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CLINICAL—PANCREAS

Regular Use of Aspirin or Non-Aspirin Nonsteroidal Anti-Inflammatory Drugs Is Not Associated With Risk of Incident Pancreatic Cancer in Two Large Cohort Studies

Natalia Khalaf,[1,*] **Chen Yuan**,[2,3,*] Tsuyoshi Hamada,[2] Yin Cao,[4,5,6] Ana Babic,[2] Vicente Morales-Oyarvide,[2] Peter Kraft,[2] Kimmie Ng,[2] Edward Giovannucci,[2] Shuji Ogino,[2,3,7] Meir Stampfer,[2] Barbara B. Cochrane,[8] JoAnn E. Manson,[3,9] Clary B. Clish,[10] Andrew T. Chan,[4,5,10,11] Charles S. Fuchs,[12] and Brian M. Wolpin[2]

[1]Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, Boston, Massachusetts; [2]Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts; [3]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts; [4]Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; [5]Division of Gastroenterology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; [6]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts; [7]Program of MPE Molecular Pathological Epidemiology, Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [8]School of Nursing, University of Washington, Seattle, Washington; [9]Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [10]Broad Institute of Massachusetts Institute of Technology and Harvard University, Cambridge, Massachusetts; [11]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; and [12]Yale Cancer Center at Yale School of Medicine and Smilow Cancer Hospital, New Haven, Connecticut

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BACKGROUND & AIMS: Use of aspirin and/or non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) reduces the risk of several cancers, but it is not clear if use of these drugs is associated with risk of pancreatic cancer. **METHODS:** We evaluated aspirin and non-aspirin NSAID use and risk of pancreatic adenocarcinoma in 141,940 participants from the Health Professionals Follow-up Study and Nurses' Health Study using multivariable-adjusted Cox proportional hazards regression. We considered several exposure classifications to model differing lag times between NSAID exposure and cancer development. We also conducted a nested case–control study of participants from 3 prospective cohorts using conditional logistic regression to evaluate pre-diagnosis levels of plasma salicylurate, a major metabolite of aspirin, in 396 pancreatic cancer cases and 784 matched individuals without pancreatic cancer (controls). **RESULTS:** In the prospective cohort study, 1122 participants developed pancreatic adenocarcinoma over 4.2 million person-years. Use of aspirin or non-aspirin NSAIDs was not associated with pancreatic cancer risk, even after considering several latency exposure classifications. In a pre-planned subgroup analysis, regular aspirin use was associated with reduced pancreatic cancer risk among participants with diabetes (relative risk, 0.71; 95% CI, 0.54–0.94). In the nested case–control study, pre-diagnosis levels of salicylurate were not associated with pancreatic cancer risk (odds ratio, 1.08; 95% CI, 0.72–1.61; P_{trend} 0.81; comparing participants in the highest quintile with those in the lowest quintile of plasma salicylurate). **CONCLUSIONS:** Regular aspirin or non-aspirin NSAID use was not associated with future risk of pancreatic cancer in participants from several large prospective cohort studies. A possible reduction in risk for pancreatic cancer among people with diabetes who regularly use aspirin should be further examined in preclinical and human studies.

Keywords: NHS; Chemoprevention; Salicyluric Acid; Inflammation.

Pancreatic cancer is the third leading cause of cancer-related death in the United States (US).[1] Surgery provides the only potential for cure, but most patients present with advanced disease that is not amenable to surgical resection. Therefore, chemoprevention and early detection strategies are extremely important for reducing mortality from pancreatic cancer, particularly in at-risk populations, such as those with new-onset diabetes, inherited predisposition, or pancreatic cystic neoplasms.[1–3]

Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) used primarily for the prevention and treatment of cardiovascular disease, but whose long-term use has been associated with a reduction in overall cancer risk.[4]

***Authors share co-first authorship.**

Abbreviations used in this paper: **BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DM, diabetes mellitus; EDIP, empirical dietary inflammatory pattern; HPFS, Health Professionals Follow-up Study; IL6, interleukin-6; NHS, Nurses' Health Study; NSAID, nonsteroidal anti-inflammatory drug; QC, quality control; RR, relative risk; sTNFR-2, soluble tumor necrosis factor receptor-2; TNFαR2, tumor necrosis factor α receptor 2; WHI-OS, Women's Health Initiative-Observational Study.**

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EDITOR'S NOTES

BACKGROUND AND CONTEXT

An association between incident pancreatic cancer and regular use of aspirin and/or non-aspirin NSAIDs remains poorly defined. Identifying preventative agents for pancreatic cancer would be of great importance given its extremely high mortality rate.

NEW FINDINGS

Regular use of aspirin or non-aspirin NSAIDs was not associated with pancreatic cancer risk, even after considering several latency exposure classifications. However, in a pre-planned subgroup analysis, regular aspirin use was associated with reduced pancreatic cancer risk among participants with diabetes.

LIMITATIONS

The association of regular aspirin use with lower pancreatic cancer risk among people with diabetes was found in a stratified analysis and will need to be confirmed in additional studies.

IMPACT

Regular aspirin or non-aspirin NSAID use was not associated with future risk of pancreatic cancer in participants from several large prospective cohort studies.

Non-aspirin NSAIDs, most commonly used for the treatment of pain and inflammation, have also been shown to reduce the risk of certain cancer types.[5] While in vitro experiments and animal studies suggest that aspirin and non-aspirin NSAIDs reduce pancreatic carcinogenesis,[6–8] human studies have yielded conflicting results.[9–14] Given inter-study variations in exposure classification and statistical methods, modest sample sizes, and short study periods in most prior investigations, there remains a critical need to examine the potential role of NSAIDs as chemopreventative agents in pancreatic cancer using large prospective study populations with updated data on NSAID use and follow-up over several decades.[15]

To investigate the association between aspirin and non-aspirin NSAID use and incident pancreatic adenocarcinoma, we conducted a prospective study within 2 large cohorts with updated ascertainment of NSAID use and potential confounding covariates over 25 years of follow-up. To further study this relationship, we evaluated the association of pre-diagnosis levels of plasma salicylurate, a major aspirin metabolite,[16,17] and future pancreatic cancer risk among cases and controls nested in 3 large prospective cohorts.

Methods

Prospective Cohort Study

Study Population. The prospective cohort study pooled participants from 2 large US cohorts, the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS). The HPFS is comprised of 51,529 male health professionals who enrolled in 1986 at ages 40–75 years, with a follow-up period from 1986 to 2012. The NHS is comprised of 121,700 registered female nurses who enrolled in 1976 at ages 30–55 years, with a follow-up period from 1980 to 2012. Both cohorts provided mailed questionnaires that collected information on demographics, medical conditions, medication usage, social and family history, and health outcomes such as cancer diagnoses. Follow-up questionnaires were sent every 2 years with follow-up rates exceeding 90%.[4] Further details on the HPFS and NHS cohorts have been previously described.[18,19] Participants with a history of cancer other than nonmelanoma skin cancer at baseline were excluded from the current study.

