Post-operative Aspirin Use and Colorectal Cancer-specific Survival in Patients with Stage I-III Colorectal Cancer

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Abstract. *Background: Recent observational studies suggest that postoperative aspirin use may improve Colorectal cancer (CRC)-specific survival and overall survival (OS). In this study, we aimed to assess the effects of aspirin use on outcomes in a predominantly Asian cohort of patients with CRC. Patients and Methods: Case records of patients undergoing curative resection for stage I-III CRC were retrieved for clinical data and patterns of aspirin use and vital data were determined from hospital electronic prescription records, hospital pharmacy dispensing records, national clinical and prescription databases. CRC-specific and recurrence-free survival (RFS) amongst aspirin users and non-users were analyzed and compared using the Cox proportional hazards model. Results: Out of 726 patients with CRC, 103 were regular aspirin users and 623 were non-users. The median age of the cohort was 65 years (range=22-94 years) and the majority of patients were Chinese (90%). Nineteen percent, 31% and 47% had stage I, II and III CRC respectively; tumor staging was unknown for 3%. After adjusting for prognostic factors (age, stage, lymph node stage, grade, lesion site, perineural invasion, lymphvascular invasion), the risk of CRC relapse or death from CRC was approximately 60% lower compared to patients who were not postoperative aspirin users (Hazard Ratio=0.38, 95% Confidence Interval=0.17-0.84, p=0.017). No benefit was observed for preoperative use of aspirin. Conclusion: In this single-Institution study, with long-term follow-up of patients with stage I-III-resected CRC, postoperative aspirin use was associated with reduced risk of relapse of and death from CRC.*

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Colorectal cancer (CRC) is the third most prevalent type of cancer worldwide, with more than 1.2 million new cases diagnosed and 600,000 deaths worldwide each year (8, 13). Coincident with the rising incidence of CRC globally, population demographics are also shifting the cancer burden to the developing world, where it exerts a disproportionately detrimental effect (12). By the year 2020, it is estimated that 70% of all new cancer cases globally will occur in lower-income countries, which are less able to manage this disease (1). Development of new cancer therapies will need to be not only effective but also affordable (3).

More recently, observational studies have suggested that aspirin may have a role in reducing risk of cancer recurrence, metastasis and cancer-specific mortality in established cancer, especially CRC (2, 6, 9, 15). In a meta-analysis of five cardiovascular trials evaluating 17,285 individuals randomized to daily aspirin *versus* no aspirin, patients with localized cancer receiving aspirin had considerably reduced risk of developing subsequent metastasis on follow-up (Hazard ratio (HR)=0.45; 95% Confidence interval (CI)=0.28-0.72) with patients with CRC experiencing the greatest risk reduction in metastasis (HR=0.26; 95% CI=0.11-0.57) (11). In a combined analysis of 1,279 patients with stage I to III CRC in the Nurses' Health Study and Health Professional's Follow-up Study, regular post-diagnosis aspirin use was associated with a reduction in CRC-specific mortality of nearly 30% (multivariate HR=0.71; 95% CI=0.53-0.95) (5).

These results were further corroborated by a Dutch case–control study by Bastiaannet *et al.* which found an improvement in overall survival between post-diagnosis aspirin users *versus* non-users (multivariate HR=0.77; 95% CI=0.63-0.95) with a multivariate HR for CRC-specific overall survival of 0.65 (95% CI=0.50-0.84) (2). McCowan *et al.* also reported similar findings in a Scottish study involving 2,990 patients. In this instance, post-diagnosis use

