Nonsteroidal Anti-inflammatory Drug Use and Protection against Colorectal Cancer in Women

Mathew J. Reeves, Polly A. Newcomb, Amy Trentham-Dietz, Barry E. Storer, and Patrick L. Remington

Abstract
Several epidemiological studies have identified an association between nonsteroidal anti-inflammatory drug (NSAID) use and colorectal cancer risk in women. We examined this association in a population-based case-control study in Wisconsin women. Between 1991 and 1992, 184 women ages 40–74 years with colorectal cancer were identified through the statewide cancer registry and 293 population-based control women were randomly selected via telephone. Regular NSAID use was defined as at least twice weekly for 12 months or longer.

After adjusting the data for age, controls were more likely than cases to report regular NSAID use (38 versus 27%). Following adjustment for age, prior sigmoidoscopy use, family history of large bowel cancer, and body mass index, women who regularly used NSAIDs were approximately one-third less likely to be diagnosed with colorectal cancer compared to women who did not use NSAIDs (odds ratio [OR], 0.65; 95% confidence interval [CI], 0.40–1.03). A statistically significant effect of duration of use was identified, although the ORs did not show a consistent trend. No significant effect of frequency of NSAID use was observed. When the type of NSAID used was examined (aspirin or nonaspirin), subjects who used nonaspirin compounds had a statistically significantly lower risk of colorectal cancer (OR, 0.43; 95% CI, 0.20–0.89), compared to nonusers, whereas aspirin users had only a small, nonsignificant reduction in cancer risk (OR, 0.79; 95% CI, 0.46–1.36). These data add support to the hypothesis that regular NSAID use is associated with lower colorectal cancer risk in women and suggest that the type of NSAID used may be important.

Introduction
Cancer of the colon and rectum is the third leading cause of cancer death in women in the United States; it was responsible for 28,200 deaths in 1994 (1). Large international differences in colorectal cancer incidence, in combination with data from immigrant studies, suggest that dietary as well as other lifestyle factors are important risk factors for colorectal cancer (2). Public health strategies to reduce the burden of colorectal cancer include various primary prevention strategies, such as increasing physical activity levels and promoting diets low in fat and high in fruits, vegetables, and fiber (3, 4). Other potential primary prevention activities include the use of pharmacological agents, namely, NSAIDs (5–7). Recent epidemiological studies have provided increasing evidence for an association between regular NSAID use and decreased colorectal cancer risk (8–17), although some conflicting results exist (18, 19).

Of the eight studies that have specifically examined the relationship between regular NSAID use and colorectal cancer in women, three reported a statistically significant reduction in cancer risk (11, 13, 16), three found a statistically nonsignificant reduction in risk (9, 10, 14), one found no effect (7), and one reported an increase in colorectal cancer risk (18). Although the evidence for a beneficial effect of NSAID use in women is strong it is certainly not definitive. Given the fact that there are considerable barriers to conducting randomized cancer prevention trials of NSAIDs, the scientific community will continue to rely on observational studies to provide further information. We therefore chose to examine the association between regular NSAID use and colorectal cancer in an ongoing population-based case-control study in women.

Subjects and Methods

Identification of Cases and Controls. Details of the design and conduct of this study have been presented previously (20). All women 40–74 years of age and residing in Wisconsin who had a new diagnosis of invasive cancer of the colon or rectum reported to the Wisconsin Cancer Reporting System, a statewide, mandatory population-based cancer registry, between 1991 and 1992 were eligible for this study. This series of colorectal cancer cases was part of an ongoing study of cancer in women, which also included a large series of breast cancer cases (21). Information available from the Cancer Reporting System included cancer site, histology, extent of disease, demographics, and follow-up physician. According to an institutionally approved protocol, the physician listed on the record for each eligible case was contacted by mail to obtain permission to contact the patient. To identify incident cases, cancer

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cases reported to the registry more than 2 years after initial diagnosis were excluded. Eligibility was further limited to cases with listed telephone numbers and Wisconsin driver’s licenses (if younger than 65). The overall response rate of the colorectal cancer case series during this period was estimated to be at least 74% of living eligible case subjects (20).

