A Prospective Study of Aspirin Use and the Risk of Pancreatic Cancer in Women

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See “Notes” following “References.”

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Pancreatic cancer, the fourth leading cause of cancer-related mortality in the United States (1), is a rapidly fatal malignancy with limited effective treatment. Nonetheless, other than cigarette smoking, few risk factors have been consistently linked to the risk of pancreatic cancer. Clearly, further studies are needed to identify potential causes and chemopreventive agents for the disease.

There is considerable evidence that nonsteroidal anti-inflammatory drugs (NSAIDs), particularly aspirin, reduce the risk of several cancers and premalignant lesions. Observational and intervention studies (2) consistently demonstrate the value of these drugs as chemopreventive agents for colorectal neoplasia. Although the mechanism by which aspirin reduces the risk of neoplasms remains unclear, the oncostatic effect is thought to be based in part on its anti-inflammatory actions, mediated by the inhibition of cyclooxygenase 2: NSAIDs indirectly inhibit the biosynthesis of prostaglandins by blocking the enzyme prostaglandin G/H synthetase (3). Two isoforms of cyclooxygenase have been identified: cyclooxygenase 1 and cyclooxygenase 2 (4,5). Although cyclooxygenase 1 plays a central role in platelet aggregation and protection of stomach mucosa and is expressed in most tissues, cyclooxygenase 2 is induced by various cytokines and mitogenic factors and is found in high concentrations in tissues undergoing inflammatory and wound healing processes as well as in some neoplasms (6). Both cyclooxygenase 1 and cyclooxygenase 2 initiate the production of biologically important prostanoids, which are involved in cell signaling (7).

Numerous experimental studies (3) also indicate that NSAIDs can influence tumorogenesis, apoptosis, and angiogenesis.

In vitro experiments and limited animal studies (8,9) suggest that aspirin and NSAIDs inhibit pancreatic carcinogenesis. To date, few studies have examined the associations between analgesic use and pancreatic cancer in humans, and the results have been inconsistent. A recent prospective study of U.S. women (10) reported a statistically significant inverse association between current aspirin use and the risk of pancreatic cancer, although the analysis was limited by the small number of patients studied (n = 80). Moreover, updated aspirin use (beyond the baseline measure) and past use were not assessed.

We conducted a prospective study in a large cohort of women with 18 years of follow-up and detailed periodic assessment of aspirin use to further define the possible preventive effects of aspirin for pancreatic cancer with particular emphasis on the effects of dosage and duration of aspirin use. In this cohort, aspirin data were elicited before any diagnosis of pancreatic cancer, thus avoiding potential biases that may occur when obtaining such information from pancreatic cancer patients or their next of kin.

Background: In vitro experiments and limited animal studies suggest that aspirin and nonsteroidal anti-inflammatory drugs may inhibit pancreatic carcinogenesis. Because few studies have examined the association between aspirin use and pancreatic cancer in humans and the results have been inconsistent, we examined the relationship between aspirin use and the development of pancreatic cancer in the Nurses’ Health Study.

Methods: Among 88,378 women without cancer at baseline, we documented 161 cases of pancreatic cancer during 18 years of follow-up. Aspirin use was first assessed at baseline in 1980 and updated biennially thereafter. All statistical tests were two-sided. Results: Participants were classified according to history of aspirin use. In a multivariable analysis, the risk of pancreatic cancer was not associated with current regular aspirin use (defined as two or more standard tablets per week; relative risk [RR] = 1.20, 95% confidence interval [CI] = 0.87 to 1.65), compared with use of fewer than two tablets per week. Increasing duration of regular aspirin use, compared with non-use, was associated with a statistically significant increase in risk: Women who reported more than 20 years of regular aspirin use had an increased risk of pancreatic cancer (RR = 1.58, 95% CI = 1.03 to 2.43; \( P_{\text{trend}} = .01 \)). Among women who reported aspirin use on at least two of three consecutive biennial questionnaires compared with consistent non-users of aspirin, the risk increased with dose (one to three tablets per week: RR = 1.11, 95% CI = 0.70 to 1.76; four to six tablets per week: RR = 1.29, 95% CI = 0.70 to 2.40; seven to 13 tablets per week: RR = 1.41, 95% CI = 0.76 to 2.61; and \( \geq 14 \) tablets per week: RR = 1.86, 95% CI = 1.03 to 3.35) \( P_{\text{trend}} = .02 \). Conclusion: Extended periods of regular aspirin use appear to be associated with a statistically significantly increased risk of pancreatic cancer among women.
PATIENTS AND METHODS