Assessment of Aspirin Use. Information on aspirin use was collected at baseline (HPFS, 1986; NHS, 1980) and updated biennially via questionnaires, with the exception of the NHS 1986 questionnaire when aspirin use was not ascertained. Both baseline questionnaires asked yes/no aspirin use and yes/no use of 2 or more 325-mg equivalent aspirin tablets per week. Starting in 1992 for HPFS and 1980 for NHS, additional aspirin use details such as dose and frequency of aspirin use were elicited. We defined a standard tablet of aspirin as 325 mg and a low-dose tablet as 81 mg. Similar to prior studies,[4] regular aspirin users were defined as participants who on average used aspirin (either standard or low-dose) at least 2 times per week. Detailed information on aspirin use in these cohorts have been described previously.[4,14,20,21]

Assessment of Non-Aspirin NSAID Use. Information on non-aspirin NSAID use was collected at baseline (HPFS, 1986; NHS, 1990) and updated biennially via questionnaires. Non-aspirin NSAIDs were listed as "anti-inflammatory analgesics" other than aspirin on the study questionnaires and included examples such as ibuprofen (Advil, Motrin, Nuprin), Aleve, Naprosyn, Celebrex, and Vioxx. Regular non-aspirin NSAID users were participants who responded "yes" to regular use on questionnaires, defined as at least 2 doses per week.

Assessment of Empirical Dietary Inflammatory Pattern (EDIP) Scores. To better understand the role of systemic inflammation in the association between NSAID use and pancreatic cancer risk, we used an empirical dietary inflammatory pattern (EDIP) score that measures dietary inflammatory potential. Derivation of the EDIP score has been described previously.[22] In brief, investigators identified a dietary pattern most predictive of 3 plasma inflammatory biomarkers, interleukin-6 (IL6), C-reactive protein (CRP), and tumor necrosis factor α receptor 2 (TNFαR2), using 39 predefined food groups by reduced rank regression models followed by stepwise linear regression analyses. The EDIP score is the weighted sum of 18 component food groups: 9 anti-inflammatory and 9 pro-inflammatory. A higher score indicates greater dietary inflammatory potential. In addition, the score was validated in 2 independent cohorts in which it significantly predicted plasma levels of IL6, CRP, and TNFαR2.[22,23] For participants in our prospective cohort study, we calculated EDIP scores from the current questionnaire cycle based on food-frequency questionnaire data collected since 1986 for HPFS and 1984 for NHS.

Nested Case-Control Study

Study Population. We measured pre-diagnosis plasma levels of salicylurate from nested pancreatic cancer cases and controls from the HPFS, NHS, and Women's Health Initiative-Observational Study (WHI-OS) cohorts. WHI-OS is a prospective cohort comprised of 93,676 healthy postmenopausal

women who enrolled between 1994–1998 at 40 US clinics. Participants completed a baseline clinic questionnaire followed by annual mailed questionnaires.

Plasma was collected from 18,225 men in the HPFS (1993–1995), 32,826 women in the NHS (1989–1990), and 93,676 women in the WHI-OS (1994–1998). HPFS cohort members who responded positively to an invitation letter were sent a blood kit for collection. NHS participants were asked if they were willing to have blood samples collected in the 1988 questionnaire, and those who responded "yes" were mailed a separate letter of invitation. Blood specimen collection was part of the routine follow-up activities for those enrolled in the WHI-OS.

Two control participants were matched to each pancreatic cancer case by year of birth, cohort, smoking status (never, past, current), fasting status (<8 hours, ≥8 hours), and month/year of blood draw.[24] Control subjects in our nested case-control study had no history of cancer other than non-melanoma skin cancer and were alive at the time of the matched case's pancreatic cancer diagnosis. Pancreatic cancer cases diagnosed with pancreatic cancer within 1 year of blood draw and their matched controls were excluded to account for the possibility of reverse causation, in which persons might have used aspirin for cancer-related symptoms such as pain.[14]

Assessment of Salicylurate Levels. All patient samples were analyzed at the Broad Institute of the Massachusetts Institute of Technology and Harvard University (Cambridge, MA), where laboratory personnel were blinded to sample identity (case, control, or quality control [QC)]. Liquid chromatography–tandem mass spectrometry was used to measure plasma salicylurate levels. Details regarding metabolite profiling via this method have been previously described.[24,25] To test for reproducibility, mean intra-assay coefficient of variation for blinded QC samples were calculated for salicylurate across 3 ethylenediaminetetraacetic acid QC plasma pools and 3 heparin QC plasma pools. The mean coefficients of variation for salicylurate across QC plasma pools was 11%, indicating good reproducibility. Further details regarding blood draw methods, plasma transportation and storage, and metabolite profiling have been previously described.[24] In a prior study of circulating metabolites, we included subjects from the Physician's Health Study I. However, these subjects were excluded from the current analyses as the blood collection in Physician's Health Study I was conducted when all participants were taking aspirin as part of the run-in for the trial prior to their randomization to aspirin or placebo. Therefore, measured salicylurate levels would not accurately reflect long-term aspirin exposure.

Pancreatic Cancer Cases

Pancreatic cancer cases were identified by self-report, next of kin, or the computerized National Death Index.[26] The diagnosis was confirmed by review of medical records, death certificates, or cancer registry data by physicians who were blinded to the exposure status of cases. Among the 1122 participants who developed pancreatic cancer over the follow-up period, 904 (81%) were confirmed to have adenocarcinoma by record review. Pancreatic cancer cases with known histologies other than adenocarcinoma were excluded. Remaining cases known to have pancreatic cancer without a further confirmed histologic subtype were maintained in the analyses because approximately 90% of pancreatic cancers are of adenocarcinoma histology.[27,28] Pancreatic cancer cases were included through 2012 for the cohort study and 2010 for the nested case-control study.

Assessment of Covariates

Covariate data were collected at baseline and in follow-up questionnaires, including age, race, sex, body mass index (BMI), diabetes mellitus (DM) status, smoking status, alcohol intake, physical activity level, and multivitamin use.[29] Average weekly energy expenditure from self-reported activity levels was converted to metabolic equivalent of task hours per week, as described in detail in prior work.[30] Fasting period prior to blood draw was also collected for participants in the nested case-control study.

Statistical Analysis

For the cohort study, we calculated person-years of follow-up from ascertainment date of aspirin or non-aspirin NSAID use to date of incident pancreatic cancer diagnosis, death, or end of follow-up, whichever occurred first. To comprehensively evaluate the potential association of NSAID use with pancreatic cancer risk, 4 approaches to exposure classification were considered, including current, latent, baseline, and cumulative use. As used by previous studies from these cohorts,[4,14,31] these approaches take into account differing time intervals during which medication use may impact disease development.

For the current exposure analyses, NSAID use was a simple update taken from the most recent questionnaire cycle before each follow-up interval. For the latency exposure analyses, the association between NSAID use and pancreatic cancer was examined with a latency period of 6–8 years between reported exposure and cancer diagnosis. Although studies suggest at least a decade elapses between formation of the tumor-initiating clone and a pancreatic cancer diagnosis,[32] the exact time period over which pancreatic cancer develops has not been clearly delineated.[33] Therefore, a 6–8 year latency period was chosen a priori based on a reasonable lag period during which pre-invasive or early invasive disease is likely to be present and for consistency with prior studies in our cohorts.[4] For the baseline analyses, NSAID use was derived directly from baseline questionnaires (HPFS 1986 or 1992; NHS 1980 for aspirin use and 1990 for non-aspirin NSAID use). For the cumulative analyses, the mean weekly intake of aspirin and non-aspirin NSAIDs was calculated by taking the average from all available questionnaires beginning with baseline until the beginning of each follow-up interval.

