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Long-term use of low-dose aspirin for cancer prevention: A 20-year longitudinal cohort study of 1,506,525 Hong Kong residents

Amy Lam[1] | Ziyu Hao[1] | Karen Yiu[2] | Stephen Chan[3] | Francis Chan[4] | Joseph Sung[5] | Kelvin Tsoi[1,2]

[1]Jockey Club School of Public Health and Primary Care, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, Hong Kong SAR

[2]Stanley Ho Big Data Decision Analytics Research Centre, The Chinese University of Hong Kong, Hong Kong, Hong Kong SAR

[3]State Key Laboratory of Translational Oncology, Department of Clinical Oncology, Sir YK Pao Centre for Cancer, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, Hong Kong SAR

[4]Department of Medicines and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, Hong Kong SAR

[5]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore

Correspondence
Joseph Sung, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore.
Email: josephsung@ntu.edu.sg

Kelvin Tsoi, Jockey Club School of Public Health and Primary Care, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, Hong Kong SAR.
Email: kelvintsoi@cuhk.edu.hk

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Abstract

Long-term use of low-dose aspirin has been demonstrated to reduce cancer risk, but the duration of necessary medication use remains uncertain. This study aimed to investigate the long-term chemoprotective effect of aspirin among the Chinese population. This population-based study included all aspirin users between 2000 and 2019. Aspirin users were age-sex matched with non-users at a 1:2 ratio. Cancer incidence and mortality were the main outcomes measured. Survival analyses with the Fine–Gray modelling were performed. The chemoprotective effects were measured by the sub-distribution hazard ratios (SHR) with control for the competing risks. A total of 538,147 aspirin users and 968,378 non-users were included, with a mean age of 64.8 years, 9,543,399 person-years of follow-up and 90% of users with 80 mg aspirin. The long-term use of aspirin was associated with a reduced risk of cancer (SHR 0.92, 95% CI 0.91–0.94) and a reduced risk of cancer mortality (SHR 0.80, 95% CI 0.79–0.82). Stronger chemopreventive effects were observed among those who used aspirin for more than 10 years, including risk reductions for lung (SHR 0.56, 95% CI 0.51–0.60), breast (SHR 0.34, 95% CI 0.29–0.38) and colorectal (SHR 0.37, 95% CI 0.33–0.40) cancers, but not for bladder cancer and leukaemia. Low-dose use of aspirin was associated with lower risk of cancer among Chinese. The association was even stronger for those using aspirin for more than 10 years. Prescription of aspirin may be started as early as at age of 40, as the chemoprotective effect also applied for early cancers.

KEYWORDS
aspirin, cancer, cancer prevention

What's New?

Low-dose aspirin use over an extended period is associated with a reduced risk of colorectal cancer (CRC) and potentially other malignancies. Duration of use to derive such benefits,

however, remains unclear. This retrospective study examined low-dose aspirin use for possible chemoprotective effects among individuals in Hong Kong. Analyses show a link between long-term aspirin use and decreased risk of common cancers, including CRC, liver cancer and breast cancer. The association is notably strong for aspirin use of 10 years or longer. The findings suggest that initiation of low-dose aspirin at ages as young as 40 could help protect against cancer.

1 | INTRODUCTION

Evidence demonstrates aspirin reduces the risk of most gastrointestinal (GI) cancers,[1] including colorectal cancer, stomach cancer, hepatobiliary tract cancer and pancreatic cancer, and some non-GI cancers including lung cancer, breast cancer, endometrial cancer, ovarian cancer and prostate cancer.[2] The benefit of low-dose aspirin is also associated with reduced risk of colorectal cancer incidence and mortality,[3,4] with benefits on cancer risk reduction observed with at least 3 years of aspirin use.[4] Recently, a 20-year Danish cohort study with 1,909,531 individuals from the nationwide registries demonstrated that the long-term use of low-dose aspirin marginally benefits several cancers, such as breast, liver and colon, but not for the overall cancer risk.[5]

Many of these studies[1] were conducted in Western countries, but more studies were coming up for the Asian regions, including China,[6,7] Hong Kong,[8,9] Korea[10,11] and Japan.[12] However, these studies were usually limited by the sample size or the duration of follow-up. A population-based longitudinal study is needed to demonstrate the chemoprotective effect of aspirin in different specific types of cancer in Asians as the disease burden can be different from Caucasian populations, such as nasopharyngeal cancer and oesophageal cancer.[13] Although these studies suggested the chemoprotective benefits of GI cancer, evidence of aspirin use for other non-GI cancers is still uncertain.[2,14]

Long-term use of aspirin for lower risk of cancer has been suggested,[1,5] but the definition of long-term use is always unclear among healthcare professionals. It implies further discussions on the early start of aspirin among the general population or the early stop of aspirin for those at risk of ulcer bleeding. Therefore, we conducted this population-based cohort study in Hong Kong to further explain the long-term effect of aspirin use for cancer prevention.

