**Nonsteroidal anti-inflammatory drugs, statins and pancreatic cancer risk: a population-based case-control study**

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# ABSTRACT

***Purpose:*** Studies suggest that aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs) and statins may reduce risk of some cancers. However, findings have been conflicting as to whether these agents reduce the risk of pancreatic cancer.

***Methods:*** We used data from the Queensland Pancreatic Cancer Study, a population-based case-control study. In total 704 cases and 711 age- and sex-matched controls were recruited. Participants completed an interview in which they were asked about history of NSAID and statin use. We included 522 cases and 653 controls who had completed the medication section of the interview in this analysis. Unconditional multivariable logistic regression was used to estimate associations between medication use and pancreatic cancer.

***Results:*** We found no consistent evidence of an association between use of NSAIDs or statins and risk of pancreatic cancer. There was some suggestion of a protective effect in infrequent users of selective COX-2 inhibitors, but no association in more frequent users. We did not find evidence of protective effects in analyses stratified by sex, smoking status, time between diagnosis and interview or presence / absence of metastases.

***Conclusions:*** Overall our results do support the hypothesis that use of NSAIDs or statins may reduce the odds of developing pancreatic cancer.

***Key words:* pancreatic cancer, NSAIDs, COX-2 inhibitor, statin, aspirin, paracetamol**

**Introduction**

In 2012, pancreatic cancer was the 10th most common cancer and the 4th leading cause of cancer-related death in developed countries [[1](#_ENREF_1)]. Despite advances in chemotherapy and surgical treatment, the 5-year survival rate is lower than five percent [[2](#_ENREF_2)]. Understanding risk factors may identify opportunities for prevention or early diagnosis.

There is compelling evidence that factors including advancing age, Jewish ethnicity, family history of pancreatic cancer, history of chronic pancreatitis, diabetes, ABO blood group, cigarette smoking and obesity are associated with increased risk of developing pancreatic cancer [[3-8](#_ENREF_3)]. Some, although not all, studies have reported that a history of allergy, physical activity, and consumption of folate, fruit and vegetables may have a protective effect [[9-12](#_ENREF_9)].

There is some evidence to suggest that use of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, may be associated with decreased risk of pancreatic cancer [[13-18](#_ENREF_13)]. These agents, in particular nonselective NSAIDs, may act by inhibiting both cyclooxygenase COX-1 and COX-2 enzymes and prostaglandin synthesis [[15](#_ENREF_15)], thereby influencing apoptosis, cell proliferation and angiogenesis. Despite the biologically plausible mechanisms, findings from epidemiological studies are inconsistent. Two meta-analyses in which the primary exposure of interest was NSAIDs found no association between pancreatic cancer and either aspirin or other NSAIDs [[19](#_ENREF_19), [20](#_ENREF_20)]. However, there was significant heterogeneity in the estimates. A later study [[17](#_ENREF_17)] suggested that long-term use of NSAIDs (>2 years) may have a protective effect.

Aspirin has been trialled for prevention of cardiovascular disease. In a pooled analysis of eight randomized trials [[21](#_ENREF_21)], daily aspirin use reduced pancreatic cancer mortality after five years of the scheduled trial treatment. However, only 48 cases were included and a subsequent analysis including the same trials but using a different statistical approach found no effect of aspirin on risk of pancreatic cancer [[22](#_ENREF_22)].

Statins, used to manage hypercholesterolemia, may also have chemopreventive properties. A number of biologically plausible mechanisms by which statins might reduce risk of cancer have been proposed. These include inhibition of the mevalonate pathway and suppression of tumour growth and metastasis by reducing inflammation [[23](#_ENREF_23), [24](#_ENREF_24)]. However, the epidemiological evidence for an association between use of statins and pancreatic cancer is unclear. Two meta-analyses did not support a protective effect of statin use on pancreatic cancer but there was significant heterogeneity in the overall estimate [[25](#_ENREF_25), [26](#_ENREF_26)]. Two later studies found a significant inverse association between statin use risk of pancreatic cancer in men [[27](#_ENREF_27), [28](#_ENREF_28)].

In light of the inconsistency in previous findings, we have explored the association between NSAIDs, statins and pancreatic cancer risk, using data from a large population-based case-control study in Australia.

# METHODS

The Queensland Pancreatic Cancer Study (QPCS) is a population-based case-control study examining genetic and environmental risk factors for pancreatic cancer. The Human Research Ethics Committees of the QIMR Berghofer Medical Research Institute and all participating hospitals throughout Queensland (Australia) reviewed and approved the study, and informed consent was obtained from all participants.

## Participants

Detailed information about the recruitment and data collection procedures have been published previously [[3](#_ENREF_3), [29](#_ENREF_29)]. In brief, cases were residents of Queensland aged 18 years and over who were diagnosed with pancreatic cancer between 1st January 2007 and 31st June 2011. They were identified and recruited using a rapid ascertainment approach through a state-wide network of clinicians and the population-based Queensland Cancer Registry. The median time between diagnosis and interview was 65 days [[3](#_ENREF_3)]. Controls were randomly selected from the Australian Electoral Roll (voting is compulsory for Australians 18 years of age and over) and were frequency matched to cases by sex and age (within 5 years).

In total 705 cases were recruited, approximately 35% of all those notified to the Queensland Cancer Registry. Reasons for case non-participation were: the patient died before we were able to send the invitation – 51%; the doctor refused to allow access to the patient – 11%; the patient refused – 16%; the patient was unable to be contacted – 12%; the patient was diagnosed outside of eligibility period – 9%; cognitive impairment – 1% [[3](#_ENREF_3)]. We approached 1543 potential controls. Among these, 6% were ineligible or dead, 39% refused, 8% were unable to be contacted, and 1% failed to complete the interview at a satisfactory standard. A total of 711 controls were recruited (46% of those eligible) [[3](#_ENREF_3)]. For this analysis we excluded participants who did not complete the medication history section of the questionnaire, leaving 522 cases (74%) and 653 controls (92%) in the analysis.

## Interview questions

Data were collected during direct interviews; for most exposures we asked cases to exclude the year prior to diagnosis and controls the year prior to interview.

