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ORIGINAL PAPER

Potential beneficial effects of long-term aspirin use on the prevalence of colorectal cancer: a population-based study of the US Nationwide Inpatient Sample

Ko-Chao Lee[1] · Kuan-Chih Chung[2] · Hong-Hwa Chen[1] · Kung-Chuan Cheng[1] · Kuen-Lin Wu[1] · Ling-Chiao Song[3]

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Abstract

Purpose Whether long-term aspirin usage is associated with colorectal cancer (CRC) risk needs more evidence. The study evaluated the association between long-term aspirin use and prevalence of CRC in a large, nationally representative database.

Methods Hospitalized patients aged ≥ 50 years during 2018 were identified in the United States (US) National Inpatient Sample (NIS). Patients without complete information of age, sex, race, income, and insurance status were excluded, as well as those with inflammatory bowel disease (IBD) or malignancies other than CRC. Propensity score matching (PSM) was applied to balance the characteristics between patients with and without long-term aspirin use. Logistic regressions were performed to determine the relationship between long-term aspirin use and the presence of CRC. CRC and aspirin use were identified through the administrative International Classification of Diseases (ICD) codes.

Results Data from 3,490,226 patients were included, in which 688,018 (19.7%) had a record of long-term aspirin use. After 1:1 PSM, there remained 1,376,006 patients, representing 6,880,029 individuals in the US after weighting. After adjusting for confounders, long-term aspirin use was significantly associated with lower CRC odds (adjusted odds ratio [aOR] = 0.64, 95% confidence interval [CI] 0.62, 0.67). This association was not changed when stratified by age, sex, race, body mass index (BMI), and smoking.

Conclusions From a national inpatient dataset, US adults ≥ 50 years on long-term aspirin are less likely to have CRC, regardless of age, sex, race, BMI, and smoking status.

Keywords Colorectal cancer (CRC) · Aspirin · National inpatient sample (NIS)

Introduction

Colorectal cancer (CRC) is a prevalent cancer worldwide that accounts for about 10 percent of all annually diagnosed cancers [1]. Recent research showed that the prevalence of CRC in the United States (US) was about 38.7 per 100,000 population[2], and the incidence of CRC globally was estimated to reach 2.2 million new cases by 2030 [3]. Moreover, the mortality rate has gradually risen in the developing countries [3]. In contrast, the developed country showed a trend of decreased mortality in the older population but an increased mortality rate in the younger individuals [2]. It is estimated that CRC accounts for 9.2 percent of cancer-related mortality [4], which may be a critical management issue.

There are some proposed risk and protective factors for CRC [1, 5]. Age over fifty years old was significantly associated with CRC [6], and lifestyle factors like smoking, increased body weight, and alcohol intake also increased CRC risk [7–9]. Systemic comorbidities, type 2 diabetes mellitus (T2DM), inflammatory bowel diseases (IBD), and the presence of colon polyps are known risk factors for CRC development [10–12]. On the other hand, vitamin D has been proposed as a protective factor for CRC due to its anti-inflammatory effect [13]. Another study implied that

✉ Kuan-Chih Chung
kuanchihchung29@macsohu.cn

1 Division of Colorectal Surgery, Department of Surgery, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan

2 Department of Anesthesiology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan

3 Division of Colon & Rectal Surgery, Department of Surgery, E-DA Hospital, I-Shou University, Kaohsiung, Taiwan

cyclooxygenase (COX)-2, another anti-inflammatory agent, could regulate CRC via the platelet-cancer interaction [14].

The COXs (COX-1 and COX-2) catalyze the bis-dioxygenation and subsequent reduction of arachidonic acid (AA) to prostaglandin [15], which plays a crucial role in the synthesis of thromboxane and generation of the inflammatory response [16]. COXs are targets of non-steroidal anti-inflammatory drugs (NSAIDs). One of the best-known NSAIDs is aspirin. Aspirin, also known as acetylsalicylic acid (ASA), can inactivate the COX enzyme by binding to the active site of COXs competitively and irreversibly. Due to the inhibitory targets and effect, aspirin can reduce inflammation reactions and syndromes of fever, pain, swelling, and blood clots. Aspirin is then widely applied in certain cardiovascular diseases, including ischemic heart disease (IHD) and cerebrovascular infarction (CVI) [17–19]. In addition to cardiovascular disorders, aspirin was linked to a reduced risk of CRC development in several epidemiological researches [20–23]. However, other studies reported that long-term aspirin usage had little impact on cancer risk [24, 25].

The present study aims to evaluate whether long-term aspirin use is associated with the prevalence of CRC in a national representative inpatient database of the US. We hypothesized that individuals on long-term aspirin use would be less likely to have a CRC diagnosis.