2 | METHODS

2.1 | Study design and data sources

This retrospective cohort study followed the standard guidelines of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[15] This study utilised electronic medical records from the Hospital Authority, which covered full patient activities for long-term chronic disease management in public hospitals for the entire population.[16]

2.2 | Subject recruitment and data extraction

The aspirin group included any patients who were (i) over 18 years old, (ii) without cancer history and (iii) prescribed aspirin for any indications between January 2000 and June 2019 under the Hospital Authority. Data from the Hospital Authority covers all medical services offered by public hospitals serving the entire population in Hong Kong, including outpatient clinics, inpatient services and day-patient services. The non-aspirin group included patients who received medical services from the Hospital Authority but had never been prescribed aspirin between 2000 and 2020. The aspirin users were randomly age-sex matched with non-users at a ratio of 1:2 for obtaining a sample population. Age-matching with 2 years older or younger was allowed. The date of matching was defined as the first prescription record of aspirin (Figure S1). Non-users who died before the matching date were excluded to reduce the immortal time bias.[17,18] To avoid reverse causation bias in aspirin prescription after a cancer diagnosis, patients who were prescribed aspirin for less than 6 months due to death or cancer were excluded. In case a patient suspended the prescription of aspirin for any reasons, the duration of aspirin use was discounted. Non-users who died or experienced cancer event within 6 months after matching date were also excluded. The primary purpose of aspirin prescription in the cohort is mainly to prevent cardiovascular and cerebrovascular diseases. Other medical information, including demographics, clinical records and dispensing records were retrieved until June 2020. Clinical diagnosis, procedures and the causes of death were classified in the form of the International Classification of Disease (ICD-9-CM or ICD-10) (Table S1). Definitions of the comorbidities were listed (Table S2).

2.3 | Study outcome

Any cancer incidence until the end of June 2020 was included as the primary outcome and cancer-related mortality was defined as the secondary outcome, including the top 10 cancer sites by the International Agency for Research on Cancer (IARC), the World Health Organization and other common cancers in Asia, such as nasopharyngeal, head and neck cancers. The cancer diagnoses were based on ICD-9-CM.

For a patient with more than one cancer diagnosis during the follow-up, all cancer incidences were counted separately.

2.4 | Statistical analysis

Baseline demographics in the aspirin and non-aspirin groups were presented. Standardised mean difference (SMD), presented in absolute value, was used to compare the difference in means or proportions with a consideration of combined standard deviation.[19] The SMD is less sensitive to sample size than traditional hypothesis testing and thus more appropriate for population-based cohorts. Propensity scores (PS) on individual risk factors were developed by the logistic regression model and inverse probability of treatment weighting (IPTW) was used to adjust for the imbalance of the baseline characteristics (Figure S2). Survival analyses with the Fine–Gray model[20] were fitted with the baseline characteristics from IPTW and concurrent use of other medication during the follow-up period. For the medication use during the follow-up period, proton pump inhibitors (PPI), statins, insulin were considered for any cancer-related outcomes, while oral anticoagulants and histamine-2 receptor antagonists (H2RA) were considered for bleeding outcome. The stabilisation of the weighted model was conducted to avoid excessive weighting.[21] Time to event was defined as the time from the date of aspirin use for 6 months to the date of cancer diagnosis, with censoring time considered on the mortality or at the end of follow-up until June 2020. Patients may early stop the aspirin due to bleeding risk, or start the aspirin at old age, so the duration of aspirin use was further categorised as <5 years, 5–9 years and ≥10 years. Subgroup analyses across different age groups of starting aspirin were considered in the survival analyses.

Primary survival analysis was conducted using a Fine–Gray model with IPTW and stabilisation. Sensitivity analyses on the Fine–Gray models with different ways of confounding controls were conducted, including (1) IPTW and no stabilisation, (2) PS matching with the 1-to-1 nearest neighbour algorithm and (3) model adjustment without IPTW or PS matching. The final model was further compared with the traditional Cox-proportional hazard model. Statistical significance was indicated by SMD greater than 0.1.[22] Additional sensitivity analysis on (1) re-categorising aspirin users with less than 180 days of aspirin prescription and (2) excluding aspirin users with less than 180 days of aspirin prescription were done. All statistical analyses were performed using R version 3.6.3 and SAS version 9.4.

3 | RESULTS

3.1 | Patient characteristics

A total of 583,079 aspirin users without cancer history were identified from 8,711,300 patients in the Hospital Authority between January 2000 and June 2019. After the exclusion of 3956 (0.7%) early cancer diagnoses and 40,976 (7%) mortalities from other diseases within 6 months of aspirin prescription, the final cohort included 538,147 aspirin users and matched with a total of 968,378 subjects who were not prescribed aspirin (Figure 1). Therefore, the total sample size of this study was 1,506,525. The mean age of the cohort was 64.8 years (SD = 14.3 years) with 53.8% male. Among the aspirin users, only 10,950 (2.0%) of them received high dose of aspirin for more than 300 mg a day. Aspirin users showed to have more comorbidities at the baseline, including hypertension (78% vs. 39), diabetes (34% vs. 17%), dyslipidaemia (49% vs. 16%), coronary artery disease (40% vs. 3.4%), heart failure (8.1% vs. 1%) and cardiac dysrhythmia (13% vs. 1.5%). During the follow-up period, aspirin users also demonstrated having more concurrent use of gastric protective agents (including H2RA and PPI), statin, oral anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs) and insulin. After the adjustment for the imbalance of baseline characteristics, no statistically significant difference was observed in the comorbidities (Table 1). Among the aspirin users, 330,564 (61.4%) were prescribed aspirin for less than 5 years, 127,680 (23.7%) for a duration between 5 and 9 years and 79,903 (14.8%) for at least 10 years.