Population-based control subjects were identified from two sources. Women under 65 years of age were randomly selected from Wisconsin driver’s license files, whereas women 65–74 years of age were randomly selected from a roster of eligible Medicare beneficiaries compiled by the U.S. Health Care Financing Administration. Control subjects were frequency matched in 5-year age groups to the distribution of the larger series of breast cancer cases identified for the ongoing parallel study (21), but the selection was otherwise made at random. Eligible control subjects had to have a listed telephone number, no previous history of large bowel cancer, and either a current Wisconsin driver’s license (for women <65 years of age) or a Medicare card (for women ≥65 years of age). The overall response rate for control subjects completing the study interview was 90% during this period (20).

Data Collection and Exposure Definition. A 25-min telephone interview was used to obtain information on demographic factors, medical and reproductive histories, height, weight, family history of cancer, current alcohol consumption (defined as the intake during the most recent decade of life), lifetime tobacco use, early life (adolescent) physical activity, and a limited number of dietary variables (i.e., an index of vitamin A intake based on the self-reported consumption of liver, raw and cooked carrots, and spinach).

Women were asked the following question regarding previous NSAID use: “Have you ever regularly taken anti-inflammatory drugs, such as aspirin, ibuprofen, indocin, feldene, ponstel, butazolidin, or others?” For the purpose of data collection, regular NSAID use was defined as taking at least one tablet, twice weekly or more for a month or longer. Nonsteroidal anti-inflammatory drugs were defined as any of the following standard classes: salicylates (e.g., salicylic acid or acetylsalicylic acid), propionic acids (e.g., ibuprofen or naproxen), fenemates (e.g., mefenamic acid), pyrazolones (e.g., phenylbutazone), piroxicam, indomethacin, and sulindac sulfone. Women who reported taking acetaminophen were not regarded as NSAID users. Information on duration of NSAID use was obtained for all regular users. For women who reported using NSAIDs at 2 least years prior to the date of interview, further information was obtained on the frequency and dose of NSAID used. Finally, BMI was calculated using self-reported weight in kg 5 years prior to interview and tallest-ever height in m (BMI = weight/height²). Information on the women’s personal and family history of colon or rectal cancer was obtained at the end of the interview to maintain blinding.

Statistical Analysis. Only exposure status prior to the assigned reference date was used in the analysis. For cases, this was the date of colorectal cancer diagnosis. For comparability, control subjects were assigned a reference date that corresponded to the average time from diagnosis to interview for the case group (13 months; Ref. 20). Since the age distribution of the cases and controls differed (the mean age of the cases was 64.5 years, compared to 57.1 years for the controls), all descriptive statistics were age adjusted. The age distribution of the cases was used as the standard for categorical variables, whereas age-adjusted least square means were calculated for continuous variables using the general linear models procedure in SAS (SAS Institute Inc., SAS Campus Drive, Cary, NC).

For the purpose of analysis, regular NSAID use was defined as taking at least one tablet twice weekly or more for at least 12 months. The relationship between prior regular NSAID use and colorectal cancer risk was evaluated by calculating adjusted ORs and 95% CIs, using multivariable logistic regression (22, 23). Age (specified in 5-year groups), prior sigmoidoscopy use, family history of colorectal cancer, and BMI (specified as quintiles) were all regarded as a priori confounders and included in all models. Other variables of interest, such as smoking or alcohol use, were included in the final model only if they were shown to be important confounding variables (determined by looking for a meaningful change in the regression coefficient for regular NSAID use after each variable was deleted from the model). Overall model goodness-of-fit was evaluated by calculating the Hosmer-Lemeshow goodness-of-fit chi² statistic (23). Finally, the effect of duration and frequency of NSAID use, as well as the type of NSAID used (i.e., aspirin or nonaspirin) were also evaluated in a multivariable analysis.