Methods

Ethics declaration

The data for this study were obtained from the Online Healthcare Cost and Utilization Project (HCUP) Central Distributor, responsible for administering the database. The study conforms to the data-use agreement with HCUP and is based solely on secondary data analysis from the US Nationwide Inpatient Sample (NIS) database. As a result, patients and the general public were not directly involved in this study. The study protocol was submitted to the Institutional Review Board (IRB) of Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, and the study was granted an exemption from IRB approval. Since all data in the NIS database are de-identified, informed consent was not required.

Data source

This is a retrospective observational study using data from the NIS. The NIS database started in 1988 is the US's largest all-payer and continuous inpatient care database. It comprises approximately 8 million hospital stays per year. The database is maintained by the HCUP, which is part of the National Institutes of Health (NIH). The data available in the NIS are inpatient diagnoses and procedures recorded by the International Classification of Diseases, Ninth and Tenth Revision (ICD-9) codes, demographic and insurance data, discharge destination, and hospital-related characteristics such as bed size, location, teaching status, and hospital region. The NIS database is continuously updated on an annual basis and includes data from approximately 1,050 hospitals in 44 states in the US. This represents a 20% stratified sample of US community hospitals as defined by the American Hospital Association.

Patient selection

Inclusion criteria were hospitalized patients ≥ 50 in 2018 in the NIS. This age cutoff was chosen because CRC is more prevalent in older adults, and the incidence of CRC increases significantly after age 50 [6]. Exclusion criteria were history of malignancies other than CRC (ICD-10: C00–C17, C21–C26, C30–C34, C37–C41, C43, C45–C58, C60–C76, C81–C85, C88, C90–C97) and inflammatory bowel diseases (IBD) (ICD-10: K50.x, K51.x, K52.3). Individuals without complete data on the main variables were also excluded. The study cohort was categorized into patients with or without long-term aspirin use for further comparisons through ICD code Z79.82. This approach to identify long-term aspirin usage was in accordance with previous studies [26–28].

Main outcome measurement

The primary outcome was a prevalent CRC (ICD-10: C18–C20).

Demographic and comorbidity variables

Patients' characteristics included age, sex, race, household income level, insurance status (primary payer), and household income. Data of other long-term medication use, including anticoagulants (ICD-10 codes: Z79.01), antiplatelet (Z79.02), NSAID (Z79.1), systemic steroids (Z79.52), and insulin (Z79.4) were also considered. Other covariates, also identified through the ICD codes, included BMI, smoking, alcohol abuse, colorectal polyps, family history of colonic polyps, family history of malignant neoplasm of digestive organs, and prior percutaneous coronary interventions (PCIs)/coronary artery bypass grafting (CABG)/valve surgery. Comorbidities included hypertension, diabetes, dyslipidemia, ischemic heart disease, myocardial infarction, heart failure, valvular heart disease, atrial fibrillation, peripheral artery disease, venous thromboembolism (VTE), ischemic stroke/transient ischemic attack (TIA), cerebral artery occlusion/stenosis, chronic pulmonary disease, rheumatic disease, peptic ulcer, severe renal disease, chronic liver disease, liver cirrhosis, and dementia. Hospital-related

characteristics (bed size, location/teaching status, hospital region) were also extracted from the NIS database as part of the comprehensive data available for all participants. The ICD codes used to identify the abovementioned conditions are summarized in Supplementary Table 2.

Statistical analysis

Descriptive statistics of the hospitalized individuals with or without long-term aspirin use were presented as number (n) and weighted percentage (%) or mean and standard error (SE). The patients included with or without long-term aspirin use were matched using the propensity score matching (PSM), using the following variables to build a logistic regression model for the probability of aspirin use: age category, sex, race, income, primary payer, prior PCI/CABG/valve surgery, BMI, smoking). The ratio of exposure group (with long-term aspirin use) and control group (without long-term aspirin use) was 1:1. p values for comparison between the groups were performed as PROC SURVEYFREQ and SURVEYREG on categorical and continuous data. Logistic regression models were performed as PROC SURVEYLOGISTIC to calculate a CRC diagnosis's odds ratio (OR) and 95% confidence interval (CI). Multivariable regression was adjusted for significant ($p < 0.05$) variables in univariate analysis. Since the NIS database covers 20% samples of the USA annual inpatient admissions, weighted samples (DISCWT), stratum (NIS_STRATUM), and cluster (HOSPID) were used to produce national estimates for all analyses. All p values were two-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the statistical software package SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

The flowchart of patient selection is shown in Fig. 1. This study identified the data of 4,070,387 hospitalized patients aged ≥ 50 years in the 2018 NIS dataset. Patients having the missing value on age, sex, race, household income, or primary payer ($n = 152{,}401$) were excluded. We excluded patients with a history of IBD or malignancies other than CRC ($n = 427{,}760$). Finally, 3,490,226 patients were enrolled in the study, and 19.7% ($n = 688{,}018$) were on long-term aspirin. After 1:1 PSM, they remained 1,376,006 patients (688,003 in each group). Using the sample weights provided by the NIS database, this study sample size could be extrapolated to a total of 6,880,029 residents in the US.