3.2 | Cancer incidence and mortality

A total of 103,547 (6.9%) cancer cases were observed over 9,543,399 person-years in this cohort study. Lung cancer was the most common cancer with 2884 (1.5%) and 8590 (1.6%) cases in the aspirin and non-aspirin groups, respectively, followed by breast cancer (1060 (1.1%) vs. 4565 (1.7%)) and colorectal cancer (2119 (1.1%) vs. 7023 (1.3%)). The cumulative cancer incidences were comparable between aspirin and non-aspirin groups (13.5% vs. 13.3%) and decreased to 9.8% when aspirin was prescribed for more than 10 years (Table 2). Similarly, the cumulative cancer mortalities were also comparable (6.7% vs. 6.2%) and decreased to 4.1% for the long-term use of aspirin. Aspirin was associated with risk reduction in all cancer incidence (SHR 0.92, 95% CI 0.91–0.94). When aspirin was used for less than 5 years, the chemoprotective effects were only shown on stomach, liver, colorectal, breast and other gynaecological cancers. The cancer risk was further lowered for those who were prescribed aspirin for 10 years or more (SHR 0.43, 95% CI 0.41–0.45). The long-term benefit of aspirin was demonstrated in many types of cancer, except bladder cancer and leukaemia (Tables 3 and S3). Aspirin was associated with reduced all cancer mortality (SHR 0.80, 95% CI 0.79–0.82). The risk reduction in cancer mortality was even stronger for those with a longer duration of aspirin use across many cancer types. (Table S4).

3.3 | Subgroup analyses across different starting ages on aspirin

A total of 18,461 patients (3.4%) started aspirin before the age of 40 years, contributing to 149,820 person-years. Early use of aspirin reduced the risk of liver cancer (SHR 0.30, 95% CI 0.16–0.55), stomach cancer (SHR 0.11, 95% CI 0.04–0.32) and ovarian cancer (SHR 0.46, 95% CI 0.26–0.80) (Figure 2; Table S5). A total of 381,746

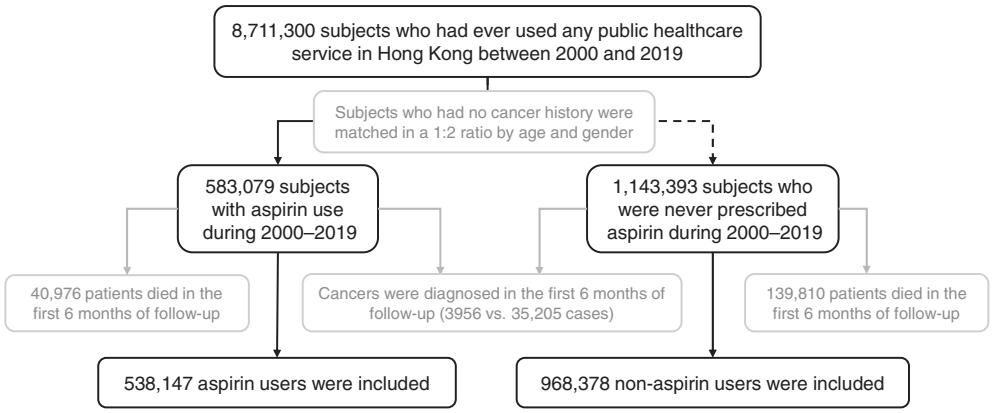

FIGURE 1 Flowchart of cohort matching for aspirin and non-aspirin groups. (*) Not available due to the small number of cancer incidences.

TABLE 1 Baseline characteristics between aspirin and non-aspirin groups.

