Journal of Drug Abuse
ISSN: 2471-853X

Open Access Research Article

Aspirin Use and Risk of Pancreatic Ductal Adenocarcinoma: A Large Case-Control Study

Zahra Momayez Sanat[1], Sahar Masoudi[1], Seidamir Pasha Tabaeian[2], Maryam Jameh Shorani[3], Majid Soruri[1], Akram Pourshams[1,4,5*]

[1]*Department of Medical Sciences, Tehran University of Medical Sciences, Tehran, Iran*

[2]*Department of Internal Medicine, Iran University of Medical Sciences, Tehran, Iran*

[3]*Department of Internal Medicine, Zanjan University of Medical Sciences, Zanjan, Iran*

[4]*Department of Oncology, Tehran University of Medical Sciences, Tehran, Iran*

[5]*Department of Gastroenterology, Guilan University of Medical Sciences, Rasht, Iran*

ABSTRACT

Background: Pancreatic Ductal Adeno Carcinoma (PDAC) is one of the deadliest cancers, with a five-year survival rate of approximately 5%. The incidence and mortality rates of PDAC are increasing and the results of medical treatments remain unsatisfactory. Some conflicting evidence suggests that aspirin intake may reduce the risk of PDAC. This study aimed to evaluate the association between regular low-dose aspirin use (80 mg aspirin tablets, 5-7 tablets/week) and the risk of PDAC.

Methods: This prospective, hospital based, case control study was performed on 470 PDAC patients (case group) and 526 controls, who were matched in terms of gender and age, in Tehran, Iran from 2011 to 2018. The participants were interviewed regarding the patterns of aspirin use. Data are expressed as mean ± SD or frequency and percentage as appropriate. Differences in frequency between the case and control groups were evaluated based on the analysis of the contingency table (χ^2 test and Fisher's exact test). The propensity score models were designed to calculate the Odds Ratios (OR) and 95% Confidence Intervals (95% CIs) for PDAC with respect to aspirin use, adjusted for age, gender, smoking status, opium use, diabetes mellitus, place of residence and family history of cancer in first-degree relatives.

Results: About 60% of PDAC patients were male in this study. Nearly 30% of PDAC patients had a family history of cancer in one of their first-degree relatives, 26% were smokers, 16% were opium users and 15% had a history of diabetes. Aspirin was used by 22.5% of PDAC patients and 18.06% of the controls. Aspirin use (OR: 1.037, 95% CI: 0.95–1.12) was not associated with PDAC. A possible reduction in the risk of PDAC was reported in individuals who used aspirin for more than 10 years (OR: 0.927, 95% CI: 0.86-0.99).

Received:	16-September-2022	**Manuscript No:**	IPJDA-22-14471
Editor assigned:	19-September-2022	**PreQC No:**	IPJDA-22-14471 (PQ)
Reviewed:	04-October-2022	**QC No:**	IPBJR-22-14471
Revised:	02-February-2023	**Manuscript No:**	IPJDA-22-14471 (R);
Published:	09-February-2023	**DOI:**	10.21767/2471-853X.23.9.06

Corresponding author: Akram Pourshams, Department of Gastroenterology, Guilan University of Medical Sciences, Rasht, Iran; E-mail: akrampourshams@gmail.com

Citation: Sanat ZM, Masoudi S, Tabaeian P, Shorani MJ, Soruri M, et al. (2023) Aspirin Use and Risk of Pancreatic Ductal Adenocarcinoma: A Large Case-Control Study. J Drug Abuse. 9:06.

Conclusion: Overall, aspirin use was not associated with a reduced risk of PDAC. Based on the results, long term aspirin use may play a role in PDAC prevention.

Keywords: Pancreatic ductal adenocarcinoma; Pancreatic cancer; Aspirin; Case control study

INTRODUCTION

Pancreatic Ductal Adeno Carcinoma (PDAC) is deadly cancer, with rising incidence and mortality rates worldwide [1]. In 2017, nearly 441,000 deaths caused by PDAC were reported worldwide. There was a 2.3-fold increase in the global incidence and mortality of PDAC from 1990 to 2017, indicating both ageing and growth of the population and the increased prevalence of obesity and diabetes, which are two main risk factors for PDAC [2-4]. The five-year survival rate of PDAC has slightly improved in the past four decades from 3%in 1970 to 5% today [5,6]. PDAC is diagnosed frequently at an advanced stage when surgical resection is not possible and chemoraditaion is not effective enough [6]. Considering the slow progress in the management of PDAC burden, efforts are being made today to find early detecting markers and introduce potential chemo-preventive agents. Aspirin is a Non-Steroidal Anti-Inflammatory Drug (NSAID), primarily used for the prevention and treatment of cardiovascular disease [7]. However, its long-term use has been associated with a reduction in the overall cancer risk due to its antioxidant and anti-inflammatory properties and inhibition of Cyclooxygenase-2 (COX-2) pathway with increased expression in PDAC [8-10]. According to laboratory studies, inhibition of COX-2 activity may be an effective preventive approach against PDAC [11,12]. Nevertheless, the association between aspirin use and the risk of PDAC is inconsistent in clinical studies [13-16]. Therefore, the present study aimed to evaluate the association between low-dose aspirin use (80 mg aspirin tablets, 5-7 tablets per week) and the risk of PDAC.