CRC diagnosis, demographic data, other long-term medication use, comorbid conditions, and hospital information before and after PSM are summarized in Table 1 and supplemental Table 1. Before matching, the mean age of all hospitalized subjects was 70.3 years; 52.2% were females, and 72.9% were Whites. Concerning demographics, compared with subjects who had no history of long-term aspirin use, the patients with long-term aspirin use were older, had a larger proportion of male, White, insurance covered by Medicare/Medicaid, BMI over 30 kg/m^2, smoking, alcohol abuse, family history of malignant neoplasm of digestive organs, and having prior PCI/CABG/valve surgery. Patients with long-term aspirin use had a larger proportion of long-term anticoagulants, antiplatelet, NSAID, systemic steroids, and insulin usage. Except for VTE, rheumatic disease, chronic liver disease, and liver cirrhosis, patients with long-term aspirin use had a larger proportion in each comorbid condition (Supplemental Table 1).

After PSM, the proportion of age, other long-term medication use (except for systemic steroids), alcohol abuse, colorectal polyps, family history of colonic polyps, family history of malignant neoplasm of digestive organs, prior PCI/CABG/valve surgery, comorbidities (except for peptic ulcer), hospital location/teaching status, and hospital region were still significantly different between the two groups (Table 1).

The effects of aspirin on CRC are listed in Table 2. In univariate analyses, long-term aspirin use was significantly associated with decreased risk of CRC diagnosis (OR, 0.55; 95% CI 0.53–0.57). In the multivariable analysis, after adjustment for all the relevant confounders in the univariate analysis with significant difference ($p < 0.05$), long-term use of aspirin was associated with a reduced risk for CRC diagnosis (adjusted OR, 0.64; 95% CI 0.62–0.67) (Table 2).

We further performed stratified analyses by age in category, sex, race, BMI, and smoking adjusted. Compared to individuals without long-term aspirin use, those on long-term aspirin had lower odds for CRC diagnosis among subgroups aged < 70 years (adjusted OR = 0.60) and ≧70 years (adjusted OR = 0.60 vs 0.68). In addition, long-term use of aspirin was associated with lower prevalent CRC regardless of sex, race, BMI, and smoking status (Table 3).

Discussion

The study queried an extensive, nationally representative inpatient database on the potential association between long-term aspirin usage and the presence of CRC. The results revealed that hospitalized US adults on long-term aspirin use are 36% less likely to have prevalent CRC, regardless of age, sex, race, BMI, and smoking status. Although strictly causal inference cannot be made, our findings are noteworthy for their contribution to the literature due to the usage of a national dataset, the substantial sample size retrieved, and the comprehensive adjustment for numerous covariates.

