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BRIEF ARTICLES

Non-steroidal anti-inflammatory drugs and statins in relation to colorectal cancer risk

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Abstract

AIM: To investigate the association between individual or combined use of non-steroidal anti-inflammatory drugs (NSAIDs) or statins and colorectal cancer risk.

METHODS: In a population-based case-control study in women, we examined the association between NSAIDs and statin use and the risk of colorectal cancers. We further investigated whether the use of statins modifies the protective effect of NSAIDs. Female cases (n = 669) of colorectal cancer aged 50-74 years were identified from a statewide registry in Wisconsin during 1999-2001. Community control women (n = 1375) were randomly selected from lists of licensed drivers and Medicare beneficiaries. Medication use and risk factor information were gathered during a structured telephone interview. A multivariable logistic regression model was used to calculate odds ratio (OR) and 95% confidence interval (CI).

RESULTS: Overall, NSAIDs users had a 30% reduction in risk of colorectal cancer (95% CI: 0.56-0.88). Statin use was not associated with colorectal cancer risk (OR = 1.17, 95% CI: 0.74-1.85), regardless of structural type (lipophilic or hydrophilic), duration of use, or recency. There was no evidence of an interaction between NSAIDs and statins and colorectal cancer risk (P-interaction = 0.28).

CONCLUSION: Although our results confirm the inverse association between NSAIDs use and colorectal cancer risk, they do not support a risk reduction in statin users, or an interaction effect of combined NSAIDs and statin use.

Key words: Non-steroidal anti-inflammatory drugs; Statin; Colorectal cancer; Cancer prevention; Chemoprevention

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INTRODUCTION

There is strong evidence for a reduced risk of colorectal cancer in regular users of non-steroidal anti-inflammatory drugs (NSAIDs)[1,2] and some promising but inconsistent observational data regarding a role of statins in this risk[3-11]. An interaction between the use of NSAIDs and statin on the risk of colorectal cancer is suggested by both *in vivo* and *in vitro* studies[5,12,13].

NSAIDs induce apoptosis in colon cancer cells[14,15]. By blocking cyclooxygenase enzymes, they also inhibit prostaglandin production, which is known to promote tumor angiogenesis and cell proliferation[1]. Statins have anti-neoplastic effects through both HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) dependent and independent processes[13,16,17]. Inhibition of the prenylation of cell signaling proteins, as well as the anti-inflammatory and anti-oxidative properties of statins, are thought to be responsible for their anti-cancer effects[16]. Augmentation of sulindac or celecoxib induced apoptosis by Lovastatin in colon cancer cell lines and

the increased activation of caspase-3, a pro-apoptotic protein, in combined statin and NSAIDs use[12,18], suggest a synergistic anti-cancer effect. These observations have also been supported by some observational data[5].

The purpose of this study was to investigate the effects of NSAIDs and statin use in relation to colorectal cancer in a population-based case-control study in women. We also investigated whether the use of statins modified the relationship between NSAIDs and statins.

MATERIALS AND METHODS

Female cases (n = 669) of colorectal cancer aged 50-74 years were identified from the Wisconsin cancer reporting system, the statewide tumor registry, during 1999-2001. Registry reports included stage, histology and limited treatment information. Of the 1038 eligible cases, 170 (16.4%) were deceased, 19 (1.8%) were not contacted due physicians' disapproval, 22 (2.1%) could not be located and 154 (14.8%) declined to participate, resulting in a 65% response rate. We also excluded four cases with unreliable interviews. Community control (n = 1375) women were randomly selected to match the age distribution of cases from two sampling frames: lists of licensed drivers (age < 65 years) and Medicare beneficiaries (age ⩾ 65 years). Women were ineligible as controls if they reported a history of colorectal cancer. The response rate for controls was 79%.

Structured telephone interviews were conducted to obtain information regarding medication use, including NSAIDs and statins, and other factors (Table 1). We considered the most commonly used statins that were approved by the Food and Drug Administration from 1995 through 2000. Having ever used NSAIDs or statins was confined to subjects who reported using the medications for at least 30 d. We defined the duration of each period of NSAIDs or statin use. Use of these preparations within one year before the reference year was considered as current use. We categorized statins according to whether they were lipophilic (simvastatin, lovastatin and fluvastatin) or hydrophilic (pravastatin), as it has been suggested that the anti-cancer activity of statins might be limited to the ones with lipophilic structure[16].

