-use).

eTable 3. Duration of Aspirin Use* and Risk of Hepatocellular Carcinoma in Women (1980-2012) and Men (1986-2012) in the Pooled NHS and HPFS cohorts (n=133,371)

	Duration of Aspirin Use*, years				P_{trend}[1]
	Never-use (*Ref.*)	< 5 years	5 to < 10 years	≥ 10 years	
Cases / Person-Years	38 / 1,510,602	23 / 816,080	16 / 627,575	31 / 1,277,931	--
Model 1[∂], HR (95% CI)	1	0.83 (0.49-1.41)	0.60 (0.33-1.09)	0.51 (0.31-0.85)	0.037
Model 2[‡], HR (95% CI)	1	0.87 (0.51-1.48)	0.59 (0.33-1.08)	0.51 (0.30-0.86)	0.031
Model 3[§], HR (95% CI)	1	0.90 (0.53-1.52)	0.62 (0.34-1.13)	0.55 (0.32-0.93)	0.033

Abbreviations: NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; PY, person-years; HR, Hazard Ratio; CI, confidence interval; Ref., reference

*Categories of aspirin use duration were compared to individuals reporting never-use of aspirin (reference group).

[∂] Model 1 was conditioned on age (continuous years) and year of questionnaire return and sex/cohort.

[‡] Model 2 = Model 1 + race (white vs. non-white), body mass index (continuous kg/m^2), 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.

[§] Model 3 = Model 2 + regular use of non-aspirin nonsteroidal anti-inflammatory drugs (NSAID; ≥2 tablets per week vs. no), assessed as a time-varying covariate.

[1] P-trend calculated using continuous duration of aspirin use (months) among aspirin users, compared to the lowest reported duration of use.

eTable 4. Time Since Discontinuation of Aspirin* and Risk of Incident Hepatocellular Carcinoma (HCC) in the Pooled NHS and HPFS Cohorts (n=133,371)

	Current aspirin use	Discontinued < 8 years	Discontinued ≥ 8 years	Never aspirin use	P_{trend}[1]
Cases / Person-Years	32 / 1,873,462	12 / 321,405	29 / 917,564	35 / 1,119,758	--
Model 1[∂], HR[2] (95% CI)	1 (*Ref.*)	1.33 (0.61-2.91)	1.66 (0.99-2.78)	2.25 (1.37-3.68)	0.003
Model 2[‡], HR (95% CI)	1	1.30 (0.59-2.85)	1.77 (1.06-2.97)	2.16 (1.30-3.57)	0.006
Model 3[§], HR, 95% CI)	1	1.36 (0.62-2.99)	1.86 (1.11-3.11)	2.07 (1.25-3.43)	0.009

Abbreviations: HR, hazard ratio; CI, confidence interval; Ref., reference

*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, using methods previously described in these cohorts[17-18].

[2]Hazard ratios (HR) are for individuals in each category compared to subjects in the reference category (never aspirin use).

[1]P-trend calculated using continuous elapsed time in months since last regular aspirin use, among prior aspirin users.

[∂] Model 1 was conditioned on age (continuous years) and year of questionnaire return and sex/cohort.

[‡] Model 2 = Model 1 + race (white vs. non-white), body mass index (continuous kg/m^2), 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.

[§] Model 3 = Model 2 + regular use of non-aspirin nonsteroidal anti-inflammatory drug (NSAID) use (≥2 NSAID tablets per week vs. no), which was assessed as a time-varying covariate.

eTable 5. Joint Analysis of Aspirin Dose and Duration of Use and Risk of Incident HCC in the Pooled NHS and HPFS Population (n=133,371)

	Dose* (tablets/week)	**Duration of Aspirin Use**		
		0 years	**>0 to <5 years**	**≥5 years**
Cases of HCC *Multivariable HR‡, 95% CI*	**0**	35 1 (*Reference*)	--	--
	Up to 1.5	--	11	13
			1.05 (0.52-2.12)	0.70 (0.37-1.30)
	1.5 to < 5	--	11	16
			0.91 (0.47-1.76)	0.41 (0.21-0.77)
	≥ 5	--	15	7
			0.71 (0.35-1.43)	0.25 (0.11-0.58)

Abbreviations: HCC, hepatocellular carcinoma; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; PY, person-years; HR, Hazard Ratio; CI, confidence interval

*Dose of aspirin defined by cumulative average aspirin tablets consumed per week, updated at each biennial questionnaire.
‡ Multivariable Cox proportional hazards regression model conditioned on age (years) and year of questionnaire return, with further adjustment for sex, race (white vs. non-white), body mass index (continuous kg/m^2), alcohol intake (0 – 4.9 g/day, 5-14.9 g/day, ≥15 g/day), smoking status (current vs. prior vs. never), physical activity (< 3 metabolic equivalent (MET)-hours/week, 3 to 8.9 MET-hours/week, ≥ 9 MET-hours/week), diabetes (yes vs. no), hypertension (yes vs. no), dyslipidemia (yes vs. no), and regular multivitamin use (≥2 tablets per week vs. no), with all relevant covariates were updated over time.

eTable 6. Regular Use* of Non-Aspirin Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)[1] or Acetaminophen* and Risk of Hepatocellular Carcinoma (HCC) in the Pooled NHS and HPFS Cohorts (n=133,371)

	Non-aspirin NSAIDs[1]		**Acetaminophen**		
	Non-Regular use	*Regular use**	*Non-Regular use*	*Regular use**	
Cases/Person-years	94 / 3,048,136	14 / 1,184,052	69 / 2,480,708	39 / 1,751,481	
Age-adjusted HR (95%CI)	1 (*Ref.*)	1.26 (0.92-1.73)	1 (*Ref.*)	0.76 (0.46-1.26)	
Model 2‡; (95%CI)	1	1.11 (0.80-1.54)	1	0.85 (0.52-1.40)	
Model 3§; (95% CI)	1	1.09 (0.78-1.51)	1	0.89 (0.54-1.46)	

Abbreviations: HCC, hepatocellular carcinoma; NHS, Nurses' Health Study; HPFS, Health Professionals Follow-up Study; PY, person-years; HR, Hazard Ratio; CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; Ref., reference

[1]Nonaspirin NSAID use was a composite category, that included both ibuprofen (e.g. Advil, Motrin, etc.) and other nonaspirin NSAIDs (e.g. Aleve, Naprosyn, Relafen, Ketofen, Anaprox, etc).
*Regular use of all medications was defined as self-reported use at least 2 or more times per week, updated at each biennial questionnaire. Non-regular use was defined as use of that medication less than 2 times per week.
‡ Model 2 was conditioned on age (years) and year of questionnaire return, with further adjustment for sex, race (white vs. non-white), body mass index (continuous kg/m^2), 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.
§ Model 3 = Model 2 + regular aspirin use, defined as use of aspirin at least 2 or more times per week. Non-regular aspirin use was defined as use of aspirin less than 2 times per week. All relevant variables were assessed as time-varying covariates.

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