Am J Cancer Res 2024;14(12):5921-5934
www.ajcr.us /ISSN:2156-6976/ajcr0161026

Original Article

Aspirin use reduces cancer risk in betel nut chewers: a nationwide population-based cohort study

Peng Tien[1*], Zen Lang Bih[2*], Wan-Ming Chen[3,4], Ben-Chang Shia[3,4], Szu-Yuan Wu[5,6,7,8,9,10#], Ching-Wen Chiang[1#]

[1]Department of Otorhinolaryngology, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan 265, Taiwan; [2]Department of Emergency Medicine, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan 265, Taiwan; [3]Graduate Institute of Business Administration, College of Management, Fu Jen Catholic University, Taipei 242, Taiwan; [4]Artificial Intelligence Development Center, Fu Jen Catholic University, Taipei 242, Taiwan; [5]Department of Food Nutrition and Health Biotechnology, College of Medical and Health Science, Asia University, Taichung 413, Taiwan; [6]Division of Radiation Oncology, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan 265, Taiwan; [7]Big Data Center, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan 265, Taiwan; [8]Department of Healthcare Administration, College of Medical and Health Science, Asia University, Taichung 413, Taiwan; [9]Cancer Center, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan 265, Taiwan; [10]Centers for Regional Anesthesia and Pain Medicine, Taipei Municipal Wan Fang Hospital, Taipei Medical University, Taipei 116, Taiwan. [*]Equal contributors and co-first authors. [#]Equal contributors.

Received October 9, 2024; Accepted November 10, 2024; Epub December 15, 2024; Published December 30, 2024

Abstract: Betel nut chewing, common in several Asian populations, is linked to increased cancer risk, including oral, esophageal, gastric, and hepatocellular carcinoma. Aspirin shows potential as a chemopreventive agent. This study investigates the association between aspirin use and cancer risk among betel nut chewers. Betel nut chewers aged 18 and older were included, with aspirin use defined as at least 28 cumulative defined daily doses (cDDDs). Propensity score matching and Cox proportional hazards models, adjusted for time-varying covariates, were used to assess cancer risk. The study included 46,302 betel nut chewers, equally divided between aspirin users and non-users. Aspirin use was associated with a 31% reduction in overall cancer risk (adjusted hazard ratio [aHR], 0.69; 95% confidence interval [CI], 0.66 to 0.73; P<0.0001). A dose-response relationship was observed, with higher cDDDs of aspirin corresponding to greater reductions in cancer risk. The highest quartile of aspirin use (Quartile 4) showed a 62% reduction in cancer risk (aHR, 0.38; 95% CI, 0.34 to 0.41; P<0.0001). Daily aspirin intensity was also associated with a significant reduction in cancer risk, with doses greater than 1 DDD showing an aHR of 0.54 (95% CI, 0.47 to 0.61; P<0.0001) compared to 1 DDD or less. Aspirin use significantly reduces cancer risk among betel nut chewers in a dose-dependent manner. These findings suggest aspirin as a potential chemopreventive agent in high-risk populations, warranting further investigation.

Keywords: Betel nut chewing, aspirin, cancer prevention, population-based cohort, chemoprevention

Introduction

Betel nut chewing, prevalent in several Asian populations, is strongly associated with an increased risk of oral cancer, esophageal squamous cell carcinoma (ESCC), gastric cancer, and hepatocellular carcinoma (HCC) [1-6]. The carcinogenic potential of betel nut is particularly concerning in regions like Taiwan, where its use is widespread [1-6]. Emerging evidence further implicates betel nut chewing in the development of pancreatic, pharyngeal, lung, and cervical cancers, suggesting it as a multifaceted carcinogen affecting various organs [6-12]. Betel nut chewers have a 1.5-fold increased risk of pancreatic cancer and approximately a threefold higher risk of pharyngeal cancer compared to non-chewers [6, 13, 14]. Additionally, those who chew betel nuts and smoke face a 1.4-fold increased risk of lung cancer, and women in this group have a 1.6-fold higher risk of cervical cancer, likely due to the immunosuppressive effects of betel nut alkaloids that may facilitate persistent HPV infec-

tions [6, 13, 14]. Habitual chewers also have a 2.2-fold increased risk of stomach cancer [6, 13, 14].

Aspirin has demonstrated significant promise as a chemopreventive agent against various cancers, supported by extensive data from numerous studies [8, 15-21]. Meta-analyses of randomized controlled trials and observational studies consistently show that regular aspirin use significantly reduces the incidence of several types of cancer [15, 20]. For instance, long-term aspirin use is linked to a 24% reduction in colorectal cancer incidence and a 35% reduction in mortality [22]. Similarly, aspirin is associated with a 20-30% reduction in the risk of esophageal, stomach, and breast cancers [22-25]. Notably, daily aspirin use for over five years reduces the risk of colorectal cancer by approximately 30-40% [6, 13, 14, 26].

Betel nut chewing induces chronic inflammation in the oral mucosa, esophagus, and liver due to alkaloids like arecoline, which cause oxidative stress and DNA damage [1-6, 27, 28]. This chronic inflammatory state fosters a conducive environment for cancer development [29]. Aspirin, by mitigating this inflammation [15-17], could potentially reduce the carcinogenic effects of betel nut. Furthermore, aspirin's anti-platelet properties may help prevent metastasis, as platelets can shield circulating tumor cells from immune detection and facilitate their adhesion to the endothelium, promoting metastasis [15, 18, 19]. Therefore, aspirin might offer a novel approach to reducing cancer risk in betel nut chewers, who are at high risk due to the combined effects of betel nut and tobacco use. Given the wide range of cancers associated with betel nut chewing, identifying effective preventive strategies is crucial. Our study explores the potential role of aspirin in mitigating cancer risk within this high-risk population, offering new insights into cancer prevention strategies tailored for individuals with compounded carcinogenic exposures. By leveraging data from a large, real-world cohort, we aim to inform targeted approaches to address the unique cancer risks faced by betel nut chewers, potentially guiding public health interventions and clinical practices in regions with a high prevalence of betel nut use.

Methods

Study population

We conducted a population-based cohort study utilizing data from the Taiwan National Health Insurance Research Database (NHIRD) covering the period from 2008 to 2021. The NHIRD is an invaluable resource for epidemiological research, providing extensive medical claims data for all National Health Insurance beneficiaries in Taiwan, including detailed information on diagnoses, procedures, prescriptions, demographics, and enrollment profiles [30-35]. The data is anonymized using unique patient identifiers and linked to the death registry and Taiwan Cancer Registry, enabling accurate determination of vital status and causes of death for each patient [36-38]. Additionally, the Health Promotion Administration of the Ministry of Health and Welfare in Taiwan initiated an oral cancer screening program in 2004, allowing us to identify high-risk individuals based on betel nut chewing habits by linking the National Oral Cancer Screening database with the NHIRD [39]. Consequently, our study population included betel nut chewers identified from this linked data, representing over 99% of the Taiwanese population.

Our study aimed to examine the association between aspirin use and cancer risk among betel nut chewers aged 18 and older. We utilized data from the Taiwan NHIRD and the National Oral Cancer Screening database, excluding individuals with incomplete age data. Aspirin use was defined as the intake of at least 28 cumulative defined daily doses (cDDDs) of aspirin [40, 41]. The index date was set as the date when a patient first reached 28 cDDDs of aspirin use. The observation period for each betel nut chewer began on the index date and continued until a cancer diagnosis or the end of the study period (December 31, 2022), whichever came first. Patients prescribed at least 28 cDDDs of aspirin during follow-up were classified as the case group (aspirin users), while those prescribed fewer than 28 cDDDs formed the control group (aspirin nonusers). The follow-up duration was defined as one year after the initial aspirin use or cohort entry. To our knowledge, this study is the first to explore the relationship between aspirin use and cancer risk in betel nut chewers, aiming to provide critical

insights into the impact of aspirin on cancer incidence in this population.

Our study employed stringent exclusion criteria to ensure the robustness of our findings. We excluded individuals from the cohort if they met any of the following conditions: (1) a cancer diagnosis within one year of the index date, (2) missing data on sex or age, or being under 18 years of age, (3) a follow-up period of less than one year, or (4) a diagnosis of any other type of cancer within one year prior to cohort entry. These criteria were designed to eliminate potential confounders and to ensure that the observed association between aspirin use and cancer risk was accurately reflected in our results. The study protocols were reviewed and approved by the Institutional Review Board of Tzu-Chi Medical Foundation (IRB number: IRB109-015-B).

PSM and study covariates

To account for potential confounding factors, we incorporated various covariates into our analysis. Participants were stratified into four age groups according to their age on the index date: 18-49, 50-59, 60-69, and ≥70 years. The index date for aspirin users was defined as the first instance of aspirin consumption at a dose of at least 28 cDDDs. For matched non-users, variables recorded at the corresponding index date were utilized.