Population for Analysis. One hundred eighty-four incident cases of carcinoma of the colon and rectum and 293 population-based control women were initially identified and interviewed between September 1990 and March 1992. For missing information, the final model was based on 182 cases and 286 controls. Information concerning the frequency and dose of NSAID use was not collected for 83 subjects [34 of 182 case-patients (19%) and 49 of 293 controls (17%)] who were regular NSAID users but were not taking the drug 2 years prior to the interview.

Results

Descriptive frequencies, including age-adjusted prevalences for the control subjects for sigmoidoscopy, family history, BMI, and NSAID use are summarized in Table 1. Control subjects reported more prior sigmoidoscopy use compared to cases (age-adjusted prevalence of use was 51% for controls compared to 39% for cases). As expected, a family history of colon cancer was more commonly reported by the cases. Nineteen % of cases reported a positive family history for colorectal cancer, compared with an age-adjusted prevalence of 12% for the control subjects. Cases tended to be heavier than controls (Table 1), although a relatively high proportion of control subjects (24%) were found in the highest quintile of BMI (≥28.3).

Overall, 27% of case-patients reported regular NSAID use of at least 12 months duration, compared with an age-adjusted prevalence of 38% for the control subjects. Case and control subjects reported using NSAIDs with similar frequency (the age-adjusted mean number of times per week was 10.4 for cases and 9.7 for controls). However, cases tended to report longer duration of NSAID use than controls; the age-adjusted mean duration of NSAID use for cases was 6.3 years (range, 1–41), compared to 4.5 years (range, 1–46) for controls. This difference was not statistically significant (P = 0.20).

The results of the final multivariable model, which included age, sigmoidoscopy use, family history, and BMI, are shown in Table 1. Following multivariable adjustment, women who reported ever having used NSAIDs regularly for at least 12 months were approximately one-third less likely to be diagnosed with colorectal cancer, as compared with nonusers (OR, 0.65; 95% CI, 0.40–1.03). Neither recent alcohol consumption nor smoking were significant in the final model, and adjusting for these variables did not change the parameter estimate for NSAID use (data not shown). Adjusting the final model for vitamin A consumption and early life (adolescent) physical activity also did not alter the results (data not shown).
to only 394 subjects (150 cases and 244 controls). No significant

Table 2. Similarly, no statistically significant relationship was

(i.e. identified when duration was evaluated as a continuous vari-

tively (Table 2). No statistically significant relationship was

number of times per week that NSAIDs were taken and the total

frequency of NSAID use (specified as <7 times per week, 7

number of aspirin doses [calculated as the product of the

years, 2 to <5 years, and 5 years) was found to be signif-

cantly associated with colorectal cancer risk in the multivari-

test for the effect of frequency of NSAID use: LRCS

Table 2

Table 1. Age-adjusted descriptive frequencies for 184 colorectal cancer cases and 293 population-based control subjects and adjusted ORs and 95% CIs for the risk of colorectal cancer based on a multivariable logistic regression modela

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases, % (n = 184)</th>
<th>Controls, % (n = 293)</th>
<th>Adjusted OR</th>
<th>95% CI (OR)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sigmoidoscopy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>61</td>
<td>49</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39</td>
<td>51</td>
<td>0.6</td>
<td>0.4-0.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Family History</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>81</td>
<td>88</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>19</td>
<td>12</td>
<td>1.8</td>
<td>1.0-3.2</td>
<td>0.05</td>
</tr>
<tr>
<td>BMI (quintiles)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (&lt;21.4)</td>
<td>14</td>
<td>23</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (21.4 to &lt;23.4)</td>
<td>15</td>
<td>20</td>
<td>1.0</td>
<td>0.5-2.1</td>
<td>0.92</td>
</tr>
<tr>
<td>3 (23.4 to &lt;25.7)</td>
<td>27</td>
<td>18</td>
<td>2.2</td>
<td>1.2-4.3</td>
<td>0.02</td>
</tr>
<tr>
<td>4 (25.7 to &lt;28.3)</td>
<td>24</td>
<td>14</td>
<td>2.4</td>
<td>1.2-4.8</td>
<td>0.01</td>
</tr>
<tr>
<td>5 (28.3)</td>
<td>20</td>
<td>24</td>
<td>1.4</td>
<td>0.7-2.8</td>
<td>0.32</td>
</tr>
<tr>
<td>NSAID useb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>73</td>
<td>62</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27</td>
<td>38</td>
<td>0.65</td>
<td>0.40-1.03</td>
<td>0.07</td>
</tr>
</tbody>
</table>