MATERIALS AND METHODS

The recruitment methods of case and control groups have been extensively explained in the literature and briefly described here [17]. The case group (patients with pathology proven PDAC) and control group (individuals with similar referral patterns and gastrointestinal motility disorders or biliary stone disease with a normal pancreas and no other cancers or organ failure), matched by gender and age, were recruited from Shariati Hospital (a tertiary referral hospital) in Tehran, Iran, between December 2011 and January 2018. Individuals who were suspected of having pancreatitis were invited to participate in this case control study. Upon enrolment, written informed consent was obtained from the participants. Next, bio-sample collection and Endoscopic Ultra Sonography (EUS) were performed for the patients. If a mass or cystic lesion was detected, Fine Needle Aspiration (FNA) was performed. The obtained samples were then reviewed by two expert pathologists, who were blinded to the questionnaire data. All participants with histologically confirmed PDAC were included in the study. For data collection, a valid and reliable, structured questionnaire was used by a few trained interviewers before performing EUS [18]. The participants were asked regarding the regular use of aspirin (80 mg aspirin tablets, 5-7 tablets/week). For each episode of use, the name of drug, date of drug use onset and duration and frequency of drug use were recorded. Data are expressed as mean ± SD or frequency and percentage as appropriate. Differences in frequency between the case and control groups were evaluated by analysis of contingency table (Fisher's exact test and χ^2 test). The propensity score models were used to statistically mimic randomization and calculate the Odds Ratios (OR's) and 95% Confidence Intervals (95% CIs) for PDAC in terms of aspirin use and duration of consumption, adjusted for age, gender, smoking status, opium use, diabetes mellitus, place of residence and family history of cancer in first-degree relatives. The propensity score can be estimated using a logistic regression model, in which treatment status is regressed on observed baseline characteristics. The propensity score aims to present an unbiased estimate of treatment effect, adjusted for confounding factors in non-randomized and observational studies [19,20]. All statistical analyses were performed in STATA version 11 (STATA Corp., College Station, TX, USA). P-value less than 0.05 was considered significant. It has been previously shown that cigarette smoking, opium use (>1 year), long-term diabetes mellitus (>2 years) and a family history of cancer in first-degree relatives with no obesity were associated with an increased risk of PDAC development in our population [21,22].

RESULTS

A total of 470 new incident cases of histologically confirmed PDAC and 526 hospital controls were enrolled in this study. Descriptive characteristics of PDAC cases and controls are presented in **Table 1**. Nearly 60% of the patients were male. The mean age of the patients was 64.10 ± 11.55 years and 80% of them were urban inhabitants. Approximately 30% of patients had a history of cancer in their first-degree relatives, 26% smoked and 16% used opium. Moreover, 15% of the patients had a history of diabetes for more than two years. The PDAC patients were more likely to be smokers, opium users and rural inhabitants. Also, the case group had a higher frequency of a previous diagnosis of diabetes mellitus and a family history of cancer in their first-degree relatives compared to the controls.

Table 1: Descriptive characteristics of pancreatic cancer cases and controls.