Table I. *Clinical characteristics of patients stratified by aspirin use.*

Characteristics		Aspirin usage after operation		*p*-Value[a]
	Total (N=726)	No (N=634)	Yes (N=92)	
Median (range) age at operation, years	65 (22-94)	64 (22-94)	71 (43-91)	-
Gender, N (%)				0.085
Female	321 (44)	288 (45)	33 (36)	
Male	405 (56)	346 (55)	59 (64)	
Ethnicity, N (%)				<0.001
Chinese	650 (90)	571 (90)	79 (86)	
Malay	28 (4)	25 (4)	3 (3)	
Indian	18 (2)	9 (1)	9 (10)	
Other	30 (4)	29 (5)	1 (1)	
Stage, N (%)				0.32
I	136 (19)	114 (18)	22 (24)	
II	226 (31)	196 (31)	30 (33)	
III	342 (47)	304 (48)	38 (41)	
Unknown	22 (3)	20 (3)	2 (2)	
Lymph node stage: number of lymph nodes				0.013
N0: 0	380 (52)	327 (52)	53 (58)	
N1: 1-3	186 (26)	157 (25)	29 (32)	
N2: ≥4	160 (22)	150 (24)	10 (11)	
Tumor grade, N (%)				0.77
Undifferentiated/poorly differentiated	36 (5)	30 (5)	6 (7)	
Moderately differentiated	589 (81)	515 (81)	74 (80)	
Well differentiated	77 (11)	67 (11)	10 (11)	
Unknown	24 (3)	22 (3)	2 (2)	
Lesion site, N (%)				0.36
Left	590 (81)	512 (81)	78 (85)	
Right	136 (19)	122 (19)	14 (15)	
Perineural invasion, N (%)				0.45
No	576 (79)	500 (79)	76 (83)	
Yes	113 (16)	101 (16)	12 (13)	
Not reviewed	37 (5)	33 (5)	4 (4)	
Vascular embolism, N (%)				0.10
No	521 (72)	449 (71)	72 (78)	
Yes	177 (24)	161 (25)	16 (17)	
Not reviewed	28 (4)	24 (4)	4 (4)	

[a]Two-sided *p*-values based on Chi-square test/Fisher's exact test, excluding unknowns.

was associated with lower risk of CRC-specific mortality after adjusting for other prognostic factors (HR=0.58, 95% CI=0.45-0.75, $p<0.01$) (9).

To date, data supporting the adjuvant benefit of aspirin in the secondary prevention of CRC has been derived exclusively from Western cohorts. In order to assess the effects of postoperative aspirin use in a cohort of mainly Asian patients undergoing curative CRC resections at our Center, we performed an analysis of 726 patients who underwent curative surgery at our Hospital during 2006 and 2007.

Patients and Methods

Case records of all patients undergoing curative resection for stage I-III CRC at the Singapore General Hospital (SGH) and National Cancer Centre Singapore (NCC) were retrieved and manually culled for clinical data. Patterns of aspirin use were extracted from the SGH and NCC pharmacy database, and the National Electronic Patient and Drug Database (EMRX). Vital status and the death date for patients were obtained from hospital records and supplemented with data from the National Death Registry Database.

In order to control for potential confounding factors that may influence outcomes, patients with familial adenomatosis polyposis

Table II. *Univariate analysis for colorectal cancer-specific survival.*

Characteristics	Events/patients	HR (95% CI)	*p*-Value
Age at operation in years (10-year increment)	181/726	0.99 (0.88-1.12)	0.88
Age group, years			
<40	2/15	1	-
40-55	41/136	2.33 (0.56-9.64)	0.24
55-70	77/331	1.85 (0.45-7.52)	0.39
>70	61/244	2.14 (0.52-8.74)	0.29
Gender			
Female	82/321	1	-
Male	99/405	0.94 (0.70-1.26)	0.66
Race			
Chinese	166/650	1	-
Malay	8/28	1.28 (0.63-2.62)	0.49
Indian	5/18	1.01 (0.42-2.46)	0.98
Other	2/30	0.51 (0.13-2.06)	0.35
Stage			
I	9/136	1	-
II	36/226	2.61 (1.26-5.44)	0.010
III	136/342	7.86 (4.00-15.44)	<0.001
Lymph node stage: number of lymph nodes			
N0: 0	44/380	1	-
N1: 1-3	60/186	3.24 (2.19-4.79)	<0.001
N2: ≥4	77/160	5.86 (4.03-8.52)	<0.001
Tumor grade			
Undifferentiated/poorly differentiated	18/36	1	-
Moderately differentiated	143/589	0.30 (0.19-0.49)	<0.001
Well differentiated	20/77	0.32 (0.17-0.60)	<0.001
Lesion site			
Left	151/590	1	-
Right	30/136	0.84 (0.56-1.24)	0.37
Perineural invasion			
No	119/576	1	-
Yes	55/113	3.16 (2.29-4.37)	<0.001
Vascular embolism			
No	100/521	1	-
Yes	74/177	2.70 (1.99-3.65)	<0.001
Aspirin use before/after operation			
No	153/623	1	-
Yes	28/103	1.06 (0.71-1.58)	0.78
Aspirin use before operation			
No	162/678	1	-
Yes	19/48	1.76 (1.09-2.83)	0.020
Aspirin use after operation			
No	160/634	1	-
Yes	21/92	0.81 (0.51-1.28)	0.37

CI: Confidence interval; HR: hazard ratio.

coli syndrome (FAP), Lynch syndrome, history of inflammatory bowel disease, R1 or R2 resections, synchronous tumors, mucinous and signet ring cell tumors, as well as stage IV disease, were excluded from our analysis. Eligible patients who developed systemic metastases within six months of diagnosis were re-classified as having stage IV CRC, and also excluded from the study.