a Descriptive frequencies for control subjects were adjusted to the age distribution of the cases. The final multivariable model was based on 468 observations (182 cases and 286 controls) and included age, sigmoidoscopy, family history, BMI, and NSAID use. Hosmer-Lemeshow goodness-of-fit statistic = 6.54 (8 d.f.); P = 0.59.

b Defined as taking at least one NSAID tablet twice weekly or more for 12 months or longer.

The duration of regular NSAID use (specified as <2 years, ≥2 years to <5 years, and ≥5 years) was found to be significantly associated with colorectal cancer risk in the multivariable model [LRCS test = 10.3 (3 d.f.), P = 0.016; Table 2]. However, the ORs did not follow a consistent dose-dependent trend between increased duration of use and lower cancer risk; the ORs for women who reported regular NSAID use of <2 years, ≥2 to <5 years, and ≥5 years 0.7, 0.3, and 1.1, respectively (Table 2). No statistically significant relationship was identified when duration was evaluated as a continuous variable (i.e., years; P = 0.65).

Information on frequency of NSAID use was available for only 394 subjects (150 cases and 244 controls). No significant relationship between the likelihood of colorectal cancer and frequency of NSAID use (specified as <7 times per week, ≥7 to <14 times per week, and ≥14 times per week) was identified in the multivariable analysis [LRCS = 4.3 (3 d.f.); P = 0.23; Table 2]. Similarly, no statistically significant relationship was identified when frequency was evaluated as a continuous variable (i.e., number of times NSAIDs were consumed per week; P = 0.10). We also found no relationship between the lifetime number of aspirin doses [calculated as the product of the number of times per week that NSAIDs were taken and the total duration of use (in weeks)] and the risk of colorectal cancer (data not shown). It should be noted that the OR estimates for both duration and frequency effects are imprecise (as indicated by the wide CIs) due to the relatively small number of women in each group (Table 2).

Of the 137 subjects who were classified as regular NSAID users, 87 (64%) reported using aspirin or other salicylates, 35 (25%) reported using propionic acid derivatives (such as ibuprofen or naproxen), and the remaining 15 (11%) used various other nonaspirin NSAIDs. Whether the type of NSAID drug used was an important factor was examined by classifying regular NSAID users into two groups (aspirin users and nonaspirin users) and repeating the multivariable analysis. After adjusting for the same confounding variables, subjects who used nonaspirin NSAIDs regularly were significantly less likely to be diagnosed with colorectal cancer (OR = 0.43; 95% CI = 0.20-0.89), compared to subjects who did not use NSAIDs. In contrast, subjects who reported using aspirin regularly had a statistically nonsignificant 21% lower risk of colorectal cancer (OR = 0.79; 95% CI = 0.45-1.36) (Table 3). However, there was no statistically significant difference between the OR estimates for regular aspirin and nonaspirin users (P = 0.16).
Table 3  Age-adjusted descriptive frequencies and adjusted Odds Ratios (OR) and 95% confidence intervals (CI) for the effect of the type of NSAID used on the risk of colorectal cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases, % (n = 184)</th>
<th>Controls, % (n = 293)</th>
<th>Adjusted OR</th>
<th>95% CI (OR)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of NSAID used</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>73</td>
<td>62</td>
<td>1.0</td>
<td></td>
<td>0.40</td>
</tr>
<tr>
<td>Aspirin</td>
<td>21</td>
<td>22</td>
<td>0.79</td>
<td>0.46-1.36</td>
<td>0.03</td>
</tr>
<tr>
<td>Nonaspirin*</td>
<td>6</td>
<td>16</td>
<td>0.43</td>
<td>0.20-0.89</td>
<td></td>
</tr>
</tbody>
</table>

*Descriptive frequencies for control subjects were adjusted to the age distribution of the cases. Results are based on a multivariable logistic regression models that also adjusted for age, sigmoidoscopy use, family history, and BMI.

