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Original article

Low-dose acetylsalicylic acid for cancer prevention considering risk factors: a retrospective cohort study

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ABSTRACT

Purpose: Aspirin (acetylsalicylic acid) has been reported to protect against certain cancers. However, patient-related risk factors may moderate protective effects, including excess weight, smoking, risky alcohol use, and diabetes. We explore the cancer-risk relationship between aspirin intake and those four factors.
Methods: Retrospective cohort study of cancers, aspirin intake, and four risk factors in persons aged ≥50 years. Participants received medication during 2007–2016, and cancers were diagnosed in 2012–2016. Adjusted hazard ratios (aHR) for 95% confidence intervals (95%CI) were calculated for aspirin intake and risk factors using Cox proportional hazard modeling.
Results: Of 118,548 participants, 15,793 consumed aspirin, and 4003 had cancer. Results indicated a significant protective effect of aspirin against colorectal (aHR: 0.7; 95%CI: 0.6–0.8), pancreatic (aHR: 0.5; 95%CI: 0.2–0.9), prostate (aHR: 0.6; 95%CI: 0.5–0.7) cancers and lymphomas (aHR: 0.5; 95%CI: 0.2–0.9), and also, although not significantly, against esophageal (aHR: 0.5; 95%CI: 0.2–1.8), stomach (aHR: 0.7; 95%CI: 0.4–1.3), liver (aHR: 0.7; 95%CI: 0.3–1.5), breast (aHR: 0.8; 95%CI: 0.6–1.0), and lung and bronchial (aHR: 0.9; 95%CI: 0.7–1.2) cancers. Aspirin intake was not significantly protective against leukemia (aHR: 1.0; 95%CI: 0.7–1.4) or bladder cancer (aHR: 1.0; 95%CI: 0.8–1.3).
Conclusions: Our results suggest that aspirin intake is associated with a reduced incidence of colorectal, pancreatic, and prostate cancers and lymphomas.
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Introduction

Aspirin (acetylsalicylic acid) has long been known to prevent cardiovascular and cerebrovascular diseases [1,2], with daily administration of low doses proven to be beneficial in preventing the recurrence of cardiovascular events [3]. More recently, long-term aspirin intake has also been demonstrated to significantly reduce cancer risk [4,5]. Aspirin intake has been reported specifically to have a protective effect against colorectal cancer [6], with Patrignani et al. [7], for instance, demonstrating a potent chemopreventive effect against colorectal cancer in adults aged 50–59 years. In relation to gastrointestinal cancers, long-term use of aspirin has been shown to be associated with reduced gastric cancer incidence and mortality [8], and also to have a protective effect against stomach cancer [9], while a recent study in the United Kingdom confirms the protective effect of aspirin against esophageal cancer [10]. Low-dose aspirin has likewise been associated with a significantly lower risk of hepatocellular carcinoma [11] and pancreatic cancer [12], while aspirin and metformin combined have been reported to have independent protective associations in the case of lung and bronchial cancers [13]. For non-Hodgkin lymphoma and breast cancer, Liebow et al. [14] concluded that risk was lowered by aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs).

Abbreviations and acronyms: 95%CI, 95% confidence interval; aHR, adjusted hazard ratio; BMI, body mass index; DDD, defined daily dose; HR, hazard ratio

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However, while aspirin is reported to protect against certain cancers, its protective effects require further research [15], as certain patient-related lifestyle and comorbidity risk factors may moderate those protective effects. Excess weight, smoking, and risky alcohol use are all documented as elevating cancer risk [16,17], while a relationship has also been reported between diabetes and the risk of cancer, especially pancreatic cancer [18].

The aim of this study, conducted in Lleida (Catalonia, Spain), was to analyze the association between aspirin intake and different cancers, considering excess weight or obesity, smoking, risky alcohol use, and diabetes as patient-related risk factors.

Methods

Study population

A retrospective cohort study was carried out of aspirin intake for the period January 1, 2007, to December 31, 2016, considering individual risk factors and specific cancers. The study was based on data available from the Catalan Health Service (CatSalut), which, as of January 1, 2007, provided care to 118,548 inhabitants aged more than or equal to 50 years in Lleida (Catalonia, Spain). The Lleida Population-based Cancer Registry furnished data on cancer cases diagnosed during the study period, and demographic characteristics of the study participants, including age and sex, were obtained from the CatSalut system.