To investigate the association between aspirin use and cancer onset while controlling for potential confounders, we employed propensity score matching (PSM) to minimize confounding effects when comparing cancer risk between aspirin users and non-users. Matching variables included age, sex, income level, urbanization status, smoking status, alcohol-related diseases, and specific comorbidities such as diabetes, hyperlipidemia, hypertension, chronic obstructive pulmonary disease, tuberculosis, asthma, upper respiratory tract infection, hepatitis B, hepatitis C, liver cirrhosis, inflammatory bowel disease, familial adenomatous polyposis, urinary tract infection, Parkinson's disease, pregnancy, pneumonia, cystic fibrosis, obesity, coronary artery disease, cardiac arrhythmia, stroke or transient ischemic attack, peripheral vascular disease, and congestive heart failure. Additionally, medication use - including non-aspirin NSAIDs, statins, and metformin - as well as the Charlson Comorbidity Index (CCI) score, were considered in the matching process (**Table 1**).

Comorbidities were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or Tenth Revision, Clinical Modification (ICD-10-CM) codes, based on either one inpatient visit or two or more outpatient visits within the year preceding the index date. To avoid repetitive adjustments in the multivariate analysis, repeat comorbidities were excluded from CCI calculations. We employed a time-dependent Cox proportional hazards model, adjusted for relevant covariates, to compare cancer incidence between aspirin users and non-users within the Betel Nut Chewers cohort. This model accounted for changes in aspirin use over the study period, with non-use periods of at least three months classified as unexposed. Aspirin exposure status was updated quarterly, enabling dynamic adjustment for time-varying covariates and providing a more precise estimate of cancer risk. To address the potential for competing risks, we used the Fine and Gray method, which allowed us to estimate the subdistribution hazard of cancer while considering mortality as a competing event, thereby offering a more nuanced understanding of the relationship between aspirin use and cancer incidence [42].

To reduce disparities between patient groups, we utilized the greedy method for propensity score matching, employing a caliper width of 0.1 to achieve a 1:1 matching ratio [43]. This approach involves selecting controls with identical background covariates deemed essential by the investigator for controlling confounding factors. Continuous variables are reported as means with standard deviations or medians with interquartile ranges, depending on the data distribution.

Aspirin exposure

In this study, aspirin exposure was assessed using prescription data from the NHIRD, classified according to the Anatomical Therapeutic Chemical (ATC) system [44]. Collected information included drug type, dosage, administration route, prescription date, and the number of pills dispensed. Given that patients may have modified their aspirin use over time, we treated aspirin use as a time-varying covariate in the Cox proportional hazards model [45]. The cumula-

Table 1. Baseline characteristics of betel nut chewers with and without aspirin use after propensity score matching

	Non-Aspirin use group N = 23,151		Aspirin use group N = 23,151		ASMD
	N	%	N	%	
Age (mean ± SD)	57.19 ± 12.57		57.07 ± 11.65		0.0100
Age, median (IQR), years	57.00 (50.00, 66.00)		57.00 (49.00, 66.00)		
Age Group, years					0.0780
18-49	5,408	23.4%	6,183	26.7%	
50-59	7,546	32.6%	7,251	31.3%	
60-69	6,361	27.5%	6,116	26.4%	
≥70	3,836	16.6%	3,601	15.6%	
Sex					0.0553
Female	5,883	25.4%	5,333	23.0%	
Male	17,268	74.6%	17,818	77.0%	
Income					0.0250
Low income	327	1.4%	345	1.5%	
≤20,000	15,366	66.4%	15,133	65.4%	
20,001-30,000	3,587	15.5%	3,675	15.9%	
30,001-45,000	2,425	10.5%	2,567	11.1%	
>45,000	1,446	6.3%	1,431	6.2%	
Urbanization					0.0053
Rural	8,941	38.6%	8,880	38.4%	
Urban	14,210	61.4%	14,271	61.6%	
Coexisting comorbidities					
Diabetes	5,319	23.0%	5,256	22.7%	0.0067
Hyperlipidemia	15,224	65.8%	14,076	60.8%	0.1030
Hypertension	7,268	31.4%	7,357	31.8%	0.0084
Chronic obstructive pulmonary disease	2,946	12.7%	2,962	12.8%	0.0018
Tuberculosis	183	0.8%	182	0.8%	0.0000
Asthma	1,386	6.0%	1,327	5.7%	0.0111
Upper respiratory tract infection	13,494	58.3%	13,142	56.8%	0.0308
Hepatitis B	486	2.1%	467	2.0%	0.0056
Hepatitis C	277	1.2%	263	1.1%	0.0056
Liver cirrhosis	3,360	14.5%	3,104	13.4%	0.0317
Inflammatory bowel disease	145	0.6%	139	0.6%	0.0038
Familial adenomatous polyposis	144	0.6%	144	0.6%	0.0000
Urinary tract infection	2,193	9.5%	2,063	8.9%	0.0194
Parkinson's disease	140	0.6%	157	0.7%	0.0100
Pregnancy	11	0.1%	14	0.1%	0.0043
Pneumonia	641	2.8%	645	2.8%	0.0012
Cystic fibrosis	0	0.0%	0	0.0%	0.0000
Obesity	180	0.8%	178	0.8%	0.0011
Coronary artery disease	7,435	32.1%	8,317	35.9%	0.0805
Cardiac arrhythmia	342	1.5%	488	2.1%	0.0475
Stroke or transient ischemic attack	3,590	15.5%	3,931	17.0%	0.0399
Peripheral vascular disease	445	1.9%	474	2.1%	0.0093
Congestive heart failure	808	3.5%	1,073	4.6%	0.0578

Habitus					
Ever or current smoking	20,951	90.5%	21,113	91.2%	0.0243
Alcohol-related diseases	807	3.5%	754	3.3%	0.0127
Medication use					
Non-Aspirin NSAIDs	12,537	54.2%	11,970	51.7%	0.0491
Statins	3,563	15.4%	3,963	17.1%	0.0469
Metformin	3,291	14.2%	3,230	14.0%	0.0078
CCI scores					
Mean (SD)	1.27 ± 1.33		1.28 ± 1.40		
Median (Q1-Q3)	1.00 (0.00, 2.00)		1.00 (0.00, 2.00)		
CCI score categories					0.0481
0	9,101	39.3%	9,647	41.7%	
≥1	14,050	60.7%	13,504	58.3%	
Aspirin, cDDD					
Nonuse	23,151	100.0%	0	0.0%	
Q1	0	0.0%	5,540	23.9%	
Q2	0	0.0%	5,455	23.6%	
Q3	0	0.0%	5,888	25.4%	
Q4	0	0.0%	6,268	27.1%	
Aspirin dosage					
Nonuse	23,151	100.0%	0	0.0%	
< median	0	0.0%	10,995	47.5%	
≥ median	0	0.0%	12,156	52.5%	
Daily intensity of dosage					
nonuse	23,151	100.0%	0	0.0%	
≤1 DDD	0	0.0%	20,790	89.8%	
>1 DDD	0	0.0%	2,361	10.2%	

Abbreviations: ASMD, Absolute Standardized Mean Difference; SD, Standard Deviation; IQR, Interquartile Range; CCI, Charlson Comorbidity Index; cDDD, Cumulative Defined Daily Dose; DDD, Defined Daily Dose.

tive dose of aspirin was calculated by multiplying the number of pills dispensed by the prescribed dose, dividing by the days' supply, and converting the result into cDDDs based on the World Health Organization's defined daily dose (DDD) for aspirin. Patients were stratified into four subgroups according to quartiles of cDDDs. The daily intensity of aspirin dosage was also analyzed, comparing the risk of cancer among betel nut chewers receiving dosages greater than 1 DDD versus those receiving 1 DDD or less. Aspirin nonuse was defined as fewer than 28 cDDDs to exclude occasional use, while aspirin use was defined as at least 28 cDDDs [40, 41].

Sensitivity analysis

We conducted a sensitivity analysis to assess the impact of aspirin use on cancer risk across various subgroups, including age, sex, non-aspirin NSAID use, statin use, and metformin use.