Cox proportional hazards regression models conditioned on age and questionnaire cycle were used to calculate hazard ratios as estimates for age- and multivariable-adjusted relative risks (RRs) and 95% confidence intervals (95% CIs) for the association between NSAID use and pancreatic cancer risk. Multivariable models were adjusted for potential confounding factors including sex/cohort, race, BMI, DM, smoking, alcohol use, multivitamin use, and physical activity level ascertained from the most current follow-up questionnaire cycle. In analyses with aspirin use as the main exposure of interest, regular non-aspirin NSAID use (yes/no/missing) as derived from the most recent questionnaire cycle was included as a covariate in multivariable analyses. Similarly, in analyses with non-aspirin NSAID use as the main exposure of interest, regular

aspirin use (yes/no) as derived from the most recent questionnaire cycle was controlled for in multivariable analyses.

Using a propensity score previously constructed within our study cohorts to account for overall comorbidity status,[34] we further adjusted for comorbidities and lifestyle factors that may be associated with NSAID use, including calorie intake and history of high cholesterol, stroke, hypertension, or heart disease. Linear trends by frequency and duration of NSAID use were calculated by using the median of each category as a continuous variable in Cox regression models. We were not able to assess the association between the frequency of non-aspirin NSAID use (ie, tablets per week) and pancreatic cancer risk because this information was not consistently collected in the cohorts.

Stratified analyses were performed by history of diabetes and BMI, based on the findings of prior studies[14,35], as well as by EDIP scores. *P* values for interaction were calculated by entering into the model a cross-product term of regular NSAID use and stratified covariates. In keeping with prior studies on diabetes and pancreatic cancer,[34,36–38] diabetes status was further classified as long-term (>4 years) or short-term (≤4 years) based on time from diabetes diagnosis date to most current questionnaire cycle.

Salicylurate is an abundant circulating metabolite of aspirin and has been used as a measure of aspirin exposure.[16,17] Nevertheless, the optimal plasma level of salicylurate to mark specific quantities of aspirin intake is unknown. Therefore, for the nested case-control study, subjects were categorized into quintiles based on the distribution of plasma salicylurate levels among controls. The lowest quintile for plasma salicylurate levels was denoted as quintile 1, and the highest quintile was denoted as quintile 5.

To evaluate the association of plasma salicylurate levels and pancreatic cancer risk, we performed conditional logistic regression with conditioning on matching factors (age, sex/cohort, smoking status, fasting time prior to blood draw, and month/year of blood draw) and adjusting for potential confounding factors (race, BMI, diabetes, alcohol use, multivitamin use, physical activity, and non-aspirin NSAID use). *P* values for trend were calculated by entering the log-transformed salicylurate values as continuous variables into logistic regression models. Stratified analyses by time interval between blood

Table 1. Baseline Characteristics of HPFS and NHS Participants by Regular Aspirin Use

	HPFS		NHS		Combined	
Characteristics[b]	Nonregular user	Regular user[a]	Nonregular user	Regular user[a]	Nonregular user	Regular user[a]
No. of participants	34,795	14,529	62,033	30,583	96,828	45,112
Age, *y*						
Mean (*SD*)	53.7 (9.7)	56.4 (9.7)	46.7 (7.3)	46.9 (7.1)	49.2 (8.9)	50.0 (9.2)
Race (%)						
White	88.8	95.1	96.8	98.4	93.9	97.3
Black	1.1	0.6	2.1	1.0	1.7	0.9
Other	3.7	2.4	1.1	0.6	2.1	1.2
Unknown	6.4	1.9	0	0	2.3	0.6
BMI, kg/m^2						
Mean (*SD*)	24.9 (5.0)	25.1 (5.2)	24.2 (4.4)	24.7 (4.7)	24.5 (4.6)	24.8 (4.9)
<25.0	46.3	42.6	61.4	62.1	56.0	55.9
25.0–29.9	43.6	46.2	21.4	24.5	29.3	31.5
30.0–34.9	6.6	7.4	6.8	8.8	6.8	8.3
≥35.0	1.2	1.4	2.8	4.1	2.2	3.2
Missing	2.3	2.4	7.6	0.5	5.7	1.1
Tobacco smoking (%)						
Never	46.3	40.7	44.2	41.5	45.0	41.3
<5 pack-years	4.2	4.2	9.7	9.6	7.8	7.9
5–19 pack-years	17.2	18.7	20.2	21.3	19.1	20.4
20–39 pack-years	16.3	20.3	17.6	18.9	17.1	19.4
≥40 pack-years	9.0	13.7	6.9	7.4	7.6	9.4
Missing	7.0	2.4	1.4	1.3	3.4	1.6
Alcohol use, *grams/day*						
Mean (*SD*)	10.8 (15.0)	12.7 (16.3)	6.1 (10.3)	6.9 (10.9)	7.9 (12.6)	8.8 (13.2)
Multivitamin use (%)	38.4	49.4	29.1	38.2	32.4	41.8
Physical activity (*MET-hours/week*)						
Mean (*SD*)	21.2 (30.0)	20.4 (28.8)	14.4 (21.7)	13.5 (18.9)	17.3 (25.8)	16.1 (23.4)
Diabetes mellitus (%)	2.9	4.0	2.4	2.4	2.6	2.9
Regular non-aspirin NSAID use (%)	4.7	7.3	31.9	44.2	20.4	30.5

BMI, body mass index; HPFS, Health Professionals Follow-up Study; kg, kilogram; MET, metabolic equivalent of task; m, meter; NHS, Nurses' Health Study; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.
[a]Average of 2 tablets of 81 mg of aspirin per week or greater.
[b]All variables derived from baseline questionnaires (HPFS 1986; NHS 1980) except for physical activity, which was derived from 1986 questionnaires in both cohorts, and non-aspirin NSAID use, which was derived from 1990 questionnaire in NHS.

Table 2. Association Between Regular Aspirin Use and Incident Pancreatic Cancer

	HPFS		NHS		Combined Population	
	Nonregular users	Regular users	Nonregular users	Regular users	Nonregular users	Regular users
Current exposure[a]						
No. cases	214	201	379	328	593	529
Person-years	585,954	501,314	1,899,575	1,227,923	2,485,529	1,729,236
Age-adjusted RR (*95% CI*)	1	0.91 (0.75, 1.10)	1	1.01 (0.87, 1.18)	1	0.99 (0.88, 1.11)
Multivariable RR (*95% CI*)[b]	1	0.87 (0.71, 1.06)	1	0.99 (0.85, 1.15)	1	0.95 (0.84, 1.07)
Latency exposure[a]						
No. cases	163	165	357	288	520	453
Person-years	443,434	336,911	1,529,058	875,400	1,972,492	1,212,311
Age-adjusted RR (*95% CI*)	1	1.08 (0.87, 1.35)	1	1.14 (0.98, 1.34)	1	1.14 (1.00, 1.29)
Multivariable RR (*95% CI*)[b]	1	1.03 (0.82, 1.29)	1	1.12 (0.95, 1.31)	1	1.09 (0.96, 1.24)
Baseline exposure[a]						
No. cases	159	144	365	209	524	353
Person-years	456,511	323,807	1,818,540	891,565	2,275,051	1,215,372
Age-adjusted RR (*95% CI*)	1	1.08 (0.86, 1.36)	1	1.14 (0.96, 1.36)	1	1.14 (1.00, 1.31)
Multivariable RR (*95% CI*)[b]	1	1.02 (0.81, 1.29)	1	1.14 (0.96, 1.35)	1	1.10 (0.95, 1.26)

CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; RR, relative risk.
[a]Current exposure, aspirin use obtained from the most recent questionnaire cycle; Latency exposure, 6–8 year latency period for reported aspirin exposure; Baseline exposure, aspirin use obtained from baseline questionnaires (HPFS 1992; NHS 1980).
[b]Multivariate models conditioned on age (months) and questionnaire cycle and adjusted for sex/cohort, race (white, black, other, unknown), BMI in kg/m^2 (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0, missing), DM (yes/no), smoking in pack-years (never, <5, 5–19, 20–39, ≥40, missing), alcohol intake in grams/day (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, ≥30.0, missing), multivitamin use (yes/no), physical activity (quintiles by sex), and regular non-aspirin NSAID use (yes/no/missing).

collection and cancer diagnosis (1–<5 years, ≥5–<10 years, and ≥10 years) were performed. We assessed the possibility of a nonlinear association between salicylurate level and pancreatic cancer risk by using the likelihood ratio test, comparing the model with linear and cubic spline terms to the model with linear terms only.[39] Values outside of 2 standard deviations from the log-transformed overall mean salicylurate level were excluded from this analysis to reduce the influence of extreme values.

All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC), and 2-sided *P* values of <.05 were considered statistically significant. Study protocols were approved by the Human Research Committee at Brigham and Women's Hospital.

Results

Prospective Cohort Study

At baseline, 141,940 participants met inclusion criteria and nearly 32% were regular aspirin users (Table 1). In total, 1122 participants developed pancreatic adenocarcinoma over 4.2 million person-years of follow-up (Table 2).

In pooled analyses of HPFS and NHS participants, we identified no association between regular aspirin use and pancreatic cancer risk when regular aspirin use was classified as current (adjusted RR, 0.95; 95% CI, 0.84–1.07), latent (adjusted RR, 1.09; 95% CI, 0.96–1.24) or baseline exposure (adjusted RR, 1.10; 95% CI, 0.95–1.26; Table 2). Analysis of each cohort (HPFS or NHS) individually yielded similar results (all $P_{\text{heterogeneity}}$ >.30; Table 2).

To better understand the associations of aspirin and non-aspirin NSAID use with pancreatic cancer risk independently, we divided participants into 4 groups: no regular aspirin or non-aspirin NSAID use, regular aspirin use only, regular non-aspirin NSAID use only, and regular use of both aspirin and non-aspirin NSAIDs. No associations between regular aspirin use, non-aspirin NSAID use, or combination aspirin/non-aspirin NSAID use was identified with pancreatic cancer risk (Table 3).

We next conducted stratified analyses by BMI and diabetes status. The association of regular aspirin and non-aspirin NSAID use and pancreatic cancer risk was similar across BMI categories (Supplementary Table 1), without a significant change in results after sensitivity analysis excluding underweight participants (BMI <18.5; data not shown).

Amongst the 1122 participants who developed pancreatic cancer, 212 (19%) had diabetes at diagnosis. On stratified analysis by diabetes status, regular aspirin use was associated with a lower risk of pancreatic cancer among participants with diabetes (current exposure analysis: adjusted RR, 0.71; 95% CI, 0.54–0.94; Table 4). A similar association was not identified for non-aspirin NSAID use (current exposure analysis: adjusted RR, 1.02; 95% CI, 0.74–1.41; Table 4). In further classifying participants by duration of diabetes (long-term >4 years or short-term ≤4 years), we found similar results (data not shown). To explore whether the reduced risk of pancreatic cancer among cases with diabetes who reported regular aspirin use was related to aspirin's anti-inflammatory properties,

Table 3. Association Between Regular NSAID Use and Incident Pancreatic Cancer

	Nonregular users of any NSAIDs	Regular users		
		Aspirin only	Non-aspirin NSAIDs only	Combination aspirin and non-aspirin NSAIDs
Current exposure[a]				
No. cases	366	347	144	137
Person-years	1,194,055	953,905	498,385	398,622
Age-adjusted RR (*95% CI*)	1	0.97 (0.83, 1.12)	0.98 (0.81, 1.19)	0.95 (0.78, 1.16)
Multivariable RR (*95% CI*)[b]	1	0.92 (0.79, 1.07)	1.01 (0.83, 1.23)	0.93 (0.76, 1.14)
Latency exposure[a]				
No. cases	288	287	127	98
Person-years	884,265	624,929	349,878	238,050
Age-adjusted RR (*95% CI*)	1	1.16 (0.99, 1.37)	1.15 (0.93, 1.42)	1.13 (0.89, 1.42)
Multivariable RR (*95% CI*)[b]	1	1.10 (0.93, 1.30)	1.17 (0.94, 1.45)	1.09 (0.86, 1.38)
Baseline exposure[a]				
No. cases	339	213	110	44
Person-years	1,096,358	518,317	463,658	136,654
Age-adjusted RR (*95% CI*)	1	1.15 (0.97, 1.37)	0.86 (0.69, 1.07)	1.03 (0.75, 1.42)
Multivariable RR (*95% CI*)[b]	1	1.07 (0.89, 1.27)	0.88 (0.71, 1.10)	0.99 (0.72, 1.36)

CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; NSAIDs, nonsteroidal anti-inflammatory drugs; RR, relative risk.
[a]Current exposure, NSAID use obtained from the most recent questionnaire cycle; Latency exposure, 6–8 year latency period for reported NSAID exposure; Baseline exposure, NSAID use obtained from baseline questionnaires (HPFS 1992; NHS 1980 for aspirin use and 1990 for non-aspirin NSAID use).
[b]Multivariate models conditioned on age (months) and questionnaire cycle and adjusted for sex/cohort, race (white, black, other, unknown), BMI in kg/m^2 (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0, missing), diabetes mellitus (yes/no), smoking in pack-years (never, <5, 5–19, 20–39, ≥40, missing), alcohol intake in grams/day (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, ≥30.0, missing), multivitamin use (yes/no), and physical activity (quintiles by sex).

we conducted stratified analysis by a dietary inflammatory (EDIP) score. Notably, diabetic participants in the top tertile of EDIP score, which reflects a high inflammatory diet, had a decreased risk of pancreatic cancer with regular aspirin use (RR, 0.58; 95% CI, 0.37–0.89; $P_{\text{interaction}}$ .04; Supplementary Table 2).