The included cancers were esophageal, stomach, colorectal, liver, pancreatic, lung and bronchial cancers, leukemia, breast (only women), prostate, and bladder cancers and lymphomas. Person-years at risk were calculated at the study outset (January 1, 2007) and up to December 31, 2016, or to the date of cancer diagnosis or death. This period ensured that cancer cases detected in 2012 had the opportunity to be exposed to aspirin for more than or equal to 5 years. Only individuals on medication in 2007 were included in the cohort.

Data on aspirin intake were obtained from the volume of aspirin dispensed by pharmacies. In Catalonia, drugs are dispensed in pharmacies on presentation of a doctor's prescription. Drugs administered to hospitalized patients and prescribed by private providers are not recorded in the CatSalut system, and so were not included in this study.

Figure 1 shows a flowchart of the study population. At the outset, the pharmacy database documented a total of 724,070 individuals who had received at least a prescription of any medication. After excluding individuals who did not reside in the Lleida region, individuals aged under 50 years at the study outset, individuals who only commenced any medication intake after 2007, and a small number of individuals with incomplete risk factor data, we were left with a final sample composed of 118,548 inhabitants.

Data collection

Information on cancer diagnoses obtained from the Lleida Population-based Cancer Registry using five consecutive years of incidence data (2012–2016) was validated by checking medical records. Hospital and pathology records were used as the main information sources. Cancers were identified in accordance with the definitions of the International Association of Cancer Registries, the International Agency for Research on Cancer, and the European Network of Cancer Registries.

Evaluated at baseline were excess weight or obesity, smoking, and risky alcohol use as lifestyle risk factors, and diabetes as a

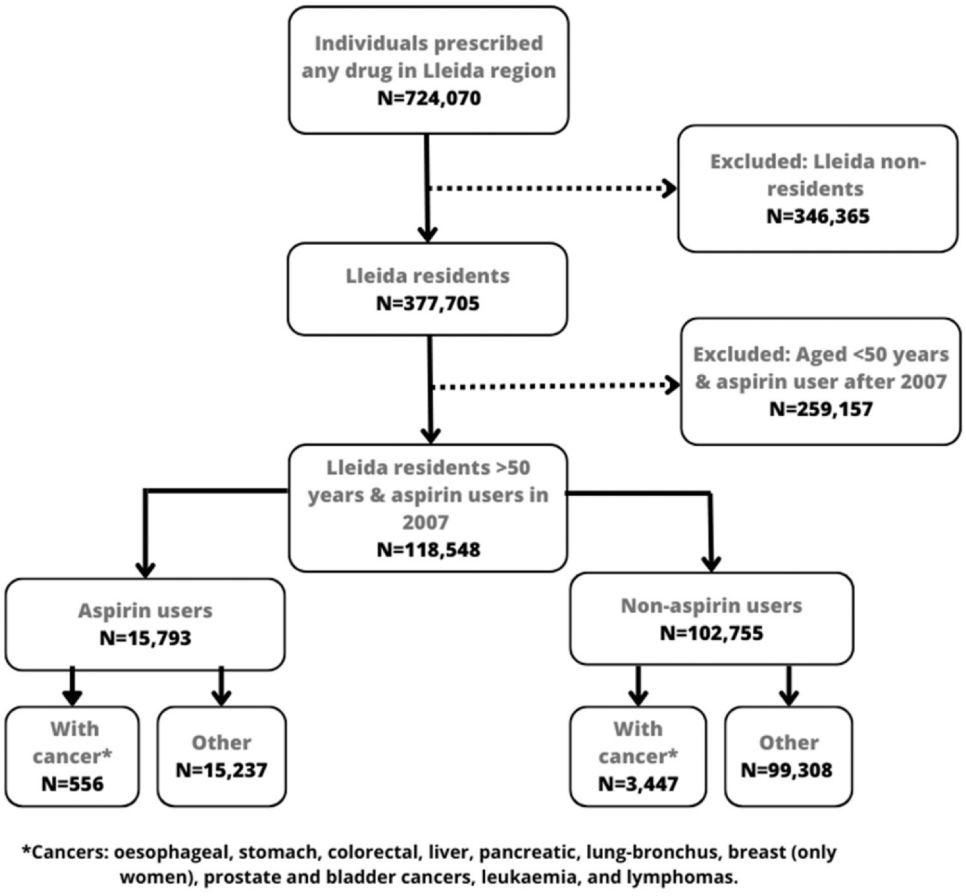

Fig. 1. Flowchart of subjects included in the analysis.