Study Cohort

In 1976, the Nurses’ Health Study enrolled 121,700 female registered nurses aged 30 to 55 years to gather, through mailed questionnaires, information on their health status, medical history, and known and suspected risk factors for cancer and coronary heart disease. Follow-up questionnaires were sent biennially to cohort participants thereafter. Further details of the cohort are reported elsewhere (11–13).

Ascertainment of Aspirin and NSAID Use

Information on aspirin use was first collected at baseline in 1980 and updated biennially thereafter with the exception of 1986. In 1980, we ascertained current aspirin use (defined as aspirin use in most weeks) from the study participants and provided space for participants to fill in the number of tablets taken each week and to indicate for how many years they had used aspirin. In 1982, we asked if they currently took aspirin at least once per week and provided prespecified categories of the total amount of aspirin use per week (1–3, 4–6, 7–14, or ≥15 adult tablets). In 1984 and 1988, we queried the average number of days per month of aspirin use (none, 1–4, 5–14, 15–21, or ≥22 days/month) and, on days they did take aspirin, the number of tablets usually taken (never take it, 1, 2, 3–4, 5–6, or ≥7 tablets). In 1990 and 1992, only the number of days per month of aspirin use was assessed (none, 1–4, 5–14, 15–21, or ≥22 days/month) but not the number of aspirin tablets per day. In 1994 and 1996, women were asked whether they had regularly used aspirin (two or more times per week) in the past 2 years, how frequently they had used aspirin (<1 day/month, 1–3 days/month, 1–2 days/week, 3–4 days/week, 5–6 days/week, or daily) and how many tablets per week, on average (0, 0.5–2, 3–5, 6–14, or ≥15 tablets per week). Early in the study, most women used standard-dose tablets (325 mg per tablet); however, to reflect overall trends in consumption of low-dose or baby aspirin (81 mg per tablet), the 1994 and 1996 questionnaires asked participants to convert use of four baby aspirin to one adult tablet when choosing their responses. Some regrouping of responses, therefore, was required to adjust for the differing ways in which aspirin-use habits were recorded between 1980 and 1998 (14). On the basis of a previous analysis of this cohort, women who reported taking two or more standard aspirin tablets per week were defined as regular users, whereas those who reported less aspirin use were defined as non-regular users (14). To elicit the reasons for aspirin use, a short questionnaire was sent in 1990 to 100 participants in the Nurses’ Health Study who reported taking one to six aspirin per week (90% response) and to 100 women who reported taking seven or more aspirin per week (92% response) on the 1980, 1982, and 1984 questionnaires (14). The major reasons for use among women taking one to six aspirin and seven or more aspirin per week were headache (32% and 18%, respectively), arthritis and other musculoskeletal pain (30% and 50%), a combination of headache and musculoskeletal pain (16% and 15%), cardiovascular disease prevention (9% and 8%), and other reasons (13% and 9%) (14).

In 1980, participants were also asked whether they were currently taking nonsteroidal analgesics other than aspirin (Motrin, Indocin, Tolectin, and Clinoril) in most weeks. In addition, users were asked to provide the number of years they had used the drugs and the number of tablets taken per week. Non-aspirin NSAID use was not reassessed until 1990. In 1990 and 1992, we asked for the frequency of non-aspirin NSAID use (none, 1–4, 5–14, 15–21, or ≥22 days per month) and, in 1994 and 1996, we assessed regular use of non-aspirin NSAIDs (two or more times per week).