Table 4. Association Between Regular Aspirin and Non-Aspirin NSAID Use and Incident Pancreatic Cancer Stratified by Diabetes Status

	Aspirin[a]			Non-aspirin NSAIDs[a]		
Diabetes status	Nonregular users	Regular users	$P_{\text{interaction}}$[c]	Nonregular users	Regular users	$P_{\text{interaction}}$[c]
Diabetes			0.05			0.91
No						
No. cases	483	427		570	224	
Person-years	2,332,301	1,566,450		1,964,554	810,961	
Age-adjusted RR (*95% CI*)	1	1.03 (0.90, 1.17)		1	0.99 (0.84, 1.16)	
Multivariable RR (*95% CI*)[b]	1	1.01 (0.89, 1.16)		1	1.03 (0.88, 1.21)	
Yes						
No. cases	110	102		143	57	
Person-years	153,227	162,786		183,406	86,047	
Age-adjusted RR (*95% CI*)	1	0.75 (0.57, 1.00)		1	0.97 (0.71, 1.34)	
Multivariable RR (*95% CI*)[b]	1	0.71 (0.54, 0.94)		1	1.02 (0.74, 1.41)	

CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; RR, relative risk.
[a]Current exposure, aspirin and non-aspirin NSAID use obtained from the most recent questionnaire cycle.
[b]Multivariate models conditioned on age (months) and questionnaire cycle and adjusted for sex/cohort, race (white, black, other, unknown), BMI in kg/m^2 (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0, missing), smoking in pack-years (never, <5, 5–19, 20–39, ≥40, missing), alcohol intake in grams/day (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, ≥30.0, missing), multivitamin use (yes/no), physical activity (quintiles by sex), and regular use of aspirin (yes/no) or non-aspirin NSAID (yes/no/missing) depending on the primary exposure.
[c]Tests for interaction performed by entering into the model a cross-product term of regular aspirin or non-aspirin NSAID use (yes/no) and diabetes mellitus (yes/no).

Table 5. Association Between Duration of Aspirin and Non-Aspirin NSAID Use and Incident Pancreatic Cancer

	Years of regular aspirin use[a]				Years of regular non-aspirin NSAID use[a]			
	0–5	6–10	>10	P_{trend}[d]	0–5	6–10	>10	P_{trend}[d]
HPFS								
No. cases	188	105	122		343	51	21	
Person-years	609,899	267,456	209,913		944,461	101,844	40,963	
Age-adjusted RR (95% CI)	1	0.95 (0.74, 1.21)	1.11 (0.86, 1.44)	0.48	1	1.12 (0.82, 1.51)	1.13 (0.71, 1.78)	0.44
Multivariable RR (95% CI)[b]	1	0.91 (0.71, 1.16)	1.04 (0.80, 1.35)	0.87	1	1.08 (0.79, 1.46)	1.12 (0.71, 1.78)	0.53
Multivariable RR (95% CI)[c]	1	0.90 (0.70, 1.16)	1.03 (0.79, 1.36)	0.90	1	1.08 (0.79, 1.47)	1.12 (0.70, 1.77)	0.54
NHS								
No. cases	274	149	284		397	147	68	
Person-years	1,725,215	536,512	865,772		1,402,465	486,964	194,236	
Age-adjusted RR (95% CI)	1	1.13 (0.93, 1.39)	1.30 (1.09, 1.55)	0.002	1	1.04 (0.86, 1.26)	1.02 (0.78, 1.33)	0.86
Multivariable RR (95% CI)[b]	1	1.15 (0.93, 1.41)	1.34 (1.12, 1.60)	0.001	1	1.04 (0.86, 1.27)	1.01 (0.77, 1.33)	0.89
Multivariable RR (95% CI)[c]	1	1.16 (0.94, 1.42)	1.36 (1.14, 1.64)	0.001	1	1.05 (0.87, 1.28)	1.04 (0.79, 1.36)	0.76
Combined								
No. cases	462	254	406		740	198	89	
Person-years	2,335,113	803,967	1,075,685		2,346,926	588807	235199	
Age-adjusted RR (95% CI)	1	1.07 (0.91, 1.25)	1.21 (1.05, 1.40)	0.005	1	1.02 (0.87, 1.20)	1.00 (0.80, 1.26)	0.97
Multivariable RR (95% CI)[b]	1	1.05 (0.90, 1.23)	1.23 (1.06, 1.42)	0.003	1	1.06 (0.90, 1.25)	1.05 (0.83, 1.32)	0.62
Multivariable RR (95% CI)[c]	1	1.06 (0.91, 1.24)	1.23 (1.06, 1.42)	0.004	1	1.07 (0.91, 1.26)	1.06 (0.84, 1.33)	0.56

CI, confidence interval; HPFS, Health Professionals Follow-up Study; NSAIDs, nonsteroidal anti-inflammatory drugs; NHS, Nurses' Health Study; RR, relative risk.
[a]Cumulative exposure, NSAID use obtained from mean weekly intake over all available questionnaires.
[b]Multivariate models conditioned on age (months) and questionnaire cycle and adjusted for sex/cohort, race (white, black, other, unknown), BMI in kg/m^2 (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0, missing), diabetes mellitus (yes/no), smoking in pack-years (never, <5, 5–19, 20–39, ≥40, missing), alcohol intake in grams/day (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, ≥30.0, missing), multivitamin use (yes/no), physical activity (quintiles by sex), and regular use of aspirin (yes/no) or non-aspirin NSAID (yes/no/missing) depending on the primary exposure.
[c]Multivariate models further adjusted for calorie intake, and history of high cholesterol, stroke, hypertension, or heart disease (angina pectoris, coronary bypass/angioplasty/stent, myocardial infarction).
[d]Tests for trend conducted using the median value of each category as a continuous variable.

We next examined the duration of regular NSAID use and risk of pancreatic cancer, noting a modest increase in risk with long-term regular aspirin use in the combined population of HPFS and NHS participants (RR 1.23; 95% CI, 1.06–1.42; P_{trend} .003) that was not seen among regular non-aspirin NSAID users (Table 5). After adjustment for potential comorbidities in long-term aspirin users, including history of high cholesterol, stroke, hypertension, or heart disease, our results remained largely unchanged (Table 5). Although RRs were more pronounced in NHS cohort participants compared with HPFS cohort participants, the *P* value for heterogeneity was .18, supporting no statistically significant heterogeneity across the 2 study cohorts.

We also investigated whether the average number of aspirin tablets taken per week was associated with pancreatic cancer risk. When considering current, latency, baseline, and cumulative exposure classifications, we identified no association between the frequency of aspirin use and pancreatic cancer risk (all adjusted P_{trend} >.05; Supplementary Table 3). Similarly, we found no association between frequency of aspirin use and pancreatic cancer risk when stratified by diabetes status (data not shown). The association between the frequency of non-aspirin NSAID use and pancreatic cancer risk could not be assessed, as this level of detail was not consistently collected in cohort questionnaires.