comorbidity risk factor, with the corresponding data extracted from eCAP (used by primary care physicians to record patient medical data). Body mass index (BMI), calculated from patient weight and height data (BMI = weight(kg)/height(m)^2), was categorized as follows: 18.5–24.9 normal weight; 25–29.9 overweight; and rater than 30 obese [19]. International ICD-10 coding as follows was used: diabetes mellitus, E10-E14; risky alcohol use, F10.9; and smoking, Z72.0. Risky alcohol use was defined as > 40 g/day and > 24 g/day intake for men and women, respectively [20]. Smokers were defined as those who started smoking for more than or equal to 5 years before the study outset (information included in eCAP).

Exposure

According to the Anatomical Therapeutic Chemical classification system, aspirin as medication is categorized as A01AD05 (acetylsalicylic acid). Aspirin intake was evaluated for each patient based on the defined daily dose (DDD) and accumulated study-period dose (in milligram). The DDD is a technical unit of measurement reflecting the daily adult maintenance dose for the main drug indication and a given administration route. DDD values for active ingredients are established by the World Health Organization and published on its Collaborating Center for Drug Statistics Methodology website [19,21].

Aspirin exposure, defined as daily consumption for more than or equal to 5 years [22] of between 75 mg and 250 mg [23,24] and determined from computerized pharmacy data, was calculated as the DDD total dispensed to an individual during the study period. If aspirin intake was suspended for a period and later started again, the DDD as consumed in the later period was considered.

Statistical analysis

Descriptive analyses evaluated the association between baseline characteristics, aspirin exposure, and outcomes. The crude hazard ratio (HR) was calculated to determine the association between aspirin intake and cancer risk. Cox proportional hazard modeling was used to estimate the effect of aspirin intake on each cancer, adjusted HR (aHR) by sex, age, aspirin intake, excess weight or obesity, smoking, risky alcohol use, and diabetes, and reporting the corresponding 95% confidence intervals (CI). Probability values for the statistical tests were two-tailed, and a CI that did not contain 1.0 was regarded as statistically significant, indicating that results with wide CIs needed to be interpreted with care. All statistical analyses were performed using R (R Core Team, 2019), an open-source programming language and environment for statistical analysis and graphic representation.

Ethics

This study was approved by the IDIAP Jordi Gol Clinical Research Ethics Committee (CEIC 21/190-P). As a retrospective cohort study based on patient information anonymized for research purposes, no written informed consent was necessary. All statistical calculations were carried out in accordance with relevant guidelines and regulations.

Results

Patient characteristics

From a total sample of 118,548 individuals aged more than or equal to 50 years for the period 2007–2016, 15,793 (13.3%) had used aspirin for more than or equal to 5 years, and 102,755 (86.7%) had not used aspirin (Table 1). The largest age subgroup in the aspirin group was 70–79 years (31.6%), followed by similar numbers in the 60–60 (23.2%) and 80–89 (28.1%) age groups. The largest age subgroup in the nonaspirin group was 50–59 years (30.2%). Men predominated in the aspirin group (54.1%), but not in the nonaspirin group (43.6%). The median daily aspirin dose was 85 mg (interquartile range: 75–110 mg).

Table 1
Characteristics of patients in the aspirin and nonaspirin groups

	All subjects n = 118,548 n (%)	Aspirin group n = 15,793 n (%)	Nonaspirin group n = 102,755 n (%)
Age, years			
50–59	32,684 (27.6)	1675 (10.6)	31,009 (30.2)
60–69	29,434 (24.8)	3668 (23.2)	25,766 (25.1)
70–79	25,828 (21.8)	4988 (31.6)	20,840 (20.3)
80–89	22,254 (18.8)	4451 (28.2)	17,803 (17.3)
90-	8348 (7.0)	1011 (6.4)	7337 (7.1)
Sex, male	53,340 (45.0)	8550 (54.1)	44,790 (43.6)
Aspirin, dosage		> 75 mg	NA
BMI			
Normal weight	27,254 (23.0)	1985 (12.6)	25,269 (24.6)
Overweight	42,489 (35.8)	5630 (35.6)	36,859 (35.9)
Obese	48,805 (41.2)	8178 (51.8)	40,627 (39.5)
Smoking, yes	12,367 (10.4)	2463 (15.6)	9904 (9.6)
Risky alcohol use, yes	2795 (2.4)	442 (2.8)	2353 (2.3)
Diabetes, yes	4645 (3.9)	1420 (9.0)	3225 (3.1)
Cancers, all	4003 (3.4)	556 (3.5)	3447 (3.4)

BMI = body mass index; NA = not applicable.