Endpoints

The primary endpoint of this study was the incidence of cancers, confirmed through certification records in the Registry for Catastrophic Illness Patients [46]. Secondary endpoints included the risk of specific cancer types. To account for potential unmeasured confounding, we assessed the risk of nine negative control outcomes (NCOs) [47], including conditions such as dog bite (ICD-9: E906; ICD-10: W54.0), wrist/hand fracture (ICD-9: 814; ICD-10: S62), ingrown nail (ICD-9: 703; ICD-10: L60.0), ganglion (ICD-9: 727.4; ICD-10: M67.4), ankle sprain (ICD-9: 845, 905.7; ICD-10: S93.4), otitis externa (ICD-9: 380.0-380.2; ICD-10: H60), viral warts (ICD-9: 078.1; ICD-10: B07), atopic dermatitis (ICD-9: 690.12, 691.8, 692.3-692.9; ICD-10: L20, L25, L85.3), and conjuncti-

vitis (ICD-9: 706.8, 360.14, 370; ICD-10: H16). These conditions, unlikely to be influenced by aspirin use, could nonetheless be impacted by differences in healthcare utilization or other unmeasured confounders. Each outcome was evaluated both individually and as part of a composite measure.

Statistical analysis

In this study, we collected patient characteristics, including age, sex, comorbidities, medication use, and aspirin dosage. Participants were stratified into age groups in 10-year intervals, and baseline characteristics between aspirin users and non-users were compared using appropriate statistical tests. Categorical variables were analyzed with chi-squared tests, continuous variables with t-tests, and medians with Wilcoxon rank-sum tests. The cohort study baseline was defined as the start of follow-up.

To ensure adequate statistical power, we conducted a power calculation based on an anticipated effect size of 0.75 for the primary outcome (cancer risk), assuming a two-sided alpha of 0.05 and a sample size of 46,302. This analysis indicated that our study had over 90% power to detect statistically significant differences.

To examine the association between aspirin use and cancer risk, incidence rates (IRs), incidence rate ratios (IRRs), and adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) were calculated using Cox regression models, adjusting for confounders such as age, sex, income level, urbanization status, smoking, alcohol-related diseases, specific comorbidities, medication use, and CCI scores. The cumulative incidence of cancers was estimated via the Kaplan-Meier method and compared using log-rank tests. The daily intensity of aspirin dosage was evaluated by categorizing patients into two groups: those taking more than 1 DDD and those taking 1 DDD or less. This classification allowed for the analysis of the relationship between daily aspirin dosage intensity and cancer risk, with results presented as Kaplan-Meier cumulative incidence curves. Statistical analyses were conducted using SAS for Windows (version 9.4), with a two-sided *P*-value of less than 0.05 indicating statistical significance.

Results

Baseline characteristics

Table 1 presents the baseline characteristics of 46,302 betel nut chewers, equally divided between aspirin users and non-users (n = 23,151 each). The mean age was similar between groups (57.07 ± 11.65 years for users vs. 57.19 ± 12.57 years for non-users, ASMD = 0.010). The majority were male (74.6% non-users vs. 77.0% users, ASMD = 0.0553) and aged 50-69 years. Income, urbanization, smoking habits, and comorbidities were well-matched, minimizing confounding. Slight differences in medication use, such as higher statin use among aspirin users, were observed but remained within acceptable ASMD limits.

Cancer risk outcomes

As shown in Supplementary Table 1, cancer incidence was lower in aspirin users (11.1%) compared to non-users (15.2%) (P<0.0001). Aspirin use was associated with reduced risk across several cancers, including hepatocellular carcinoma (1.3% users vs. 1.8% non-users, P<0.0001) and lung cancer (1.6% users vs. 2.1% non-users, P<0.0001). The median follow-up was 8 years for both groups, providing robust data on long-term cancer risk. **Figure 1** shows that aspirin use significantly reduces cancer risk in betel nut chewers, as indicated by the lower cumulative incidence of cancer compared to non-users.

Cancer risk reduction by adjusted hazard ratios

Supplementary Table 2 demonstrates the impact of aspirin use on cancer incidence among betel nut chewers. Overall cancer incidence was significantly reduced with an adjusted HR of 0.69. Gastric cancer showed the greatest reduction among specific cancers, with an HR of 0.56, followed by gynecological cancers (HR 0.66) and breast cancer (HR 0.69). Colorectal cancer had an HR of 0.70, and HCC showed a reduction with an HR of 0.72. Esophageal and prostate cancers both had an HR of 0.73, while lung cancer showed an HR of 0.74. Other cancers had an HR of 0.76, head and neck cancer had an HR of 0.77, and pancreatic cancer showed the smallest reduction with an HR of 0.82.

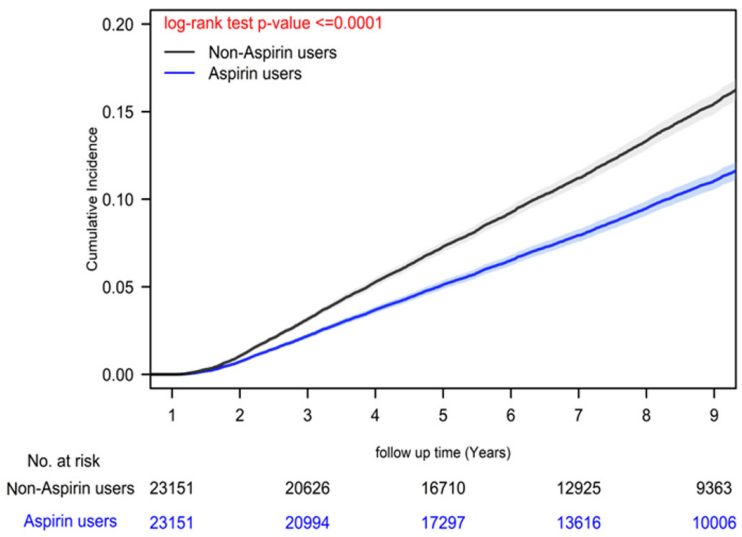


Figure 1. Kaplan-Meier cumulative incidence curves for cancer risk in betel nut chewers with and without aspirin use.

Cox proportional hazards regression model for cancer risk

The aHR for cancer incidence in the aspirin use group was 0.69 (95% CI, 0.66 to 0.73; P< 0.0001), indicating a 31% reduction in cancer risk compared to non-users (**Table 2**).

Further stratification by cDDD of aspirin revealed a dose-dependent relationship. The adjusted HR for the highest quartile of aspirin cDDD (Quartile 4) was 0.38 (95% CI, 0.34 to 0.41; P<0.0001), suggesting a 62% reduction in cancer risk. The HRs for the other quartiles were similarly reduced, with Quartile 3 at 0.82 (95% CI, 0.76 to 0.89; P<0.0001) and Quartile 2 at 0.88 (95% CI, 0.81 to 0.95; P = 0.0019). **Figure 2** demonstrates a clear dose-response relationship, with higher cumulative doses of aspirin associated with greater reductions in cancer risk. Supplementary Figure 1 also highlights that betel nut chewers with aspirin use above the mean cumulative dose have a significantly lower cancer risk compared to those below the mean.

Daily intensity of aspirin use also influenced cancer risk, with a greater than 1 defined daily dose (DDD) associated with a lower HR of 0.54 (95% CI, 0.47 to 0.61; P<0.0001), compared to an HR of 0.71 (95% CI, 0.67 to 0.75; P<0.0001) for those using 1 DDD or less. Supplementary Figure 2 shows that daily aspirin doses greater than 1 DDD are associated with lower cancer incidence than doses of 1 DDD or less.

The competing risk analysis, conducted using the Fine and Gray method, confirmed the robustness of these findings by accounting for the competing risk of death. The adjusted HR for aspirin use in this analysis remained consistent, reinforcing the protective effect of aspirin against cancer in this high-risk population. These results highlight the significant dose-dependent protective effect of aspirin on cancer risk among betel nut chewers, with both higher cumulative doses and daily intensities offering greater reductions in risk. Supplementary Figure 3 reinforces that higher cumulative aspirin doses correspond to lower cancer risk.

Incidence rates and incidence rate ratios for cancer risk

Aspirin use was associated with a lower cancer incidence rate, with 132.53 events per 100,000 person-years compared to 188.48 events per 100,000 person-years in non-users, yielding an IRR of 0.70 (95% CI, 0.67 to 0.74; P<0.0001) (**Table 3**).

Aspirin use significantly reduced cancer incidence among betel nut chewers, with an IRR of 0.70 (95% CI, 0.67 to 0.74; P<0.0001). The highest reduction was in the fourth quartile of cumulative aspirin dose (IRR 0.44, 95% CI, 0.40 to 0.48; P<0.0001). Daily doses above 1 DDD showed a greater reduction (IRR 0.58, 95% CI, 0.51 to 0.65; P<0.0001) compared to 1 DDD or less (IRR 0.72, 95% CI, 0.68 to 0.76; P<0.0001). These results highlight the significant impact of higher aspirin doses and daily intensity in reducing cancer risk.