Participants were asked about their height and weight; these were used to compute body mass index (BMI, kg/m2). Alcohol consumption was recorded as the number of alcoholic drinks consumed during each decade, and average weekly consumption over adulthood was calculated. Participants reported their history of diabetes and the year of onset if present. We asked participants whether they had smoked more than 100 cigarettes, cigars or pipes over their lifetime. Positive responses led to further detailed questions to enable calculation of pack-years of smoking. [[3](#_ENREF_3)].

All participants in this analysis self-reported their use of medications. Participants were asked, “Have you ever taken low-dose aspirin for your heart?” and if the answer was yes, it was followed by “At what age did you first start?” We then asked participants if they had taken any of the following drugs over the past 5 years, excluding during the last year: regular dose aspirin, paracetamol, ibuprofen, diclofenac, naproxen, indomethacin, tenoxicam, piroxicam, phenylbutazone, diflunisal, ketoprofen, sulindac, celecoxib, rofecoxib, and meloxicam. Possible answers were never, occasionally, ~1 per month, 2-3 per month, ~1 per week, 2-3 per week, 4-7 per week or 2+ per day. Participants were also asked whether they had ever taken statins and, if yes, for age at first use. We did not ask about the specific type of statin. All questions were supplemented with generic and brand names of medication to facilitate recall.

## Statistical analysis

Distributions of the following variables were examined: age at interview, sex, education level, pack years of smoking, alcohol use, diabetes history, and body mass index one year prior to diagnosis **[Table 1]**. The Chi-squared test was used to test for significant differences between cases and controls.

We constructed aspirin use variables as follows. We firstly analysed ever users of low-dose aspirin and, for users, duration of use as <5 and ≥5 years of use. Use of regular-dose aspirin was dichotomised into ever versus never use (in the last 5 years) due to the small number of regular-dose aspirin users in this study. The reference groups for these analyses were non-users of low-dose aspirin and non-users of regular aspirin, respectively. Sensitivity analyses in which the reference category included those who had never used aspirin of any type did not alter the results. In a further analysis, we tested the association between pancreatic cancer and intake of (1) only low dose aspirin; (2) only regular dose aspirin; and (3) combination of these two types of aspirins. The reference category was never-users of any aspirin.

The following categories of NSAIDs were created, based on their active ingredients: (1) selective COX-2 inhibitors (including celecoxib, rofecoxib, meloxicam); (2) nonselective COX-1/COX-2 inhbitors (including regular-dose aspirin, ibuprofen, diclofenac, naproxen, indomethacin, tenoxicam, piroxicam, phenylbutazone, diflunisal, ketoprofen, and sulindac); and (3) all non-aspirin NSAIDs. Participants were asked to record the use of multiple different medications. If they had used more than one medication within a particular drug class, they were assigned the frequency category of the most frequently used medication. Categories were combined if necessary to allow sufficient numbers for analysis. The reference groups for these analyses were non-users of selective COX-2 inhibitors, non-users of nonselective COX-2 inhibitor, and non-users of all non-aspirin NSAIDs, respectively. Sensitivity analyses in which we changed the reference category for all analyses to never users of any NSAIDs did not alter the results.

We examined the association between statin use and pancreatic cancer risk, using the same approach as for low-dose aspirin. The reference group for this analysis was non-users of statins. Finally, we analysed frequency of paracetamol use. While paracetamol appears to have minimal peripheral anti-inflammatory activity and it is unlikely that it would influence risk of pancreatic cancer, it was included to help elucidate whether any associations with NSAIDs were due to differential requirement for pain relief between cases and controls.

Multivariable unconditional logistic regression was used to compute the odds ratios (ORs) with 95% confidence intervals (95% CI) for the association between pancreatic cancer risk and medication use. All reported results are adjusted for age, sex, pack-years of smoking, alcohol use, diabetes history and adult BMI as they were either matching factors or known to be associated with risk of pancreatic cancer. Cholesterol-lowering drugs (statins) are often taken in combination with aspirin for prevention of cardiovascular disease [[14](#_ENREF_14)]; thus we also investigated the impact of mutual adjustment for aspirin or statins in the multivariate models. However, the ORs were not substantially changed so results from this analysis have not been presented. We further assessed the effects of adjustment for other potential confounding variables (including education level, physical activity and history of pancreatitis) but they have not been included in the models as they did not appreciably change the OR estimates (<10% difference). Mutual adjustment for aspirin, non-aspirin NSAIDs or paracetamol did not alter the results.

Finally, we conducted analyses stratified by sex, smoking (ever/never), presence of metastases at diagnosis and time since diagnosis (< 3 months vs ≥ 3 months) **[Tables S 1-4]**. All analyses were performed using SAS version 9.4.

# RESULTS

The mean ages of cases and controls were 65.3 years and 66.6 years respectively **[Table 1]**. A higher proportion of cases than controls smoked (p < 0.0001), were heavy drinkers (p < 0.0001), had lower education levels (p = 0.0095) and were diabetic (p = 0.0086). Compared with those included in the study, those excluded were older (mean age 70 vs 66 years), more likely to be never drinkers (34% vs 26%), and more likely to have had no education beyond high school (59% vs 43%).

We found no consistent protective effect of any of the NSAIDs examined **[Table 2]**. Although there was some suggestion that infrequent users of selective COX-2 inhibitors were at reduced risk of pancreatic cancer, there was no trend with increasing frequency of use. There was some suggestion that use of any NSAID more than 4 times per week was associated with an increased risk of pancreatic cancer, although the OR decreased and was not significant after adjustment for confounders. Stratifying by sex, smoking, presence of metastases or time since diagnosis did not alter the results **[Tables S1-S4]**. Use of statins and paracetamol were not associated with pancreatic cancer risk, either overall or in stratified analyses **[Tables 2, S 1-4]**.

# DISCUSSION

This study does not support the hypothesis that use of aspirin or other NSAIDs lowers pancreatic cancer risk. Statins and paracetamol use were not associated with pancreatic cancer risk, either overall or in stratified analyses.