Regarding risk factors for the aspirin and nonaspirin groups (Table 1), 87.4% and 75.4% of patients were overweight or obese, 15.6% and 9.6% were smokers, and 2.8% and 2.3% were risky alcohol users, respectively, while diabetes was diagnosed in 9.0% and 3.1%, respectively. Finally, 556 (3.5%) aspirin group patients and 3447 (3.4%) nonaspirin group patients were diagnosed with cancer.

Cancer incidences

The cumulative incidence of each of the cancers was calculated for all patients and for the aspirin and nonaspirin groups (Table 2).

The HRs in Table 2 suggest a protective effect of aspirin for most cancers. However, the results are not statistically significant. Furthermore, in the cases of lung and bronchial cancer (HR: 0.72; 95% CI: 0.53–0.96) and bladder cancer (HR: 0.76; 95% CI: 0.61–0.96), the HRs are statistically significant.

Cox regression, with aHR values, resulted in a variation in outcomes (Table 3). Aspirin intake had a suggestive protective effect against four cancers: colorectal cancer (aHR: 0.7; 95%CI: 0.6–0.8), pancreatic cancer (aHR: 0.5; 95%CI: 0.2–0.9), prostate cancer (aHR: 0.6; 95%CI: 0.5–0.7), and lymphomas (aHR: 0.5; 95%CI: 0.2–0.9). It was also suggestive of a possible reduced incidence, but not to a significant degree, for five cancers: esophageal cancer (aHR: 0.6; 95%CI: 0.2–1.9), stomach cancer (aHR: 0.7; 95%CI: 0.4–1.3), liver cancer (aHR: 0.7; 95%CI: 0.3–1.5), breast cancer (aHR: 0.8; 95%CI: 0.6–1.0), and lung and bronchial cancer (aHR: 0.9; 95%CI: 0.7–1.2). Finally, for leukemia (aHR: 1.0; 95%CI: 0.7–1.4) and bladder cancer (aHR: 1.0; 95%CI: 0.8–1.3), aspirin intake was not significant. Figure 2 graphically depicts the aHR values for aspirin intake associated with each cancer type.

Men, in general, showed a greater risk than women of developing any of the studied cancer types, while the age group showing the highest incidence of cancer was 70–89 years.

Discussion

This retrospective study confirmed that aspirin intake may be associated with a reduced incidence of colorectal, pancreatic, and prostate cancers and lymphomas, and to a lesser degree (the effect

Table 2
Total cases for each cancer, person-years at risk, and hazard ratios for cancer incidence for the aspirin and nonaspirin groups