Negative control outcomes

In our analysis of negative control outcomes, we evaluated the risk of nine events unrelated to aspirin use, including dog bites and wrist/hand fractures, to assess potential confounding. The adjusted hazard ratio (aHR) for all negative control outcomes was 1.01 (95% CI, 0.97

Table 2. Cox proportional hazards regression model for cancer risk in betel nut chewers with and without aspirin use following propensity score matching

Subgroup	Reference Group	Crude HR (95% CI)		*P*-value	Adjusted HR* (95% CI)		*P*-value	Adjusted HR# (95% CI)		*P*-value
Aspirin Use	Non-Aspirin Use Group	1	-	-	1	-	-	1	-	-
Aspirin Use Group		0.70	(0.66, 0.73)	<0.0001	0.69	(0.66, 0.73)	<0.0001	0.69	(0.66, 0.73)	<0.0001
Cumulative Defined Daily Dose (cDDD)	Non-Aspirin Use Group	1	-	-	1	-	-	1	-	-
Aspirin, cDDD, Quartile 1		0.89	(0.75, 0.94)	<0.0001	0.94	(0.87, 0.97)	0.0483	0.94	(0.87, 0.97)	0.0439
Aspirin, cDDD, Quartile 2		0.88	(0.81, 0.95)	0.0013	0.89	(0.82, 0.97)	0.0050	0.88	(0.81, 0.95)	0.0019
Aspirin, cDDD, Quartile 3		0.86	(0.79, 0.93)	0.0002	0.83	(0.76, 0.9)	<0.0001	0.82	(0.76, 0.89)	<0.0001
Aspirin, cDDD, Quartile 4		0.41	(0.37, 0.45)	<0.0001	0.37	(0.34, 0.41)	<0.0001	0.38	(0.34, 0.41)	<0.0001
Aspirin, cDDD (Overall)	Non-Aspirin Use Group	1	-	-	1	-	-	1	-	-
Aspirin, cDDD < Median		0.85	(0.79, 0.9)	<0.0001	0.91	(0.86, 0.97)	0.0052	0.90	(0.85, 0.96)	0.0020
Aspirin, cDDD ≥ Median		0.58	(0.55, 0.62)	<0.0001	0.55	(0.51, 0.58)	<0.0001	0.55	(0.51, 0.58)	<0.0001
Daily Intensity of Dosage	Non-Aspirin Use Group	1	-	-	1	-	-	1	-	-
Daily Dose ≤1 DDD		0.72	(0.68, 0.76)	<0.0001	0.71	(0.68, 0.75)	<0.0001	0.71	(0.67, 0.75)	<0.0001
Daily Dose >1 DDD		0.54	(0.47, 0.61)	<0.0001	0.55	(0.48, 0.62)	<0.0001	0.54	(0.47, 0.61)	<0.0001

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; cDDD, Cumulative Defined Daily Dose; DDD, Defined Daily Dose. *The time-varying Cox proportional hazards model, incorporating aspirin use as a dynamic variable, was adjusted for all covariates listed in **Table 1**. #The Fine and Gray method was employed to estimate the hazard of cancer risk while accounting for competing risks of death.

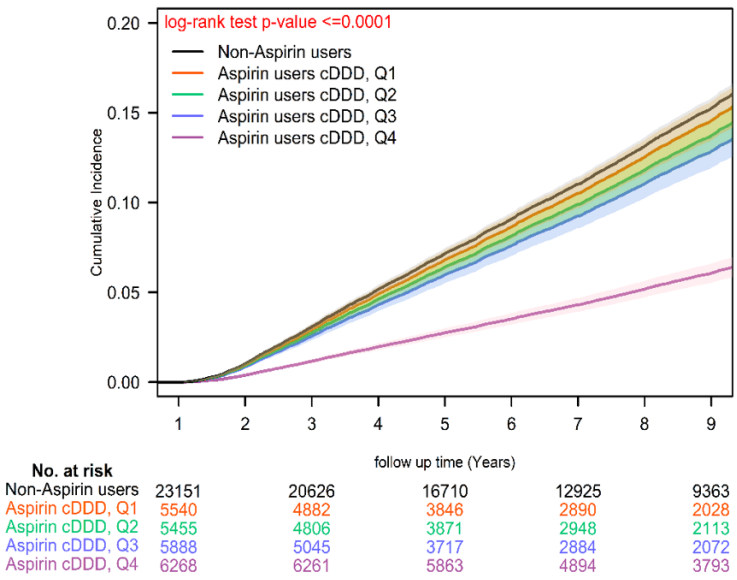


Figure 2. Kaplan-Meier cumulative incidence curves for cancer risk in betel nut chewers by different levels of aspirin cumulative defined daily dose.

to 1.05; P = 0.4908), indicating no significant association between aspirin use and these outcomes (Supplementary Table 3). Stratification by cumulative defined daily doses (cDDD) revealed that hazard ratios remained near 1.00 across all quartiles, with Quartile 4 showing a slightly elevated HR of 1.03 (95% CI, 0.98 to 1.07). These findings, also illustrated in Supplementary Figure 4, confirm that the association between aspirin use and cancer risk is unlikely to be influenced by unmeasured confounding factors related to healthcare utilization or other biases.

Sensitivity analysis

Supplementary Figure 5 demonstrates that aspirin use consistently reduced cancer risk across all subgroups. The adjusted hazard ratios (HRs) were similar across age groups: 0.68 (95% CI, 0.64 to 0.73) for ages 18-49, 0.70 (95% CI, 0.65 to 0.74) for 50-59, 0.71 (95% CI, 0.66 to 0.76) for 60-69, and 0.72 (95% CI, 0.66 to 0.79) for those 70 and older. The HRs were 0.69 (95% CI, 0.65 to 0.73) for males and 0.70 (95% CI, 0.64 to 0.76) for females. Among those using non-aspirin NSAIDs, the HR was 0.72 (95% CI, 0.68 to 0.76); for statin users, 0.68 (95% CI, 0.63 to 0.74); and for metformin users, 0.70 (95% CI, 0.65 to 0.75). These findings affirm the consistent protective effect of aspirin across different age groups, sexes, and concurrent medication use.

Discussion

Our study, utilizing a real-world population-based cohort design, provides novel insights into the association between aspirin use and cancer risk among betel nut chewers, a group at high risk for various malignancies [20]. This research is the first to report on the IRs, IRRs, and aHRs of cancers specifically within this population, highlighting several key findings (**Tables 2** and **3**). Aspirin use was associated with a 31% reduction in overall cancer risk (aHR 0.69, 95% CI, 0.66 to 0.73) compared to non-users, with a clear dose-response relationship. Higher cDDDs of aspirin corresponded to a greater reduction in cancer risk, with the highest quartile showing a 62% reduction in risk (aHR 0.38, 95% CI, 0.34 to 0.41) (**Table 2**). Daily aspirin intensity also played a significant role; individuals consuming more than 1 DDD had a substantially lower cancer risk (aHR 0.54, 95% CI, 0.47 to 0.61) compared to those taking 1 DDD or less (aHR 0.71, 95% CI, 0.67 to 0.75). Importantly, our use of competing risk analysis with the Fine and Gray method confirmed the robustness of these findings, reinforcing aspirin's protective effect against cancer even when accounting for competing mortality risks. Combined with rigorous sensitivity analyses and evaluation of negative control outcomes (Supplementary Table 3 and Supplementary Figure 5), our study underscores the potential of aspirin as a chemopreventive agent in high-risk populations like betel nut chewers, offering valuable evidence for targeted cancer prevention strategies in regions with high prevalence of betel nut chewing.

Aspirin reduces cancer risk through several key molecular pathways, as evidenced by preclinical and laboratory studies. It primarily inhibits COX-2, thereby reducing pro-inflammatory prostaglandin production, a crucial factor in tumor progression [15-17]. Aspirin's anti-platelet effects prevent circulating tumor cells from

Table 3. Incidence rates and incidence rate ratios for cancer risk

	Events	Person-years	IR (per 100,000 person-year)	IRR*	95% CI for IRR	*P-Values*
Aspirin use						
Nonuse (≤28 cDDD)	3,526	187,077.6	188.48	Ref.		
>28	2,570	193,913.4	132.53	0.70	(0.67, 0.74)	<0.0001
Aspirin use (cDDD)						
Nonuse (≤28 cDDD)	3,526	187,077.6	188.48	Ref.		
Aspirin, cDDD, Quartile 1	640	42,635.3	150.11	0.80	(0.73, 0.87)	<0.0001
Aspirin, cDDD, Quartile 2	705	43,107.3	163.55	0.87	(0.8, 0.94)	0.0006
Aspirin, cDDD, Quartile 3	697	44,082.0	158.11	0.84	(0.77, 0.91)	<0.0001
Aspirin, cDDD, Quartile 4	528	64,088.8	82.39	0.44	(0.4, 0.48)	<0.0001
Aspirin use (cDDD)						
Nonuse (≤28 cDDD)	3,526	187,077.6	188.48	Ref.		
Aspirin, cDDD < Median	1,345	85,742.6	156.86	0.83	(0.78, 0.89)	<0.0001
Aspirin, cDDD ≥ Median	1,225	108,170.8	113.25	0.60	(0.56, 0.64)	<0.0001
Aspirin use (Daily Intensity of Dosage)						
Nonuse (≤28 cDDD)	3,526	187,077.6	188.48	Ref.		
Daily Dose ≤1 DDD	2,319	170,754.9	135.81	0.72	(0.68, 0.76)	<0.0001
Daily Dose >1 DDD	251	23,158.6	108.38	0.58	(0.51, 0.65)	<0.0001