The location of the index CRC was defined as a right-sided lesion if it arose proximal to the splenic flexure. Lesions at or distal to the splenic flexure were considered left-sided. We defined synchronous CRC as tumors being found at the index operation for CRC or diagnosed within 12 months after resection of the index CRC. Stage of disease was evaluated by plain chest radiographs/computed tomography of the thorax, abdomen and pelvis. Clinical and pathologic staging of disease was according to American Joint Committee on Cancer Staging Manual, seventh edition (7), with review of the biopsies or resected specimen. Aspirin use was stratified and analyzed according to pre- and postoperative use. Mortality data and the cause of death were

Table III. *Univariate analysis for recurrence-free survival.*

Characteristics	Events/patients	HR (95% CI)	*p*-Value
Age at operation in years (every 10-year increment)	226/726	0.97 (0.87-1.08)	0.55
Age Group, years			
<40	2/15	1	-
40-55	51/136	3.15 (0.77-12.95)	0.11
55-70	99/331	2.44 (0.60-9.88)	0.21
>70	74/244	2.60 (0.64-10.60)	0.18
Gender			
Female	97/321	1	-
Male	129/405	1.08 (0.83-1.40)	0.59
Race			
Chinese	206/650	1	-
Malay	9/28	1.09 (0.56-2.13)	0.80
Indian	6/18	0.92 (0.41-2.07)	0.84
Others	5/30	0.95 (0.39-2.31)	0.91
Stage			
I	14/136	1	-
II	46/226	2.19 (1.21-3.99)	0.010
III	165/342	6.24 (3.62-10.78)	<0.001
Lymph Node Stage: Number of lymph nodes			
N0: 0	60/380	1	-
N1: 1-3	76/186	2.99 (2.13-4.19)	<0.001
N2: ≥4	90/160	5.12 (3.69-7.11)	<0.001
Tumor grade			
Undifferentiated/ poorly differentiated	22/36	1	-
Moderately differentiated	182/589	0.28 (0.18-0.44)	<0.001
Well differentiated	21/77	0.25 (0.13-0.45)	<0.001
Lesion site			
Left	187/590	1	-
Right	39/136	0.88 (0.62-1.24)	0.46
Perineural invasion			
No	149/576	1	-
Yes	68/113	3.27 (2.45-4.36)	<0.001
Vascular embolism			
No	131/521	1	-
Yes	87/177	2.49 (1.90-3.26)	<0.001
Aspirin use before/ after operation			
No	191/623	1	-
Yes	35/103	1.04 (0.72-1.48)	0.851
Aspirin use before operation			
No	204/678	1	-
Yes	22/48	1.56 (1.01-2.43)	0.046
Aspirin use after operation			
No	198/634	1	-
Yes	28/92	0.86 (0.58-1.27)	0.44

CI: Confidence interval; HR: hazard ratio.

obtained from the Singapore Cancer Registry. Study end-points analyzed were CRC-specific survival (CSS) and recurrence-free survival (RFS). CSS was calculated from the date of operation for CRC to the date of CRC-related death. RFS was calculated from the date of operation to the date of first recurrence or CRC-related death. Overall survival (OS) was calculated from the date of operation for CRC to the date of death from any cause. Patients who were still alive or lost to follow-up were censored at their last follow-up date. All non-CRC-related deaths were censored at the date of death.

Patients were analyzed for outcomes according to postoperative aspirin use. Univariate and multivariate analyses were based on the Cox proportional hazards model. Tumor stage, lymph node stage, tumor grade, lesion site, perineural invasion and vascular embolism were added to the final multivariate model for age and aspirin use, respectively, to account for their confounding effects. Proportional hazards assumptions were checked by Schoenfeld's global test. A *p*-value of less than 0.05 was considered statistically significant. All analyses were performed using the Stata Statistical Software, Release 11.0 (StataCorp. 2009,College Station, Texas, USA).