	Cancer incidence						
Cancers	All n = 118,548 n (%)	PYAR n (%)	Aspirin group n = 15,793 n (%)	PYAR n (%)	Non-aspirin group n = 102,755 n (%)	PYAR n (%)	HR (95%CI)
Esophagus	26	197	3	25	29	172	0.72
	(0.02)	(0.02)	(0.02)	(0.02)	(0.03)	(0.02)	(0.21–2.51)
Stomach	122	938	18	155	117	783	0.77
	(0.10)	(0.09)	(0.11)	(0.11)	(0.08)	(0.09)	(0.5–1.31)
Colorectal	1083	8305	134	1069	1138	7236	0.81
	(0.91)	(0.84)	(0.83)	(0.75)	(0.82)	(0.85)	(0.7–1.011)
Liver	54	431	7	56	53	375	0.88
	(0.05)	(0.04)	(0.04)	(0.04)	(0.04)	(0.04)	(0.38–2.02)
Pancreas	85	617	9	71	89	546	0.77
	(0.07)	(0.06)	(0.05)	(0.05)	(0.06)	(0.06)	(0.37–1.61)
Lung- bronchus	347	2614	59	478	365	2136	0.72
	(0.29)	(0.26)	(0.37)	(0.34)	(0.26)	(0.25)	(0.53–0.96)
Leukemia	281	2104	54	430	272	1674	0.81
	(0.24)	(0.21)	(0.34)	(0.30)	(0.20)	(0.20)	(0.56–1.05)
Breast (women)	635	4862	55	414	681	4448	0.86
	(0.54)	(0.49)	(0.34)	(0.29)	(0.49)	(0.52)	(0.64–1.16)
Prostate (men)	779	6005	113	884	803	5121	0.81
	(0.66)	(0.61)	(0.78)	(0.62)	(0.58)	(0.60)	(0.66–1.00)
Bladder	475	3651	96	772	467	2879	0.76
	(0.40)	(0.37)	(0.60)	(0.54)	(0.34)	(0.34)	(0.61–0.96)
Lymphoma	116	891	8	56	123	835	0.96
	(0.10)	(0.09)	(0.05)	(0.04)	(0.09)	(0.10)	(0.45–2.08)

95%CI = 95% confidence interval; HR = hazard ratio; PYAR = person-years at risk.

was not statistically significant), with a reduced incidence of esophageal, stomach, liver, breast, and lung and bronchial cancers. Excess weight or obesity, smoking, risky alcohol use, and diabetes were also associated with the risk of most cancers.

Several recent studies have reported an association between aspirin intake and specific cancers, although not all reported similar outcomes. Tsoi et al. [4], in analyzing different cancers, demonstrated that aspirin was protective against liver, colorectal, and pancreatic cancers, but was a risk factor for breast cancer. Other studies have demonstrated low-dose aspirin intake to be associated with lower risks of breast cancer [25], colorectal cancer [22,26,27], esophageal cancer [28], stomach cancer [10], liver cancer [11], and pancreatic cancer [12].

However, most published studies on the impact of aspirin intake have focused on a specific cancer and have not taken into account lifestyle and comorbidity risk factors. In contrast, our study considers several different cancers and individual risk factors, and our findings corroborate the literature in highlighting the protective effect of aspirin while contrasting this positive effect with the negative effects of individual risk factors.

Our findings regarding the possible association between aspirin intake and cancer were statistically significant for colorectal, pancreatic, and prostate cancers and lymphomas. The significant association we found for colorectal cancer corroborates the protective effective of around 30% against colorectal cancer reported elsewhere [29–31]. Likewise, our finding of a lower risk of pancreatic cancer has

Table 3
Cancer hazard ratios adjusted for sex, age, aspirin intake, BMI, smoking, risky alcohol use, and diabetes