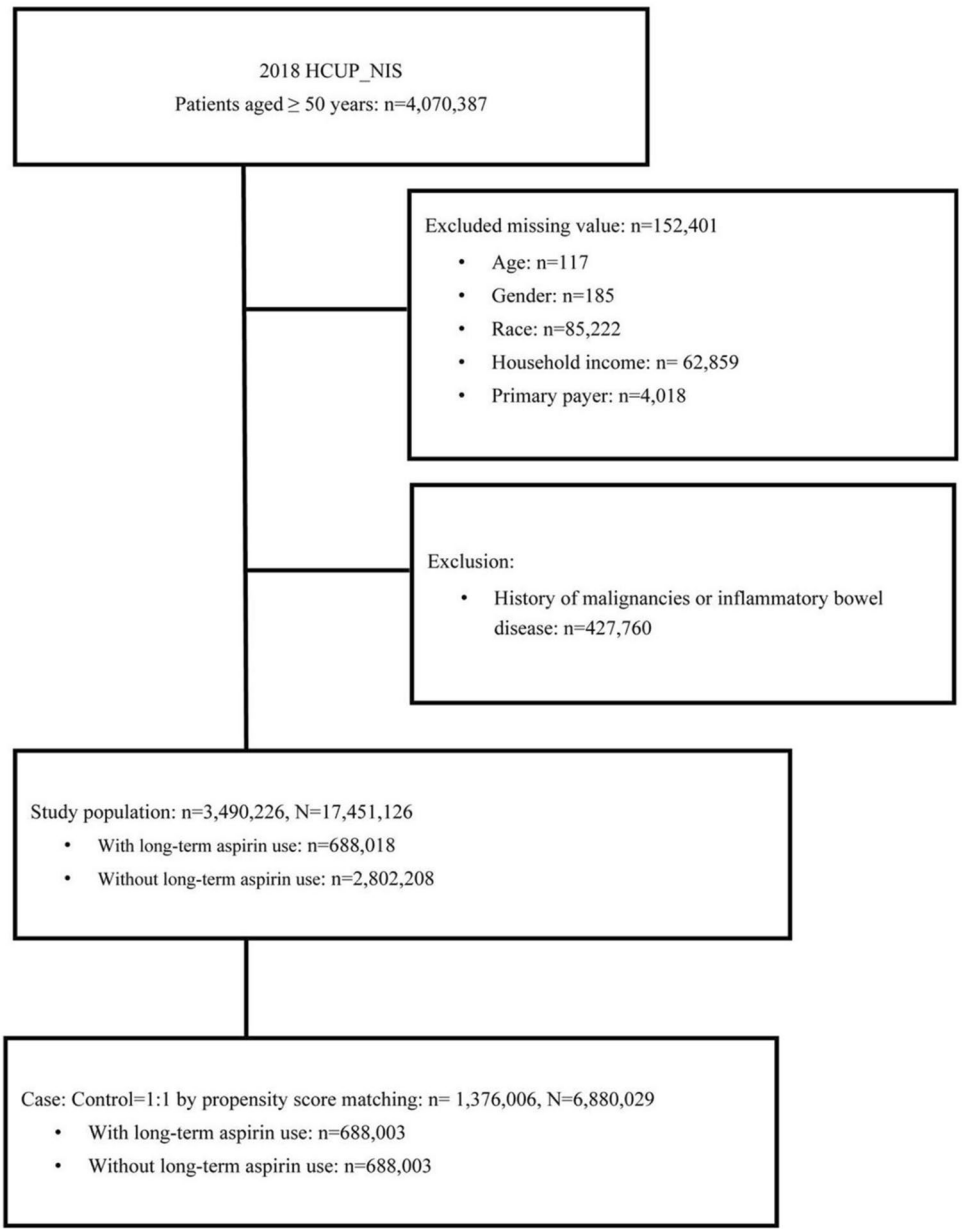

Fig. 1 Flowchart of patient selection

The mechanism underlying the relationships between aspirin use and lowered CRC chance is likely through the mediation of the COX system, as proposed in the previous reports [29, 30]. COX-1, found ubiquitously, generates prostanoids in response to various physiological cues [31, 32]. In contrast, COX-2, typically expressed at low levels in specific organs, can be induced at inflammation, infection, and cancer sites, producing prostanoids associated with disease processes [33–35]. In carcinogenesis, COX-2 is consistently upregulated in 70–80% of esophageal, gastric, and colorectal carcinomas [36, 37]. Additionally, inflammatory cells, vascular endothelium, and fibroblasts near cancer sites exhibit markedly elevated COX-2 expression compared to healthy colon tissues [38]. CRC cells frequently display 2 to 50-fold COX-2 overexpression relative to normal mucosa, supported by Roelofs et al.'s finding of COX-2 mRNA overexpression in 80% of colorectal cancer tissues, while β2-microglobulin and glyceraldehyde-3-phosphate dehydrogenase mRNA levels were expressed at 70% and 40% in colon neoplastic tissue [39–41]. These findings collectively confirm COX-2 as overexpressed in CRC cells, underpinning its role in the mechanism underlying the relationship between long-term aspirin and CRC risk reduction.

Although studies [21, 23] have investigated the effect of aspirin on CRC risk reduction in the general population, few prior reports have assessed the relationship between aspirin use and CRC prevalence or incidence in the subgroups of age, sex, race, and obesity or smoking status, as evaluated

