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

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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.

Abstract

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the increased activation of caspase-3, a pro-apoptotic protein, in combined statin and NSAIDs use\cite{2,3}, suggest a synergistic anti-cancer effect. These observations have also been supported by some observational data\cite{3}.

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 \( \geq 65 \) 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\cite{4}.

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% lipophilic and 2% hydrophilic) (Table 2).

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 (\( \geq 3 \) 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\cite{5}.

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

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

| Characteristic | Cases (\( \eta = 657 \)) | Controls (\( \eta = 1342 \)) |
|---------------|---------------------------|-----------------------------|
| Education     |                           |                             |
| No high school diploma | 95 (14.8)              | 119 (11.8)                   |
| High school diploma     | 312 (48.7)            | 632 (40.9)                   |
| 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 (78.0)             | 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)             | 308 (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.
Table 2  Multivariable OR of colorectal cancer associated with statin and NSAIDs use

| Cases n (%) | Controls n (%) | OR¹  | 95% CI¹ | OR²  | 95% CI² |
|-------------|----------------|------|---------|------|---------|
| NSAIDS      |                |      |         |      |         |
| Never       | 462 (71.9)     | 837  | 0.70    | 1.00 | Reference |
| Ever        | 181 (28.1)     | 480  | 0.69    | 0.55-0.86 | 0.70 | 0.56-0.88 |
| Former      | 41  | 109  | 0.74    | 0.50-1.11 | 0.77 | 0.51-1.15 |
| Current     | 140 (21.8)     | 371  | 0.68    | 0.53-0.86 | 0.70 | 0.53-0.88 |
| Duration (yr) |         |      |         |      |         |
| < 1         | 8  | 25  | 0.71    | 0.30-1.65 | 0.71 | 0.38-1.69 |
| 1-4         | 85  | 233  | 0.70    | 0.52-0.93 | 0.70 | 0.52-0.94 |
| ≥ 5         | 88  | 222  | 0.68    | 0.51-0.92 | 0.71 | 0.52-0.96 |
| Lipophilic use |       |      |         |      |         |
| Never use   | 453 (92.6)     | 1114 | 1.00    | Reference | 1.00 | Reference |
| Ever use    | 36 (7.4)       | 81   | 1.03    | 0.66-1.60 | 1.17 | 0.74-1.85 |
| Former      | 4  | 9   | 1.63    | 0.49-5.44 | 1.93 | 0.56-6.06 |
| Current     | 32  | 72   | 0.97    | 0.60-1.55 | 1.09 | 0.67-1.78 |
| Hydrophilic use |       |      |         |      |         |
| Never use   | 30 (6.1)       | 64   | 0.96    | 0.51-1.80 | 1.07 | 0.56-2.03 |
| Ever use    | 7  | 14   | 1.10    | 0.60-2.00 | 1.27 | 0.68-2.38 |
| Type        |                |      |         |      |         |
| Never use   | 462 (71.9)     | 837  | 1.00    | Reference | 1.00 | Reference |
| Ever use    | 181 (28.1)     | 480  | 0.69    | 0.55-0.86 | 0.70 | 0.56-0.88 |
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| ≥ 5         | 88  | 222  | 0.68    | 0.51-0.92 | 0.71 | 0.52-0.96 |

¹Adjusted for age and reference year. ²Adjusted 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.

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. Our study was restricted to women, but there are no reported gender effects on the association of drugs with colorectal cancer risk. 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.

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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.

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Peer review
This is a retrospective case-controlled study investigating if NSAIDs or 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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