aHR (95%CI)											
	Esophagus	Stomach	Colorectal	Liver	Pancreas	Lung-bronchus	Leukemia	Breast	Prostate	Bladder	Lymphoma
Female	-	-	-	-	-	-	-	-	NA	-	-
Male	4.3	1.9	1.9	2.2	1.7	3.8	1.6	NA	-	6.0	1.1
	(1.6–11.8)	(1.3–2.8)	(1.7–2.2)	(1.2–4.0)	(1.1–2.7)	(3.0–5.0)	(1.3–2.0)			(4.7–7.8)	(0.7–1.7)
Age [50–59]	-	-	-	-	-	-	-	-			
Age [60–69]	0.6	2.1	1.7	2.7	1.7	1.9	3.8	1.0	3.5	1.5	1.4
	(0.2–1.8)	(1.1–4.0)	(1.4–2.0)	(1.2–6.1)	(0.9–3.4)	(1.4–2.6)	(2.4–6.2)	(0.8–1.3)	(2.7–4.3)	(1.1–1.9)	(0.8–2.3)
Age [70–79]	1.0	3.7	2.0	3.2	2.4	2.5	5.8	0.9	5.2	2.6	1.9
	(0.4–2.7)	(2.0–6.8)	(1.7–2.4)	(1.4–7.6)	(1.3–4.5)	(1.8–3.3)	(3.6–9.3)	(0.7–1.1)	(3.4–5.5)	(2.0–3.5)	(1.2–3.0)
Age [80–89]	1.4	4.1	1.5	2.1	2.4	1.5	7.3	0.8	3.5	2.1	0.8
	(0.4–3.9)	(2.2–7.7)	(1.3–1.9)	(0.8–5.6)	(1.2–4.7)	(1.0–2.2)	(4.5–11.8)	(0.6–1.0)	(1.8–3.1)	(1.6–2,8)	(0.4–1.7)
Age [90–]	NA	2.5	0.4	1.0	1.0	0.4	1.3	0.2	0.2	0.6	NA
		(0.9–7.1)	(0.2–0.7)	(0.2–8.2)	(0.2–4.6)	(0.1–1.2)	(0.4–3.9)	(0.1–0.4)	(0.1–0.9)	(0.2–1.3)	
Aspirin intake	0.6	0.7	0.7	0.7	0.5	0.9	1.0	0.8	0.6	1.0	0.5
	(0.2–1.9)	(0.4–1.3)	(0.6–0.8)	(0.3–1.5)	(0.2–0.9)	(0.7–1.2)	(0.7–1.4)	(0.6–1.0)	(0.5–0.7)	(0.8–1.3)	(0.2–0.9)
BMI, normal	-	-	-	-	-	-	-	-			
BMI, overweight	1.4	1.4	1.5	1.0	1.4	0.8	1.2	1.5	1.9	1.2	1.0
	(0.4–4.0)	(0.8–2.5)	(1.2–1.8)	(0.5–2.2)	(0.4–2.7)	(0.6–1.1)	(0.8–1.7)	(1.1–1.9)	(1.5–2.5)	(0.9–1.6)	(0.6–1.7)
BMI, obese	0.8	1.3	1.5	1.1	1.4	0.7	1.3	1.9	2.2	1.2	1.2
	(0.3–2.6)	(0.7–2.2)	(1.3–1.9)	(0.5–2.4)	(0.7–2.8)	(0.5–1.0)	(0.9–1.8)	(1.5–2.4)	(1.7–2.8)	(0.9–1.7)	(0.7–2.0)
Smoking	2.4	1.0	1.4	1.6	1.4	1.7	0.9	1.1	1.0	1.8	0.8
	(1.0–5.6)	(0.6–1.7)	(1.2–1.8)	(0.8–3.2)	(0.8–2.6)	(1.4–2.2)	(0.6–1.4)	(0.7–1.6)	(0.8–1.1)	(1.5–2.3)	(0.4–1.6)
Risky alcohol use	2.1	1.0	1.4	1.2	1.2	2.1	2.0	0.8	0.8	1.0	1.5
	(0.5–9.9)	(0.3–3.2)	(1.1–1.9)	(0.3–4.9)	(0.4–4.0)	(1.4–3.1)	(1.2–3.7)	(0.3–2.4)	(0.6–1.2)	(0.7–1.6)	(0.5–4.1)
Diabetes	1.9	1.1	1.0	0.9	3.4	0.9	0.7	0.7	1.0	1.1	0.3
	(0.4–8.6)	(0.6–2.4)	(0.7–1.3)	(0.2–3.5)	(1.3–5.0)	(0.5–1.5)	(0.4–1.3)	(0.4–1.2)	(0.8–1.4)	(0.7–1.6)	(0.1–1.8)

95%CI = 95% confidence interval; aHR = adjusted hazard ratio; BMI = body mass index; NA = not applicable.