Our study was consistent with other studies [[16](#_ENREF_16), [19](#_ENREF_19), [20](#_ENREF_20)] in that we found no association between non-aspirin NSAIDs use and risk of pancreatic cancer, either overall or within subgroups defined by sex, smoking status or presence of metastases. Indications of an increase in the risk of pancreatic cancer among people who used NSAIDs at high frequency were likely due to reverse causality. Although we asked participants to report use prior to their diagnosis of pancreatic cancer, it is possible that this finding reflects analgesic use for the treatment of symptoms arising prior to diagnosis or that cases’ perception of their use was influenced by use since diagnosis. In support of this possible explanation we found that the effect of high NSAIDs use was stronger, albeit not significantly so, in those with longer time since diagnosis.

A large body of epidemiological evidence suggests that the use of NSAIDs, particularly selective COX-2 inhibitors, may prevent a number of different cancers, including cancers of the colon/rectum [[30-33](#_ENREF_30)] and breast [[34](#_ENREF_34)]. Animal and in vitro studies also indicated potential protective effects for this medication in prostate [[35](#_ENREF_35), [36](#_ENREF_36)] and lung cancers [[37](#_ENREF_37)]. *In vivo* and *in vitro* studies [[38-44](#_ENREF_38)] have demonstrated upregulation of COX-2 expression in human pancreatic cancer tissues as compared to healthy pancreatic tissues. Selective COX-2 inhibitors have been studied in pancreatic cancer *in vivo* and *in vitro* [[45-47](#_ENREF_45)] but their use has not been adequately investigated in epidemiological studies. To the best of our knowledge, there has been only one epidemiological study that analysed this class of NSAIDs in pancreatic cancer prevention [[17](#_ENREF_17)]. It found some suggestion of a possible protective effect of selective COX-2 inhibitors, although only a small number of participants used these drugs and the association was not statistically significant. We found a significant protective effect in infrequent users of selective COX-2 inhibitors, but the lack of effect in more frequent users suggests that this is likely to be a chance finding. Despite the relatively large sample size in our study, only a small proportion was regular users of selective COX-2 inhibitors, limiting our ability to detect an effect. This may have been partially driven by the withdrawal of rofecoxib from the market in late 2004. Furthermore, we only asked about use in the previous 5 years and it is possible that longer-term use is needed before any protective effect is seen.

We found no overall effect of aspirin, whether taken for cardioprophylaxis or analgesia, on pancreatic cancer. Two meta-analyses reported no association between aspirin use and pancreatic cancer risk [[19](#_ENREF_19), [20](#_ENREF_20)] and other studies published subsequently support these findings [[17](#_ENREF_17), [18](#_ENREF_18)]. However, other findings suggest that there may a protective effect, including an individual patient data analysis of randomised trials [[14](#_ENREF_14), [16](#_ENREF_16), [21](#_ENREF_21)]. Differences in the definitions of regular aspirin use or in the proportion of users may be at least partially responsible for the heterogeneity of the findings, but we could find no consistent pattern according to the frequency of use in controls. Ongoing large trials of aspirin may help to clarify the role of aspirin in prevention of pancreatic cancer [[48](#_ENREF_48)].

Despite the plausible antitumorigenic mechanism of statins, our results did not find any evidence for an association between statin use and pancreatic cancer risk, irrespective of the duration of treatment. Our findings are consistent with a number of recent studies [[23](#_ENREF_23), [25](#_ENREF_25), [26](#_ENREF_26), [49](#_ENREF_49), [50](#_ENREF_50)]. In contrast, [a](#_ENREF_39) protective effect between statin use and pancreatic cancer risk in male smokers has been documented [[28](#_ENREF_28)] but there was no assessment of duration and no adjustment for BMI which is likely to have significantly confounded the relationship. It has been suggested that the doses of statins used in hypercholesterolemia may be insufficient to influence cancer development, with chemopreventive effects possibly only seen at high doses [[23](#_ENREF_23), [26](#_ENREF_26)]. Even if this is the case it is unlikely that statins would be used for prevention of cancer due to the risks of toxicity associated with high-dose use. [[51](#_ENREF_51)]

This is one of the largest case-control studies of pancreatic cancer conducted, and we had comprehensive measurement of confounders. We used direct interviews to elicit information from participants and used generic and brand names of medications to facilitate recall. Nevertheless, both differential and non-differential misclassification of exposure is possible. It is challenging for people to remember timing and frequency of medication use, and case recall may have been influenced by more recent use to manage pain associated with cancer, particularly since the median time from diagnosis to interview was approximately 2 months, despite our rapid ascertainment approach. It is also possible that pre-diagnostic symptoms led to anti-inflammatory use in cases. The response fraction in controls was approximately 50%. If the participating controls were healthier than the overall population, they may have been less likely to use analgesics which could have under-estimated a true protective effect. The response fraction in cases was also low, largely because many patients died before we were able to contact them. If use of NSAIDs was associated with survival the effect estimates would have been biased. Our analyses stratified by time since diagnosis and presence / absence of metastases suggested that the estimates did not vary according to disease severity, suggesting that any effect of survivor bias is likely to have been small.

In summary, our study observed no inverse association between aspirin, non-aspirin NSAIDs, paracetamol or statins and risk of pancreatic cancer. We documented a significant protective association with infrequent use of selective COX-2 inhibitors but no consistent trend.

