Prognostic and predictive biomarkers in colorectal cancer. Towards precision medicine

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PART TWO

Treatment of colon cancer and predictive biomarkers

CHAPTER 6

Aspirin use after diagnosis improves survival in older adults with colon cancer: a retrospective cohort study

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ABSTRACT

Background

Preclinical studies have shown aspirin might prolong survival due to inhibition of tumor growth and metastases in colon cancer patients. To date, however, it is unclear whether aspirin, prescribed as an adjuvant therapy, can influence the prognosis of colon cancer patients. An effective and well-tolerated adjuvant therapy would be a major clinical advancement, particularly in older cancer patients. The aim of this study was to assess survival in relation to aspirin use after diagnosis in older colon cancer patients.

Methods

Subgroup analysis of a previously published cohort and retrospective study of 536 patients aged 70 years and older diagnosed with colon cancer registered in the Eindhoven Cancer Registry (ECR) between 1998 and 2007, linked to prescriptions of low dose aspirin (80 mg) registered in the community pharmacy database of the PHARMO record linkage system.

Survival was analyzed with user status as a time-dependent covariate. Multivariable Poisson regression survival models were used to study the effect of aspirin on Overall Survival (OS).

Results

Overall, 107 patients (20.0%) started aspirin after being diagnosed with colon cancer; 429 patients (80.0%) were not prescribed aspirin. In total 339 patients (63.2%) died at the end of follow up. Aspirin use after diagnosis was associated with a better OS with a Rate Ratio (RR) of 0.51 (95% CI 0.38-0.70 $p<0.001$). Multivariable proportional hazards regression analysis revealed aspirin use was associated with overall survival (adjusted RR 0.59 (95% CI 0.44-0.81, $p=0.001$)).

Conclusions

Aspirin use after the diagnosis of colon cancer in older patients was associated with better survival. These results suggest that low dose aspirin could be used as an effective adjuvant therapy in older colon cancer patients.

INTRODUCTION

Nearly half of all patients with colon cancer are above 70 years of age and this age group is expanding as a result of increasing life expectancy [2]. Approximately fifty percent of all patients undergoing colorectal cancer surgery are known to develop a relapse and die of metastatic disease [1;3;4]. The introduction of adjuvant chemotherapy has significantly improved the prognosis of colon cancer patients. However, the effect of adjuvant chemotherapy on older patients is less clear. Some studies have suggested lack of survival benefit with adjuvant chemotherapy in patients older than 65 years [5]. Other studies, however, have suggested that older patients do benefit similar from chemotherapy, but that they are less frequently treated [4;6]. Undertreatment with adjuvant chemotherapy of older patients often occurs because of co-morbidities and patient preferences [7]. Due to underrepresentation in clinical trials there is no treatment consensus for elderly patients with colon cancer.

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in preventing colorectal cancer [8-10]. Aspirin inhibits cyclooxygenase-2 (COX-2), which is expressed in 70% of the colorectal tumors and increases with disease stage [11;12]. COX-2 plays an important role in colorectal carcinogenesis, invasion, angiogenesis and metastasis. Several studies have shown that this COX-2 effect can be reversed by selective COX-2 inhibitors [13]. It is not clear whether aspirin can influence the prognosis of patients with colorectal cancer, but in animal models aspirin and NSAIDs with activity against the COX-2 isoenzyme have shown to inhibit tumor progression and increase survival [14]. Besides, clinical studies have shown an association between aspirin and prognosis as well. A recent study in patients with stage I-III colorectal cancer selected from two nationwide health professional cohorts in the U.S. showed that regular aspirin use after the diagnosis of colorectal cancer compared with non-users was associated with a lower risk of colorectal cancer-specific and overall mortality, especially among individuals with tumors that overexpress COX-2 [11].

The number of colon cancer patients is increasing and there is a strong need for therapeutic improvement, especially in elderly patients, who are less frequently treated with standard chemotherapy. The aim of this study was to assess the association of aspirin use after the diagnosis of colon cancer on survival in patients aged 70 years and older.