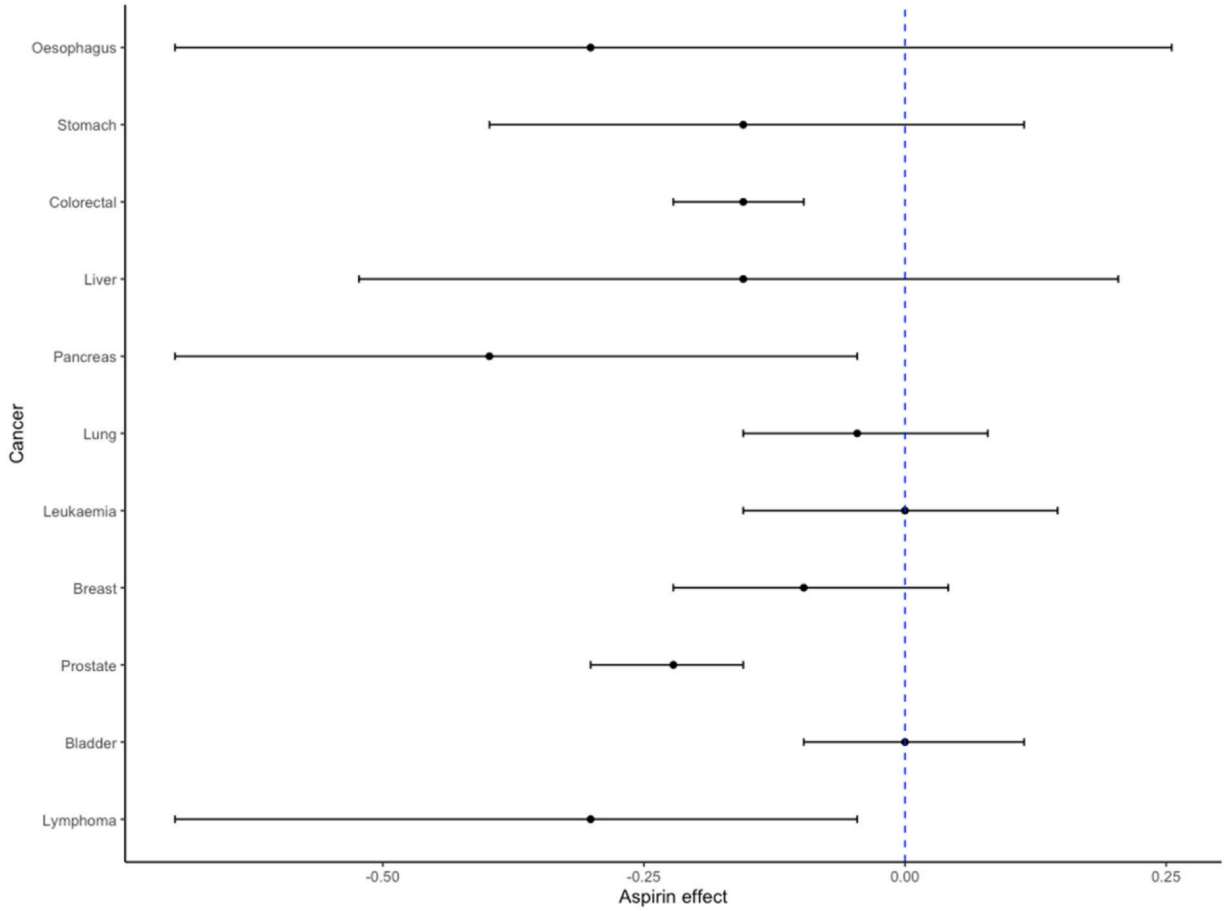

Fig. 2. Aspirin and cancer risk: adjusted hazard ratios (logarithmic scale).

elsewhere been expressed in terms of an incidence reduction of 50% [4]. This reduced incidence may be due to the fact that aspirin inhibits proliferation and stimulates pancreatic cancer cell apoptosis by inactivating the P13K/Akt/mTOR signaling pathway [32]. Our finding regarding prostate cancer in men corroborates the reduction of 40% reported elsewhere [33], attributable to aspirin-suppressing prostate cancer cell invasion by reducing MMP-9 activity and uPA expression and decreasing IKK-β-mediated NF-kB activation [34]. Finally, although there is relatively little literature in this area, aspirin intake has also been significantly associated with a lower risk of lymphomas. While a protective effect of 50% has been reported for both Hodgkin and non-Hodgkin lymphomas [35], other results are contradictory, as aspirin intake has been reported to decrease the incidence of Hodgkin lymphoma [36], but to increase the incidence of non-Hodgkin lymphoma [37]. Further studies are clearly needed to explore the association between the lymphomas and certain drugs, as was done in a recent study that reported an association between the use of dipyridamole and a lower risk of lymphoid neoplasms [38].

We also found suggestive protective effects of aspirin for esophageal, stomach, liver, breast, and lung and bronchial cancers, although the effects were not statistically significant. For esophageal cancer, a protective effect of around 50% has been reported elsewhere for aspirin intake [4,28], and the fact that our result for this cancer was not statistically significant may be due by the small number of included cases. For stomach cancer, our study indicated a 30% lower incidence, corroborating another study that recently reported a significant protective effect of 32% [39]. A similar protective effect of around 30% was obtained for liver cancer [11]; this effect can be attributed to inhibition of the AMPK-TOR (activated protein kinase - target-of-rapamycin) pathway and suppression of mTORC1 (mechanistic target of rapamycin complex 1) activity [40]. Our finding of a lower breast cancer risk corroborates a finding elsewhere [41], although our result was not significant. Finally, we found no significant association of aspirin intake with bladder cancer or leukemia.