	Overall cohort			Propensity score weighted[a]		
	Aspirin group	Non-aspirin group		Aspirin group	Non-aspirin group	
	N = 538,147	*N* = 968,378	SMD[b]	*N* = 709,165	*N* = 722,290	SMD[b]
Male, *N* (%)	280,021 (52.0)	530,361 (54.8)	0.055	351,192 (49.5)	361,273 (50.0)	0.010
Age, mean (SD)	67.2 (14.1)	63.4 (14.2)	**0.267**	66.4 (15.0)	64.3 (14.0)	**0.148**
Smoker, *N* (%)	24,320 (4.5)	29,820 (3.1)	0.075	27,162 (3.8)	31,190 (4.3)	0.025
Alcohol use, *N* (%)	2034 (0.4)	2875 (0.3)	0.014	2628 (0.4)	2447 (0.3)	0.005
History of disease, *N* (%)[c]						
Hypertension	417,938 (77.7)	375,016 (38.7)	**0.859**	462,412 (65.2)	442,021 (61.2)	0.083
Diabetes	183,771 (34.1)	166,571 (17.2)	**0.395**	201,779 (28.5)	192,677 (26.7)	0.040
Dyslipidaemia	264,119 (49.1)	152,721 (15.8)	**0.761**	223,717 (31.5)	205,636 (28.5)	0.067
Coronary artery disease	215,377 (40.0)	33,057 (3.4)	**0.991**	15,519 (2.2)	11,785 (1.6)	0.041
Stroke	84,205 (15.6)	11,063 (1.1)	**0.542**	3376 (0.5)	2598 (0.4)	0.018
Heart failure	43,691 (8.1)	8490 (0.9)	**0.355**	11,556 (1.6)	5921 (0.8)	0.074
Cardiac dysrhythmia	67,287 (12.5)	14,882 (1.5)	**0.439**	17,369 (2.4)	9394 (1.3)	0.085
Peripheral artery disease	9437 (1.8)	3675 (0.4)	**0.134**	5293 (0.7)	3505 (0.5)	0.033
Chronic kidney disease	97,790 (18.2)	80,877 (8.4)	**0.293**	102,548 (14.5)	83,270 (11.5)	0.087
Renal replacement therapy	6104 (1.1)	1351 (0.1)	**0.125**	1916 (0.3)	1022 (0.1)	0.028
Peptic ulcer disease	20,992 (3.9)	22,635 (2.3)	0.090	21,257 (3.0)	17,688 (2.4)	0.034
History of H. pylori infection	6729 (1.3)	7586 (0.8)	0.047	7107 (1.0)	6347 (0.9)	0.013
Liver disease	24,003 (4.5)	38,427 (4.0)	0.024	30,123 (4.2)	28,854 (4.0)	0.013
Medication use during follow-up, *N* (%)[d]						
Histamine-2 receptor antagonist	356,719 (66.3)	187,824 (19.4)	**1.076**	458,486 (64.7)	162,511 (22.5)	**0.939**
Proton pump inhibitor	210,368 (39.1)	76,186 (7.9)	**0.792**	226,210 (31.9)	62,740 (8.7)	**0.603**
Statin	334,559 (62.2)	233,598 (24.1)	**0.832**	359,249 (50.7)	273,609 (37.9)	**0.259**
Non-steroidal anti-inflammatory drugs	77,018 (14.3)	109,581 (11.3)	**0.090**	105,864 (14.9)	94,680 (13.1)	0.052
Oral anticoagulant	37,983 (7.1)	12,522 (1.3)	**0.291**	32,151 (4.5)	9321 (1.3)	**0.194**
Insulin	44,238 (8.2)	22,589 (2.3)	**0.266**	41,342 (5.8)	26,522 (3.7)	**0.102**

Note: Statistically significant results, highlighted in bold, were given at $p < 0.05$. Significant difference is identified when the SMD is greater than 0.1.[22]

[a]Propensity scores were developed by the logistic regression for the imbalance baseline characteristics. The weighted model is further stabilised to avoid excessive weighting.

[b]Standardised mean difference (SMD) is used to compare the difference between the groups.

[c]History of disease is defined as any disease that was diagnosed before the index date, that is, 6 months after aspirin initiation or the date of matching with non-users.

[d]Medication use for at least 6 months during the follow-up period.

TABLE 2 Cumulative cancer incidence and mortality for all cancer.

	Overall	Aspirin group	Duration of aspirin used			Non-aspirin group
			<5 years	5–9 years	≥10 years	
	N = 1,506,525	*N* = 538,147	*N* = 330,564	*N* = 127,680	*N* = 79,903	*N* = 968,378
Cancer incidence						
Number of cancers (%)	103,547 (6.9)	38,367 (7.1)	25,719 (7.8)	8982 (7.0)	3666 (4.6)	65,180 (6.7)
Person-years	9,543,399	3,510,052	1,534,393	947,144	1,028,515	6,033,347
Incidence/100,000 person-years	1085	1093	1676	948	356	1080
Cumulative incidence (95% CI)	13.7% (13.5%–13.9%)	13.5% (13.2%–13.8%)	14.3% (14.0%–14.6%)	14.9% (14.4%–15.4%)	9.8% (9.0%–10.7%)	13.3% (13.1%–13.5%)
Cancer mortality						
Number of deaths (%)	48,923 (3.3)	18,920 (3.5)	13,100 (4.0)	4283 (3.6)	1537 (1.9)	30,003 (3.1)
Mortality/100,000 person-years	501	528	824	445	149	485
Cumulative mortality (95% CI)	6.6% (6.5%–6.7%)	6.7% (6.6%–6.9%)	7.7% (7.4%–7.9%)	8.3% (7.9%–8.7%)	4.1% (3.8%–4.4%)	6.2% (6.1%–6.3%)

TABLE 3 Cancer incidence and sub-distribution hazard ratio by aspirin used.