METHODS

Patients

The central patient database of PHARMO, which links to more than 10 databases using different medical record linkage algorithms, was recently combined with data from the

Eindhoven Cancer Registry (ECR) [15]. From the PHARMO database, prescriptions of low dose aspirin (80 mg) were selected and linked to patients diagnosed with colorectal cancer, registered in the ECR between 1998 and 2007. In total, 4481 colorectal cancer patients were included in this database. We performed a subgroup analysis on this previously published cohort, comprising specifically patients 70 years and older, diagnosed with colon cancer, who used aspirin only after diagnosis or who never used aspirin (n=536).[1] The date of prescription and date of diagnosis were compared to assess whether the aspirin was prescribed only after the diagnosis. Nonusers were defined as patients who were never used prescribed aspirin. Patients who were prescribed aspirin after diagnosis were defined as users.

Statistics

Vital status of patients was established either directly from the patient's medical record or through linkage of cancer registry data with the municipal population registries, which record information on the vital status of their inhabitants. Follow-up started at 30 days from diagnosis of colorectal cancer (T0), as information concerning the prescriptions in hospital was unknown. Follow-up was until the last contact date or date of death. Users were defined as patients who had at least 1 prescription for aspirin for at least 14 days; patients who were prescribed aspirin for less than 14 days were defined as nonusers. Time-dependent survival analyses were used to assess survival. Patients were defined as nonusers from T0 to first use and user from first use to the end of the follow-up. Poisson regression survival models were used to study the effect of aspirin on overall survival. In multivariable proportional hazards regression analysis adjustments were made for sex, age (continuous), stage (pathological stage and clinical stage if pathological stage was unknown), adjuvant chemotherapy (yes/no), co-morbidity (yes/no), surgery (yes/no), grade, localization of the tumor, and year of diagnosis. Finally, stratified analyses were performed for type of co-morbidity, chemotherapy, grade, stage, surgery and localization of the tumor.

RESULTS

Overall, 536 patients aged 70 years and older diagnosed with colon cancer between 1998 and 2007 were included in the analyses. There were 107 patients (20%) who started low-dose aspirin (80 mg) after diagnosis and 429 patients (80%) who did not use prescribed aspirin before or after diagnosis. Table I shows the patient baseline characteristics; Median age was 77.6 (SD 5.3) years. Patients who used aspirin were significantly younger than patients without aspirin use. Non-users were more likely to be diagnosed with stage IV colon cancers compared to aspirin users. Also, aspirin users were more often diagnosed

Table I: Baseline Characteristics of Study Population

	Overall N=536	%	Aspirin + N=107	%	Aspirin – N=429	%	*P*-value
Age,Mean (SD[a])	77.6 (5.3)		76.6 (4.9)		77.8 (5.4)		0.04
Sex							0.57
Female	258	48.1	48	44.9	210	49.0	
Male	278	51.9	59	55.1	219	51.0	
Grade							0.87
I	69	12.9	13	12.1	56	13.1	
II	311	58.0	64	59.8	247	57.6	
III	84	15.7	18	16.8	66	15.4	
Unknown	72	13.4	12	11.2	60	14.0	
Stage							<0.01
I	89	16.6	25	23.4	64	14.9	
II	212	39.6	53	49.5	159	37.1	
III	115	21.5	24	22.4	91	21.2	
IV	85	15.9	2	1.9	83	19.3	
Unknown	35	6.5	3	2.8	32	7.5	
Chemotherapy							0.25
Yes	68	12.7	10	9.3	58	13.5	
No	468	87.3	97	90.7	371	86.5	
Radiotherapy							0.86
Yes	9	1.7	2	1.9	7	1.6	
No	527	98.3	105	98.1	422	98.4	
Surgery							<0.01
Yes	463	86.4	105	98.1	358	83.4	
No	73	13.6	2	1.9	71	16.6	
Pulmonary							0.15
Yes	67	12.5	9	8.4	58	13.5	
No	469	87.5	98	91.6	371	86.5	
Cardiovascular							0.35
Yes	244	45.5	53	49.5	191	44.5	
No	292	54.5	54	50.5	238	55.5	
Diabetes							0.64
Yes	62	11.6	11	10.3	51	11.9	
No	474	88.4	96	89.7	378	88.1	
Comorbidity							0.86
0-1	439	81.9	87	81.3	352	82.1	
2+	97	18.1	20	18.7	77	17.9	

[a] SD=Standard Deviation

with stage I colon cancer. Most of the patients did not receive chemotherapy (87%) or radiotherapy (98%). This was similar in both groups. Aspirin users more frequently underwent surgery compared to non-users. There were no differences in co-morbidities between the two groups.