Nested Case-Control Study

For pancreatic cancer cases in the nested case-control study, the median time between blood collection and cancer diagnosis was 8 years. Demographic and clinical data for 396 pancreatic cancer cases and 784 matched controls are shown in Supplementary Table 4. Participants with salicylurate levels in the highest quintile (quintile 5) had an adjusted odds ratio for pancreatic cancer of 1.08 (95% CI,

Table 6. Odds Ratio of Pancreatic Cancer by Prediagnosis Plasma Salicylurate Levels

	Quintiles of plasma salicylurate					
	1 (lowest)	2	3	4	5 (highest)	P_{trend}[c]
No. cases/controls	79/156	82/157	80/157	66/157	89/157	
OR (*95% CI*)[a]	1	1.04 (0.71, 1.52)	1.01 (0.69, 1.49)	0.83 (0.56, 1.23)	1.11 (0.75, 1.64)	.56
OR (*95% CI*)[b]	1	1.09 (0.74, 1.62)	1.04 (0.70, 1.54)	0.80 (0.53, 1.20)	1.08 (0.72, 1.61)	.81

CI, confidence interval; OR, odds ratio.
[a]OR (95% CI) from conditional logistic regression models conditioned on matching factors (year of birth, cohort, smoking status, fasting status, and month of blood draw).
[b]OR (95% CI) from conditional logistic regression models conditioned on matching factors and adjusted for race (white, black, other, unknown), BMI in kg/m^2 (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0, missing), diabetes mellitus (yes/no), alcohol intake in grams/day (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, ≥30.0, missing), multivitamin use (yes/no), physical activity (quintiles by sex), and regular non-aspirin NSAID use (yes/no/missing).
[c]Tests for trend conducted using the log-transformed metabolite as a continuous variable.

0.72–1.61; P_{trend} .81) compared with those in the lowest quintile (quintile 1; Table 6). Stratified analysis by diabetes status could not be performed because of limited sample size. Restricted cubic spline regression confirmed that a nonlinear association between salicylurate level and pancreatic cancer risk was not present ($P_{nonlinearity}$ .48).

We also conducted a stratified analysis by the time interval between blood collection and cancer diagnosis and found no association between salicylurate level and pancreatic cancer risk (all P_{trend} >.30; Supplementary Table 5). No heterogeneity in pancreatic cancer risk by plasma salicylurate level was identified across the 3 cohorts ($P_{heterogeneity}$ .84; Figure 1).

Discussion

In a pooled analysis of 2 large prospective cohorts, we identified no association between regular aspirin or non-aspirin NSAID use and incident pancreatic cancer. This lack of association was consistent across several analytic approaches that accounted for a range of time periods between NSAID use and development of cancer. We also found no association between pre-diagnosis plasma salicylurate levels, an abundant circulating metabolite of aspirin, and pancreatic cancer risk in a nested case-control study from 3 prospective cohorts. Therefore, the primary results from these studies do not support an association between regular use of aspirin or non-aspirin NSAIDs and future risk of pancreatic cancer in a large population of US subjects.

Prior studies of aspirin use and pancreatic cancer risk have yielded mixed results.[9–14] Several case-control studies have suggested a reduced risk for pancreatic cancer among aspirin users,[9,10] while other studies have indicated no association.[11] In a large prospective study from the Cancer Prevention Study II Nutrition Cohort, no association was found between regular (325 mg) aspirin use (daily, daily current use of <5 years, and daily current use of ≥5 years) and pancreatic cancer.[13] Similarly, in a prior prospective study of NHS participants that included 161 pancreatic cancer cases, no association was identified between regular aspirin use and pancreatic cancer risk.[14] Differing results across studies could be because of differences in timing of

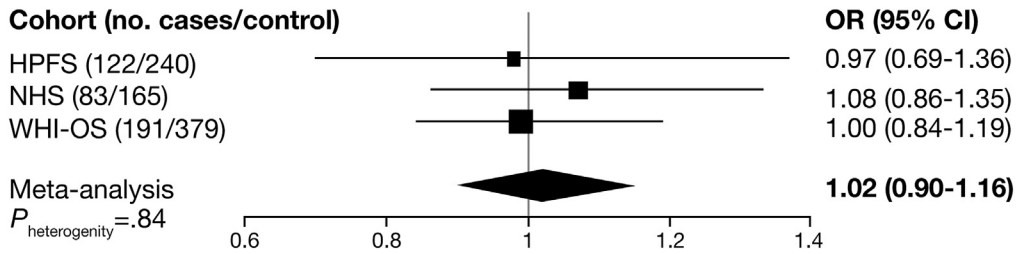

Figure 1. Forest plot and meta-analysis of odds ratios for pancreatic cancer per standard deviation increase in plasma salicylurate by cohort. CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; OR, odds ratio; WHI-OS, Women's Health Initiative-Observational Study. *Solid squares* and *horizontal lines* indicate cohort-specific multivariable-adjusted ORs and 95% CIs, respectively, per standard deviation increase in plasma salicylurate. Area of the solid square reflects the cohort-specific weight (inverse of the variance). Diamond represents the meta-analysis multivariable-adjusted OR and 95% CI. Vertical line indicates an OR of 1.0. Overall response (95% CIs) from conditional logistic regression models conditioned on matching factors (year of birth, cohort, smoking status, fasting status, and month of blood draw) and adjusted for race (white, black, other, unknown), BMI in kg/m^2 (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0, missing), diabetes mellitus (yes/no), alcohol intake in grams/day (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, ≥30.0, missing), multivitamin use (yes/no), physical activity (quintiles), and regular non-aspirin NSAID use (yes/no/missing).

aspirin exposure ascertainment in relation to cancer risk and differences in aspirin doses.[40,41] In our primary analyses, we defined regular aspirin use as a minimum of 2 tablets of low-dose aspirin per week, noting no association between regular aspirin use and pancreatic cancer risk. However on subsequent analyses, we similarly did not identify an association between higher numbers of aspirin tablets per week and pancreatic cancer risk. Furthermore, we investigated multiple exposure classifications with differing lag times between aspirin use and incident pancreatic cancer and again saw no association between regular aspirin use and pancreatic cancer risk.

Randomized, placebo-controlled trials have been conducted of aspirin use with cardiovascular disease endpoints. Several of these studies have also evaluated cancer incidence or mortality by treatment arm. In a report from the Women's Health Study that randomized patients to placebo or 100 mg of aspirin every other day for 10 years, no difference in risk of pancreatic cancer was seen between the aspirin and placebo arms (N = 51 cases; RR, 1.43; 95% CI, 0.81–2.49).[42] In a subsequent pooled analysis of randomized controlled trials, a reduced risk of pancreatic cancer death was suggested during study treatment, but only after a latent period of 5 years of aspirin use and with only 45 pancreatic cancer deaths available for the analysis.[43]

Although few prior studies have been conducted, available prospective data have not supported an association between non-aspirin NSAID exposure and risk of pancreatic cancer. In concordance with these prior studies,[40,44,45] regular non-aspirin NSAID use was not associated with pancreatic cancer risk within our study cohorts. These findings were consistent after considering multiple exposure classifications to account for the possible influence of differing time intervals between non-aspirin NSAID use and cancer risk.

In a pre-planned subgroup analysis, we identified a nearly 30% lower risk for pancreatic cancer with regular aspirin use among participants with diabetes. Diabetes is a known risk factor for pancreatic cancer[46,47] and leads to increased systemic inflammation.[48] In a previously published nested case-control study in NHS, women with high baseline levels of soluble tumor necrosis factor receptor-2 (sTNFR-2) who used aspirin/NSAIDs regularly had a reduced risk of incident colon cancer.[49] A similar effect of aspirin/NSAID use on colon cancer risk was not seen among women with low baseline levels of sTNFR-2, suggesting that the reduced cancer risk with regular aspirin/NSAID use was most prominent among participants with increased systemic inflammation. Although highly exploratory, we noted that regular aspirin use was associated with reduced pancreatic cancer risk primarily among diabetic participants expected to have higher systemic inflammation, based upon a previously validated dietary inflammatory index.[22,23] These findings support that the effects of aspirin on pancreatic tumorigenesis in the setting of hyperglycemia and diabetes should be further investigated.