Table IV. *Multivariate analysis for recurrence-free survival (aspirin use after operation).*

Characteristics	HR (95% C.I.)	*p*-Value
Aspirin use after operation		
No	1	-
Yes	0.38 (0.17-0.84)	0.017
Aspirin use after operation		
No	1	-
Yes	1.36 (1.04-1.79)	0.026
Age Group		
<40	1	-
40-55	5.31 (1.26-22.31)	0.023
55-70	4.58 (1.11-18.93)	0.035
>70	5.59 (1.35-23.13)	0.018
Stage		
I	1	-
II	1.95 (1.06-3.58)	0.032
III	2.20 (0.29-16.92)	0.45
Lymph Node Stage		
Number of lymph nodes		
N0: 0	1	-
N1: 1-3	1.81 (0.24-13.38)	0.56
N2: ≥4	2.53 (0.33-19.21)	0.37
Tumor grade		
Undifferentiated/ poorly differentiated	1	-
Moderately differentiated	0.44 (0.26-0.75)	0.002
Well differentiated	0.62 (0.31-1.22)	0.17
Lesion site		
Left	1	-
Right	1.06 (0.74-1.52)	0.75
Perineural invasion		
No	1	-
Yes	2.05 (1.5-2.81)	<0.001
Vascular embolism		
No	1	-
Yes	1.46 (1.08-1.97)	0.015
No. of events=214; No. of patients=678		

CI: Confidence interval; HR: hazard ratio.

Results

This study was approved by the Institution Ethics committee ref: 2009/907/B. A total of 961 cases were reviewed and 726 patients with CRC met the eligibility criteria for analysis. Out of these 726 patients, 103 (14%) were regular aspirin users, with 92 using aspirin postoperatively and 48 patients using aspirin preoperatively. The characteristics of patients who were postoperative aspirin users and non-users are summarized in Table I. The median age of eligible patients at the time of diagnosis was 65 years (range=22-94 years) and the majority of patients were Chinese (90%). Majority of the patients had stage II (31%) and stage III (47%) CRC. Tumor staging was unknown for 3% of patients. Left-sided colonic tumors were more frequent (81%) and 81% of patients had tumors that were moderately differentiated. Twenty-one percent of patients had tumors with peri-neural invasion and 28% with vascular embolism.

Comparing characteristics of postoperative aspirin users with non-users (Table I), postoperative aspirin users were more likely to be elderly ($p<0.001$), Indian ($p<0.001$) and to have lower TNM nodal status ($p=0.013$).

Later tumor stage ($p=0.010$ for stage II; $p<0.001$ for stage III), increased lymph node stage ($p<0.001$), higher tumor grade ($p<0.001$), perineural invasion ($p<0.001$), vascular embolism ($p<0.001$) and use of aspirin before surgery were associated with poorer CSS and RFS on univariate analysis, with the proportional hazards assumption being satisfied for all univariate models (Tables II and III).

Overall, patients who used aspirin postoperatively had an improved RFS but this was not found to be statistically significant ($p=0.44$) (Figure 1). After adjusting for prognostic factors (age group, aspirin use before surgery, tumor stage, lymph node stage, tumor grade, lesion site, perineural invasion and vascular embolism), the risk of death from CRC in patients who used aspirin after surgery was 30% lower compared to patients who had not (HR=0.71, 95% CI=0.43-1.16, $p=0.17$), but this failed to show any statistical significance. A final multivariate model was evaluated with age group, aspirin use after surgery, tumor stage, lymph node stage, tumor grade, lesion site, perineural invasion and vascular embolism analyzed in a backward fashion. The risk of recurrence of and death from CRC in patients who used aspirin after surgery was approximately 60% lower compared to patients who had not (HR=0.38, 95%CI=0.17-0.84, $p=0.017$) (Table IV).

Analysis of preoperative aspirin use showed that preoperative aspirin users were at a higher risk of CRC-specific death on univariate analysis (HR=1.7, 95% CI=1.09-2.83). RFS for preoperative aspirin users (HR=1.56, 95% CI=1.01-2.43) was also higher (Tables II and III).

Analysis according to postoperative/preoperative aspirin use ('ever use') showed no statistically significant differences in CSS and RFS between aspirin ever-users and non-users, after adjusting for prognostic factors (age group, tumor stage, lymph node stage, tumor grade, lesion side, perineural invasion and vascular embolism). Proportional hazards assumption was verified.