Survival with time-varying covariate

Between 1998 and 2007, 339 patients (63.2%) died during follow-up, and 197 patients were still alive in 2007. For all patients with colon cancer, aspirin use after the diagnosis was associated with a significant reduction in overall mortality (Rate Ratio (RR) 0.51 (95% CI 0.38-0.70 $p<0.001$)). Multivariable analysis revealed that aspirin use was also associated with better survival when adjusted for sex, stage, age, adjuvant chemotherapy, co-morbidity, incidence year, surgery and grade (adjusted RR 0.59 (95% CI 0.44-0.81, $p=0.001$)). Figure 1 shows the OS curve for aspirin users and non-users. Stratification for various factors, as shown in Figure 2, revealed survival gain was present in all strata. The greatest association between aspirin use and survival was in patients with higher disease stage and grade, and in patients who did not receive chemotherapy (adjusted RR for no chemotherapy: 0.71, 95% CI 0.64-0.79, $p<0.001$). Because older patients are frequently known to have co-morbidities we also stratified for this possible confounder. Again, the association between aspirin use and survival persisted in patients with diabetes (adjusted RR 0.53, 95% CI 0.32-0.86, $p=0.01$), cardiovascular disease (adjusted RR 0.69, 95% CI 0.59-0.79, $p<0.001$), no cardiovascular disease (adjusted RR 0.77, 95% CI 0.66-0.89, $p=0.001$) and absence of pulmonary disease (adjusted RR 0.72, 95% CI 0.64-0.80, $p<0.001$).

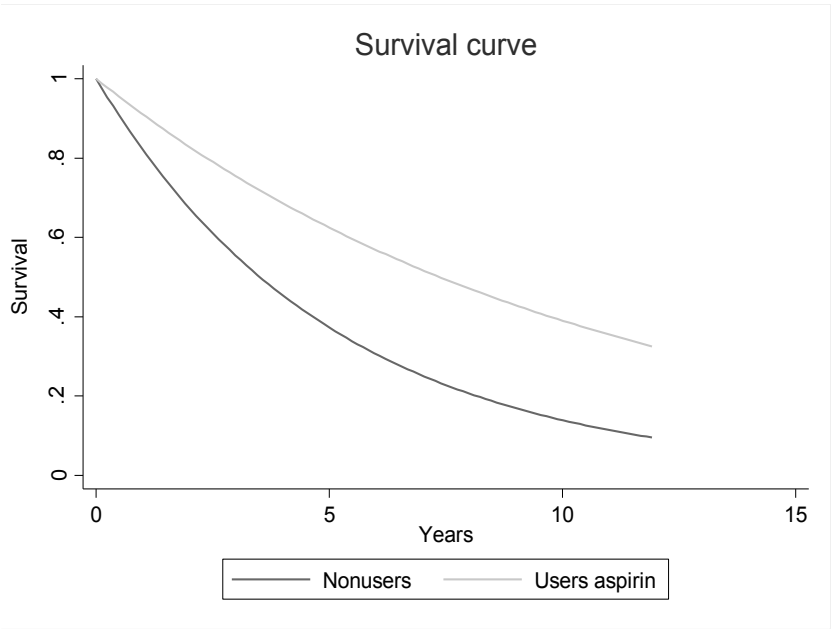

Figure 1: Survival Curve for Overall Survival in Older Colon Cancer Patients According to Use of Aspirin.