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Table 1. Characteristics of included participants

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **Controls (N= 653)**  **N (%)** | **Cases (N= 522)**  **N (%)** | **P value** |
| **Age, mean (range), years** | 66.62 (34 – 92) | 65.31 (29 – 89) | 0.04 |
| **Sex**  Men  Women | 387 (59.3)  266 (40.7) | 321 (61.5)  201 (38.5) | 0.44 |
| **Pack years of smoking**  Never  < 15 pack-year  15 – 29 pack-year  ≥30 pack-year | 320 (49.5)  131 (20.3)  80 (12.4)  116 (17.9) | 188 (36.3)  91 (17.6)  86 (16.6)  153 (29.5) | <0.0001 |
| **Alcohol use**  Never drinkers  Past drinkers but no drink last year  <1 drinks/week  1-3 drinks/week  4-7 drinks/week  8-21 drinks/week  ≥21 drinks/week | 176 (27.0)  31 (4.8)  30 (4.6)  76 (11.7)  102 (15.7)  151 (23.2)  85 (13.1) | 133 (25.6)  48 (9.3)  21 (4.1)  45 (8. 7)  53 (10.2)  95 (18.3)  124 (23.9) | <0.0001 |
| **Diabetes**  Never  < 3 years  3 years or over | 567 (86.8)  19 (2.9)  67 (10.3) | 424 (81.5)  25 (4.8)  71 (13.7) | 0.04 |
| **Education level**  No further education  Technical college/diploma  Trade certificate/apprentice  University degree  Other | 281 (43.3)  99 (15.3)  121 (18.6)  107 (16.5)  41 (6.3) | 226 (43.7)  116 (22.4)  76 (14.7)  66 (12.8)  33 (6.4) | 0.01 |
| **Body Mass Index at age 20**  < 18.5 kgm-2  18.5 – 24.9 kgm-2  25 – 29.9 kgm-2  30 – 34.9 kgm-2  ≥35 kgm-2 | 94 (15.4)  398 (65.0)  99 (16.2)  16 (2.6)  5 (0.8) | 52 (11.1)  323 (68.9)  75 (16.0)  12 (2.6)  7 (1.5) | 0.26 |
| **Adult Body Mass Index**  < 18.5 kgm-2  18.5 – 24.9 kgm-2  25 – 29.9 kgm-2  30 – 34.9 kgm-2  ≥35 kgm-2 | 11 (1.7)  220 (34.0)  255 (39.4)  115 (17.8)  47 (7.3) | 9 (1.8)  137 (27.2)  205 (40.8)  105 (20.9)  47 (9.3) | 0.12 |

Table 2. Associations between medication use and risk of pancreatic cancer

|  | **N (%)1** | | **Age- and sex-adjusted ORs (95% CI)** | **Fully adjusted ORs2 (95% CI)** |
| --- | --- | --- | --- | --- |
| **Controls** | **Cases** |
| **Low dose aspirin**  No low dose aspirin  Yes  <5 years of use  ≥5 years of use | 411 (63.0)  241 (37.0)  85 (13.1)  151 (23.3) | 344 (65.9)  178 (34.1)  59 (11.5)  112 (21.8) | 1  0.95 (0.74-1.23)  0.88 (0.61-1.28)  0.96 (0.71-1.30) | 1  0.81 (0.61-1.06)  0.76 (0.51-1.12)  0.81 (0.59-1.11) |
| **Regular dose aspirin**  No regular dose aspirin  Yes | 582 (89.1)  71 (10.9) | 456 (87.4)  66 (12.64) | 1  1.14 (0.80-1.64) | 1  1.23 (0.84-1.79) |
| **Aspirin**  No aspirin  Low dose aspirin only  Regular dose aspirin only  Low & regular aspirin | 365 (56.0)  217 (33.3)  46 (7.1)  24 (3.7) | 297 (56.9)  159 (30.5)  47 (9.0)  19 (3.6) | 1  0.97 (0.74-1.27)  1.22 (0.79-1.89)  1.00 (0.54-1.87) | 1  0.81 (0.61-1.08)  1.27 (0.80-2.01)  1.00 (0.52-1.91) |
| **All non-aspirin NSAIDs**  Never  Occasionally  2/month to 3/week  4+/week | 417 (63.9)  141 (21.6)  35 (5.4)  60 (9.2) | 329 (63.0)  98 (18.8)  23 (4.4)  72 (13.8) | 1  0.82 (0.60-1.11)  0.76 (0.44-1.32)  1.48 (1.02-2.15) | 1  0.93 (0.67-1.27)  0.65 (0.36-1.16)  1.36 (0.92-2.01) |
| **Selective COX-2 inhibitors only**  Never  Occasional use to ~1/week  2+/week | 568 (87.7)  53 (8.2)  27 (4.2) | 459 (89.1)  22 (4.3)  34 (6.6) | 1  0.51 (0.31-0.86)  1.60 (0.95-2.69) | 1  0.45 (0.26-0.78)  1.46 (0.84-2.52 ) |
| **Nonselective COX-1/COX-2 inhibitors**  Never  Occasional use to ~1/week  2/month to 3/week  4+/week | 413 (63.3)  171 (26.2)  30 (4.6)  39 (6.0) | 334 (64.0)  121 (23.2)  23 (4.4)  44 (8.4) | 1  0.82 (0.62-1.09)  0.86 (0.48-1.52)  1.31 (0.83-2.07) | 1  0.94 (0.70-1.26)  0.76 (0.42-1.39)  1.18 (0.73-1.92) |
| **Paracetamol**  Never  Occasionally  1/ month to 3/month  1/week to 3/ week  4+/week | 205 (31.4)  246 (37.7)  55 (8.4)  50 (7.7)  97 (14.9) | 177 (33.9)  190 (36.4)  29 (5.6)  41 (7.9)  85 (16.3) | 1  0.87 (0.66-1.15)  0.59 (0.36-0.98)  0.95 (0.60-1.50)  1.09 (0.76-1.56) | 1  0.94 (0.70-1.26)  0.68 (0.41-1.15)  0.96 (0.59-1.56)  0.92 (0.62-1.36) |
| **Statins**  No  Yes  <5 years of use  ≥5 years of use | 410 (63.4)  237 (36.6)  67 (10.4)  167 (25.9) | 323 (63.3)  187 (36.7)  48 (9.5)  132 (26.2) | 1  1.06 (0.83-1.36)  0.94 (0.63-1.40)  1.07 (0.81-1.41) | 1  0.95 (0.73-1.25)  0.81 (0.53-1.24)  0.98 (0.73-1.33) |

1Percentages may not add up to 100% due to rounding or missing responses

2Adjusted for age, sex, pack years of smoking (Never, < 15 pack-year, 15 – 29 pack-year, ≥30 pack-year), alcohol use (Never drinkers, Past drinkers but no drink last year, <1 drinks/week, 1-3 drinks/week, 4-7 drinks/week, 8-21 drinks/week, >21 drinks/week), diabetes (no, <3 years, ≥3 years) and adult Body Mass Index (<18.5 kg/m2, 18.5 – 25 kg/m2, 25 – 30 kg/m2, 30 – 35 kg/m2, ≥ 35 kg/m2).