	Aspirin group	Non-aspirin group	SHR (95% CI)[a] across different durations of aspirin used[b]			
Site of cancer	*N* (%)	*N* (%)	Overall	<5 years	5–9 years	≥10 years
Colorectal cancer	6427 (1.2)	11,205 (1.2)	**0.78 (0.76–0.81)**	**0.92 (0.89–0.95)**	**0.63 (0.60–0.67)**	**0.37 (0.33–0.40)**
Liver cancer	2737 (0.5)	6282 (0.7)	**0.67 (0.64–0.70)**	**0.76 (0.72–0.79)**	**0.55 (0.50–0.60)**	**0.30 (0.26–0.34)**
Stomach cancer	2017 (0.4)	3114 (0.3)	**0.79 (0.75–0.84)**	**0.93 (0.87–0.99)**	**0.61 (0.55–0.68)**	**0.37 (0.31–0.44)**
Pancreatic cancer	1327 (0.3)	2132 (0.2)	**0.85 (0.79–0.91)**	0.97 (0.90–1.05)	**0.78 (0.69–0.87)**	**0.37 (0.30–0.45)**
Gallbladder cancer	1496 (0.3)	1914 (0.2)	1.02 (0.95–1.10)	**1.15 (1.07–1.24)**	**0.85 (0.76–0.96)**	**0.59 (0.49–0.71)**
Oesophageal cancer	710 (0.1)	1243 (0.1)	1.02 (0.93–1.12)	**1.14 (1.03–1.26)**	**0.84 (0.71–0.99)**	**0.55 (0.42–0.71)**
Lung cancer	8647 (1.6)	13,907 (1.4)	1.01 (0.99–1.04)	**1.14 (1.11–1.18)**	**0.85 (0.81–0.89)**	**0.56 (0.51–0.60)**
Prostate cancer	3166 (1.1)	5330 (1.0)	**0.95 (0.91–1.00)**	**1.10 (1.05–1.16)**	**0.81 (0.75–0.87)**	**0.47 (0.41–0.53)**
Breast cancer	2806 (1.1)	6442 (1.5)	**0.76 (0.73–0.79)**	**0.87 (0.84–0.91)**	**0.63 (0.58–0.68)**	**0.34 (0.29–0.38)**
Cervical cancer	328 (0.1)	665 (0.2)	**0.80 (0.70–0.91)**	**0.87 (0.76–1.00)**	**0.72 (0.57–0.91)**	**0.50 (0.35–0.71)**
Ovarian cancer	267 (0.1)	670 (0.2)	**0.71 (0.62–0.81)**	**0.80 (0.70–0.93)**	**0.47 (0.34–0.63)**	**0.54 (0.38–0.76)**
Corpus uteri cancer	496 (0.2)	1178 (0.3)	**0.65 (0.58–0.72)**	**0.76 (0.68–0.85)**	**0.60 (0.48–0.74)**	NA
Kidney cancer	902 (0.2)	1230 (0.1)	0.93 (0.85–1.02)	**1.11 (1.01–1.22)**	**0.67 (0.56–0.79)**	**0.36 (0.27–0.48)**
Bladder cancer	883 (0.2)	991 (0.1)	**1.24 (1.12–1.36)**	**1.38 (1.24–1.53)**	0.96 (0.81–1.13)	0.97 (0.78–1.21)
Head and neck cancer	1422 (0.3)	1974 (0.2)	**2.50 (2.34–2.67)**	**3.00 (2.81–3.19)**	**1.16 (1.01–1.33)**	**0.62 (0.49–0.79)**
Thyroid cancer	362 (0.1)	801 (0.1)	**0.82 (0.72–0.93)**	1.01 (0.89–1.14)	**0.63 (0.49–0.80)**	NA
Skin cancer	1259 (0.2)	1632 (0.2)	**0.91 (0.84–0.98)**	0.99 (0.91–1.07)	**0.86 (0.76–0.98)**	**0.54 (0.44–0.67)**
Bone and soft tissue cancer	1566 (0.3)	2210 (0.2)	**0.90 (0.84–0.96)**	1.00 (0.93–1.07)	**0.81 (0.72–0.91)**	**0.50 (0.42–0.61)**
Leukaemia	732 (0.1)	1184 (0.1)	**1.16 (1.06–1.28)**	**1.19 (1.07–1.31)**	1.17 (0.99–1.37)	1.00 (0.81–1.22)
Non-Hodgkin lymphoma	1145 (0.2)	2143 (0.2)	0.97 (0.90–1.05)	1.05 (0.97–1.14)	0.90 (0.80–1.02)	**0.60 (0.50–0.72)**
Multiple myeloma	865 (0.2)	801 (0.1)	**1.32 (1.20–1.47)**	**1.58 (1.42–1.76)**	0.90 (0.76–1.07)	**0.68 (0.52–0.87)**
All cancer	38,367 (7.1)	65,180 (6.7)	**0.92 (0.91–0.94)**	**1.08 (1.07–1.10)**	**0.72 (0.70–0.73)**	**0.43 (0.41–0.45)**

Note: Statistically significant results, highlighted in bold, were given at $p < 0.05$. NA: not available due to the small number of cancer incidences.
[a]Sub-distribution hazard ratio (SHR) was developed by the Fine–Gray model with propensity score weighting, and competing risk adjustments for death.
[b]Duration of aspirin use is defined by the total duration of aspirin prescription during the follow-up period.