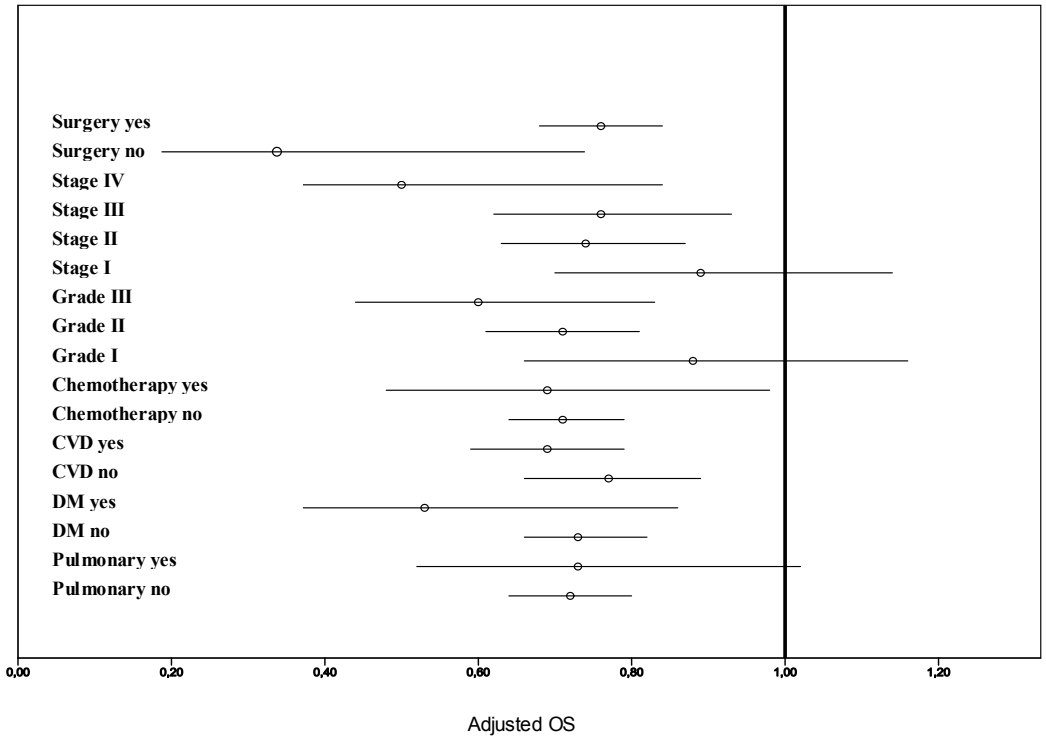

Figure 2: Adjusted Rate Ratio (RR) with 95% Confidence Interval (CI) for Aspirin Use for Older Colon Cancer Patients Stratified for Sex, Stage, Age, Adjuvant chemotherapy, Co-morbidity, Incidence year, Surgery and Grade.
CVD, Cardiovascular disease; DM, diabetes mellitus

DISCUSSION

Here we report an independent strong association of improved survival in older patients who used aspirin after colon cancer diagnosis. This effect also persisted after adjusting for several confounders and was present in most strata of colon cancer.

Since 1968, it has been suggested that aspirin could be a possible preventive agent for colorectal cancer [16]. Only recently, aspirin has been mentioned as a possible adjuvant agent for colorectal cancer [11]. Our study implicates that aspirin could be an effective adjuvant agent in the treatment of colorectal cancer, especially in older, chemo-naive colon cancer patients, as aspirin use was associated with a clinically and statistically significant increase in overall survival. To our knowledge, this is the first report that focuses on older colon cancer patients specifically.

Our results are consistent with results by Chan *et al.*, who found an improved OS of 0.79 (95% CI 0.65-0.97) for regular aspirin users compared to non-users in a cohort study of 1279 patients diagnosed with stage I-III colorectal cancer [11]. In our study as-

pirin users had a RR of 0.51 (95% CI 0.38-0.70, p<0.001) for OS. A major strength of this investigation is the use of a time-dependent covariate in the survival analyses and the large number of patients enrolled in the PHARMO database, which gave us the unique opportunity to assess older colon cancer patients specifically. By using two validated databases we have avoided the possibility of recall bias, which will be more likely with the use of questionnaires to assess aspirin use.

Our results underscore the findings found in cardiovascular prevention trials, where long-term aspirin use was associated with fewer deaths due to cancer. Hazard ratios in these studies ranged from 0.63-0.85, which correspond with our findings, in favor of aspirin use to reduce cancer death. Benefit increased with treatment duration and was consistent across the various populations included in these studies [9;10]. Nevertheless, we assessed aspirin as adjuvant treatment, starting after diagnosis of colon cancer, whereas these studies investigated aspirin use in the preventive setting, including aspirin use before diagnosis. Our results suggest that aspirin use after cancer diagnosis is associated with a survival advantage, when compared to aspirin use before diagnosis. Also, the slightly greater survival advantage for older aspirin users in our cohort might be explained by the undertreatment of these elderly patients with adjuvant chemotherapy, while younger patients receive chemotherapy more often, with good results. Therefore, the absolute effect of aspirin could be higher in older colon cancer patients who, without chemotherapy, have a higher a-priori chance of developing metastases. This is also reflected in the larger effect of aspirin on survival in older colon cancer patients without chemotherapy (HR 0.71) and the previously published data where the largest survival gain of aspirin use after diagnosis was found in older colon cancer patients, when compared to other age categories [1]. Furthermore, the expression of COX-2 may increase with older age and this could be the reason for the larger effect of aspirin on survival in older colon cancer patients [17].