No benefit was observed on OS ($p=0.41$), with the Kaplan–Meier curve showing a trend for a lower death rate in the first five years in postoperative aspirin users, with a cross-over of curves and a higher incidence of death after five years (Figure 2). Analysis of CSS, however, did not show any increase in CRC-related deaths (Figure 3), implying that the higher incidence of death after five years was largely attributable to non-cancer-related deaths.

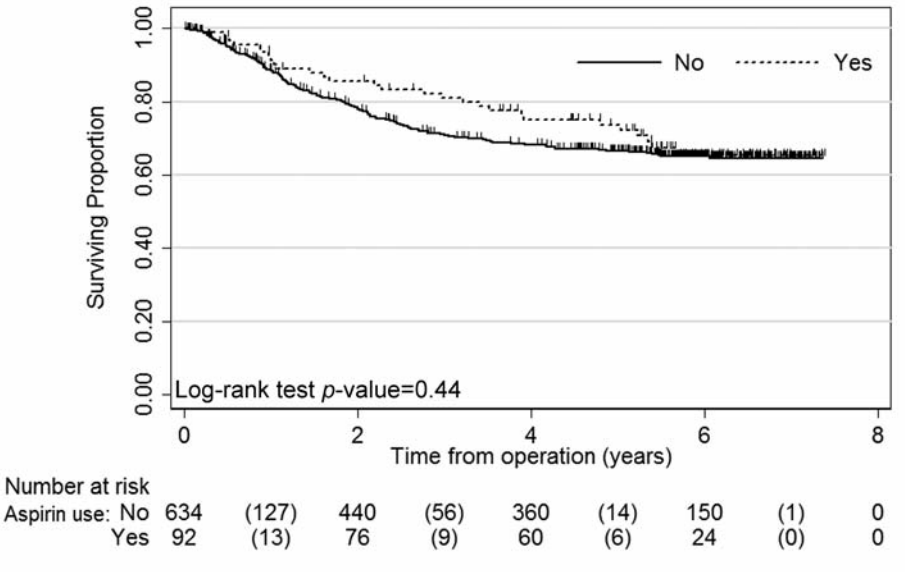

Figure 1. *Kaplan-Meier recurrence-free survival graph stratified by post-operative Aspirin use.*

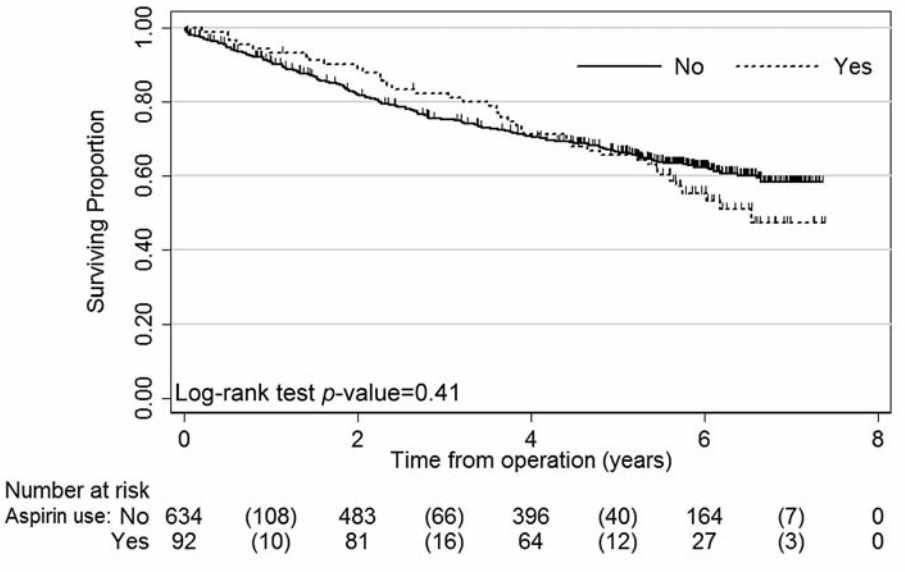

Figure 2. *Kaplan-Meier overall survival graph stratified by post-operative Aspirin use.*

Discussion

In this single-center analysis of 726 patients, with stringent long-term follow-up, our data suggest that postoperative aspirin use significantly improves cancer outcomes in patients with established non-metastatic CRC. After adjusting for risk factors, postoperative aspirin use was associated with an improvement in RFS, with a trend towards improvement in CSS. As far as we are aware of, this is the first study to investigate the benefits of postoperative aspirin use in a cohort of Asian patients with CRC, and these findings are consistent with observational data from Western cohorts. The magnitude of aspirin benefit in our study (HR=0.38, 95% CI=0.17-0.84, p=0.017) was noted to be higher than in other Western studies, however, the confidence intervals were wider, reflecting the smaller number of events in our study.