Participants characteristics	Total (n=996)	Cases (n=470)	Controls (n=526)	P-value
Age (years), mean ± SD	63.38 ± 12.47	64.10 ± 11.55	62.74 ± 13.22	0.072
BMI (kg/m^2) ± SD	26.29 ± 5.93	26.18 ± 5.05	26.73 ± 5.89	0.147
Gender				
Male	597 (59.94%)	284 (60.43%)	313 (59.51%)	0.767
Female	399 (40.06%)	186 (39.57%)	213 (40.49%)	
Education				
Illiterate	379 (38.05%)	180 (38.30%)	199 (37.83%)	0.513
Less or high school graduate	495 (49.70%)	227 (48.30%)	268 (50.95%)	
Advanced degree	122 (12.25%)	63 (13.40%)	59 (11.22%)	
Residence				
Rural	155 (15.64%)	92 (19.66%)	63 (12.05%)	0.001
Urban	836 (84.36%)	376 (80.34%)	460 (87.95%)	
Marital status				
Single	19 (1.91)	5 (1.06%)	14 (2.66%)	0.154
Married	795 (79.82%)	382 (81.28%)	413 (78.52%)	
Divorced or Widowed	182 (18.27%)	83 (17.66%)	99 (18.82%)	
Family history of any cancer (first degree)				
Yes	251 (25.20%)	138 (29.36%)	113 (21.48%)	0.004
No	745 (74.80%)	332 (70.64%)	413 (78.52%)	
Diabetes mellitus history (>2 years)				
Yes	117 (11.75%)	70 (14.89%)	47 (8.94%)	0.004
No	879 (88.25%)	400 (85.11%)	479 (91.06%)	
Smoking status				
Current	219 (21.99%)	123 (26.17%)	96 (18.25%)	0.011
Quit more than 5 y	104 (10.44%)	46 (9.79%)	58 (11.03%)	
Never	673 (67.57%)	301 (64.04%)	372 (70.72%)	
Opium use				
More than 1 year	134 (13.45%)	74 (15.74%)	59 (11.22%)	0.036
Never	862 (86.55%)	396 (84.26%)	467 (88.78%)	

The results regarding the aspirin intake of the study population are presented in **Table 2**. Low-dose aspirin intake was not associated with a reduced risk of PDAC (adjusted OR (aOR): 1.037, 95% CI: 0.95-1.12). According to the results, the advantages of aspirin intake in PDAC prevention are being highlighted after 10 years (aOR: 0.927, 95% CI: 0.86-0.99) (**Table 3**).

Table 2: Description of Aspirin use and duration among cases and controls.

	Total	Cases	Controls	P-value
		Aspirin use		
Never	795 (79.82%)	364 (77.45%)	431 (81.94%)	0.077
Ever	201 (20.18%)	106 (22.55%)	95 (18.06%)	
		Duration of use (years)		
Never	793 (80.10%)	363 (77.23%)	430 (81.75%)	0.322
≤ 1	43 (4.34%)	23 (4.90%)	20 (3.83%)	
01-May	69 (6.97%)	34 (7.25%)	35 (6.70%)	
05-Oct	57 (5.76%)	31 (6.61%)	26 (4.98%)	
>10	28 (2.83%)	17 (3.62%)	11 (2.11%)	

Table 3: Pancreatic cancer odds ratios according to duration of aspirin use.

Variables	Adj OR*	CI 95%	P for trend
Aspirin intake Never	Ref	-	
Ever	1.037	0.95-1.12	-
Never Aspirin use	Ref	-	
Aspirin user ≤ 1y	1.028	0.88-1.19	0.044
Aspirin user 1-5 y	1.015	0.88-1.16	
Aspirin user 5-10 y	0.954	0.82-1.11	
Aspirin user >10 y	0.927	0.86-0.99	

Note: *Propensity score matching by (age, gender, smoking, opium use, diabetes mellitus, residence and family history of any cancer in their first degree relatives).

DISCUSSION

PDAC accounted for 466,000 deaths in 2020 and it was the seventh leading cause of cancer related mortality in both males and females [23]. The incidence, prevalence and mortality of PDAC have increased by 55%, 63% and 53% in the last 25 years, respectively [24]. Both the incidence and mortality rates of PDAC have been either stable or increased globally, suggesting the increasing prevalence of obesity and diabetes mellitus, although advances in diagnostic and cancer registration modalities may be also effective in some countries [25]. It has been proposed that the mortality rates of PDAC surpass those of breast cancer. This type of cancer may become the third leading cause of cancer death following lung and colorectal cancers in 28 European countries by 2025 [26]. With the translation of emerging technologies to early diagnostic tools and more effective therapies for PDAC, it is crucial to prevent PDAC. Aspirin, with antioxidant and anti-inflammatory properties and inhibition of COX-2 pathway, is considered a chemoprophylaxis agent for PDAC management however, the association between aspirin use and the risk of PDAC is inconsistent in clinical studies. The results of the present study on the ineffectiveness of low dose aspirin in reducing the incidence of PDAC are consistent with the results of most relevant clinical studies. In this regard, Cook et al., in a clinical trial on women, showed that daily low-dose aspirin use (100 mg) over 10 years did not reduce the PDAC risk [27]. Moreover, Choi et al. evaluated the association between the use of aspirin and PDAC in a nested case-control study on a 12-year Korean nationwide cohort [28]. They recruited 827 PDAC patients and 4,135 matched controls in their study. Aspirin use (aOR: 0.84, 95% CI: 0.70-1.01, P=0.068) was not associated with a decreased risk of PDAC. Additionally, Khalaf et al. evaluated aspirin use and the risk of PDAC in 141,940 participants from the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS). They defined 325 mg aspirin as the standard dose and 81 mg aspirin as the low dose. Also, regular aspirin users used aspirin (either standard or low-dose) at least twice per week on average. They also measured the pre-diagnosis plasma levels of salicylurate (a circulating metabolite of aspirin) in 396 nested PDAC cases and 784 controls from the HPFS, NHS and women's health initiative-observational study cohorts. They did not find any association between regular aspirin use and incident PDAC in