Smoking History and Other Risk Factors

Smoking status and history of smoking were obtained at baseline and in all subsequent questionnaires. Current smokers also reported intensity of smoking (average number of cigarettes smoked per day) on each questionnaire. Past smokers reported when they last smoked, and the time since quitting was calculated for those who quit during follow-up. In a previous study (15), we examined the relationship between smoking and pancreatic cancer risk in detail; the strongest associations were observed in analyses of total pack-years smoked within the previous 15 years. Participants were asked about history of diabetes at baseline and in all subsequent questionnaires. Because pancreatic cancer is frequently associated with profound weight loss, we did not adjust for weight change or most recent body mass index but used baseline body mass index (1976, the start of the cohort), which was the most important weight risk factor for pancreatic cancer in this cohort (16). Other questions relevant to the association between aspirin use and pancreatic cancer provided information on the study participants’ age and physical activity.

Ascertainment of Pancreatic Cancer and Deaths

We included pancreatic cancers reported on the biennial questionnaires between the return of the 1980 questionnaire and June 1, 1998. With permission from study participants, pancreatic cancer was confirmed through physicians’ review of the nurses’ medical records. If permission was denied, we attempted to confirm the self-reported cancer with an additional letter or phone call. We also searched the National Death Index to identify deaths among the nonrespondents to each 2-year questionnaire. The computerized National Death Index is a highly sensitive method for identifying death in this cohort (17). For all deaths attributable to pancreatic cancer, we requested permission from family members (subject to state regulation) to review the medical records. Pancreatic cancer was considered the cause of death if the medical records or autopsy report confirmed fatal pancreatic cancer or if pancreatic cancer was listed as the underlying cause of death without another more plausible cause.

Statistical Analysis

We excluded participants who did not respond to the baseline questionnaire or did not provide information on aspirin use on the baseline questionnaire and all participants who reported a baseline history of cancer (with the exception of nonmelanoma skin cancer). We computed person-years of follow-up to the date of diagnosis of pancreatic cancer, death from any cause, or the end of the study period (June 1, 1998), whichever occurred first. After these exclusions, 88,378 women were eligible for follow-up, and 1,475,262 person years were accrued. Among these 88,378 women without cancer at baseline, we documented 161 cases of pancreatic cancer during 18 years of follow-up. Because the use of analgesics might have been triggered by early symptoms associated with pancreatic cancer, we excluded the first 2
years of follow-up, in secondary analyses, for all study participants after their first report of analgesic use.

The primary analysis used incidence rates with person-years of follow-up in the denominator. We used relative risk as the measure of association; relative risk was defined as the incidence of pancreatic cancer among participants who reported regular use of aspirin divided by the incidence among participants without such a report. We examined relative risks according to duration of regular aspirin use defined as duration before baseline (as reported on the 1980 questionnaire) plus years of regular use after 1980. Regular use of aspirin was defined as the use of two or more tablets per week. In subanalyses, we examined whether regular use of five or more tablets of aspirin per week influenced pancreatic cancer risk. Because data on the use of such high doses of aspirin were not available before 1980 (aspirin use was assessed as years of prior use of two or more tablets per week in 1980), the maximal report on duration of regular aspirin intake, defined as five or more tablets per week, did not exceed 18 years in these analyses. To more accurately assess the influence of aspirin dose among relatively consistent aspirin users, we calculated the average aspirin dose among women who reported any aspirin use on at least two of three consecutive biennial questionnaires (1980, 1982, and 1984) and compared their incidence of pancreatic cancer to that among women who reported no aspirin use on at least two of the same three consecutive questionnaires.

Using Cox proportional hazards models, we adjusted for other potential risk factors for pancreatic cancer, including a history of diabetes and level of physical activity. We also conducted stratified analyses to determine whether the influence of aspirin use was modified by body mass index and included an interaction term of body mass index with dosage into the model to test for statistical significance. The data conformed to proportional hazards assumptions, and all statistical tests were two-sided (α = .05).

RESULTS

During 18 years and 1,475,262 person-years of follow-up, 161 women were diagnosed with pancreatic cancer. Baseline characteristics of the 88,378 women who completed the baseline aspirin questionnaire in 1980 and provided information on regular aspirin use are shown in Table 1. At baseline, 43% of the participants reported any current, regular use of aspirin, defined as two or more aspirin tablets per week. Women who reported current aspirin use were generally similar to women who did not take aspirin. However, there was a higher prevalence of obesity and diabetes mellitus among participants who reported higher doses or regular aspirin use.