We identified a modestly increased risk of pancreatic cancer with long-term aspirin use of more than 10 years. Prior studies have shown a nonsignificant trend towards increased pancreatic cancer risk with longer duration of aspirin and non-aspirin NSAID use,[50,51] but additional work is required to confirm these findings. Although we noted similar findings after adjustment for comorbid conditions related to cardiovascular disease, residual confounding among long-term users cannot be excluded, particularly because several pancreatic cancer risk factors are enriched within long-term aspirin users, such as tobacco use and obesity.

The current study has several important strengths. Notably, detailed information on aspirin and non-aspirin NSAID use was obtained prospectively and longitudinally from over 140,000 people residing throughout the US over a 25-year period. This led to the capture of a large number of pancreatic cancer cases and the ability to examine multiple latency periods between NSAID use and development of pancreatic cancer. Furthermore, we prospectively collected extensive information for lifestyle factors and other conditions, allowing for robust control for confounding and examination of effect modification by obesity and diabetes. In our nested case-control study, we examined the association of aspirin with future pancreatic cancer risk by quantitating a central plasma metabolite of the drug. Importantly, plasma samples were drawn prior to cancer diagnosis and cases that developed cancer within 1 year of blood draw were excluded, greatly reducing the likelihood of reverse causation bias, in which aspirin may have been ingested to mitigate symptoms from a soon-to-be-diagnosed pancreatic cancer.

This study also has limitations. Our study population was predominately white, and participants in HPFS and NHS were all employed within health care fields. Of note, WHI-OS had greater racial diversity without the eligibility criteria for health care professionals. Plasma salicylurate was measured at a single point in time and has a relatively short half-life of approximately 1 hour,[52,53] such that low salicylurate levels could be seen even among regular aspirin users depending on timing of blood draw in relation to medication usage. Nevertheless, our results were consistent across the analyses of self-reported aspirin use and risk of incident pancreatic cancer in the prospective cohort study. Although our subgroup analyses were pre-planned based on prior data and included only 2 stratification covariates, the association of regular aspirin use with lower pancreatic cancer risk among people with diabetes will need to be confirmed in additional studies.

In conclusion, we conducted 2 large, prospective studies on aspirin and non-aspirin NSAID use and pancreatic cancer risk, using both longitudinal self-report of NSAID use and a major circulating metabolite of aspirin measured in pre-diagnosis blood samples. We did not identify an association of regular aspirin use and pancreatic cancer risk in the full patient population, but the observed reduction in risk among people with diabetes should be further investigated in preclinical and human studies.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2017.12.001.

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Reprint requests
Address requests for reprints to: Brian M. Wolpin, MD, MPH, 450 Brookline Avenue, Boston, MA 02215. e-mail: bwolpin@partners.org; fax: (617) 632-5370.

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Author contributions: N.K. and C.Y. contributed to data acquisition, data analysis and interpretation, literature review, and drafting and critically revising the manuscript. T.H., Y.C., A.B., V.M., P.K., K.N., E.G., S.O., M.S., B.C., J.M., A.C., and C.F. contributed to study design, data acquisition, and critically revising the manuscript for important intellectual content. C.B.C. contributed to data acquisition and analysis, and technical and material support. B.W. contributed to study design, data acquisition, data interpretation, and drafting and critically revising the manuscript. All authors gave final approval of the version to be published.

Conflicts of interest
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Supplementary Table 1. Association Between Regular Aspirin and Non-Aspirin NSAID Use and Incident Pancreatic Cancer Stratified by BMI Category

	Aspirin[a]			Non-aspirin NSAIDs[a]		
BMI (kg/m^2)	Nonregular users	Regular users	$P_{interaction}$[c]	Nonregular users	Regular users	$P_{interaction}$[c]
			.39			.87
< 25						
No. cases	275	223		330	100	
Person-years	1,328,114	838,685		1,078,903	392,459	
Age-adjusted RR (*95% CI*)	1	0.97 (0.81, 1.16)		1	0.87 (0.69, 1.09)	
Multivariable RR (*95% CI*)[b]	1	0.96 (0.80, 1.15)		1	0.92 (0.73, 1.16)	
25–29.9						
No. cases	225	218		282	124	
Person-years	810,948	636,008		808,818	335,903	
Age-adjusted RR (*95% CI*)	1	0.97 (0.80, 1.17)		1	1.07 (0.86, 1.33)	
Multivariable RR (*95% CI*)[b]	1	0.93 (0.77, 1.13)		1	1.11 (0.89, 1.39)	
≥ 30						
No. cases	91	87		101	56	
Person-years	316,693	250,537		254,981	167,297	
Age-adjusted RR (*95% CI*)	1	0.97 (0.71, 1.31)		1	0.87 (0.62, 1.22)	
Multivariable RR (*95% CI*)[b]	1	0.98 (0.72, 1.33)		1	0.89 (0.63, 1.25)	

BMI, body mass index; CI, confidence interval; kg, kilogram; m, meter; NSAIDs, nonsteroidal anti-inflammatory drugs; RR, relative risk.

[a]Current exposure, aspirin and non-aspirin NSAID use obtained from the most recent questionnaire cycle.

[b]Multivariate models conditioned on age (months) and questionnaire cycle and adjusted for sex/cohort, race (white, black, other, unknown), diabetes mellitus (yes/no), smoking in pack-years (never, <5, 5–19, 20–39, ≥40, missing), alcohol intake in grams/day (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, ≥30.0, missing), multivitamin use (yes/no), physical activity (quintiles by sex), and regular use of aspirin (yes/no) or non-aspirin NSAID (yes/no/missing) depending on the primary exposure.

[c]Tests for interaction performed by entering into the model a cross-product term of regular aspirin and non-aspirin NSAID use (yes/no) and BMI (continuous).

Supplementary Table 2. Association Between Regular Aspirin Use and Incident Pancreatic Cancer by Diabetes Status and Stratified by Dietary Inflammatory Score

		Aspirin use[a]		
EDIP Score	No. cases	Nonregular users	Regular users RR (*95% CI*)[b]	$P_{interaction}$[c]
Tertile 1 (lowest)				.29
Diabetes: no	277	1	0.92 (0.72, 1.18)	
Diabetes: yes	42	1	0.84 (0.42, 1.71)	
Tertile 2				.55
Diabetes: no	270	1	1.02 (0.80, 1.31)	
Diabetes: yes	73	1	0.94 (0.56, 1.58)	
Tertile 3 (highest)				.04
Diabetes: no	295	1	1.08 (0.85, 1.36)	
Diabetes: yes	93	1	0.58 (0.37, 0.89)	

CI, confidence interval; EDIP, empirical dietary inflammatory pattern; RR, relative risk.
[a]Current exposure, aspirin use obtained from the most recent questionnaire cycle.
[b]Multivariate models conditioned on age (months) and questionnaire cycle and adjusted for sex/cohort, race (white, black, other, unknown), BMI in kg/m^2 (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0, missing), diabetes mellitus (yes/no), smoking in pack-years (never, <5, 5–19, 20–39, ≥40, missing), alcohol intake in grams/day (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, ≥30.0, missing), multivitamin use (yes/no), physical activity (quintiles by sex), and regular non-aspirin NSAID use (yes/no/missing).
[c]Tests for interaction performed by entering into the model a cross-product term of regular aspirin use (yes/no) and diabetes mellitus (yes/no).