Table S 1. Associations between medication use and risk of pancreatic cancer, stratified by sex

|  | **Men** | | | **Women** | | |
| --- | --- | --- | --- | --- | --- | --- |
|  | **N (%)1** | | **Fully adjusted ORs2**  **(95% CI)** | **Prevalence (%)1** | | **Fully adjusted ORs 2**  **(95% CI)** |
| **Controls** | **Cases** | **Controls** | **Cases** |
| **Low dose aspirin**  No low dose aspirin  Yes  <5 years of use  ≥5 years of use | 237 (61.4)  149 (38.6)  49 (12.7)  99 (25.7) | 209 (65.1)  112 (34.9)  40 (12.6)  68 (21.5) | 1  0.76 (0.53-1.08)  0.86 (0.53-1.41)  0.66 (0.43-1.00) | 174 (65.4)  92 (34.6)  36 (13.7)  52 (19.9) | 135 (67.2)  66 (32.8)  19 (9.6)  44 (22.2) | 1  0.91 (0.58-1.42)  0.62 (0.32-1.22)  1.12 (0.66-1.91) |
| **Regular dose aspirin**  No regular dose aspirin  Yes | 337 (87.1)  50 (12.9) | 272 (84.7)  49 (15.3) | 1  1.27 (0.81-1.99) | 245 (92.1)  21 (7.9) | 184 (91.5)  17 (8.5) | 1  1.01 (0.48-2.15) |
| **Aspirin**  No aspirin  Low dose aspirin only  Regular dose aspirin only  Low & regular aspirin | 207 (53.6)  130 (33.7)  30 (7.8)  19 (4.9) | 174 (54.2)  98 (30.5)  35 (10.9)  14 (4.4) | 1  0.78 (0.54-1.14)  1.43 (0.82-2.50)  0.86 (0.40-1.85) | 158 (59.4)  87 (32.7)  16 (6.0)  5 (1.9) | 123 (61.2)  61 (30.4)  12 (6.0)  5 (2.5) | 1  0.86 (0.54-1.37)  0.80 (0.33-1.97)  1.53 (0.39-6.02) |
| **All non-aspirin NSAIDs**  Never  Occasionally  2/month to 3/week  4+/week | 265 (68.5)  68 (17.6)  20 (5.2)  34 (8.8) | 201 (62.6)  63 (19.6)  14 (4.4)  43 (13.4) | 1  1.33 (0.87-2.04)  0.68 (0.32-1.45)  1.33 (0.79-2.24) | 152 (57.1)  73 (27.4)  15 (5.6)  26 (9.8) | 128 (63.7)  35 (17.4)  9 (4.5)  29 (14.4) | 1  0.51 (0.30-0.87)  0.51 (0.19-1.33)  1.27 (0.68-2.38) |
| **Selective COX-2 inhibitors only**  Never  Occasional use to ~1/week  2+/week | 348 (90.6)  24 (6.3)  12 (3.1) | 286 (90.5)  10 (3.2)  20 (6.3) | 1  0.42 (0.19-0.92)  1.82 (0.83-3.98) | 220 (83.3)  29 (11.0)  15 (5.7) | 173 (86.9)  12 (6.0)  14 (7.0) | 1  0.46 (0.21-1.01)  1.14 (0.50-2.59) |
| **Nonselective COX-1/COX-2 inhibitors**  Never  Occasional use to ~1/week  2/month to 3/week  4+/week | 248 (64.1)  98 (25.3)  16 (4.1)  25 (6.5) | 199 (62.0)  82 (25.6)  13 (4.1)  27 (8.4) | 1  1.15 (0.79-1.67)  0.75 (0.33-1.69)  1.01 (0.54-1.88) | 165 (62.0)  73 (27.4)  14 (5.3)  14 (5.3) | 135 (67.2)  39 (19.4)  10 (5.0)  17 (8.5) | 1  0.60 (0.36-1.01)  0.69 (0.27-1.77)  1.44 (0.65-3.22) |
| **Paracetamol**  Never  Occasionally  1/ month to 3/month  1/week to 3/ week  4+/week | 143 (37.0)  152 (39.3)  25 (6.5)  26 (6.7)  41 (10.6) | 121 (37.7)  126 (39.3)  14 (4.4)  23 (7.2)  37 (11.5) | 1  1.05 (0.73-1.51)  0.81 (0.39-1.71)  0.98 (0.51-1.87)  0.76 (0.43-1.34) | 62 (23.3)  94 (35.3)  30 (11.3)  24 (9.0)  56 (21.1) | 56 (27.9)  64 (31.8)  15 (7.5)  18 (9.0)  48 (23.9) | 1  0.66 (0.39-1.12)  0.52 (0.24-1.13)  0.77 (0.35-1.69)  0.88 (0.49-1.58) |
| **Statins**  No  Yes  <5 years of use  ≥5 years of use | 237 (61.7)  147 (38.3)  38 (9.9)  108 (28.2) | 196 (62.2)  119 (37.8)  29 (9.3)  86 (27.7) | 1  0.97 (0.69-1.38)  0.89 (0.51-1.56)  0.98 (0.67-1.43) | 173 (65.8)  90 (34.2)  29 (11.1)  59 (22.6) | 127 (65.1)  68 (34.9)  19 (9.9)  46 (24.0) | 1  0.93 (0.59-1.46)  0.72 (0.35-1.46)  1.00 (0.60-1.66) |

1Percentages may not add up to 100% due to rounding or missing responses

2Adjusted for age, sex, pack years of smoking (Never, < 15 pack-year, 15 – 29 pack-year, ≥30 pack-year), alcohol use (Never drinkers, Past drinkers but no drink last year, <1 drinks/week, 1-3 drinks/week, 4-7 drinks/week, 8-21 drinks/week, >21 drinks/week), diabetes (no, <3 years, ≥3 years) and adult Body Mass Index (<18.5 kg/m2, 18.5 – 25 kg/m2, 25 – 30 kg/m2, 30 – 35 kg/m2, ≥ 35 kg/m2).