Using data from the baseline 1980 report only, we examined the association between regular aspirin use, defined as two or more tablets per day, and the risk of pancreatic cancer. Participants who reported regular aspirin use at baseline, compared with those who reported using fewer than two tablets per week, experienced an increased risk of pancreatic cancer (RR = 1.43, 95% CI = 1.05 to 1.95) after adjusting for age, cigarette smoking, history of diabetes mellitus, body mass index, and nonvigorous physical activity.

We used reports that were updated biennially to examine the influence of current aspirin use on the risk of pancreatic cancer. Current regular aspirin use, defined as the use of two or more tablets per week at the beginning of each 2-year follow-up cycle, was not statistically significantly associated with the risk of pancreatic cancer when compared with non-regular use (Table 2). Adjustment for other known risk factors did not substantially alter this estimate (multivariable RR = 1.20, 95% CI = 0.87 to 1.65). Increasing current doses of aspirin, compared with non-use, did not change these risks (P_trend = .41). When we decreased the number of categories of aspirin dosage to four by using seven or more tablets per week as the highest category and subjected the data to multivariable analysis, the risks associated with all dosage categories and the P_trend remained statistically nonsignificant.

We also examined the influence of increasing duration of regular aspirin use (defined as two or more tablets per week) on the risk of pancreatic cancer. Prolonged regular use of two or more tablets per week appeared to increase the risk of pancreatic cancer (P_trend = .01). Participants who reported the use of two or more tablets per week for more than 20 years, compared with women who never regularly consumed aspirin at this dose, experienced a statistically significantly increased risk of pancreatic cancer (multivariable RR = 1.58, 95% CI = 1.03 to 2.43).

We similarly assessed the influence of non-aspirin NSAID use on the risk of pancreatic cancer. Women who reported any current other NSAID use, compared with non-users, had a statistically nonsignificant increased risk of pancreatic cancer (RR = 1.20, 95% CI = 0.79 to 1.80). Because of limited statistical power, we could not examine the association be-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline No. of aspirin tablets per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of individuals</td>
<td></td>
</tr>
<tr>
<td>Age, y (SD)</td>
<td></td>
</tr>
<tr>
<td>Height, inches (SD)</td>
<td></td>
</tr>
<tr>
<td>% with baseline body mass index ≥30</td>
<td></td>
</tr>
<tr>
<td>% with history of diabetes</td>
<td></td>
</tr>
<tr>
<td>% current smokers</td>
<td></td>
</tr>
<tr>
<td>Avg. No. (SD) of pack-years of smoking</td>
<td></td>
</tr>
<tr>
<td>Total physical activity, h/weekdays only (SD)</td>
<td></td>
</tr>
</tbody>
</table>

*Age was standardized according to eight categories (<44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, ≥75 y) as of 1980. Data are means (standard deviation [SD]), unless otherwise indicated.

†Body mass index is weight (in kilograms) divided by the square of height (in meters).

‡Pack-years were calculated for former and current smokers only.
The number of cases of pancreatic cancer is shown. RR = relative risk; CI = confidence interval. Multivariable risks from proportional hazards models are adjusted for age in years, follow-up cycle, history of diabetes (yes/no), smoking status in six categories (never, quit ≥15 years ago, quit <15 years ago and smoked ≥25 pack-years in past 15 years, current smoker who smoked ≥25 pack-years in past 15 years, and current smoker who smoked >25 pack-years in past 15 years), quintiles of nonvigorou physical activity in metabolic equivalents per week (i.e., the caloric need per kilogram body weight per hour of activity, divided by the caloric need per kilogram per hour at rest), and 1976 body mass index in five categories (<21, 21–22.9, 23–24.9, 25–28.9, and ≥29 kg/m²).

† Non-regular use is defined as use of any aspirin dose of fewer than two tablets per week.
‡ All statistical tests were two-sided.

Table 2. Association between updated regular aspirin use (defined as use of ≥2 tablets per week) and incident pancreatic cancer*.