Abbreviations: IR, Incidence Rate; IRR, Incidence Rate Ratio; CI, Confidence Interval; cDDD, Cumulative Defined Daily Dose; DDD, Defined Daily Dose. *The IRR was calculated using Poisson regression models, adjusted for all covariates listed in **Table 1**.

evading the immune system and metastasizing [15, 18, 19]. Additionally, aspirin inhibits the NF-κB pathway, which is often overactive in cancers, thus decreasing the expression of genes involved in tumor survival and growth [8, 20, 26, 48]. It also interferes with the Wnt/β-catenin signaling pathway, reducing cell proliferation and contributing to its anti-cancer effects [20, 49, 50]. These mechanisms highlight aspirin's potential as a chemopreventive agent in high-risk populations [8, 15-20, 26, 48-50], like betel nut chewers. While these effects are supported by preclinical studies [8, 16-19, 26, 48-50], our study is the first to clinically demonstrate aspirin's protective effects against cancer in betel nut chewers, paving the way for further research to confirm these findings and explore the underlying mechanisms in more detail.

The dose-dependent effects observed with aspirin in reducing cancer risk can be explained by several biological mechanisms that are amplified with higher doses and more consistent use. The primary mechanism of aspirin's chemopreventive effect is the inhibition of COX enzymes, particularly COX-2, which is often upregulated in various cancers and is associated with promoting inflammation, cell proliferation, and angiogenesis while inhibiting apoptosis [15-17]. The extent of COX-2 inhibition, and therefore the reduction in prostaglandin production, is dose-dependent [15-17]. Higher doses of aspirin lead to greater COX-2 inhibition, resulting in a more substantial reduction in the inflammatory environment that fosters cancer development [15-17, 20]. Moreover, aspirin's ability to inhibit platelet aggregation also exhibits dose-dependent effects [15, 18, 19]. Platelets can protect circulating tumor cells from immune surveillance and facilitate their anchorage to endothelial cells, promoting metastasis [15, 18, 19]. Higher doses of aspirin more effectively inhibit platelet function, thereby reducing the risk of metastasis. This could explain why higher cDDDs of aspirin in our study were associated with greater reductions in cancer risk among betel nut chewers. Furthermore, aspirin's effects on molecular pathways involved in cancer, such as the NF-κB pathway and Wnt/β-catenin signaling, are also dose-dependent [8, 20, 26, 48-50]. These pathways play critical roles in cancer cell survival and proliferation. Higher doses of aspirin can more effectively inhibit these pathways, leading to increased cancer cell apoptosis and reduced tumor growth.

The use of competing risk analysis and negative control outcomes in our study was crucial for ensuring the validity and robustness of our findings. Competing risk analysis, particularly through the Fine and Gray method, allowed us to account for the possibility that deaths from causes other than cancer - such as cardiovascular diseases, which aspirin can influence - might alter the observed cancer incidence [42, 51]. This method provides a more accurate estimation of the relationship between aspirin use and cancer risk by considering these competing events (**Table 2**), which could otherwise lead to an overestimation of cancer risk if not properly accounted for [42, 51]. Additionally, the inclusion of negative control outcomes [47], which are not expected to be affected by aspirin use, served as a vital check against potential residual confounding or biases. By demonstrating that aspirin use did not influence these control outcomes (Supplementary Table 3), we bolstered the argument that the observed protective effects against cancer were likely genuine and not artifacts of unmeasured confounders or biases. This rigorous approach enhances the credibility of our study's conclusions regarding the role of aspirin in reducing cancer risk among betel nut chewers [42, 47, 51].

The findings from our study have significant implications for clinical practice, particularly in the prevention of cancer among high-risk populations such as betel nut chewers [3-7, 9-12]. Given the strong association between betel nut chewing and various cancers [3-7, 9-12], our research suggests that the use of low-dose aspirin could be a viable chemopreventive strategy for reducing cancer risk in this vulnerable group. Clinicians might consider incorporating aspirin into the preventive care regimen for betel nut chewers, especially those with additional risk factors such as smoking or a history of chronic inflammation. This approach could lead to a substantial reduction in cancer incidence, particularly for cancers like oral, esophageal, and gastrointestinal malignancies, which are prevalent among betel nut users (Supplementary Tables 1 and 2). From a public health perspective, our study highlights the urgent need to address the widespread use of betel nut, which remains a significant cancer risk factor in many regions, including Taiwan and other parts of Asia. Public health initiatives should focus on both reducing betel nut consumption and promoting the use of preventive measures like aspirin among those who continue to chew betel nuts. Moreover, the findings open avenues for further research into aspirin's protective effects, potentially influencing public health policies aimed at reducing cancer burden in high-risk populations. Future efforts should include larger clinical trials to confirm the effectiveness of aspirin in this context and to develop comprehensive cancer prevention strategies that incorporate lifestyle modifications, screening, and pharmacologic interventions.

Our study provides important insights into the dose-dependent effects of aspirin on cancer risk reduction among the largest betel nut chewers population, including an analysis of the optimal daily dose for maximizing protective benefits. However, there are still several limitations to consider. While we identified an optimal daily aspirin dosage of approximately 0.97 DDD that is associated with the greatest reduction in cancer risk (Supplementary Figure 6), the long-term safety of chronic aspirin use at this and higher doses remains a concern, particularly given the potential risks of gastrointestinal bleeding and hemorrhagic stroke. Although our dose-response analysis helps to mitigate concerns regarding dose optimization, the observational nature of our study cannot entirely eliminate the possibility of residual confounding, which might influence the observed associations. Additionally, our findings are based on data from the Taiwan NHIRD, which may not capture all relevant lifestyle factors or genetic predispositions that could impact cancer risk or aspirin's effectiveness. Finally, while our study is pioneering in its focus on betel nut chewers, further clinical trials are needed to confirm our findings and establish evidence-based guidelines for the use of aspirin in this high-risk population.

Conclusion

Our study demonstrates that aspirin use is associated with a significant reduction in cancer risk among betel nut chewers, a high-risk population for various malignancies. We identified a dose-response relationship, with higher cumulative doses of aspirin providing greater protective effects, reducing the hazard ratio for cancer. These findings suggest that low-dose

aspirin could be an effective chemopreventive strategy for this vulnerable group.

Acknowledgements

Lo-Hsu Medical Foundation, LotungPoh-Ai Hospital supports Szu-Yuan Wu's work (Funding Number: 110908, 10909, 11001, 11002, 11003, 11303, 11304 and 11006).

Disclosure of conflict of interest

None.

Abbreviations

aHR, Adjusted Hazard Ratio; CI, Confidence Interval; cDDD, Cumulative Defined Daily Dose; IQR, Interquartile Range; SD, Standard Deviation; N, Number; SMD, Standardized Mean Difference; HR, Hazard Ratio; IR, Incidence Rate; IRR, Incidence Rate Ratio; PSM, Propensity Score Matching; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; CCI, Charlson Comorbidity Index; DDD, Defined Daily Dose; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; NCOs, Negative Control Outcomes; ASMD, Absolute Standardized Mean Difference; ATC, Anatomical Therapeutic Chemical system.

Address correspondence to: Dr. Szu-Yuan Wu, Big Data Center, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, No. 83, Nanchang Street, Luodong Township, Yilan 265, Taiwan. E-mail: szuyuanwu53-99@gmail.com; Dr. Ching-Wen Chiang, Department of Otorhinolaryngology, Lo-Hsu Medical Foundation, Lotung Poh-Ai Hospital, Yilan 265, Taiwan. E-mail: acuteshin@gmail.com

References

[1] Huang CC, Chen WM, Shia BC, Chen M and Wu SY. The effect of statin medication on the incidence of oral squamous cell carcinoma among betel-nut chewers. Head Neck 2023; 45: 1455-1467.

[2] Lin CL, Chen WM, Shia BC and Wu SY. Statin use and its association with decreased risk of esophageal squamous cell carcinoma in betel nut chewers. Thorac Cancer 2023; 14: 2241-2250.