Table S2. Associations between medication use and risk of pancreatic cancer, stratified by smoking status

|  | **Never smoker** | | | **Ever smoker** | | |
| --- | --- | --- | --- | --- | --- | --- |
|  | **N (%)1** | | **Fully adjusted ORs2**  **(95% CI)** | **Prevalence (%)1** | | **Fully adjusted ORs 2**  **(95% CI)** |
| **Controls** | **Cases** | **Controls** | **Cases** |
| **Low dose aspirin**  No low dose aspirin  Yes  <5 years of use  ≥5 years of use | 209 (65.3)  111 (34.7)  47 (14.8)  61 (19.2) | 125 (66.5)  63 (33.5)  14 (7.6)  45 (24.5) | 1  0.79 (0.52-1.20)  0.37 (0.18-0.75)  1.07 (0.66-1.74) | 202 (60.8)  130 (39.2)  38 (11.5)  90 (27.3) | 219 (65.6)  115 (34.4)  45 (13.6)  67 (20.2) | 1  0.91 (0.63-1.31)  1.20 (0.73-1.99)  0.75 (0.49-1.16) |
| **Regular dose aspirin**  No regular dose aspirin  Yes | 291 (90.9)  29 (9.1) | 166 (88.3)  22 (11.7) | 1  1.35 (0.73-2.49) | 291 (87.4)  42 (12.6) | 290 (86.8)  44 (13.2) | 1  1.07 (0.66-1.73) |
| **Aspirin**  No aspirin  Low dose aspirin only  Regular dose aspirin only  Low & regular aspirin | 190 (59.4)  101 (31.6)  19 (5.9)  10 (3.1) | 110 (58.5)  56 (29.8)  15 (8.0)  7 (3.7) | 1  0.77 (0.49-1.21)  1.29 (0.61-2.74)  1.17 (0.42-3.24) | 175 (52.7)  116 (34.9)  27 (8.1)  14 (4.2) | 187 (56.0)  103 (30.8)  32 (9.6)  12 (3.6) | 1  0.92 (0.63-1.36)  1.15 (0.64-2.05)  0.94 (0.40-2.19) |
| **All non-aspirin NSAIDs**  Never  Occasionally  2/month to 3/week  4+/week | 206 (64.4)  75 (23.4)  11 (3.4)  28 (8.8) | 124 (66.0)  34 (18.1)  8 (4.3)  22 (11.7) | 1  0.80 (0.49-1.31)  0.97 (0.35-2.70)  1.24 (0.66-2.31) | 211 (63.4)  66 (19.8)  24 (7.2)  32 (9.6) | 205 (61.4)  64 (19.2)  15 (4.5)  50 (15.0) | 1  0.99 (0.65-1.52)  0.55 (0.27-1.12)  1.47 (0.88-2.46) |
| **Selective COX-2 inhibitors only**  Never  Occasional use to ~1/week  2+/week | 284 (89.0)  21 (6.6)  14 (4.4) | 168 (90.8)  8 (4.3)  9 (4.9) | 1  0.57 (0.23-1.41)  1.16 (0.48-2.80) | 284 (86.3)  32 (9.7)  13 (4.0) | 291 (88.2)  14 (4.2)  25 (7.6) | 1  0.39 (0.20-0.76)  1.90 (0.92-3.94) |
| **Nonselective COX-1/COX-2 inhibitors**  Never  Occasional use to ~1/week  2/month to 3/week  4+/week | 212 (66.3)  82 (25.6)  10 (3.1)  16 (5.0) | 126 (67.0)  40 (21.3)  9 (4.8)  13 (6.9) | 1  0.88 (0.55-1.40)  1.30 (0.48-3.54)  1.16 (0.52-2.60) | 201 (60.4)  89 (26.7)  20 (6.0)  23 (6.9) | 208 (62.3)  81 ((24.3)  14 (4.2)  31 (9.3) | 1  0.91 (0.62-1.33)  0.56 (0.27-1.20)  1.09 (0.59-2.02) |
| **Paracetamol**  Never  Occasionally  1/ month to 3/month  1/week to 3/ week  4+/week | 91 (28.4)  116 (36.3)  29 (9.1)  29 (9.1)  55 (17.2) | 63 (33.5)  63 (33.5)  13 (6.9)  16 (8.5)  33 (17.6) | 1  0.82 (0.52-1.31)  0.72 (0.33-1.54)  0.80 (0.39-1.65)  0.75 (0.42-1.36) | 114 (34.2)  130 (39.0)  26 (7.8)  21 (6.3)  42 (12.6) | 114 (34.1)  127 (38.0)  16 (4.8)  25 (7.5)  52 (15.6) | 1  0.98 (0.67-1.44)  0.60 (0.29-1.25)  1.24 (0.63-2.45)  1.12 (0.66-1.88) |
| **Statins**  No  Yes  <5 years of use  ≥5 years of use | 201 (63.2)  117 (36.8)  34 (10.8)  80 (25.4) | 118 (64.1)  66 (35.9)  13 (7.2)  50 (27.6) | 1  0.77 (0.50-1.17)  0.47 (0.22-1.00)  0.87 (0.55-1.38) | 209 (63.5)  120 (36.5)  33 (10.0)  87 (26.4) | 205 (62.9)  121 (37.1)  35 (10.9)  82 (25.5) | 1  1.14 (0.80-1.63)  1.14 (0.66-1.98)  1.10 (0.74-1.63) |

1Percentages may not add up to 100% due to rounding or missing responses

2Adjusted for age, sex, pack years of smoking (Never, < 15 pack-year, 15 – 29 pack-year, ≥30 pack-year), alcohol use (Never drinkers, Past drinkers but no drink last year, <1 drinks/week, 1-3 drinks/week, 4-7 drinks/week, 8-21 drinks/week, >21 drinks/week), diabetes (no, <3 years, ≥3 years) and adult Body Mass Index (<18.5 kg/m2, 18.5 – 25 kg/m2, 25 – 30 kg/m2, 30 – 35 kg/m2, ≥ 35 kg/m2).