<table>
<thead>
<tr>
<th>Aspirin use</th>
<th>No. of cases</th>
<th>Total person-years</th>
<th>Age-adjusted RR (95% CI)</th>
<th>Multivariable RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-regular use†</td>
<td>96</td>
<td>969 187</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Regular use (≥2 tablets per wk)</td>
<td>65</td>
<td>506 075</td>
<td>1.26 (0.92 to 1.73)</td>
<td>1.20 (0.87 to 1.65)</td>
</tr>
</tbody>
</table>

Duration of regular use (≥2 tablets per wk):

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of cases</th>
<th>Person-years</th>
<th>Age-adjusted RR (95% CI)</th>
<th>Multivariable RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 y</td>
<td>57</td>
<td>679 689</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>1–5 y</td>
<td>24</td>
<td>260 997</td>
<td>0.95 (0.59 to 1.54)</td>
<td>0.94 (0.58 to 1.53)</td>
</tr>
<tr>
<td>6–10 y</td>
<td>23</td>
<td>174 630</td>
<td>1.21 (0.75 to 1.96)</td>
<td>1.19 (0.73 to 1.95)</td>
</tr>
<tr>
<td>11–20 y</td>
<td>23</td>
<td>143 104</td>
<td>1.49 (0.91 to 2.35)</td>
<td>1.51 (0.92 to 2.48)</td>
</tr>
<tr>
<td>&gt;20 y</td>
<td>34</td>
<td>214 650</td>
<td>1.58 (1.03 to 2.42)</td>
<td>1.58 (1.03 to 2.43)</td>
</tr>
</tbody>
</table>

P_{trend} = .01

*The number of cases of pancreatic cancer is shown. RR = relative risk; CI = confidence interval. Multivariable risks from proportional hazards models are adjusted for age in years, follow-up cycle, history of diabetes (yes/no), smoking status in six categories (never, quit ≥15 years ago, quit <15 years ago and smoked ≥25 pack-years in past 15 years, current smoker who smoked ≥25 pack-years in past 15 years, and current smoker who smoked >25 pack-years in past 15 years), quintiles of nonvigorou physical activity in metabolic equivalents per week (i.e., the caloric need per kilogram body weight per hour of activity, divided by the caloric need per kilogram per hour at rest), and 1976 body mass index in five categories (<21, 21–22.9, 23–24.9, 25–28.9, and ≥29 kg/m²).

†Non-regular use is defined as use of any aspirin dose of fewer than two tablets per week.
‡ All statistical tests were two-sided.

We observed a monotonic increase in the risk of pancreatic cancer with increasing aspirin dose, compared with consistent non-use of aspirin (P_{trend} = .02). Women with consistent use of 14 or more tablets per week had the highest risk of pancreatic cancer (multivariable RR = 1.86, 95% CI = 1.03 to 3.35). We further considered the possibility that changing our definition of regular aspirin use to use of five or more tablets per week may influence our results and examined whether regular use of five or more tablets of aspirin per week influenced the risk of pancreatic cancer. We used reports that were updated biennially (except 1986) to determine that current use of five or more aspirin tablets per week was not statistically significantly associated with risk compared with use of fewer aspirin tablets (Table 4). However, increasing duration of regular use of this dose of aspirin was associated with a statistically significant increase in the risk of pancreatic cancer (P_{trend} = .01). Participants who regularly consumed five or more tablets of aspirin per week for more than 10 years, compared with women who never

Table 3. Association between average aspirin dose and incident pancreatic cancer among consistent users and consistent non-users of aspirin (1984–1998)*.

<table>
<thead>
<tr>
<th>Aspirin dose per wk</th>
<th>No. of cases</th>
<th>Person-years</th>
<th>Age-adjusted RR (95% CI)</th>
<th>Multivariable RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 tablets</td>
<td>25</td>
<td>214 375</td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>1–3 tablets</td>
<td>69</td>
<td>585 545</td>
<td>1.07 (0.68 to 1.70)</td>
<td>1.11 (0.70 to 1.76)</td>
</tr>
<tr>
<td>4–6 tablets</td>
<td>17</td>
<td>111 125</td>
<td>1.31 (0.71 to 2.43)</td>
<td>1.29 (0.70 to 2.40)</td>
</tr>
<tr>
<td>7–13 tablets</td>
<td>17</td>
<td>94 064</td>
<td>1.46 (0.78 to 2.72)</td>
<td>1.41 (0.76 to 2.61)</td>
</tr>
<tr>
<td>≥14 tablets</td>
<td>20</td>
<td>75 574</td>
<td>2.02 (1.12 to 3.65)</td>
<td>1.86 (1.03 to 3.35)</td>
</tr>
</tbody>
</table>