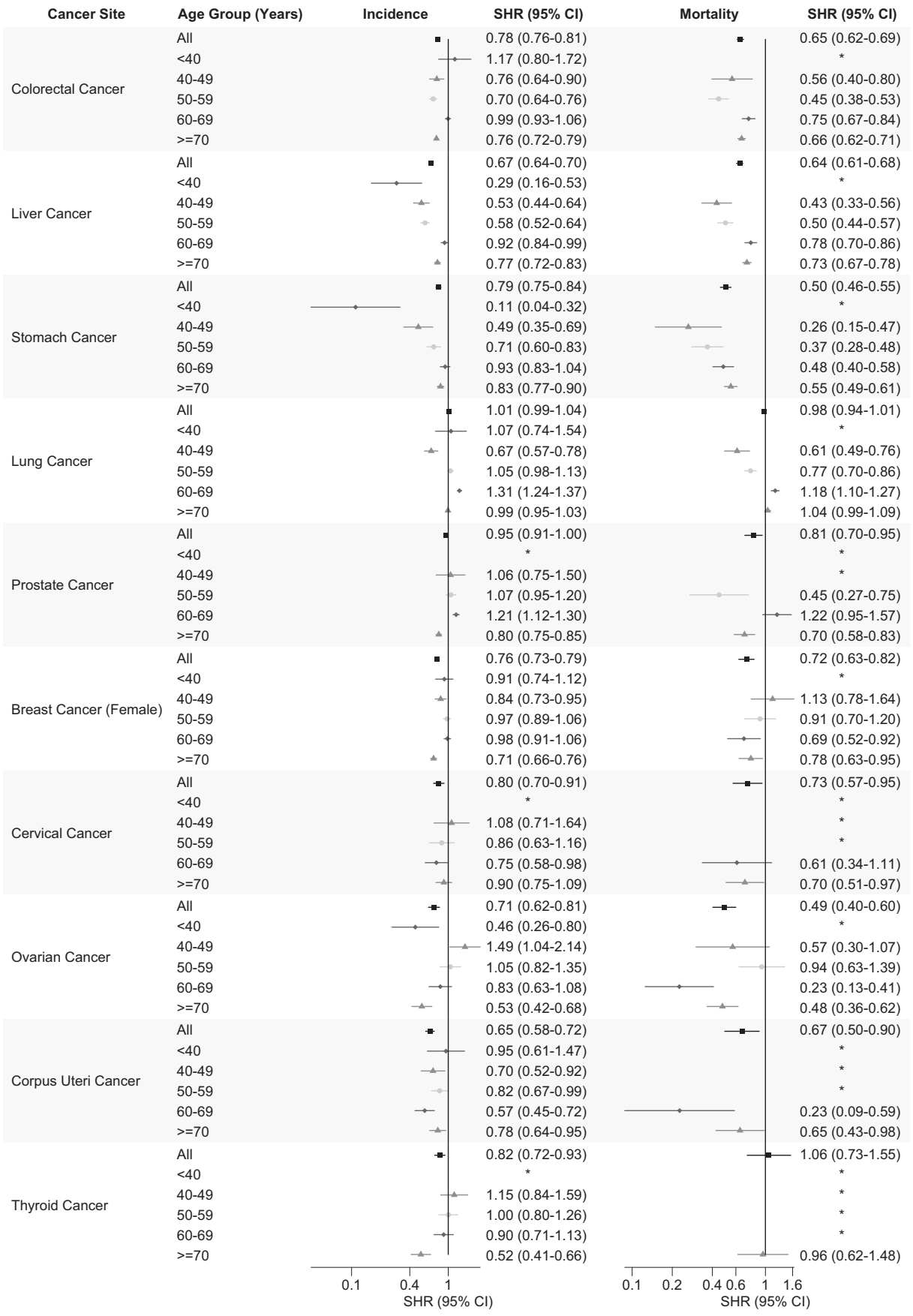

FIGURE 2 Risk of cancer incidence and mortality by the starting age of aspirin for the top 10 cancer sites by the International Agency for Research on Cancer, WHO.

patients (70.9%) started aspirin after the age of 60 years, contributing to 2,288,914 person-years. Late start of aspirin did not reduce the risk of lung, liver, stomach and colorectal cancers. In general, the use of aspirin starting from any age can reduce the risk of cancer-related mortality, especially for stomach, liver and colorectal cancers (Figure 2; Table S6).

3.4 | Sensitivity analysis

Survival analyses using the Fine–Gray models with different methods of confounding controls showed consistent results on the chemoprotective effects of long-term use of aspirin (Table S7). However, the traditional Cox proportional hazard model showed a moderate increased risk of overall cancer (HR 1.02, 95% CI 1.00–1.04), while risks of GI cancers, including colorectal, liver and stomach cancers, remained reduced. Sensitivity analysis on re-categorising (SHR 0.95, 95% CI 0.94–0.95) and excluding (SHR 0.89, 95% CI 0.88–0.91) short duration of aspirin prescription showed consistent results on overall chemoprotective effects of aspirin.

4 | DISCUSSION

In this territory-wide cohort study involving more than a million Hong Kong residents, the long-term use of low-dose aspirin is associated with a reduction in risk of various cancers such as stomach, liver, breast, ovarian and colorectum, but not for leukaemia and bladder cancers. The association is stronger for those using aspirin for more than 10 years. The chemoprotective effect of aspirin can also be demonstrated for early cancers, such as stomach, liver and breast cancers.