Odds ratios (OR) and 95% confidence intervals (CI) were calculated from multivariable logistic regression models to estimate the associations between NSAIDs and statins with the risk of colorectal cancer. We also evaluated possible interaction between NSAIDs and statin use by including a cross-product term of "ever use" of these medications in the regression model. We adjusted for the potential confounding factors (Table 1) by including them in the multivariate models.

RESULTS

Overall, 657 cases of colorectal cancer and 1342 controls were included in the analysis (Table 1). The prevalence of regular NSAIDs use in the sample was 33% (20% aspirin and 13% non-aspirin, 26% current users). The prevalence of statin use was 7% (6% current users, 5% lipophylic and 2% hydrophylic) (Table 2).

Table 1 Characteristics of women with colorectal cancer and controls n (%)

Characteristic	Cases (n = 657)	Controls (n = 1342)[1]
Education		
No high school diploma	95 (14.8)	119 (11.8)
High school diploma	312 (48.7)	632 (50.0)
Some college	143 (22.3)	312 (20.7)
College degree	91 (14.2)	257 (17.6)
Type of postmenopausal hormone therapy		
Never	417 (65.2)	696 (55.7)
Estrogen only	73 (11.4)	145 (10.9)
Estrogen and progestin only	41 (6.4)	133 (7.2)
Other combination	109 (17.0)	344 (26.2)
Family history of colorectal cancer		
No	492 (80.9)	1060 (87.2)
Yes	116 (19.1)	171 (12.8)
Body mass index (kg/m^2)		
< 25	273 (42.7)	538 (40.9)
25-30	206 (32.2)	465 (36.9)
⩾ 30	160 (25.0)	314 (22.1)
History of colorectal cancer endoscopic screening (colonoscopy/ sigmoidoscopy)		
No	429 (67.3)	816 (61.5)
Yes	208 (32.6)	455 (38.5)
Smoking history (pack-years)		
Never	311 (48.7)	677 (54.7)
< 10	101 (15.8)	208 (15.1)
10-20	53 (8.3)	127 (7.4)
⩾ 20	174 (27.2)	305 (22.9)

[1]Control percentages were age-adjusted to the cases age distribution. In this table, percentages are based on excluding unknowns in that category.

Those who had ever used NSAIDs had a 30% decrease in colorectal cancer risk (OR = 0.70; 95% CI: 0.56-0.88) compared to those who had never used NSAIDs. The risk reduction was statistically significant in current users but not in former users and there was no trend for increasing duration (P = 0.75).

Having ever used statins was not associated with colorectal cancer risk (OR = 1.17; 95% CI: 0.74-1.85) regardless of the type of statin (lipophilic or hydrophilic). Neither long term (> 3 years) nor current statin use were associated with risk.

Having ever used both NSAIDs and statins was not associated with colorectal cancer risk (OR = 0.96; 95% CI: 0.49-1.78). The association between NSAIDs use and colorectal cancer risk was not modified by use of statins (P-interaction = 0.28) (data not shown).

DISCUSSION

Our finding of a 30% reduced risk of colorectal cancer with NSAIDs use is consistent with the current evidence. The observed colorectal cancer risk reductions range from 20% to 40%, possibly due to the heterogeneity of study designs[1].

In contrast to our findings on NSAIDs use, we did not observe an association between statin use and colorectal cancer risk. This association has been examined in secondary analyses of randomized controlled trials that

Table 2 Multivariable OR of colorectal cancer associated with statin and NSAIDs use

	Cases *n* (%)	Controls *n* (%)	OR[1]	95% CI[1]	OR[2]	95% CI[2]
NSAIDS						
Never	462 (71.9)	837 (63.6)	1.00	Reference	1.00	Reference
Ever	181 (28.1)	480 (36.4)	0.69	0.55-0.86	0.70	0.56-0.88
Former	41 (6.4)	109 (8.3)	0.74	0.50-1.11	0.77	0.51-1.15
Current	140 (21.8)	371 (28.2)	0.68	0.53-0.86	0.68	0.53-0.88
Duration (yr)						
< 1	8 (1.2)	25 (1.9)	0.71	0.30-1.65	0.71	0.30-1.69
1-4	85 (13.2)	233 (17.7)	0.70	0.52-0.93	0.70	0.52-0.94
⩾ 5	88 (13.7)	222 (16.9)	0.68	0.51-0.92	0.71	0.52-0.96
Statins						
Never use	453 (92.6)	1114 (93.2)	1.00	Reference	1.00	Reference
Ever use	36 (7.4)	81 (6.8)	1.03	0.66-1.60	1.17	0.74-1.85
Former	4 (0.8)	9 (0.8)	1.63	0.49-5.44	1.93	0.56-6.06
Current	32 (6.5)	72 (6.0)	0.97	0.60-1.55	1.09	0.67-1.78
Duration (yr)						
< 3	17 (3.5)	41 (3.4)	0.96	0.51-1.80	1.07	0.56-2.03
⩾ 3	19 (3.9)	40 (3.3)	1.10	0.60-2.00	1.27	0.68-2.38
Type						
Lipophilic use	30 (6.1)	63 (5.3)	1.04	0.64-1.70	1.20	0.72-2.00
Hydrophilic use	7 (1.4)	20 (1.7)	1.06	0.43-2.63	1.10	0.44-2.77