P_{trend} = .01

*We calculated the average aspirin dose among women who reported any aspirin use on at least two of three consecutive biennial questionnaires (1980, 1982, 1984); these analyses were based on 83 976 women and 149 incident pancreatic cancer cases that occurred between 1984 and 1998. RR = relative risk; CI = confidence interval. Multivariable risks from proportional hazards models are adjusted for age in years, follow-up cycle, history of diabetes (yes/no), smoking status in six categories (never, quit ≥15 years ago, quit <15 years ago and smoked ≥25 pack-years in past 15 years, current smoker who smoked ≥25 pack-years in past 15 years, and current smoker who smoked >25 pack-years in past 15 years), quintiles of nonvigorou physical activity in metabolic equivalents per week (i.e., the caloric need per kilogram body weight per hour of activity, divided by the caloric need per kilogram per hour at rest), and 1976 body mass index in five categories (<21, 21–22.9, 23–24.9, 25–28.9, and ≥29 kg/m²).

‡ All statistical tests were two-sided.

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regularly consumed five or more tablets of aspirin per week, had an increased risk of pancreatic cancer (RR = 1.75; 95% CI = 1.18 to 2.60). Because data on the use of such high doses of aspirin were not available before 1980 (aspirin use was assessed as years of prior use of two or more tablets per week in 1980), we could not examine additional categories of use beyond 18 years.

In previous analyses of this cohort, we observed that other pancreatic cancer risk factors varied in effect by body mass index (16,18). We therefore examined the influence of body mass index at baseline on the association between updated regular aspirin use (two or more tablets per week) and the risk of pancreatic cancer. Among women of normal weight (body mass index <25 kg/m²), we observed no association between regular aspirin use and the risk of pancreatic cancer (RR = 0.84, 95% CI = 0.54 to 1.30). However, among women whose body mass index was 25 kg/m² or greater, the risk of pancreatic cancer was greater for current regular aspirin users (RR = 1.78, 95% CI = 1.08 to 2.94) than for non-regular users.

Because the use of aspirin as an analgesic may have been triggered by early symptoms associated with undiagnosed pancreatic cancer, we analyzed the relationship between regular aspirin use as assessed in 1980 and the risk of pancreatic cancer from 1982 through 1998. Despite this 2-year latency period, current regular use of aspirin, compared with current non-regular use of aspirin, was associated with a similar risk of pancreatic cancer (multivariable RR = 1.15, 95% CI = 0.83 to 1.59). Moreover, the risks associated with increasing aspirin dose among consistent aspirin users (as defined in Table 4) also remained essentially unchanged when we excluded the first 2 years of follow-up in these analyses: Women who consumed 14 or more tablets per week, compared with consistent non-users, had an increased risk of pancreatic cancer (RR = 1.74, 95% CI = 0.89 to 3.42).

**DISCUSSION**

In this prospective cohort of women, participants who reported current use of two or more standard aspirin tablets per week experienced a modest but not statistically significantly increased risk of pancreatic cancer compared with those who reported less use. Furthermore, increasing duration of regular use was associated with a statistically significant increase in risk. Among women who reported consistent aspirin use on at least two of three consecutive biennial questionnaires, we observed a statistically significant increase in the risk of pancreatic cancer with increasing aspirin dose compared with those who similarly reported non-use.