We found significant differences between the sexes, with men showing a higher risk of developing any of the studied cancers, but especially colorectal cancer. The greater incidence in men compared to women can be attributed to the fact that men are typically characterized by higher cumulative levels of tobacco and alcohol intake than women [42]. Regarding age, the 70–89 age group, with some exceptions, showed a higher incidence of cancer, corroborating evidence reported elsewhere that cancer prevalence and incidence increase up to 89 years and thereafter decrease [43].

Some significant differences were observed in the studied lifestyle (overweight or obesity, smoking, and risky alcohol use) and comorbidity (diabetes) risk factors, suggesting that certain cancers are associated with specific risks.

We found that overweight or obesity significantly increased the risk for colorectal, breast, and prostate cancers, corroborating the literature. Colorectal cancer has been significantly associated with excess weight [44], with a 1.5-fold increased risk for BMI > 30 [45] and a 1.4-fold increased risk for BMI 25–29.9 [46]. The risk of breast cancer has been reported to be 1.3 and 1.6 times greater for overweight and obese women, respectively [47], while for prostate cancer, the increased risk for overweight and obese men has been reported as 1.8 and 2.0 times, respectively [48]. Our overweight or obesity findings regarding the remaining cancers in our study also suggest an association, but not to a statistically significant degree.

Regarding smoking and risky alcohol use, we found these to be significantly associated with lung and bronchial, bladder, and colorectal cancers, and nonsignificantly associated with esophageal, stomach, liver, and pancreatic cancers. Numerous studies have demonstrated that smoking raises the incidence of lung and bronchial cancer, for example, 1.7-fold [49], and bladder cancer, for example, 1.8-fold [50], and also of colorectal cancer [51]. Regarding risky alcohol use, our results also corroborate previous findings, for example, an increased incidence of 1.6 times for colorectal cancer [52], 1.9 times for lung cancer [54], and 1.8 times for leukemia [53,54]. Our results suggest that an exhaustive analysis is necessary to confirm these associations.

Finally, we found that diabetes was significantly associated with a 3.0-fold increased incidence of pancreatic cancer, while no associations were found for the remaining cancers.

The study has some limitations. First, aspirin intake may be underestimated, as patients could potentially purchase aspirin in pharmacies without a doctor's prescription, could be prescribed aspirin in the private healthcare sector (not co-financed), or could, once they know the treatment, obtain a prescription from the public sector to benefit from the discount. Second, aspirin use may be overestimated, as patients may have obtained it from a pharmacy but may not have taken it. Third, although the cancer registry is exhaustive, cases may have been diagnosed in hospitals in other regions or may not be correctly recorded, and the registry contains few cases of certain cancers such as esophageal and liver cancer. Finally, it was not possible to study a dose–response relationship between low-dose aspirin and cancers; in 90% of cases, 100 mg/day was the maximum aspirin dose, so we could not assess the effect of higher doses for comparison with lower doses.

The strengths of this study include the fact that risk factors, such as excess weight or obesity, smoking, and risky alcohol use, were taken into account, and that several cancers were considered. Furthermore, the risk of researcher bias was minimal, as the study was based on clinical practice data and physicians were unaware of the study aims.

In conclusion, this retrospective cohort study found a clear association between aspirin intake of more than or equal to 5 years and a reduced incidence of colorectal cancer, pancreatic cancer, prostate cancer, and lymphomas, as well as a possible protective effect for esophageal, stomach, liver, breast, and lung and bronchial cancers. We also confirm an association between cancers and excess weight (overweight or obesity), smoking, and risky alcohol use as lifestyle risk factors, and between pancreatic cancer and diabetes as a comorbidity risk factor.

In general, our results indicating that aspirin is protective against certain cancers reinforce the need for public health preventive measures and patient education regarding excess weight, smoking, risky alcohol use, and diabetes as risk factors for cancer.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Consent for publication

Not applicable.

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