their pooled analysis of HPFS and NHS cohorts and the pre-diagnosis level of salicylurate was not associated with the PDAC risk. In contrast to large-scale cohort studies and clinical trials from the United States and Korea, two case-control studies from Shanghai, China and Connecticut, USA (co-authored) supported the role of regular use of aspirin in reducing the incidence of PDAC [29]. Besides, in a study from the UK, the effect of aspirin on mortality due to PDAC was only significant in patients receiving aspirin treatment for more than 7.5 years (HR: 0.28, 0.08-1.00, P=0.04); its effect did not appear to increase at aspirin doses greater than 75 mg daily [30]. Two meta-analyses of observational studies examined the association between aspirin use and PDAC incidence and mortality in the past decade [31]. In a meta-analysis (4,748 PDAC cases and 252,025 healthy controls), showed no significant association between aspirin use and the mortality risk of PDAC, however, the incidence of PDAC could slightly decrease by aspirin use (OR: 0.82, 95% CI: 0.68-0.98) with high heterogeneity (P=0.001, I2=75.6%) and this effect was not dose-dependent. Moreover, analysis of six studies suggested that if the duration of aspirin use was <5 years, it would not decrease the PDAC incidence. In another meta-analysis reported a pooled estimate of decrease in the incidence of PDAC among aspirin users (OR: 0.77, 95% CI: 0.62 to 0.96). They also assessed the relationship between aspirin use and PDAC mortality in two cohort studies and did not observe a significant association. The present results did not suggest that daily low-dose (80 mg) aspirin consumption could reduce the risk of PDAC development if the duration of aspirin use was <10 years.

CONCLUSION

The strengths of this study include accurate diagnosis of patients with PDAC by pathology, use of a prospective approach, large number of case subjects and use of a valid questionnaire. On the other hand, the limitations of this study include administration of only one dose of aspirin in Iran and the insufficient number of patients to evaluate the benefits of aspirin use for high-risk groups, such as diabetic patients. The duration-response benefit is notable and may explain the inconsistent findings reported in the literature. According to the review of several mentioned studies and the present research, the association between aspirin use and PDAC is related to the duration of aspirin use and personal risk factors. Therefore, several large scale clinical cohort trials are recommended in different countries to obtain consistent results.

REFERENCES

1. Pourshams A, Sepanlou SG, Ikuta KS, Bisignano C, Safiri S, et al. (2019) The global, regional and national burden of pancreatic cancer and its attributable risk factors in 195 countries and territories, 1990-2017: A systematic analysis for the global burden of disease study 2017. Lancet Gastroenterol Heptagon. 4(12):934-947.
2. Meisinger C, Ezzati M, Di Cesare M (2016) Trends in adult body-mass index in 200 countries from 1975 to 2014: A pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet. 387(10026):1377-1396.
3. Zhou B, Lu Y, Hajifathalian K, Bentham J, Cesare M, et al. (2016) Worldwide trends in diabetes since 1980: Pooled analysis of 751 population-based measurement studies with over 4.4 million participants. Lancet. 387(10027): 1513-1530.
4. Jemal A, Siegel R, Xu J, Ward E (2010) Cancer statistics, 2010. CA Cancer J Clin. 60(5):277-300.
5. McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, et al. (2018) Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol. 24(43):4846-4861.
6. Sheikh M, Masoudi S, Bakhshandeh R, Moayyedkazemi A, Zamani F, et al. (2020) Survival features, prognostic factors and determinants of diagnosis and treatment among Iranian patients with pancreatic cancer, a prospective study. PloS One. 15:0243511.
7. Roshandel G, Khoshnia M, Poustchi H, Hemming K, Kamangar F, et al. (2019) Effectiveness of polypill for primary and secondary prevention of cardiovascular diseases (PolyIran): A pragmatic, cluster-randomised trial. Lancet. 394(10199):672-683.
8. Ulrich CM, Bigler J, Potter JD (2006) Non-steroidal anti-inflammatory drugs for cancer prevention: Promise, perils and pharmacogenetics. Nat Rev Cancer. 6(2): 130-140.
9. Groot DD, Vries ED, Groen H, Jong SD (2007) Non-steroidal anti-inflammatory drugs to potentiate chemotherapy effects: From lab to clinic. Crit Rev Oncol Hematol. 61(1):52-69.
10. Flower RJ (2003) The development of COX-2 inhibitors. Nat Rev Drug Discov. 2(3):179-191.
11. Ali S, Banerjee S, Schaffert JM, El-Rayes BF, Philip PA, et al. (2010) Concurrent inhibition of NF-κB, cyclooxygenase-2 and epidermal growth factor receptor leads to greater anti-tumor activity in pancreatic cancer. J Cell Biochem. 110(1):171-181.
12. Xu XF, Xie CG, Wang XP, Liu J, Yu YC, et al. (2008) Selective inhibition of cyclooxygenase-2 suppresses the growth of pancreatic cancer cells *in vitro* and *in vivo*. Tohoku J Exp Med. 215(2):149-157.
13. Cao Y, Nishihara R, Wu K, Wang M, Ogino S, et al. (2016) Population-wide impact of long-term use of aspirin and the risk for cancer. JAMA Onco. 2(6):762-769.
14. Risch HA, Lu L, Streicher SA, Wang J, Zhang W, et al. (2017) Aspirin use and reduced risk of pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 26(1):68-74.
15. Khalaf N, Yuan C, Hamada T, Cao Y, Babic A, et al. (2018) 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. Gastroenterology. 154(5):1380-1390.