The nonaspirin group includes 35 women who reported using propionic acid derivatives (such as ibuprofen or naproxen) and 15 other women who used various other non-aspirin NSAID including sulindac (n = 4), indomethacin (n = 2) and piroxicam (n = 2).

Discussion

Many epidemiological studies have reported an association between NSAID use and reduced risk of colorectal cancer in both men and women (8–17). Of the eight studies that have examined the relationship in women, six reported that NSAID use was associated with a lower colorectal cancer risk (9–11, 13, 14, 16), although in only three was the effect statistically significant (11, 13, 16). Of the two other studies, one found no effect (7), whereas the other reported an increase in colorectal cancer risk in women (18). In this population-based case-control study, women who reported using NSAIDs regularly (defined as at least twice weekly for 12 months or more) had a 35% lower risk of colorectal cancer compared to nonusers. Although this estimate was imprecise, as indicated by the wide CI (a result of the relatively small size of the study), these data still add further support to the beneficial effects of NSAID use in reducing colorectal cancer risk in women. Among all the epidemiological studies that have demonstrated a protective effect of NSAID use, the magnitude of effect has been remarkably similar, typically varying between a 40 and 60% reduction in risk (9–11, 14, 15) or mortality (13, 24) for regular NSAID users. Although the majority of epidemiological studies have found a positive association between NSAID use and reduced risk of colorectal cancer, one important exception is the physicians’ health study that failed to demonstrate any protective effect of 5 years of NSAID use on colorectal cancer risk (19). Recently, a further analysis of this study using data from over 13 years of follow-up again found no benefit of aspirin use (25).

In contrast to the results of this trial however, randomized clinical trials conducted in patients with familial adenomatous polyposis have shown that the NSAID sulindac markedly reduced both the number and size of rectal and colonic polyps (26, 27).

In this study, when subjects were classified according to the type of NSAID used (either aspirin or nonaspirin NSAID), the results suggested that nonaspirin NSAIDs (mainly the propionic acid derivatives) may have greater efficacy in reducing the occurrence of colorectal cancer compared to aspirin. Subjects who reported using nonaspirin NSAIDs regularly had a statistically significant 57% lower risk of colorectal cancer compared to nonusers, whereas subjects who took aspirin regularly had only a modest, nonsignificant 21% reduction in cancer risk. The clinical and epidemiological importance of these findings are unknown. However, it is now recognized that there are two isozymes of prostaglandin synthetase (termed cyclooxygenase-1 and cyclooxygenase-2; Ref 28) and that aspirin irreversibly inhibits only cyclooxygenase-1, whereas non-aspirin NSAIDs inhibit both isozymes (29). This has led to the suggestion that nonaspirin NSAIDs or other specific inhibitors of cyclooxygenase-2 might provide greater chemoprotective activity against colorectal cancer than aspirin alone (29). It should be noted however, that two previous case-control studies did not find much difference between regular aspirin and non-aspirin NSAID use in terms of protection against colorectal cancer (12, 17). The study by Pelag et al. (12) showed a strong negative dose-response relationship between the duration of aspirin use and colorectal cancer risk, whereas the relationship between the duration of nonaspirin use and cancer risk appeared to be somewhat weaker. There was no difference in the protection afforded by aspirin and nonaspirin NSAID in the study by Logan et al. (17); compared to nonusers, the adjusted ORs for the effect of regular aspirin use and regular non-aspirin use were 0.55 and 0.56, respectively.