Table S 3. Associations between medication use and risk of pancreatic cancer, stratified by presence or absence of metastases

|  | **Non-metastatic** | | | **Metastatic** | | |
| --- | --- | --- | --- | --- | --- | --- |
|  | **N (%)1** | | **Fully adjusted ORs2**  **(95% CI)** | **Prevalence (%)1** | | **Fully adjusted ORs 2**  **(95% CI)** |
| **Controls** | **Cases** | **Controls** | **Cases** |
| **Low dose aspirin**  No low dose aspirin  Yes  <5 years of use  ≥5 years of use | 411 (63.0)  241 (37.0)  85 (13.1)  151 (23.3) | 163 (65.2)  87 (34.8)  30 (12.2)  53 (21.6) | 1  0.83 (0.58-0.87)  0.87 (0.53-1.42)  0.75 (0.49-1.13) | 411 (63.0)  241 (37.0)  85 (13.1)  151 (23.3) | 129 (67.2)  63 (32.8)  23 (12.0)  39 (20.4) | 1  0.81 (0.55-1.20)  0.79 (0.46-1.38)  0.81 (0.51-1.28) |
| **Regular dose aspirin**  No regular dose aspirin  Yes | 582 (89.1)  71 (10.9) | 220 (88.0)  30 (12.0) | 1  1.22 (0.75-1.98) | 582 (89.1)  71 (10.9) | 168 (87.5)  24 (12.5) | 1  1.19 (0.70-2.00) |
| **Aspirin**  No aspirin  Low dose aspirin only  Regular dose aspirin only  Low & regular aspirin | 365 (56.0)  217 (33.3)  46 (7.1)  24 (3.7) | 140 (56.0)  80 (32.0)  23 (9.2)  7 (2.8) | 1  0.86 (0.59-1.25)  1.38 (0.77-2.45)  0.85 (0.35-2.09) | 365 (56.0)  217 (33.3)  46 (7.1)  24 (3.7) | 115 (59.9)  53 (27.6)  14 (7.3)  10 (5.2) | 1  0.74 (0.49-1.13)  0.97 (0.49-1.90)  1.37 (0.61-3.07) |
| **All non-aspirin NSAIDs**  Never  Occasionally  2/month to 3/week  4+/week | 417 (63.9)  141 (21.6)  35 (5.4)  60 (9.2) | 156 (62.4)  46 (18.4)  12 (4.8)  36 (14.4) | 1  0.92 (0.61-1.38)  0.63 (0.30-1.32)  1.39 (0.85-2.25) | 417 (63.9)  141 (21.6)  35 (5.4)  60 (9.2) | 125 (65.1)  34 (17.7)  9 (4.7)  24 (12.5) | 1  0.84 (0.53-1.33)  0.68 (0.31-1.53)  1.21 (0.70-2.08) |
| **Selective COX-2 inhibitors only**  Never  Occasional use to ~1/week  2+/week | 568 (87.7)  53 (8.2)  27 (4.2) | 222 (89.2)  9 (3.6)  18 (7.2) | 1  0.34 (0.16-0.74)  1.58 (0.82-3.07) | 568 (87.7)  53 (8.2)  27 (4.2) | 171 (90.5)  8 (4.2)  10 (5.3) | 1  0.50 (0.23-1.11)  1.25 (0.57-2.74) |
| **Nonselective COX-1/COX-2 inhibitors**  Never  Occasional use to ~1/week  2/month to 3/week  4+/week | 413 (63.3)  171 (26.2)  30 (4.6)  39 (6.0) | 161 (64.4)  59 (23.6)  12 (4.8)  18 (7.2) | 1  0.99 (0.68-1.44)  0.71 (0.33-1.53)  0.96 (0.51-1.80) | 413 (63.3)  171 (26.2)  30 (4.6)  39 (6.0) | 123 (64.1)  42 (21.9)  9 (4.7)  18 (9.4) | 1  0.85 (0.56-1.29)  0.81 (0.36-1.82)  1.31 (0.69-2.47) |
| **Paracetamol**  Never  Occasionally  1/ month to 3/month  1/week to 3/ week  4+/week | 205 (31.4)  246 (37.7)  55 (8.4)  50 (7.7)  97 (14.9) | 82 (32.8)  93 (37.2)  17 (6.8)  18 (7.2)  40 (16.0) | 1  1.10 (0.75-1.61)  0.95 (0.50-1.80)  0.98 (0.52-1.84)  0.97 (0.58-1.60) | 205 (31.4)  246 (37.7)  55 (8.4)  50 (7.7)  97 (14.9) | 68 (35.4)  65 (33.9)  6 (3.1)  18 (9.4)  35 (18.2) | 1  0.72 (0.48-1.10)  0.29 (0.12-0.75)  0.92 (0.48-1.76)  1.03 (0.61-1.73) |
| **Statins**  No  Yes  <5 years of use  ≥5 years of use | 410 (63.4)  237 (36.6)  67 (10.4)  167 (25.9) | 154 (62.9)  91 (37.1)  26 (10.8)  60 (25.0) | 1  1.02 (0.72-1.45)  1.01 (0.60-1.72)  0.98 (0.66-1.45) | 410 (63.4)  237 (36.6)  67 (10.4)  167 (25.9) | 123 (65.4)  65 (34.6)  17 (9.1)  46 (24.7) | 1  0.86 (0.58-1.26)  0.75 (0.40-1.39)  0.86 (0.56-1.32) |

1Percentages may not add up to 100% due to rounding or missing responses

2Adjusted for age, sex, pack years of smoking (Never, < 15 pack-year, 15 – 29 pack-year, ≥30 pack-year), alcohol use (Never drinkers, Past drinkers but no drink last year, <1 drinks/week, 1-3 drinks/week, 4-7 drinks/week, 8-21 drinks/week, >21 drinks/week), diabetes (no, <3 years, ≥3 years) and adult Body Mass Index (<18.5 kg/m2, 18.5 – 25 kg/m2, 25 – 30 kg/m2, 30 – 35 kg/m2, ≥ 35 kg/m2).