A recent Danish cohort study using data from nationwide registries including 1,909,531 subjects aged 40–70 at baseline examined the association between aspirin use and cancer risk.[5] The study observed a total number of 111,316 cancer cases over 34,702,805 person-years. The study found a slightly increased risk of overall cancer risk (HR 1.04, 95% CI 1.03–1.06). The long-term use of low-dose aspirin reducing the risk of cancer is comparable to our findings at some common sites, including the liver, breast and colorectum (Table S8). However, this paper provided limited control for the competing risk of the other causes of death, such as cardiovascular disease, so the benefits of aspirin use may be underinterpreted. The current Asian cohort study further identified the benefit of aspirin on reduced risk of stomach, pancreatic, prostate and ovarian cancers. The Danish cohort found the long-term use of aspirin increased the risk of lung cancer, whereas our cohort found an increased risk of head and neck cancer, leukaemia and Hodgkin lymphoma. Both studies demonstrated the long-term use of aspirin increased the risk of bladder cancer. Another recent Norwegian study[23] and many other studies[1] suggested a reduced risk of colorectal cancer with a significant duration effect of aspirin use. Cancer incidence could be very different between the Western and Asian populations. Asian population might contribute more stomach cancer with a higher prevalence of H. pylori infection, more liver cancer with a higher proportion of hepatitis B virus carriers, and more nasopharyngeal cancer with a higher consumption of preserved food. These factors may further advance cancer incidences among Asians with the inherited genetic predisposition.[24] Therefore, this population-based study in Hong Kong may further compare the evidence from the Western population and conclude that the long-term use of aspirin can reduce the risk of many types of cancer.

Previously we reported the effect of aspirin on cancer prevention in Hong Kong as a 10-year cohort study.[16] As a sequel to that study, we further examine the effect in a 20-year cohort in the current analysis. Due to subject confidentiality and de-identified electronic health records under ethics consideration, subjects between two study cohorts cannot be matched, and therefore the current analysis should not be deemed as extension of the previous cohort study. There were some differences in the results from the two studies. Aspirin was associated with lower risk of lung cancer and leukaemia, higher risk of breast cancer and no association between aspirin use and bladder cancer and prostate cancer in the 10-year cohort study. However, in the current 20-year study, we found no association between aspirin use and lung cancer incidence, increased risk of leukaemia and bladder cancer, and reduced risk of breast cancer and prostate cancer. When we considered also the duration of aspirin use, lower risk of lung cancer incidence and no association with bladder cancer incidence were observed with a longer duration of aspirin use, which aligned with the previous findings. For prostate cancer, the previous findings showed a marginal trend of decreased risk of incidence despite non-significance (HR 0.95, 95% CI 0.88–1.03) which was indeed of similar trend to current findings (SHR 0.95, 95% CI 0.91–1.00). The lower risk of leukaemia observed in the previous study might be due to the different definition used for cancer identification, with leukaemia in the previous study including some of the codes used for non-Hodgkin lymphoma in the current study, which might lead to discrepancy in results. Indeed, our current study showed long-term use of aspirin was associated with lower risk of non-Hodgkin lymphoma which to some extent might echo the previous cohort study. While discrepancy in aspirin effect on breast cancer incidence might not be easily explained, findings on lower risk of breast cancer in the current study generally echoed with the other studies.[2]

Guidelines recommended that aspirin start at the age of 50 years as a primary prevention of colorectal cancer, including the US Preventive Services Task Force (USPSTF) in 2016. It suggests that low-dose aspirin for primary prevention of both cardiovascular disease and colorectal cancer in adults aged 50–59 years at daily low-dose aspirin for at least 10 years.[25] However, another ASPREE study comparing 19,114 elderly aspirin users with a median follow-up of 4.7 years failed to demonstrate the protective effect of aspirin against cancer in the elderly population without cardiovascular disease.[26,27] With the additional information, the USPSTF guidelines were reversed in 2022, and the recommendation on aspirin use for primary prevention of colorectal cancer was removed.[28] In this study, when the use of aspirin was less than 5 years, it demonstrated a marginally increased risk of overall cancer and a substantially increased risk of nasopharyngeal

cancer and bladder cancer. The original cancer risk outweighing the potential benefits of aspirin use may be a possible explanation. For example, it would take approximately 8 years for a lung squamous cell carcinoma to develop to a size commonly diagnosed.[29] Therefore, in those receiving short-duration of aspirin, carcinoma may exist before the start of aspirin. It also explained another observation of this study that the chemoprotective effects almost cover all types of cancer for those prescribed aspirin over 10 years. The early use of aspirin at the age of 40 years showed benefits for cancer that may appear in middle age, including stomach, liver and breast cancers. However, the benefit is not observed with nasopharyngeal cancer which is usually diagnosed before the age of 50 years. Therefore, further investigation should be conducted for the optimal starting age of aspirin use.