[1]Adjusted for age and reference year. [2]Adjusted for age, reference year, education, post menopausal hormone use, first degree family history of colorectal cancers, body mass index, history of colorectal cancer endoscopic screening, and smoking.

did not show a risk reduction among users[19]. The small number of colorectal cancer cases should be considered while interpreting these trial results as they were designed to measure cardiovascular outcomes. Observational studies have also produced inconsistent findings. While two case-control studies[5,10] reported risk reduction in long term statin users, other studies[3,4,6,9,10] did not show such an inverse association[20-25]. In a large case-controlled study[10] of 1953 cases and 2015 controls, a 50% reduction in colorectal cancer risk (OR = 0.53; 95% CI: 0.38-0.74) was observed in long term statin users (more than 5 years).The difference between databases from which the cases and controls were selected might have influenced the results. In their study, all the incident cases from northern Israel were included, while controls were recruited from a health maintenance organization, possibly making them more likely to have a healthier life style. In another population-based case-controlled study conducted in Germany[5] (537 cases and 612 controls), a 35% risk reduction (OR = 0.65; 95% CI: 0.43-0.99) was observed among statin users. However, after adjustment for NSAIDs use, the estimate did not remain statistically significant.

We also did not find any combined effect for NSAIDs and statins. To our knowledge, only two other population-based studies[3,5] have looked at the combined effect of NSAIDs and statins on colorectal cancer risk. While one[5] suggested a stronger risk reduction in combined users than we hypothesized, neither found evidence of a statistically significant interaction between NSAIDs and statin use (*P* interactions = 0.37 and 0.21, respectively).

Statin use was uncommon in our study subjects, which may have limited our ability to detect a true reduced risk. However, in another study from our group[26], with a similar design and population, a significant reduction in breast cancer risk was observed only among regular users of fluvastatin, which also had low prevalence of use. Statins are relatively new medications, therefore examining outcomes like adenomatous polyps as an intermediate step in colorectal cancer development might be a reasonable approach to evaluate both individual and combined effect of statins on colorectal cancer risk. Our study was restricted to women, but there are no reported gender effects on the association of drugs with colorectal cancer risk. The availability of detailed information, control for potential confounding factors, and reliable exposure measurements are the major strengths of our study.

In conclusion, these results support the inverse association between NSAIDs use and colorectal cancer risk in women, especially in current users. We did not detect an association between colorectal cancer risk and statin use, regardless of type (lipophilic *vs* hydrophilic), recency or duration of use. Further, there was no interaction effect of combined NSAIDs and statin use.

COMMENTS

Background

The use of non-steroidal anti-inflammatory drugs (NSAIDs) such as Aspirin is known to be inversely associated with risk of developing colorectal cancer. Some studies have suggested such an association with the use of the commonly used lipid lowering drugs, statins. There is also some experimental data suggesting a synergistic effect for these two popular drug families against colorectal cancer risk.

Research frontiers

While NSAIDs have some possible protective effect against colorectal cancer, they are not yet approved for routine use for this purpose, mainly because of their potentially fatal side effect, bleeding. Finding another protective agent that works synergistically with NSAIDs, allowing a decreased NSAIDs dose, could lower the incidence of the side effect whilst preserving the desired effect; cancer prevention. The promising evidence indicating such an effect for statins is exciting, because these drugs are a hot topic for different preventive strategies, especially in cardiovascular diseases.

Applications

The study results confirm the previously known inverse association between NSAIDs use and colorectal cancer risk.

Peer review

This is a retrospective case-controlled study investigating if NSAIDs or/and statins have chemopreventive effects in women with regard to colorectal cancer (CRC). It is well known that regular users of NSAIDs are at less risk of developing gastrointestinal cancers, including CRC. This paper supports this hypothesis.

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