Table 1 Characteristics of study population after PSM

Characteristics	Total ($n=1,376,006$)	Long-term aspirin use		p value
		Yes ($n=688,003$)	No ($n=688,003$)	
CRC diagnosis	12,776 (0.93)	4550 (0.66)	8226 (1.20)	**< 0.001**
Age, years	72.1 ± 0.04	72.2 ± 0.05	72.0 ± 0.05	**< 0.001**
50–59	205,382 (14.93)	102,696 (14.93)	102,686 (14.93)	1.000
60–69	365,465 (26.56)	182,727 (26.56)	182,738 (26.56)	
70–79	409,473 (29.76)	204,751 (29.76)	204,722 (29.76)	
80+	395,686 (28.76)	197,829 (28.75)	197,857 (28.76)	
Gender				0.967
Male	719,637 (52.30)	359,834 (52.30)	359,803 (52.30)	
Female	656,369 (47.70)	328,169 (47.70)	328,200 (47.70)	
Race				1.000
White	1,034,164 (75.16)	517,059 (75.15)	517,105 (75.16)	
Black	181,666 (13.20)	90,830 (13.20)	90,836 (13.20)	
Hispanic	95,612 (6.95)	47,818 (6.95)	47,794 (6.95)	
Others	64,564 (4.69)	32,296 (4.69)	32,268 (4.69)	
Household income				1.000
Quartile1	398,862 (28.99)	199,443 (28.99)	199,419 (28.99)	
Quartile2	380,767 (27.67)	190,368 (27.67)	190,399 (27.67)	
Quartile3	331,896 (24.12)	165,948 (24.12)	165,948 (24.12)	
Quartile4	264,481 (19.22)	132,244 (19.22)	132,237 (19.22)	
Primary payer				0.992
Medicare/medicaid	1,108,870 (80.59)	554,378 (80.58)	554,492 (80.59)	
Private including HMO	215,705 (15.68)	107,884 (15.68)	107,821 (15.67)	
Self-pay/no-charge/other	51,431 (3.74)	25,741 (3.74)	25,690 (3.73)	
Other long-term medication use				
Anticoagulants	186,179 (13.53)	91,515 (13.30)	94,664 (13.76)	**< 0.001**
Antiplatelet	104,796 (7.62)	86,207 (12.53)	18,589 (2.70)	**< 0.001**
NSAID	18,836 (1.37)	13,301 (1.93)	5535 (0.80)	**< 0.001**
Systemic steroids	39,692 (2.88)	19,883 (2.89)	19,809 (2.88)	0.797
Insulin	188,037 (13.67)	122,161 (17.76)	65,876 (9.57)	**< 0.001**
BMI, kg/m^2				0.996
< 30	1,104,672 (80.28)	552,320 (80.28)	552,352 (80.28)	
30–39	144,114 (10.47)	72,045 (10.47)	72,069 (10.48)	
40+	127,220 (9.25)	63,638 (9.25)	63,582 (9.24)	
Smoking	665,575 (48.37)	332,759 (48.37)	332,816 (48.37)	0.969
Alcohol abuse	64,129 (4.66)	24,699 (3.59)	39,430 (5.73)	**< 0.001**
Colorectal polyps	23,789 (1.73)	13,855 (2.01)	9934 (1.44)	**< 0.001**
Family history of colonic polyps	284 (0.02)	172 (0.02)	112 (0.02)	**< 0.001**
Family history of malignant neoplasm of digestive organs	11,128 (0.81)	6372 (0.93)	4756 (0.69)	**< 0.001**
Prior PCI/CABG/valve surgery	139,635 (10.15)	92,408 (13.43)	47,227 (6.86)	**< 0.001**
Comorbidities				
Hypertension	1,115,793 (81.09)	592,412 (86.11)	523,381 (76.07)	**< 0.001**
Diabetes	536,626 (39.00)	295,935 (43.01)	240,691 (34.98)	**< 0.001**
Dyslipidemia	749,033 (54.44)	433,427 (63.00)	315,606 (45.87)	**< 0.001**
Ischemic heart disease	551,435 (40.08)	340,200 (49.45)	211,235 (30.70)	**< 0.001**
Myocardial infarction	87,657 (6.37)	51,384 (7.47)	36,273 (5.27)	**< 0.001**
Heart failure	403,194 (29.30)	216,405 (31.45)	186,789 (27.15)	**< 0.001**
Valvular heart disease	161,851 (11.76)	92,386 (13.43)	69,465 (10.10)	**< 0.001**

Table 1 (continued)