[3] Tsai JF, Jeng JE, Chuang LY, Ho MS, Ko YC, Lin ZY, Hsieh MY, Chen SC, Chuang WL, Wang LY, Yu ML and Dai CY. Habitual betel quid chewing and risk for hepatocellular carcinoma complicating cirrhosis. Medicine (Baltimore) 2004; 83: 176-187.

[4] Wu MT, Lee YC, Chen CJ, Yang PW, Lee CJ, Wu DC, Hsu HK, Ho CK, Kao EL and Lee JM. Risk of betel chewing for oesophageal cancer in Taiwan. Br J Cancer 2001; 85: 658-660.

[5] Wu MT, Chen MC and Wu DC. Influences of lifestyle habits and p53 codon 72 and p21 codon 31 polymorphisms on gastric cancer risk in Taiwan. Cancer Lett 2004; 205: 61-68.

[6] Wen CP, Tsai MK, Chung WS, Hsu HL, Chang YC, Chan HT, Chiang PH, Cheng TY and Tsai SP. Cancer risks from betel quid chewing beyond oral cancer: a multiple-site carcinogen when acting with smoking. Cancer Causes Control 2010; 21: 1427-1435.

[7] Guha N, Warnakulasuriya S, Vlaanderen J and Straif K. Betel quid chewing and the risk of oral and oropharyngeal cancers: a meta-analysis with implications for cancer control. Int J Cancer 2014; 135: 1433-1443.

[8] Chen J and Stark LA. Aspirin prevention of colorectal cancer: focus on NF-kappaB signalling and the nucleolus. Biomedicines 2017; 5: 43.

[9] Sharma DC. Betel quid and areca nut are carcinogenic without tobacco. Lancet Oncol 2003; 4: 587.

[10] Akhtar S, Sheikh AA and Qureshi HU. Chewing areca nut, betel quid, oral snuff, cigarette smoking and the risk of oesophageal squamous-cell carcinoma in South Asians: a multicentre case-control study. Eur J Cancer 2012; 48: 655-661.

[11] Hung KF, Lai KC, Liu TY, Liu CJ, Lee TC and Lo JF. Asb6 upregulation by Areca nut extracts is associated with betel quid-induced oral carcinogenesis. Oral Oncol 2009; 45: 543-548.

[12] Jeng JH, Chang MC and Hahn LJ. Role of areca nut in betel quid-associated chemical carcinogenesis: current awareness and future perspectives. Oral Oncol 2001; 37: 477-492.

[13] Wang TH, Hsia SM, Shih YH and Shieh TM. Association of smoking, alcohol use, and betel quid chewing with epigenetic aberrations in cancers. Int J Mol Sci 2017; 18: 1210.

[14] Su YY, Chien CY, Luo SD, Huang TL, Lin WC, Fang FM, Chiu TJ, Chen YH, Lai CC, Hsu CM and Li SH. Betel nut chewing history is an independent prognosticator for smoking patients with locally advanced stage IV head and neck squamous cell carcinoma receiving induction chemotherapy with docetaxel, cisplatin, and fluorouracil. World J Surg Oncol 2016; 14: 86.

[15] Lichtenberger LM. Using aspirin to prevent and treat cancer. Inflammopharmacology 2024; 32: 903-908.

[16] Zhao H, Wu L, Yan G, Chen Y, Zhou M, Wu Y and Li Y. Inflammation and tumor progression: signaling pathways and targeted intervention. Signal Transduct Target Ther 2021; 6: 263.
[17] Finetti F, Travelli C, Ercoli J, Colombo G, Buoso E and Trabalzini L. Prostaglandin E2 and cancer: insight into tumor progression and immunity. Biology (Basel) 2020; 9: 434.
[18] Tao DL, Tassi Yunga S, Williams CD and McCarty OJT. Aspirin and antiplatelet treatments in cancer. Blood 2021; 137: 3201-3211.
[19] Xu XR, Yousef GM and Ni H. Cancer and platelet crosstalk: opportunities and challenges for aspirin and other antiplatelet agents. Blood 2018; 131: 1777-1789.
[20] Wang L, Zhang R, Yu L, Xiao J, Zhou X, Li X, Song P and Li X. Aspirin use and common cancer risk: a meta-analysis of cohort studies and randomized controlled trials. Front Oncol 2021; 11: 690219.
[21] Qiao Y, Yang T, Gan Y, Li W, Wang C, Gong Y and Lu Z. Associations between aspirin use and the risk of cancers: a meta-analysis of observational studies. BMC Cancer 2018; 18: 288.
[22] Garcia-Albeniz X and Chan AT. Aspirin for the prevention of colorectal cancer. Best Pract Res Clin Gastroenterol 2011; 25: 461-472.
[23] Garcia Rodriguez LA, Soriano-Gabarro M, Vora P and Cea Soriano L. Low-dose aspirin and risk of gastric and oesophageal cancer: a population-based study in the United Kingdom using The Health Improvement Network. Int J Cancer 2020; 147: 2394-2404.
[24] Bosetti C, Santucci C, Gallus S, Martinetti M and La Vecchia C. Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019. Ann Oncol 2020; 31: 558-568.
[25] Qiao Y, Yang T, Gan Y, Li W, Wang C, Gong Y and Lu Z. Associations between aspirin use and the risk of cancers: a meta-analysis of observational studies. BMC Cancer 2018; 18: 288.
[26] Pavitra E, Kancharla J, Gupta VK, Prasad K, Sung JY, Kim J, Tej MB, Choi R, Lee JH, Han YK, Raju GSR, Bhaskar L and Huh YS. The role of NF-kappaB in breast cancer initiation, growth, metastasis, and resistance to chemotherapy. Biomed Pharmacother 2023; 163: 114822.
[27] Li YC, Cheng AJ, Lee LY, Huang YC and Chang JT. Multifaceted mechanisms of areca nuts in oral carcinogenesis: the molecular pathology from precancerous condition to malignant transformation. J Cancer 2019; 10: 4054-4062.
[28] Senevirathna K, Pradeep R, Jayasinghe YA, Jayawickrama SM, Illeperuma R, Warnakulasuriya S and Jayasinghe RD. Carcinogenic effects of areca nut and its metabolites: a review of the experimental evidence. Clin Pract 2023; 13: 326-346.
[29] Chen PH, Mahmood Q, Mariottini GL, Chiang TA and Lee KW. Adverse health effects of betel quid and the risk of oral and pharyngeal cancers. Biomed Res Int 2017; 2017: 3904098.
[30] Wen CP, Tsai SP and Chung WS. A 10-year experience with universal health insurance in Taiwan: measuring changes in health and health disparity. Ann Intern Med 2008; 148: 258-267.
[31] Sun M, Chen WM, Wu SY and Zhang J. Dementia risk after major elective surgery based on the route of anaesthesia: a propensity score-matched population-based cohort study. EClinicalMedicine 2022; 55: 101727.
[32] Wu SY, Chen WM, Chen YC, Chiang MF, Lee MC and Soong RS. Effects of H1-Antihistamines on hepatocellular carcinoma risk in patients with type 2 diabetes mellitus. Diabetes Metab 2022; 49: 101393.
[33] Sun MY, Chang CL, Lu CY, Wu SY and Zhang JQ. Sarcopenia as an independent risk factor for specific cancers: a propensity score-matched asian population-based cohort study. Nutrients 2022; 14: 1910.
[34] Sun M, Lin JA, Chang CL, Wu SY and Zhang J. Association between long-term opioid use and cancer risk in patients with chronic pain: a propensity score-matched cohort study. Br J Anaesth 2022; 129: 84-91.
[35] Sun M, Chang CL, Lu CY, Zhang J and Wu SY. Effect of opioids on cancer survival in patients with chronic pain: a propensity score-matched population-based cohort study. Br J Anaesth 2022; 128: 708-717.
[36] Lin KC, Chen TM, Yuan KS, Wu ATH and Wu SY. Assessment of predictive scoring system for 90-day mortality among patients with locally advanced head and neck squamous cell carcinoma who have completed concurrent chemoradiotherapy. JAMA Netw Open 2020; 3: e1920671.
[37] Wu SY, Chang CL, Chen CI and Huang CC. Comparison of acute and chronic surgical complications following robot-assisted, laparoscopic, and traditional open radical prostatectomy among men in Taiwan. JAMA Netw Open 2021; 4: e2120156.
[38] Zhang J, Lu CY, Chen HM and Wu SY. Neoadjuvant chemotherapy or endocrine therapy for invasive ductal carcinoma of the breast with high hormone receptor positivity and human epidermal growth factor receptor 2 negativity. JAMA Netw Open 2021; 4: e211785.
[39] Huang CC, Lin CN, Chung CH, Hwang JS, Tsai ST and Wang JD. Cost-effectiveness analysis of the oral cancer screening program in Taiwan. Oral Oncol 2019; 89: 59-65.
[40] Yang YH, Chen WC, Tsan YT, Chen MJ, Shih WT, Tsai YH and Chen PC. Statin use and the risk of