Survival analyses were generally consistent over different confounding adjustment methods in the Fine–Gray models and concluded the chemoprotective effects of long-term use of aspirin. When the traditional Cox proportional hazard model was applied, a moderate increased risk of overall cancer was observed. However, this method ignored the control for the competing risks of other causes of death.[30] Therefore, we believed that survival analysis using the Fine–Gray model with sub-distribution hazard ratio[30] is more appropriate for this 20-year longitudinal cohort study with complicated mortality structures.[31] While the Fine–Gray model enabled the estimation of the risk of cancer occurrence over time through the cumulative incidence function, it is essential to ensure the cautious interpretation of SHR derived from the model. These results offered insights into the direction of association rather than the magnitude of the effect.[32] In our present analysis, the emphasis was placed on understanding the trends and patterns of aspirin's impact on the cumulative incidence of cancer. Specific numerical estimations can be cross-referenced with cause-specific hazard ratios provided in Table S7, bearing in mind that the interpretation of cause-specific hazard ratios differs from that of sub-distribution hazard ratios.

Aspirin works as cyclooxygenase (COX) inhibitor. Despite the widely reported COX-2 involvement in cancer development,[33] it should be reiterated that effect of low-dose aspirin on COX-2 inhibition is less substantial.[34] Instead, the chemoprotective effect of aspirin has been proposed to be due to its COX-1 inhibition in platelet preventing the release of inflammatory mediators and subsequently reducing COX-2 expression.[35] Apart from the COX inhibition, there has been other proposed mechanisms for aspirin chemoprotective effect, such as aspirin metabolite inhibition on cancer cell growth,[35] inhibition on inflammation-mediated carcinogenesis through NF-KB signalling inhibition and inhibition of mTOR signalling through AMPK activation.[36] Moreover, inhibition of platelet aggregation prevents the spread of cancer cells through immune elimination.[37] However, due to aspirin nature on COX inhibition, it has been well-established that aspirin increased bleeding risk, including GI bleeding and intracranial haemorrhage.[38] In the ARRIVE trial investigating aspirin effect in cardiovascular disease primary prevention in patients with average cardiovascular risk with a median follow-up time of 5 years, the risk of GI bleeding increased by double.[39] Higher risk of GI bleeding was generally observed in East Asian.[40] Our study also showed a remarkably increased risk of bleeding event adjusted with the use of gastro-protecting agents such as H2RA or PPI (Table S9).

The current study included more than a million Hong Kong residents, thus providing an extensive investigation for the long-term use of aspirin for primary cancer prevention in the Asian population, but there are still some limitations. First, the study is still restrained by its retrospective nature of observational study. Historical confounding factors are always critical for the result interpretation. We already adjusted the important confounding factors for the cancer outcomes and controlled for the competing risk of other causes of death, but time-varying covariates on these factors cannot be totally controlled in the Fine–Gray model.[41] Second, there is no information on the family history of cancer and other behavioural information, such as diet and exercise. Otherwise, the model estimation will be more accurate. Third, this study relied on the prescription records of aspirin in our healthcare system, and thus medication adherence was unknown. A previous study demonstrated good medication adherence in the population with chronic illnesses in Hong Kong.[42] Moreover, there could be a chance of an increased risk of secondary cancer due to the presence of primary cancer. However, our current analysis evaluated each cancer type independently, without considering the potential elevated risk associated with primary cancer. Finally, most of the aspirin users (98.0%) included in the current study were using low-dose aspirin. Therefore, this restricted the focus of the current study only on the chemoprotective effect of low-dose aspirin.

5 | CONCLUSION

In this 20-year longitudinal cohort study involving more than a million Hong Kong residents, the long-term use of low-dose aspirin is associated with a reduction in the risk of various types of cancers. The association is even stronger for those using aspirin for more than 10 years. The prescription of aspirin should be started as early as at 40s, as the chemoprotective effect is also applied to early cancers, such as stomach, liver and breast cancers.

AUTHOR CONTRIBUTIONS

Amy Lam: Methodology; formal analysis; writing – original draft; writing – review and editing. **Ziyu Hao:** Formal analysis; writing – review and editing. **Karen Yiu:** Writing – review and editing; supervision. **Stephen Chan:** Writing – review and editing; funding acquisition. **Francis Chan:** Writing – review and editing; funding acquisition. **Joseph Sung:** Conceptualization; writing – review and editing; supervision; funding acquisition. **Kelvin Tsoi:** Conceptualization; methodology; writing – original draft; writing – review and editing; supervision; funding acquisition.

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CONFLICT OF INTEREST STATEMENT

FC is the co-founder, non-executive board chairman, honorary chief medical officer and shareholder of GenieBiome Ltd. The company provides microbiome healthcare services and products including M3CRC and G-NiiB Immunity formulas to tackle a myriad of diseases, including the post-novel virus conditions such as difficulty in sleeping, which FC is not involved in any business negotiation process. SC received research funds from Celleron, Genorbio, Ipsen, received consultation fees from Astra-Zeneca, Eisai and MSD; received honoraria for lectures from Astra-Zeneca, BMS, Eisai, Ipsen, MSD and Roche; received travel support for attending meetings from Ipsen, Roche, Eisai, Astra-Zeneca and Novartis. Other authors declare no competing interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Data were extracted without personal identity, and informed consent of the participants was not required. Ethical approval of the study was obtained from the Joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee (reference number CREC 2019-309).

ORCID

Amy Lam https://orcid.org/0000-0003-0139-2328
Kelvin Tsoi https://orcid.org/0000-0001-5580-7686

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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