Characteristics	Total ($n=1,376,006$)	Long-term aspirin use		p value
		Yes ($n=688,003$)	No ($n=688,003$)	
Atrial fibrillation	339,974 (24.71)	166,504 (24.20)	173,470 (25.21)	**< 0.001**
Peripheral artery disease	115,599 (8.40)	66,236 (9.63)	49,363 (7.17)	**< 0.001**
VTE	40,373 (2.93)	17,118 (2.49)	23,255 (3.38)	**< 0.001**
Ischemic stroke/TIA	83,967 (6.10)	51,645 (7.51)	32,322 (4.70)	**< 0.001**
Cerebral artery occlusion/stenosis	51,004 (3.71)	32,542 (4.73)	18,462 (2.68)	**< 0.001**
Chronic pulmonary disease	350,140 (25.45)	169,220 (24.60)	180,920 (26.30)	**< 0.001**
Rheumatic disease	49,870 (3.62)	23,377 (3.40)	26,493 (3.85)	**< 0.001**
Peptic ulcer disease	25,017 (1.82)	12,529 (1.82)	12,488 (1.82)	0.815
Severe renal disease	107,439 (7.81)	57,047 (8.29)	50,392 (7.32)	**< 0.001**
Chronic liver disease	62,633 (4.55)	25,383 (3.69)	37,250 (5.41)	**< 0.001**
Liver cirrhosis	16,932 (1.23)	4960 (0.72)	11,972 (1.74)	**< 0.001**
Dementia	160,680 (11.68)	78,634 (11.43)	82,046 (11.93)	**< 0.001**
Hospital bed size				0.255
Large	664,368 (48.28)	335,190 (48.72)	329,178 (47.85)	
Medium	408,726 (29.70)	204,506 (29.72)	204,220 (29.68)	
Small	302,912 (22.01)	148,307 (21.56)	154,605 (22.47)	
Hospital location/teaching status				**0.006**
Urban teaching	944,265 (68.62)	478,718 (69.58)	465,547 (67.67)	
Urban nonteaching	299,237 (21.75)	145,543 (21.15)	153,694 (22.34)	
Rural	132,504 (9.63)	63,742 (9.26)	68,762 (9.99)	
Hospital region				**< 0.001**
Northeast	250,611 (18.21)	113,365 (16.48)	137,246 (19.95)	
Midwest	337,993 (24.56)	182,201 (26.48)	155,792 (22.64)	
South	541,009 (39.32)	269,627 (39.19)	271,382 (39.44)	
West	246,393 (17.91)	122,810 (17.85)	123,583 (17.96)	

PSM propensity score matching, *CRC* colorectal cancer, *NSAID* non-steroidal anti-inflammatory drugs, *BMI* body mass index, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft, *VTE* venous thromboembolism, *TIA* transient ischemic attack. Categorical variables are presented as unweighted counts (weighted percentage). Continuous data were presented as mean ± SE

p value < 0.05 was shown in bold

in the present analysis. Prior investigations have highlighted disparities in the impact of aspirin use on the prevention of cardiovascular diseases based on factors such as race and gender [42], as well as its role in preventing myocardial infarction with consideration for gender [43]. However, despite these variations, our study found that the substantial correlations between long-term aspirin usage and a reduced prevalence of CRC remained relatively consistent across these subgroups. This suggests that aspirin may confer a protective effect against CRC, irrespective of factors such as age, sex, race, obesity status, or smoking habits.

There are some limitations in this study. Individuals hospitalized may not entirely reflect the overall population from which CRC cases arose, which could potentially affect our findings' applicability to a broader population. Also, patients without CRC might be admitted to the hospitals due to diverse causes, potentially introducing selection bias into the data. However, in the present analysis, the control group was carefully selected from the same inpatient population of the same year. In addition, the PSM was also utilized to help reduce potential selection bias. Nevertheless, the findings should be interpreted cautiously within the specific context of hospitalized patients. Second, the study design did not allow for capturing capture the details in aspirin use, including dosage and duration, before and after diagnosis. The timeframe of CRC development in relation to aspirin usage was unclear, either. Thus, the causal inference cannot be made. Third, as with many real-world epidemiological studies, we utilized discharge codes in hospitalization records to identify aspirin use, CRC, and comorbidities. The possibility of ICD coding bias cannot be excluded. Fourth, the dose and exact duration of aspirin, anticoagulant, antiplatelet, insulin, and other NSAIDs use cannot be identified through ICD

Table 2 Univariate and multivariable analyses on the associations between long-term aspirin use and prevalent CRC diagnosis