The hypothesis that NSAIDs can reduce colorectal cancer risk is strongly supported by experimental data. Several experimental reports have documented the broad anticarcinogenic effects of NSAIDs on colon cancer both in vivo using laboratory animals, and in vitro, using cancer cell lines (30, 31). Ideally, the definition of a regular NSAID user should be based on a sound understanding of the pharmacodynamics of NSAIDs, in conjunction with an appreciation for the likely antineoplastic mechanism of action. Although many NSAIDs are recognized as having strong cystostatic effects, the exact antineoplastic mechanisms of action of these agents are still not well understood (30). Although it is widely accepted that the primary antineoplastic action of NSAIDs involves the inhibition of the cyclooxygenase pathway of arachidonic metabolism, other mechanisms may be important (32–34). In fact, some studies (31, 35) have shown poor correlation between the antiproliferative effects of NSAIDs and cyclooxygenase inhibitory activity. An understanding of the exact mechanism of action for the antiproliferative effects of NSAIDs is more than of academic interest. Because most of the complications associated with long-term NSAID therapy are associated with its antiprostaglandin activity, potential chemoprevention protocols should be based on an appropriate low dose of NSAIDs and/or the use of NSAIDs that have less potent antiprostaglandin effects (30, 36). More work is required before an appropriate dose of NSAIDs can be determined that fulfills their chemoprevention potential without incurring their deleterious side effects (36, 37).

Several studies have found that colorectal cancer risk decreases with increasing duration of NSAID use (9, 12, 15, 16, 24). This study also found a significant effect of duration of NSAID use on colorectal cancer risk, although the trend in the ORs did not fit well with the hypothesized dose-response relationship. In particular, women who reported taking NSAIDs regularly for 5 or more years did not show any benefit of NSAID use compared to nonusers (OR = 1.1). There was a relatively large proportion of cases who reported long-term
NSAID use; in fact, the mean duration of NSAID use among regular users was longer for cases (6.3 years) than controls (4.5 years). This could represent an effect of information or recall bias. It is interesting to note that in a large prospective study of aspirin use and colorectal cancer risk in women, Giovannucci et al. found that a significant reduction in colorectal cancer risk was not observed until after 20 years of continuous aspirin use. In contrast to some of the previous reports (10, 13, 24), we found no significant effect of either the frequency of NSAID use or the total number of doses of NSAID consumed on colorectal cancer risk, although this may have been related, in part, to the smaller number of women available to evaluate these effects.

The validity of the previous epidemiological studies has been criticized on several counts, including confounding and detection biases (5). It is often difficult to control for other potential confounding variables, such as physical activity and improved diet (i.e., low fat and high vegetable, fruit, and fibre intake), particularly in studies in which the hypothesis of NSAID use and decreased colorectal cancer risk was not an original primary objective. In this study, however, we were able to adjust for three commonly recognized potential confounding variables: prior sigmoidoscopy use, family history, and BMI. We also examined the effect of recent alcohol consumption, smoking, vitamin A intake, and early-life physical activity, although none of these variables were found to be important confounders.

This study has several potential limitations, including its small size and possible influence of detection bias. With respect to the latter, it has been suggested that early symptoms of colorectal cancer could result in patients avoiding NSAIDs, which would thereby lead to a spurious association between aspirin use and lower colorectal cancer risk. This form of detection bias remains a possible explanation for the results of our study, although other studies that have had the opportunity to evaluate this bias have not found much evidence for it (15, 16, 19).

In summary, this study found, a modest reduction in colorectal cancer risk among women who regularly took NSAIDs, consistent with the findings of the majority of previous observational studies. Additionally, this study found that women who took non-aspirin NSAID regularly had a markedly lower risk of colorectal cancer compared to nonusers. The clinical and epidemiological importance of this latter finding needs to be addressed in future studies. Further studies, particularly randomized prevention trials, are required before any public health recommendations can be made concerning the use of NSAID to reduce colorectal cancer risk. However, since there are significant barriers to successfully completing randomized trials of NSAID use and colorectal cancer prevention (including long follow-up duration, large size, and excessive cost), it has been suggested that trials should focus on the occurrence and progression of polyps rather than invasive tumors (37). If NSAIDs are proven to be effective chemopreventive agents for colorectal cancer prevention, any public health recommendations must take into account the potential side effects of aspirin and other NSAIDs, which include gastrointestinal bleeding and nephrotoxicity, which need to be balanced with their potential benefits of cancer and heart disease prevention.

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References


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