cirrhosis development in patients with hepatitis C virus infection. J Hepatol 2015; 63: 1111-1117.
[41] Huang YW, Lee CL, Yang SS, Fu SC, Chen YY, Wang TC, Hu JT and Chen DS. Statins reduce the risk of cirrhosis and its decompensation in chronic hepatitis b patients: a nationwide cohort study. Am J Gastroenterol 2016; 111: 976-985.
[42] Berry SD, Ngo L, Samelson EJ and Kiel DP. Competing risk of death: an important consideration in studies of older adults. J Am Geriatr Soc 2010; 58: 783-787.
[43] Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011; 10: 150-161.
[44] Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol 2005; 19: 117-125.
[45] Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME and Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. Ann Transl Med 2018; 6: 121.
[46] Shao YJ, Chan TS, Tsai K and Wu SY. Association between proton pump inhibitors and the risk of hepatocellular carcinoma. Aliment Pharmacol Ther 2018; 48: 460-468.
[47] Lipsitch M, Tchetgen Tchetgen E and Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology 2010; 21: 383-388.
[48] Zhang X, Feng H, Li Z, Guo J and Li M. Aspirin is involved in the cell cycle arrest, apoptosis, cell migration, and invasion of oral squamous cell carcinoma. Int J Mol Sci 2018; 19: 2029.
[49] Pai SG, Carneiro BA, Mota JM, Costa R, Leite CA, Barroso-Sousa R, Kaplan JB, Chae YK and Giles FJ. Wnt/beta-catenin pathway: modulating anticancer immune response. J Hematol Oncol 2017; 10: 101.
[50] Gala MK and Chan AT. Molecular pathways: aspirin and Wnt signaling-a molecularly targeted approach to cancer prevention and treatment. Clin Cancer Res 2015; 21: 1543-1548.
[51] Lau B, Cole SR and Gange SJ. Competing risk regression models for epidemiologic data. Am J Epidemiol 2009; 170: 244-256.

Supplementary Table 1. Cancer risk outcomes among betel nut chewers with and without aspirin use after propensity score matching

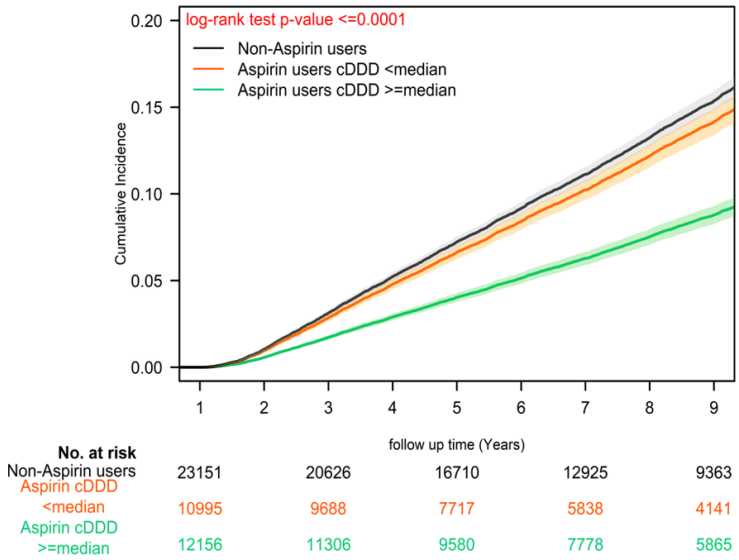
	Non-Aspirin use group N = 23,151		Aspirin use group N = 23,151		*P* Values
	N	%	N	%	
All Cancers	3,526	15.2%	2,570	11.1%	<0.0001
Cancer Type (first occurrence only)					
Pancreatic Cancer	61	0.3%	41	0.2%	0.0475
Hepatocellular Carcinoma (HCC)	416	1.8%	298	1.3%	<0.0001
Esophageal Cancer	59	0.3%	33	0.1%	0.0024
Head and Neck Cancer	342	1.5%	273	1.2%	0.0049
Gastric Cancer	163	0.7%	86	0.4%	<0.0001
Lung Cancer	481	2.1%	358	1.6%	<0.0001
Colorectal Cancer	672	2.9%	459	2.0%	<0.0001
Gynecological Cancer	19	0.1%	7	0.0%	0.0186
Breast Cancer	114	0.5%	76	0.3%	0.0057
Prostate Cancer	378	1.6%	281	1.2%	0.0001
Other Cancers	855	3.7%	676	2.9%	<0.0001
Follow up Years (mean ± SD)	8.39 ± 4.05		8.39 ± 4.04		0.9914
Follow up Years Median (IQR)	8.00 (5.00, 12.00)		8.00 (5.00, 12.00)		0.9755

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range.

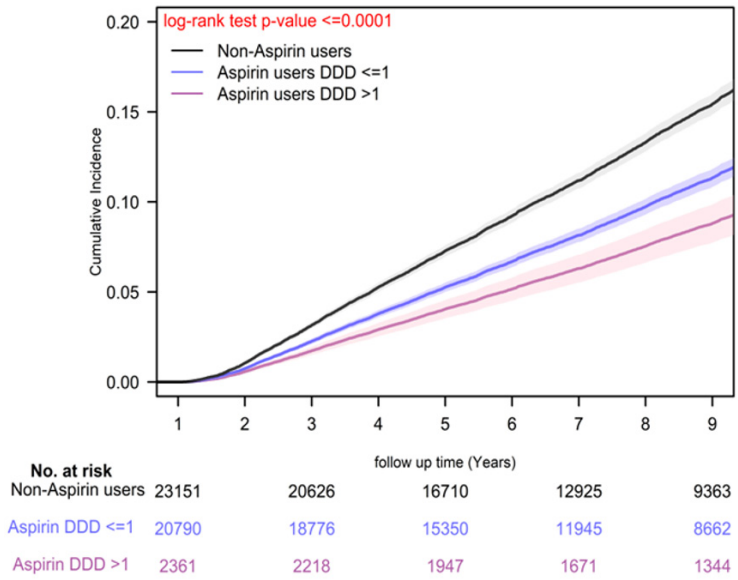
Supplementary Table 2. Cox proportional hazards model for cancer risk in betel nut chewers with and without aspirin use, stratified by cancer type

Cancer types (first occurrence only)	Crude HR (95% CI)		*P*-value	Adjusted HR* (95% CI)		*P*-value	Adjusted HR# (95% CI)		*P*-value
Aspirin Use (Ref. Non-Aspirin Use Group)									
All Cancers	0.70	(0.66, 0.73)	<0.0001	0.69	(0.66, 0.73)	<0.0001	0.69	(0.66, 0.73)	<0.0001
Pancreatic Cancer	0.80	(0.57, 1.12)	0.2020	0.83	(0.59, 1.16)	0.2718	0.82	(0.59, 1.15)	0.2587
Hepatocellular Carcinoma	0.71	(0.62, 0.81)	<0.0001	0.72	(0.63, 0.83)	<0.0001	0.72	(0.63, 0.83)	<0.0001
Esophageal Cancer	0.73	(0.52, 0.92)	0.0059	0.73	(0.52, 0.93)	0.0001	0.73	(0.52, 0.93)	0.0007
Head and Neck Cancer	0.77	(0.67, 0.89)	0.0006	0.77	(0.66, 0.89)	0.0005	0.77	(0.66, 0.89)	0.0005
Gastric Cancer	0.56	(0.44, 0.7)	<0.0001	0.56	(0.44, 0.71)	<0.0001	0.56	(0.44, 0.71)	<0.0001
Lung Cancer	0.75	(0.66, 0.84)	<0.0001	0.76	(0.67, 0.85)	<0.0001	0.74	(0.65, 0.84)	<0.0001
Colorectal Cancer	0.71	(0.63, 0.79)	<0.0001	0.71	(0.64, 0.8)	<0.0001	0.70	(0.62, 0.79)	<0.0001
Gynecological Cancer	0.58	(0.28, 1.22)	0.1513	0.64	(0.3, 1.36)	0.2420	0.66	(0.32, 1.38)	0.2731
Breast Cancer	0.66	(0.5, 0.87)	0.0031	0.70	(0.53, 0.92)	0.0108	0.69	(0.53, 0.91)	0.0084
Prostate Cancer	0.73	(0.63, 0.84)	<0.0001	0.75	(0.65, 0.86)	<0.0001	0.73	(0.63, 0.84)	<0.0001
Other Cancers	0.76	(0.7, 0.84)	<0.0001	0.77	(0.7, 0.84)	<0.0001	0.76	(0.69, 0.84)	<0.0001