Variables	CRC diagnosis			
	Crude OR (95% CI)	*p* value	Adjusted OR[a] (95% CI)	*p* value
Long-term aspirin use	0.55 (0.53, 0.57)	**< 0.001**	0.64 (0.62, 0.67)	**< 0.001**
Age, years (vs 50–59)				
60–69	1.11 (1.05, 1.17)	**< 0.001**	1.22 (1.15, 1.30)	**< 0.001**
70–79	1.13 (1.07, 1.19)	**< 0.001**	1.44 (1.35, 1.54)	**< 0.001**
80+	0.93 (0.88, 0.99)	**0.016**	1.42 (1.33, 1.53)	**< 0.001**
Gender (female vs male)	0.78 (0.76, 0.81)	**< 0.001**	0.74 (0.71, 0.77)	**< 0.001**
Race (vs White)				
Black	0.91 (0.87, 0.96)	**0.001**	1.03 (0.97, 1.10)	0.335
Hispanic	0.99 (0.92, 1.06)	0.713	1.04 (0.97, 1.13)	0.275
Others	1.20 (1.11, 1.29)	**< 0.001**	1.22 (1.08, 1.38)	**0.002**
Household income (vs quartile1)				
Quartile2	1.03 (0.99, 1.08)	0.156	0.99 (0.94, 1.04)	0.668
Quartile3	1.03 (0.98, 1.08)	0.186	0.93 (0.88, 0.98)	**0.011**
Quartile4	1.09 (1.04, 1.15)	**< 0.001**	0.92 (0.87, 0.98)	**0.013**
Primary payer (vs medicare/medicaid)				
Private including HMO	1.38 (1.32, 1.44)	**< 0.001**	1.17 (1.11, 1.24)	**< 0.001**
Self-pay/no-charge/other	0.90 (0.82, 0.99)	**0.039**	0.81 (0.73, 0.91)	**< 0.001**
Other long-term medication use (yes vs no)				
Anticoagulants	0.71 (0.67, 0.75)	**< 0.001**	0.85 (0.80, 0.91)	**< 0.001**
Antiplatelet	0.54 (0.50, 0.59)	**< 0.001**	0.84 (0.77, 0.93)	**< 0.001**
NSAID	0.58 (0.48, 0.70)	**< 0.001**	0.52 (0.42, 0.64)	**< 0.001**
Systemic steroids	0.52 (0.45, 0.60)	**< 0.001**	0.58 (0.50, 0.67)	**< 0.001**
Insulin	0.59 (0.55, 0.63)	**< 0.001**	0.85 (0.79, 0.91)	**< 0.001**
BMI (vs < 30)				
30–39	0.92 (0.87, 0.97)	**0.004**	0.93 (0.88, 0.99)	**0.025**
40+	0.58 (0.54, 0.63)	**< 0.001**	0.67 (0.62, 0.73)	**< 0.001**
Smoking (yes vs no)	0.95 (0.92, 0.98)	**0.003**	1.05 (1.01, 1.09)	**0.018**
Alcohol abuse (yes vs no)	0.50 (0.45, 0.56)	**< 0.001**	0.38 (0.33, 0.43)	**< 0.001**
Colorectal polyps (yes vs no)	3.45 (3.20, 3.73)	**< 0.001**	3.01 (2.77, 3.28)	**< 0.001**
Family history of colonic polyps (yes vs no)	7.67 (4.81, 12.21)	**< 0.001**	2.36 (1.41, 3.94)	**0.001**
Family history of malignant neoplasm of digestive organs (yes vs no)	5.72 (5.24, 6.24)	**< 0.001**	4.72 (4.25, 5.24)	**< 0.001**
Prior PCI/CABG/valve surgery (yes vs no)	0.62 (0.58, 0.67)	**< 0.001**	0.97 (0.90, 1.06)	0.510
Comorbidities (yes vs no)				
Hypertension	0.54 (0.52, 0.56)	**< 0.001**	0.77 (0.74, 0.81)	**< 0.001**
Diabetes	0.69 (0.67, 0.72)	**< 0.001**	0.93 (0.89, 0.97)	**0.001**
Dyslipidemia	0.66 (0.64, 0.68)	**< 0.001**	0.82 (0.79, 0.85)	**< 0.001**
Ischemic heart disease	0.55 (0.53, 0.57)	**< 0.001**	0.83 (0.79, 0.87)	**< 0.001**
Myocardial infarction	0.34 (0.31, 0.38)	**< 0.001**	0.43 (0.38, 0.49)	**< 0.001**
Heart failure	0.44 (0.42, 0.46)	**< 0.001**	0.68 (0.64, 0.72)	**< 0.001**
Valvular heart disease	0.55 (0.51, 0.59)	**< 0.001**	0.77 (0.72, 0.83)	**< 0.001**
Atrial fibrillation	0.66 (0.63, 0.69)	**< 0.001**	0.88 (0.83, 0.93)	**< 0.001**
Peripheral artery disease	0.71 (0.66, 0.76)	**< 0.001**	0.87 (0.81, 0.94)	**< 0.001**
VTE	1.99 (1.84, 2.15)	**< 0.001**	1.85 (1.71, 2.00)	**< 0.001**
Ischemic stroke/TIA	0.35 (0.31, 0.39)	**< 0.001**	0.41 (0.36, 0.46)	**< 0.001**
Cerebral artery occlusion/stenosis	0.37 (0.32, 0.43)	**< 0.001**	0.82 (0.70, 0.95)	**0.009**
Chronic pulmonary disease	0.54 (0.52, 0.57)	**< 0.001**	0.62 (0.59, 0.65)	**< 0.001**
Rheumatic disease	0.58 (0.52, 0.66)	**< 0.001**	0.63 (0.56, 0.71)	**< 0.001**