16. Sun J, Li Y, Liu L, Jiang Z, Liu G (2019) Aspirin use and pancreatic cancer risk: A systematic review of observational studies. Medicine. 98:e18033.
17. Shakeri R, Kamangar F, Mohamadnejad M, Tabrizi R, Zamani F, et al. (2016) Opium use, cigarette smoking and alcohol consumption in relation to pancreatic cancer. Medicine. 95(28):3922.
18. Farrokhzad S, Nedjat S, Kamangar F, Kamali M, Malekzadeh R (2014) Validity and reliability of a questionnaire designed to assess risk factors of pancreatic cancer in Iran. Arch Iran Med. 17(2):102-105.
19. Austin PC (2011) An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 46(3): 399-424.
20. Rubin DB (2010) Propensity score methods. Am J Ophthalmol. 149(1):7-9.
21. Moossavi S, Mohamadnejad M, Pourshams A, Poustchi H, Islami F, et al. (2018) Opium use and risk of pancreatic cancer: A prospective cohort study. Cancer Epidemiol Biomarkers Prev. 27(3):268-273.
22. Sanat ZM, Masoudi S, Mansouri M, Shishavan NG, Jameshorani M (2021) Diabetes mellitus, obesity and risk of pancreatic ductal adenocarcinoma: A large case-control study from Iran. Middle East J Dig Dis. 13(1):15-20.
23. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, et al. (2021) Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 71(3):209-249.
24. Lippi G, Mattiuzzi C (2020) The global burden of pancreatic cancer. Arch Med Sci. 16(4):820-824.
25. Arnold M, Abnet CC, Neale RE, Vignat J, Giovannucci EL, et al. (2020) Global burden of 5 major types of gastrointestinal cancer. Gastroenterology. 159(1):335-349.
26. Ferlay J, Partensky C, Bray F (2016) More deaths from pancreatic cancer than breast cancer in the EU by 2017. Acta Oncologica. 55(10):1158-1160.
27. Cook NR, Lee IM, Gaziano JM, Gordon D, Ridker PM, et al. (2005) Low-dose aspirin in the primary prevention of cancer: The women's health study: A randomized controlled trial. JAMA. 294(1):47-55.
28. Choi JH, Lee SH, Huh G, Chun JW, You MS, et al. (2019) The association between use of statin or aspirin and pancreatic ductal adenocarcinoma: A nested case-control study in a Korean nationwide cohort. Cancer Med. 8(17): 7419-7430.
29. Streicher SA, Yu H, Lu L, Kidd MS, Risch HA (2014) Case control study of aspirin use and risk of pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 23(7):1254-1263.
30. Rothwell PM, Fowkes FGR, Belch JF, Ogawa H, Warlow CP, et al. (2011) Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. The Lancet. 377(9759):31-41.
31. Zhang YP, Wan YD, Sun YL, Li J, Zhu RT (2015) Aspirin might reduce the incidence of pancreatic cancer: A meta-analysis of observational studies. Sci Rep. 5(15460):1-12.