In recent studies, in which prediagnosis NSAID use and survival following colorectal cancer diagnosis was evaluated, a higher reduction in colorectal cancer mortality risk after diagnosis by aspirin use was found compared to overall NSAID use [1;18;19]. These results, along with results of our study, suggest that aspirin and not overall NSAID use, which was mostly used in all previous studies[12;18], may be an important agent in improving survival in colon cancer patients.

Most studies evaluated the use of aspirin or other non-steroidal anti-inflammatory agents before diagnosis. Our study established a longer survival in aspirin users, when started after cancer diagnosis and surgery. Also, due to the large number of patients in the total cohort (4481 colorectal cancer patients) we were able to perform an analysis on older chemo-naive colon cancer patients. Although currently only hypothesis generating, our results suggest that aspirin use as an adjuvant therapy for colon cancer treatment is a clinically relevant option, especially in older adults.

Our study has limitations inherent to observational studies. First, aspirin use was not randomized, so it is possible that patients took aspirin for cancer prevention purposes. However, in the Netherlands, low dose aspirin (80 mg) is exclusively prescribed for cardiovascular risk management, and cannot be purchased 'over the counter.' Second, our data is limited to prescribed drugs. Therefore it is not possible to obtain information regarding to aspirin use or other NSAIDs at home. Third, the improved prognosis could also be explained by the reduced number of cardiac events. However, a meta-analysis for aspirin in the primary and secondary prevention of vascular disease showed a survival gain around 5% for aspirin users [20]. This minimal gain in survival cannot explain the larger survival gain associated with aspirin use in our study. Finally, there were differences in baseline characteristics of patients included in our investigation. Aspirin users more frequently underwent surgery compared to non-users, had lower stage disease and were slightly younger. However, even after adjustment for these confounders and after stratification, the effect of aspirin persisted (Figure 2). More importantly, this longer survival in aspirin users in our study and in other observational studies was consistent with the findings in randomized trials.[21] Nevertheless, residual confounding may still be present. This could only be resolved in a randomized clinical trial, one of which has already been started in Asia (ASCOLT NCT 00565708) and two trials are in preparation in Europe [22].

The exact mechanism by which aspirin exerts its activity is not completely understood. It is likely that the anti-inflammatory and chemopreventive effects of aspirin are mediated through direct inhibition of COX-1 and COX-2 [13;23;24]. Approximately 70% of colorectal tumors express COX-2 [12]. COX-2 plays an important role in colorectal carcinogenesis, invasion, angiogenesis and metastasis. Several studies have shown that this COX-2 effect can be reversed by selective COX-2 inhibitors [13]. Chan *et al.* found a much lower risk of colorectal cancer-specific and overall mortality with tumors that over express COX-2 [11]. Elevated COX-2 expression was found to be associated with tumor metastases, and multiple studies demonstrated COX-2 overexpression as a negative prognostic factor in colorectal cancer [25-27]. Also, studies have linked the COX enzyme-mediated mechanisms to the ability of tumors to initiate vascularization [28] and angiogenesis [29], probably through the production of prostaglandin by COX-2 [30]. This prostaglandin pathway may also be responsible for the regulation of apoptosis [31], and evading apoptosis is one of the key hallmarks of cancer [32]. By using aspirin, a COX-2 inhibitor, the effects of COX-2 on tumor progression can ultimately be altered in a positive way.

This is the first study focusing specifically on older colon cancer patients. Elderly patients are a frequently overlooked, understudied and often undertreated group of patients. Our findings may have important clinical implications in older adults with colorectal cancer. Demonstration of a significant therapeutic effect of a well-tolerated, inexpensive drug would be a major clinical advancement. In this study, aspirin is impli-

cated as an effective adjuvant agent, increasing overall survival in older colon cancer patients. However, a randomized trial in this age group is necessary to confirm the therapeutic role of aspirin, and is currently being developed in the Netherlands.

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