Few studies have reported on the association between the use of aspirin and NSAIDs and the risk of pancreatic cancer. In a case–control study of 194 pancreatic cancer patients and 582 age- and sex-matched control subjects, Menezes et al. (19) reported no statistically significant association between regular use of aspirin and the risk of pancreatic cancer. The authors did, however, note a statistically nonsignificant association between increased duration of use and pancreatic cancer risk (odds ratio [OR] = 1.21, 95% CI = 0.81 to 1.82 for 11 or more years of use). Coogan et al. (20) did not observe an increased risk of pancreatic cancer associated with regular NSAID use (RR = 0.8, 95% CI = 0.5 to 1.1) in their study of 504 case patients with pancreatic cancer and control subjects. In the largest case–control study, with 513 patients and 1535 control subjects, Langman et al. (21) found a statistically significantly increased risk of pancreatic cancer (OR = 1.49, 95% CI = 1.02 to 2.18) associated with aspirin and other NSAID use 13–36 months before diagnosis. In that study, which compared study subjects with seven or more prescriptions with those with no prescriptions, data on aspirin and NSAID use were recorded in the prescription drug registry before the diagnosis of pancreatic cancer. Although the authors could not exclude the possibility that case patients were taking NSAIDs because of pain related to occult, preclinical malignancy, the elevated risks persisted even after restricting analyses to prescriptions obtained more than 2 years before diagnosis of pancreatic cancer.

Two prospective studies have reported an inverse association between aspirin use and the risk of pancreatic cancer, but both were limited by a small number of case subjects and incomplete assessment of dosage and duration of aspirin and NSAID use.

<table>
<thead>
<tr>
<th>Table 4. Association between updated regular aspirin use (defined as use of ≥5 tablets of aspirin per week) and incident pancreatic cancer*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin use</strong></td>
</tr>
<tr>
<td>Use</td>
</tr>
<tr>
<td>Non-regular use†</td>
</tr>
<tr>
<td>Regular use (≥5 tablets per wk)</td>
</tr>
<tr>
<td>Duration of regular use (≥5 tablets per wk);‡</td>
</tr>
<tr>
<td>0 y</td>
</tr>
<tr>
<td>1–5 y</td>
</tr>
<tr>
<td>6–10 y</td>
</tr>
<tr>
<td>&gt;10 y</td>
</tr>
<tr>
<td><strong>P</strong></td>
</tr>
</tbody>
</table>

*The number of cases of pancreatic cancer is shown. RR = relative risk; CI = confidence interval. Multivariable risks from proportional hazards models are adjusted for age in years, follow-up cycle, history of diabetes (yes/no), smoking status in six categories (never, quit ≥15 years ago, quit <15 years ago and smoked ≥25 pack-years in past 15 years, quit <15 years ago and smoked ≥25 pack-years in past 15 years, current smoker who smoked ≥25 pack-years in past 15 years, current smoker who smoked ≥25 pack-years in past 15 years), nonvigorous physical activity in metabolic equivalents per week (i.e., the caloric need per kilogram of body weight per hour of activity, divided by the caloric need per kilogram per hour at rest), in quintiles, and 1976 body mass index in five categories (<21, 21–22.9, 23–24.9, 25–28.9, and ≥29 kg/m²).

†Duration of use was obtained from any aspirin dose of fewer than five tablets per week.

‡The number of cases of pancreatic cancer is shown. RR = relative risk; CI = confidence interval. Multivariable risks from proportional hazards models are adjusted for age in years, follow-up cycle, history of diabetes (yes/no), smoking status in six categories (never, quit ≥15 years ago, quit <15 years ago and smoked ≥25 pack-years in past 15 years, quit <15 years ago and smoked ≥25 pack-years in past 15 years, current smoker who smoked ≥25 pack-years in past 15 years, nonvigorous physical activity in metabolic equivalents per week (i.e., the caloric need per kilogram of body weight per hour of activity, divided by the caloric need per kilogram per hour at rest), in quintiles, and 1976 body mass index in five categories (<21, 21–22.9, 23–24.9, 25–28.9, and ≥29 kg/m²).

§All statistical tests were two-sided.
Using data from the National Health and Nutrition Examination Survey, Schreinemachers and Eversen (22) reported a decreased risk of pancreatic cancer (RR = 0.67, 95% CI = 0.33 to 1.67) among aspirin users from 30 patients with pancreatic cancer accrued over more than 12 years of follow-up. In a more recent prospective analysis of 80 patients with incident pancreatic cancer among women participants in the Iowa Women’s Health Study Cohort, Anderson et al. (10) reported a statistically significant inverse association between the risk of pancreatic cancer and any current aspirin use (RR = 0.57, 95% CI = 0.36 to 0.90), as well as a statistically significant trend with increasing doses of aspirin (P_trend = .005); no association was noted with the use of other NSAIDs. However, in the Iowa cohort, data on updated aspirin use and past use were not available. Consequently, the authors could not assess the effect of longer durations of aspirin use on the risk of pancreatic cancer.