Although there was a trend towards better OS in postoperative Aspirin users, this was not statistically significant, in contrast to other studies for example by

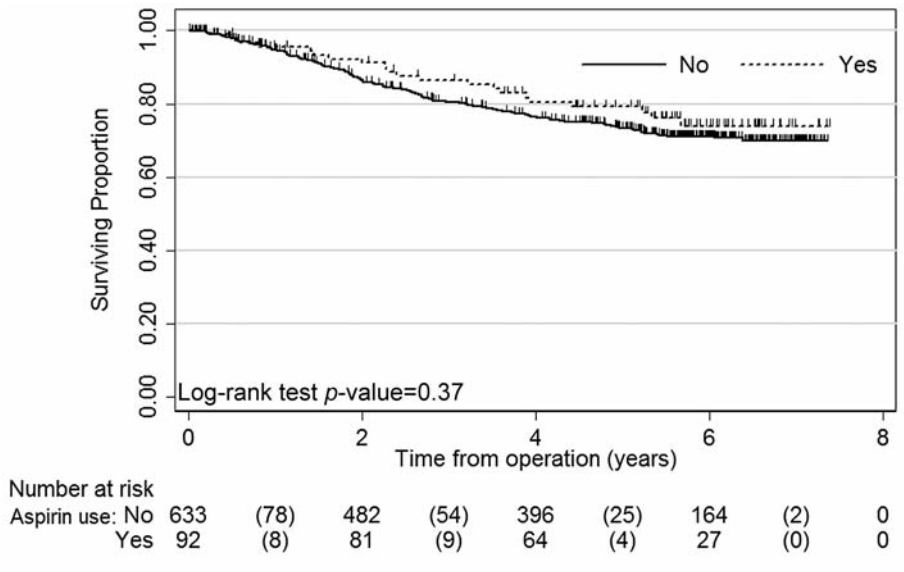

Figure 3. *Kaplan-Meier cause-specific graph stratified by post-operative Aspirin use.*

Bastiannet *et al*. (2) and Zell *et al*. (15). There may be several reasons to explain this. Firstly, the use of highly effective salvage therapies may delay death from recurrent disease. The restriction of analysis to patients who were diagnosed with CRC between 2006 and 2007 means that the majority of patients were followed-up for at least five years. Whilst this duration is adequate to detect cancer recurrences (virtually all recurrences in CRC occur within five years of surgery), it may be insufficient to capture the total death events from CRC. The advent of highly effective chemotherapy and targeted-therapies means that patients survive much longer with recurrent disease and a further minority of patients with local or systemic recurrences are still salvageable with radical metastasectomy. Secondly, because our study evaluated aspirin prescribed by physicians, it would be logical to assume that such patients were more likely to have cardiovascular comorbidities. Indeed, aspirin users had a higher median age than aspirin non-users. This is supported by the higher rate of all-cause mortality after five years amongst aspirin users, despite no deterioration in CSS.

Interestingly, our study found a slightly higher risk of cancer recurrence and death in preoperative aspirin users. This may be due to chance or due to confounding factors. For example, tumors that develop in those using aspirin preoperatively may be biologically different from tumors developing in patients not exposed to aspirin, and consequently less sensitive to aspirin intervention postoperatively. Regular aspirin use has been associated with a significant reduction in the likelihood of developing Cyclooxygenase2 (COX2)-overexpressing CRC, but not COX2-negative tumors (4).

Our study has several strengths. Firstly, we were able to retrieve detailed, updated information on all patient and tumor data because this was a single-Institution study and patients records were readily accessible and well-maintained. Pathology reports at our Center utilize synoptic reporting where tumor characteristics such as margins, LVI, PNI, lymph nodes involved and lymph nodes harvested are didactically reported (14). Secondly, aspirin usage in our study was determined from both prescription and dispensed records in a comprehensive pharmaceutical database, rather than relying on patient self-reporting. This greatly reduces the risk of recall bias. Thirdly, all hospital death data in our study were supplemented and re-verified with independent records from the Singapore Death Registry. Since death reporting in Singapore is mandatory by law, the study was able to achieve vital data of extremely high quality.