Table S 4. Associations between medication use and risk of pancreatic cancer, stratified by time since diagnosis

|  | **Diagnosed < 3 months prior to interview** | | | **Diagnosed ≥ 3 months prior to interview** | | |
| --- | --- | --- | --- | --- | --- | --- |
|  | **N (%)1** | | **Fully adjusted ORs2**  **(95% CI)** | **Prevalence (%)1** | | **Fully adjusted ORs 2**  **(95% CI)** |
| **Controls** | **Cases** | **Controls** | **Cases** |
| **Low dose aspirin**  No low dose aspirin  Yes  <5 years of use  ≥5 years of use | 411 (63.0)  241 (37.0)  85 (13.1)  151 (23.3) | 223 (65.8)  116 (34.2)  35 (10.5)  74 (22.3) | 1  0.82 (0.60-1.13)  0.71 (0.45-1.13)  0.82 (0.57-1.19) | 411 (63.0)  241 (37.0)  85 (13.1)  151 (23.3) | 120 (65.9)  62 (34.1)  24 (13.2)  38 (20.9) | 1  0.80 (0.54-1.20)  0.90 (0.52-1.55)  0.77 (0.48-1.23) |
| **Regular dose aspirin**  No regular dose aspirin  Yes | 582 (89.1)  71 (10.9) | 297 (87.6)  42 (12.4) | 1  1.23 (0.80-1.90) | 582 (89.1)  71 (10.9) | 159 (87.4)  23 (12.6) | 1  1.24 (0.73-2.11) |
| **Aspirin**  No aspirin  Low dose aspirin only  Regular dose aspirin only  Low & regular aspirin | 365 (56.0)  217 (33.3)  46 (7.1)  24 (3.7) | 194 (57.2)  103 (30.4)  29 (8.6)  13 (3.8) | 1  0.82 (0.58-1.14)  1.25 (0.74-2.12)  1.06 (0.51-2.19) | 365 (56.0)  217 (33.3)  46 (7.1)  24 (3.7) | 103 (56.6)  56 (30.8)  17 (9.3)  6 (3.3) | 1  0.82 (0.54-1.25)  1.31 (0.70-2.48)  0.94 (0.36-2.46) |
| **All non-aspirin NSAIDs**  Never  Occasionally  2/month to 3/week  4+/week | 417 (63.9)  141 (21.6)  35 (5.4)  60 (9.2) | 217 (64.0)  63 (18.6)  17 (5.0)  42 (12.4) | 1  0.96 (0.67-1.39)  0.75 (0.40-1.41)  1.18 (0.75-1.86) | 417 (63.9)  141 (21.6)  35 (5.4)  60 (9.2) | 112 (61.5)  34 (18.7)  6 (3.3)  30 (16.5) | 1  0.90 (0.56-1.42)  0.44 (0.16-1.20)  1.67 (1.00-2.79) |
| **Selective COX-2 inhibitors only**  Never  Occasional use to ~1/week  2+/week | 568 (87.7)  53 (8.2)  27 (4.2) | 301 (90.1)  12 (3.6)  21 (6.3) | 1  0.42 (0.22-0.81)  1.38 (0.74-2.57) | 568 (87.7)  53 (8.2)  27 (4.2) | 157 (87.22)  10 (5.56)  13 (7.22) | 1  0.57 (0.27-1.21)  1.62 (0.78-3.39) |
| **Nonselective COX-1/COX-2 inhibitors**  Never  Occasional use to ~1/week  2/month to 3/week  4+/week | 413 (63.3)  171 (26.2)  30 (4.6)  39 (6.0) | 217 (64.0)  81 (23.9)  17 (5.0)  24 (7.1) | 1  1.00 (0.72-1.40)  0.87 (0.45-1.67)  0.93 (0.52-1.66) | 413 (63.3)  171 (26.2)  30 (4.6)  39 (6.0) | 117 (64.29)  39 (21.43)  6 (3.30)  20 (10.99) | 1  0.84 (0.55-1.29)  0.53 (0.20-1.44)  1.59 (0.86-2.94) |
| **Paracetamol**  Never  Occasionally  1/ month to 3/month  1/week to 3/ week  4+/week | 205 (31.4)  246 (37. 7)  55 (8.4)  50 (7.7)  97 (14.9) | 120 (35.4)  118 (34.8)  16 (4.7)  29 (8.6)  56 (16.5) | 1  0.89 (0.64-1.25)  0.57 (0.30-1.07)  1.07 (0.62-1.83)  0.91 (0.58-1.41) | 205 (31.4)  246 (37.7)  55 (8.4)  50 (7.7)  97 (14.9) | 57 (31.32)  71 (39.01)  13 (7.14)  12 (6.59)  29 (15.93) | 1  1.06 (0.69-1.61)  0.89 (0.44-1.81)  0.71 (0.33-1.52)  0.94 (0.54-1.65) |
| **Statins**  No  Yes  <5 years of use  ≥5 years of use | 410 (63.4)  237 (36.6)  67 (10.4)  167 (25.9) | 211 (63.9)  119 (36.1)  32 (9.9)  82 (25.2) | 1  0.91 (0.67-1.25)  0.82 (0.50-1.33)  0.92 (0.65-1.30) | 410 (63.4)  237 (36.6)  67 (10.4)  167 (25.9) | 111 (62.01)  68 (37.99)  16 (9.04)  50 (28.25) | 1  1.02 (0.69-1.50)  0.78 (0.42-1.48)  1.10 (0.72-1.67) |

1Percentages may not add up to 100% due to rounding or missing responses

2Adjusted for age, sex, pack years of smoking (Never, < 15 pack-year, 15 – 29 pack-year, ≥30 pack-year), alcohol use (Never drinkers, Past drinkers but no drink last year, <1 drinks/week, 1-3 drinks/week, 4-7 drinks/week, 8-21 drinks/week, >21 drinks/week), diabetes (no, <3 years, ≥3 years) and adult Body Mass Index (<18.5 kg/m2, 18.5 – 25 kg/m2, 25 – 30 kg/m2, 30 – 35 kg/m2, ≥ 35 kg/m2).