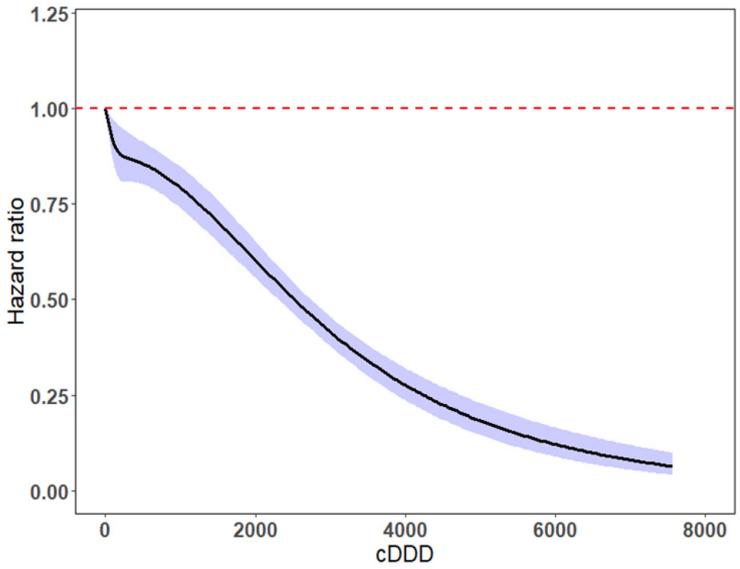
Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; cDDD, Cumulative Defined Daily Dose; DDD, Defined Daily Dose. *The time-varying Cox proportional hazards model, incorporating aspirin use as a dynamic variable, was adjusted for all covariates listed in **Table 1**. #The Fine and Gray method was employed to estimate the hazard of cancer risk while accounting for competing risks of death.



Supplementary Figure 1. Kaplan-Meier cumulative incidence curves for cancer risk in betel nut chewers by aspirin use at or above, and below the mean cumulative defined daily dose.



Supplementary Figure 2. Kaplan-Meier cumulative incidence curves for cancer risk in betel nut chewers by daily aspirin use intensity: greater than 1 defined daily dose vs. equal to or less than 1 defined daily dose.

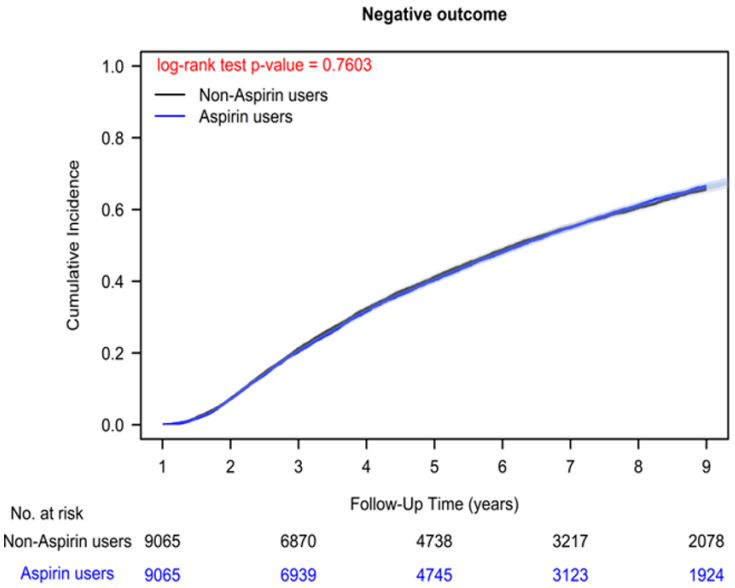


Supplementary Figure 3. Relationship between cumulative defined daily dose of aspirin use and cancer risk.

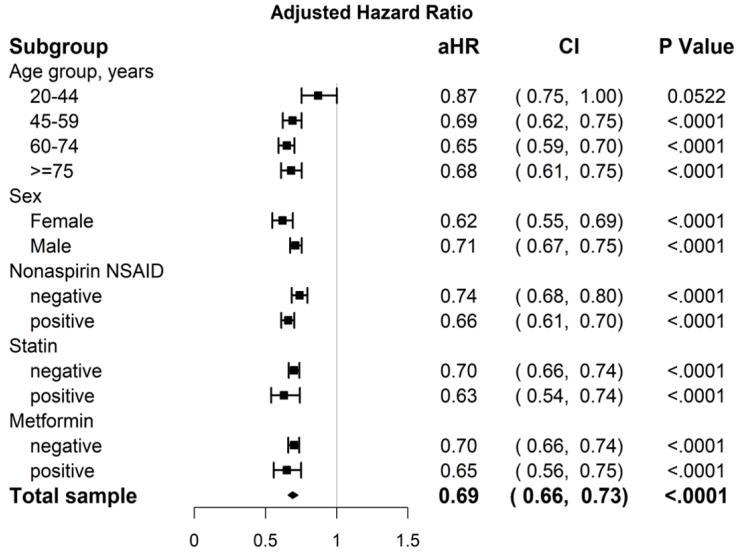
Supplementary Table 3. Cox proportional hazards model for negative outcomes in betel nut chewers with and without aspirin use

Subgroup	Reference Group	Crude HR (95% CI)		*P*-value	Adjusted HR* (95% CI)		*P*-value	Adjusted HR# (95% CI)		*P*-value
Aspirin Use	Non-Aspirin Use Group	1	-	-	1	-	-	1	-	-
Aspirin Use Group		1.01	(0.97, 1.04)	0.7607	1.02	(0.98, 1.06)	0.2812	1.01	(0.98, 1.05)	0.4908
Cumulative Defined Daily Dose (cDDD)	Non-Aspirin Use Group	1	-	-	1	-	-	1	-	-
Aspirin, cDDD, Quartile 1		1.01	(0.97, 1.06)	0.5366	1.00	(0.95, 1.04)	0.8422	1.01	(0.97, 1.06)	0.6127
Aspirin, cDDD, Quartile 2		1.00	(0.96, 1.04)	0.9179	1.00	(0.96, 1.04)	0.9412	1.00	(0.96, 1.05)	0.8663
Aspirin, cDDD, Quartile 3		1.02	(0.97, 1.06)	0.4377	1.00	(0.95, 1.04)	0.9139	1.00	(0.96, 1.05)	0.9984
Aspirin, cDDD, Quartile 4		1.01	(0.96, 1.05)	0.7438	1.01	(0.97, 1.05)	0.7028	1.03	(0.98, 1.07)	0.2682

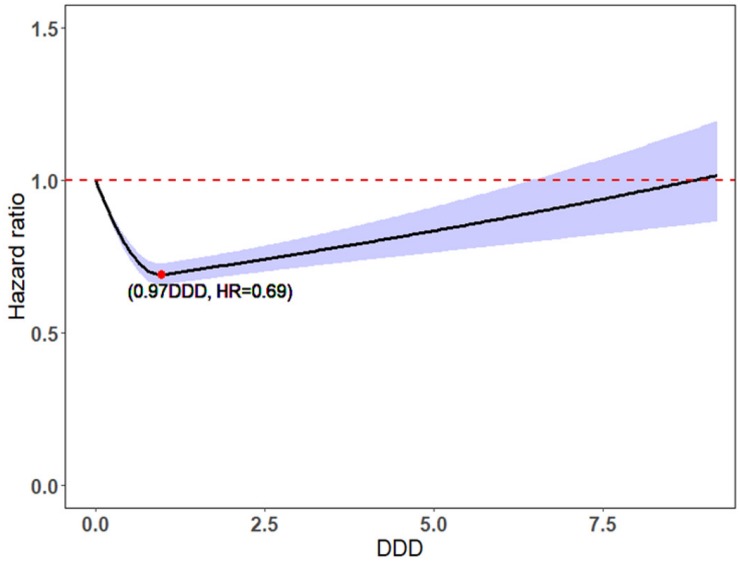
Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; cDDD, Cumulative Defined Daily Dose; DDD, Defined Daily Dose. *The time-varying Cox proportional hazards model, incorporating aspirin use as a dynamic variable, was adjusted for all covariates listed in **Table 1**. #The Fine and Gray method was employed to estimate the hazard of cancer risk while accounting for competing risks of death.



Supplementary Figure 4. Kaplan-Meier cumulative incidence curves for negative outcomes in betel nut chewers with and without aspirin use.



Supplementary Figure 5. Sensitivity analysis for cancer risk in betel nut chewers with and without aspirin use, stratified by age, sex, and medication use subgroups.



Supplementary Figure 6. Dose-response curve of daily defined dose of aspirin and hazard ratio for cancer risk among betel nut chewers.