Several limitations of our study warrant comment. Firstly, this was a retrospective cohort study, limited by a relatively small sample size of aspirin users. Secondly, we are unable to exclude the possibility that aspirin may have been prescribed by general practitioners whose prescription is not recorded in the National Prescription Database – although the numbers of such patients are deemed to be extremely small. Thirdly, we are unable to make an assessment of the effect of aspirin dose or concomitant use of other non-steroidal anti-inflammatory drug (NSAID) use on cancer outcomes. All patients included in our study were using cardioprotective doses of aspirin (100 mg daily). Although other non-aspirin NSAIDs have been variably reported to influence cancer risk, we were not able to make an accurate assessment of NSAID use since most of this use is sporadic.

We were also unable to assess the effect of compliance in patients who used aspirin. Lastly, we did not evaluate the specific effect of adjuvant or palliative chemotherapy on cancer outcomes. Because aspirin users tend to be older, with more comorbid cardiovascular disease, they are much less likely to receive chemotherapy, and would therefore be biased towards poorer outcomes.

Recently, the U.S. National Cancer Institute listed aspirin's role in cancer as one of the most provocative questions in cancer research (10). With the challenges of escalating healthcare costs and aging populations, aspirin may provide an extremely cost-effective means of reducing cancer mortality both in lower-income and developed countries, and merits further evaluation in prospective studies.

Conflicts of Interest

The Authors report no conflict of interest in regard to this study.

References

1 Ali R and Raina V: Developing innovative models for North-South cooperation in clinical research – experience from the INDOX Cancer Research Network. Ann Oncol *19*: 831-833, 2008.

2 Bastiaannet E, Sampieri K, Dekkers OM, de Craen AJ, van Herk-Sukel MP, Lemmens V, van den Broek CB, Coebergh JW, Herings RM, van de Velde CJ, Fodde R and Liefers GJ: Use of aspirin postdiagnosis improves survival for colon cancer patients. British journal of cancer *106*: 1564-1570, 2012.

3 Cavalli F: Cancer in the developing world: can we avoid the disaster? Nature clinical practice Oncology *3*: 582-583, 2006.

4 Chan AT, Ogino S and Fuchs CS: Aspirin and the Risk of Colorectal Cancer in Relation to the Expression of COX-2. New England Journal of Medicine *356*: 2131-2142, 2007.

5 Chan AT, Ogino S and Fuchs CS: Aspirin use and survival after diagnosis of colorectal cancer. JAMA: the journal of the American Medical Association *302*: 649-658, 2009.

6 Chia WK, Ali R and Toh HC: Aspirin as adjuvant therapy for colorectal cancer – reinterpreting paradigms. Nature reviews Clinical Oncol *9*: 561-570, 2012.

7 Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti A: AJCC Cancer Staging Manual. 7th ed. New York: Springer-Verlag, 2010.

8 Ferlay J, Shin H-R, Bray F, Forman D, Mathers C and Parkin DM: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International Journal of Cancer *127*: 2893-2917, 2010.

9 McCowan C, Munro AJ, Donnan PT and Steele RJ: Use of aspirin post-diagnosis in a cohort of patients with colorectal cancer and its association with all-cause and colorectal cancer specific mortality. Eur J Cancer *49*: 1049-1057, 2013.

10 National Cancer Institute: Aspirin and Cancer Risk - National Cancer Institute. National Cancer Institute, 2014.

11 Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW and Mehta Z: Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet *379*: 1591-1601, 2012.

12 Sung JJ, Lau JY, Goh KL, Leung WK, and Asia Pacific Working Group on Colorectal C: Increasing incidence of colorectal cancer in Asia: implications for screening. Lancet Oncol *6*: 871-876, 2005.

13 Weitz J, Koch M, Debus J, Hohler T, Galle PR and Buchler MW: Colorectal cancer. Lancet *365*: 153-165, 2005.

14 Wong JH, Severino R, Honnebier MB, Tom P, and Namiki TS: Number of nodes examined and staging accuracy in colorectal carcinoma. J Clin Oncol *17*: 2896-2900, 1999.

15 Zell JA, Ziogas A, Bernstein L, Clarke CA, Deapen D, Largent JA, Neuhausen SL, Stram DO, Ursin G and Anton-Culver H: Nonsteroidal anti-inflammatory drugs: effects on mortality after colorectal cancer diagnosis. Cancer *115*: 5662-5671, 2009.

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