Supplementary Table 3. Association Between Frequency of Aspirin Use and Incident Pancreatic Cancer

	Average number of aspirin tablets (325-mg equivalents) per week					
	0	1	2–5	6–15	≥16	P_{trend}[c]
Current exposure[a]						
No. cases	489	120	275	133	22	
Person-years	1,866,608	532,013	904,820	456,225	106,860	
Age-adjusted RR (*95% CI*)	1	1.13 (0.92, 1.39)	1.01 (0.87, 1.18)	0.98 (0.81, 1.19)	1.04 (0.68, 1.60)	.78
Multivariable RR (*95% CI*)[b]	1	1.15 (0.94, 1.42)	1.00 (0.86, 1.16)	0.92 (0.75, 1.11)	0.95 (0.62, 1.46)	.30
Latency exposure[a]						
No. cases	388	132	206	129	23	
Person-years	1,374,379	463,402	598,041	342,781	88,351	
Age-adjusted RR (*95% CI*)	1	1.15 (0.94, 1.41)	1.13 (0.95, 1.34)	1.13 (0.92, 1.38)	1.10 (0.72, 1.68)	.31
Multivariable RR (*95% CI*)[b]	1	1.15 (0.94, 1.41)	1.11 (0.93, 1.31)	1.04 (0.85, 1.28)	1.00 (0.66, 1.54)	.84
Baseline exposure[a]						
No. cases	404	89	150	128	52	
Person-years	1,817,112	353,200	581,053	429,559	162,456	
Age-adjusted RR (*95% CI*)	1	1.02 (0.81, 1.29)	1.08 (0.89, 1.31)	1.16 (0.95, 1.42)	1.29 (0.96, 1.72)	.04
Multivariable RR (*95% CI*)[b]	1	0.96 (0.76, 1.22)	1.03 (0.85, 1.25)	1.08 (0.88, 1.32)	1.25 (0.93, 1.68)	.09
Cumulative exposure[a]						
No. cases	250	212	362	182	33	
Person-years	1,216,390	817,537	1,147,905	553,691	131,003	
Age-adjusted RR (*95% CI*)	1	1.11 (0.92, 1.33)	1.12 (0.96, 1.32)	1.21 (1.00, 1.47)	1.29 (0.90, 1.87)	.05
Multivariable RR (*95% CI*)[b]	1	1.14 (0.95, 1.38)	1.12 (0.95, 1.32)	1.14 (0.94, 1.39)	1.25 (0.87, 1.81)	.19

CI, confidence interval; RR, relative risk.

[a]Current exposure, aspirin use obtained from the most recent questionnaire cycle; Latency exposure, 6–8 year latency period for reported aspirin exposure; Baseline exposure, aspirin use obtained from baseline questionnaires (HPFS 1992; NHS 1980); Cumulative exposure, aspirin use obtained from mean weekly intake over all available questionnaires.

[b]Multivariate models conditioned on age (months) and questionnaire cycle and adjusted for sex/cohort, race (white, black, other, unknown), BMI in kg/m^2 (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0, missing), diabetes mellitus (yes/no), smoking in pack-years (never, <5, 5–19, 20–39, ≥40, missing), alcohol intake in grams/day (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, ≥30.0, missing), multivitamin use (yes/no), physical activity (quintiles by sex), and regular non-aspirin NSAID use (yes/no/missing).

[c]Tests for trend conducted using the median value of each category as a continuous variable.

Supplementary Table 4. Baseline Characteristics of Pancreatic Cancer Cases and Matched Controls in Nested Case-Control Study

Characteristic	Cases	Controls
No. of participants	396	784
Age at blood collection, *y*		
Mean (*SD*)	64.6 (7.6)	64.4 (7.6)
Cohort study (%)		
HPFS	21.0	21.1
NHS	30.8	30.6
WHI-OS	48.2	48.3
Race (%)		
White	91.9	92.9
Black	3.5	2.5
Other	3.3	4.1
Unknown	1.3	0.5
BMI, kg/m^2		
Mean (*SD*)	26.5 (5.1)	26.2 (4.9)
<25.0	42.2	44.9
25.0–29.9	36.4	37.2
30.0–34.9	14.9	11.9
≥35.0	5.5	5.5
Missing	1.0	0.5
Tobacco use (%)		
Never	42.7	45.9
Past	44.9	43.2
Current	11.4	10.1
Missing	1.0	0.8
Alcohol use, *grams/day*		
Mean (*SD*)	8.2 (15.7)	8.0 (13.3)
Multivitamin use (%)	48.0	44.6
Physical activity (*MET-hours/week*)		
Mean (*SD*)	22.1 (36.0)	20.8 (24.0)
Diabetes mellitus (%)	6.1	4.0
Non-aspirin NSAID use (%)	19.5	22.7
Fasting time at blood collection (%)		
<4 hours	9.4	9.2
≥4–<8 hours	5.8	5.2
≥8–<12 hours	10.1	12.1
≥12 hours	71.2	71.4
Missing	3.5	2.1

BMI, body mass index; HPFS, Health Professionals Follow-up Study; kg, kilogram; MET, Metabolic Equivalent of Task; m, meter; NSAID, non-aspirin nonsteroidal anti-inflammatory drug; NHS, Nurses' Health Study; SD, standard deviation; WHI-OS, Women's Health Initiative-Observational Study.

Supplementary Table 5. Odds Ratio of Pancreatic Cancer by Prediagnosis Plasma Salicylurate Levels Stratified by Time Between Blood Collection and Cancer Diagnosis

Time between blood collection and cancer diagnosis	No. cases/ controls	Quintiles of plasma salicylurate OR (95% CI)[a]					P_{trend}[b]
		1	2	3	4	5	
1–<5 years	126/248	1	1.03 (0.48, 2.21)	0.76 (0.37, 1.54)	0.46 (0.21, 1.02)	1.08 (0.52, 2.24)	.80
≥5–<10 years	152/301	1	1.50 (0.78, 2.87)	1.65 (0.86, 3.17)	1.19 (0.62, 2.28)	0.84 (0.41, 1.70)	.32
≥10 years	118/235	1	1.18 (0.52, 2.70)	1.05 (0.45, 2.47)	0.93 (0.38, 2.28)	1.27 (0.56, 2.86)	.43

CI, confidence interval; OR, odds ratio.

[a]OR (95% CIs) from conditional logistic regression models conditioned on matching factors (year of birth, cohort, smoking status, fasting status, and month of blood draw) and adjusted for race (white, black, other, unknown), BMI in kg/m^2 (<25.0, 25.0–29.9, 30.0–34.9, ≥35.0, missing), diabetes mellitus (yes/no), alcohol intake in grams/day (0, 0.1–4.9, 5.0–14.9, 15.0–29.9, ≥30.0, missing), multivitamin use (yes/no), physical activity (quintiles by sex), and regular non-aspirin NSAID use (yes/no/missing).

[b]Tests for trend conducted using the log-transformed metabolite as a continuous variable.