Table 2 (continued)

Variables	CRC diagnosis			
	Crude OR (95% CI)	*p* value	Adjusted OR[a] (95% CI)	*p* value
Peptic ulcer disease	0.88 (0.76, 1.01)	0.060		
Severe renal disease	0.41 (0.38, 0.45)	**< 0.001**	0.53 (0.48, 0.59)	**< 0.001**
Chronic liver disease	0.96 (0.88, 1.05)	0.367		
Liver cirrhosis	1.19 (1.03, 1.38)	**0.016**	1.01 (0.87, 1.18)	0.869
Dementia	0.48 (0.44, 0.51)	**< 0.001**	0.45 (0.41, 0.49)	**< 0.001**
History of receiving CRC screening	3.23 (1.03, 10.20)	**0.045**	1.57 (0.50, 4.96)	0.443
Hospital bed size (vs large)				
Medium	0.90 (0.86, 0.93)	**< 0.001**	0.90 (0.85, 0.96)	**< 0.001**
Small	0.83 (0.79, 0.87)	**< 0.001**	0.79 (0.74, 0.84)	**< 0.001**
Hospital location/teaching status (vs urban teaching)				
Urban nonteaching	0.89 (0.85, 0.93)	**< 0.001**	0.88 (0.83, 0.94)	**< 0.001**
Rural	0.93 (0.88, 0.99)	**0.025**	0.90 (0.83, 0.96)	**0.002**
Hospital region (vs Northeast)				
Midwest	0.93 (0.88, 0.98)	**0.007**	1.03 (0.94, 1.12)	0.584
South	0.92 (0.88, 0.97)	**0.001**	0.98 (0.90, 1.07)	0.665
West	0.97 (0.91, 1.02)	0.249	0.94 (0.85, 1.03)	0.175

Long-term aspirin use by data after matching

OR odds ratio, *CI* confidence interval, *CRC* colorectal cancer, *NSAID* non-steroidal anti-inflammatory drugs, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft, *VTE* venous thromboembolism, *TIA* transient ischemic attack

p value < 0.05 was shown in bold

[a]Adjusted by related variables after matching in univariate analyses with *p*-value < 0.05

Table 3 Stratified associations between long-term aspirin use and prevalent CRC diagnosis

Subgroup	*n* (%)	Long-term aspirin use	CRC diagnosis	
			Adjusted OR[a] (95% CI)	*p* value
Age, year				
< 70	570,847 (41.5)	Yes vs no	0.60 (0.57, 0.64)	**< 0.001**
≧70	805,159 (58.5)	Yes vs no	0.68 (0.64, 0.71)	**< 0.001**
Gender				
Male	719,637 (52.3)	Yes vs no	0.66 (0.63, 0.70)	**< 0.001**
Female	656,369 (47.7)	Yes vs no	0.62 (0.58, 0.65)	**< 0.001**
Race				
White	1,034,164 (75.16)	Yes vs no	0.66 (0.63, 0.69)	**< 0.001**
Black	181,666 (13.2)	Yes vs no	0.62 (0.56, 0.69)	**< 0.001**
Hispanic	95,612 (7.0)	Yes vs no	0.70 (0.63, 0.78)	**< 0.001**
BMI				
< 30	1,104,672 (80.3)	Yes vs no	0.64 (0.61, 0.66)	**< 0.001**
≧30	271,334 (19.7)	Yes vs no	0.67 (0.61, 0.74)	**< 0.001**
Smoking				
Yes	665,575 (48.4)	Yes vs no	0.68 (0.64, 0.71)	**< 0.001**
No	710,431 (51.6)	Yes vs no	0.62 (0.59, 0.65)	**< 0.001**

OR, odds ratio, *CI* confidence interval, *CRC* colorectal cancer, *BMI* body mass index

p value < 0.05 was shown in bold

[a]Adjusted by related variables in Table 2 univariate analyses with *p* value < 0.05, including all covariate except peptic ulcer disease, chronic liver disease, and the stratified covariate

coding. Lastly, the stage and type of CRC cannot be subgrouped for further analysis.

Conclusion

In conclusion, long-term aspirin use among US adults ≥ 50 years old is associated with a lower chance of CRC. The protective effect was not modified by age, sex, race, BMI, and smoking status.

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Data availability All data use to support the findings of this study are included within the article.

Declarations

Conflict of interest The authors declare no competing of interest.

Research involving human and animals participants The study protocol was submitted to the Institutional Review Board (IRB) of Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, and the study was granted an exemption from IRB approval.

Informed consent Due to the fact that all data in the NIS database is de-identified, informed consent was not required.

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