Aspirin and NSAIDs may have several potential influences on the pancreas that could affect pancreatic carcinogenesis. Some in vitro studies reported an inhibitory effect of these compounds on the growth of pancreatic cancer cell lines (8,23), although other investigations observed essentially no effect (24). In contrast, case reports and cohort studies have suggested that aspirin and NSAIDs are associated with an increased risk of pancreatitis (25,26). Given the greater risk of pancreatic cancer among individuals with a history of pancreatitis (27), a subclinical chronic inflammation of the pancreas induced by long-term aspirin and NSAID use could elicit a modest increase in the risk of pancreatic cancer. Nonetheless, studies are needed to address the potential relationship between NSAID use and pancreatic cancer triggered through chronic pancreatitis, and these studies would have to pay particular attention to the potential for indication bias in such an association.

Another possible explanation for the observed increase in risk after several years of aspirin use may be linked with its effect on lipoxygenases. Until recently, NSAIDs, including aspirin, were believed to influence carcinogenesis mainly by inhibiting cyclooxygenases. 2 Cyclooxygenase 2 and lipoxygenases metabolize polyunsaturated fatty acids and appear to affect carcinogenesis. Recently, however, a better understanding of the complex mechanisms involved in the chemopreventive actions of NSAIDs is emerging, and other, not yet clearly defined, pathways have been hypothesized (28). An alternate pathway, as described by Ding et al. (29), for instance, could be mediated through overexpression of 5-lipoxygenase mRNA in pancreatic cancer. 5-Lipoxygenase is a procarcinogenic lipoxygenase. Currently, the extent to which NSAIDs inhibit anticarcinogenic lipoxygenases, as opposed to procarcinogenic lipoxygenases, is unclear. Any imbalances induced by NSAIDs may impact differentially on carcinogenesis in different tissues, especially in the long run, which could serve as an alternate explanation of the risk of pancreatic cancer observed in our study.

In our cohort, the higher pancreatic cancer risk associated with aspirin use seemed to be confined to women with a higher body mass index. Obesity and other symptoms of the metabolic syndrome may be associated with low-grade inflammation, with one study (30) suggesting that inflammation precedes weight gain. Thus, obesity may have served as a marker for inflammation in this cohort, a potential explanation for the observed effect modification by body mass index.

The prospective nature of our studies precluded recall bias and the need for next-of-kin respondents. Moreover, to minimize misclassification of exposure, we updated reports of drug intake biennially. Self-reports of medication use are prone to error, but we would expect such measurement error to be random by nature; thus it should only bias our results toward the null. Furthermore, multiple measures of aspirin use minimize the potential impact of such error and allow us to assess the effects of duration of aspirin use on pancreatic cancer risk. In addition, consistent with the results of randomized clinical trials, we have reported an inverse association between aspirin use and colorectal cancer and adenoma in this cohort (14), which suggests we have a reasonably valid measure of aspirin use. Finally, because identification of deaths is highly accurate in this cohort (17), differential follow-up is unlikely.

The positive association between aspirin use and the risk of pancreatic cancer could reflect analgesic use for the treatment of occult or preclinical malignancies. However, the increasing risk of pancreatic cancer with increasing duration of use, particularly after more than 20 years, makes this explanation unlikely. Moreover, our findings remained largely unchanged after we excluded the first 2 years of follow-up.

In summary, our findings do not support a protective effect of analgesics use on the risk of pancreatic cancer. Rather, aspirin appears to increase the risk of pancreatic cancer after extended periods of use. This report supports current efforts examining the potential differential effects of these agents in different tissues. Risks and benefits associated with the use of aspirin have to be weighed carefully in any recommendations made by health care providers.

REFERENCES


NOTES

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