**Supplementary Material**

**Table of Contents**

Page 2. Table S1. Study characteristics by acute pancreatitis status

Page 3. Table S2. Incidence of pancreatic cancer by year and acute pancreatitis status

Page 4. Table S3. Incidence of pancreatic cancer by year and acute pancreatitis etiology

Page 5. Table S4. Post-AP risk of PDAC in smokers and alcohol drinkers S4A. Current Smokers vs Non-smokers

Page 6. Table S4. Post-AP risk of PDAC in smokers and alcohol drinkers S4B. Alcoholics versus non-alcoholics

Page 7. Figure S1. Study cohort timeline and follow-up.

Page 8. Figure S2. Post-acute pancreatitis cumulative incidence of pancreatic cancer by smoking and alcohol status. Figure S2A. Smokers vs Non-Smokers

Page 9. Figure S2. Post-acute pancreatitis cumulative incidence of pancreatic cancer by smoking and alcohol status. Figure S2B. Alcoholics vs Non-alcoholics

Page 10. Sensitivity Analysis. Table S5. PDAC risk following AP using primary inpatient diagnosis codes:

Page 10. Sensitivity Analysis. Table S6. Risk of pancreatic cancer by acute pancreatitis status using two ICD 9 codes for pancreatic cancer and chronic pancreatitis.

Satish Munigala1, Sami Almaskeen2, Divya S. Subramaniam1, Sriya Bandi3, Benjamin Bowe4, Hong Xian5, Sunil G. Sheth6, Thomas E. Burroughs1 and Banke Agarwal8

**Table S1.** **Study characteristics by acute pancreatitis status**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Controls** | **AP group** | **CP group** | **APCP group** |
|   | Patients at risk (n) | Patients diagnosed with PDAC | Patients at risk (n) | Patients diagnosed with PDAC  | Patients at risk (n) | Patients diagnosed with PDAC  | Patients at risk (n) | Patients diagnosed with PDAC |
| 3rd year | 7099764 | 2062 (0.03%) | 27394 | 27 (0.10%) | 12545 | 18 (0.14%) | 8156 | 26 (0.32%) |
| 4th year | 6557889 | 1829 (0.03%) | 23037 | 28 (0.12%) | 10758 | 19 (0.18%) | 6888 | 16 (0.23%) |
| 5th year | 6005044 | 1704 (0.03%) | 19050 | 16 (0.08%) | 9164 | 9 (0.10%) | 5768 | 22 (0.38%) |
| 6th year | 5484040 | 1676 (0.03%) | 15594 | 15 (0.10%) | 7760 | 7 (0.09%) | 4725 | 5 (0.11%) |
| 7th year | 5027007 | 1567 (0.03%) | 12556 | 16 (0.13%) | 6584 | 7 (0.11%) | 3858 | 5 (0.13%) |
| 8th year | 4586699 | 1522 (0.03%) | 10082 | 13 (0.13%) | 5633 | 6 (0.11%) | 3087 | 6 (0.11%) |
| 9th year | 4137403 | 1321 (0.03%) | 7858 | 7 (0.09%) | 4684 | 4 (0.09%) | 2466 | 5 (0.20%) |
| 10th year | 3696791 | 1222 (0.03%) | 5992 | 7 (0.12%) | 3871 | 7 (0.18%) | 1939 | 4 (0.21%) |

AP- acute pancreatitis, CP- chronic pancreatitis, APCP- acute pancreatitis with pre-existing chronic pancreatitis, PDAC- pancreatic cancer, %- row percentage of n for each group.

**Table S2**. **Incidence of pancreatic cancer by year and acute pancreatitis status**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Follow-up period | **Incidence per 1000 person-years** | **AP group** | **CP group** | **APCP group** |
| Controls | APgroup | CP group | APCPgroup | UnadjustedHR(95% CI) | P-value | Adjusted HR\*(95% CI) | P-value | UnadjustedHR(95% CI) | P-value | AdjustedHR\*(95% CI) | P-value | UnadjustedHR(95% CI) | P-value | AdjustedHR\*(95% CI) | P-value |
| Year 3 | 0.30 | 1.07 | 1.55 | 3.47 | 3.56 (2.43-5.20) | <0.001 | 2.01 (1.36-2.96) | 0.001 | 5.14 (3.23-8.17) | <0.001 | 3.48 (2.15-5.62) | <0.001 | 11.48 (7.80-16.90) | <0.001 | 7.05 (4.74-10.51) | <0.001 |
| Year 4 | 0.29 | 1.33 | 1.91 | 2.53 | 4.59 (3.16-6.66) | <0.001 | 2.49 (1.69-3.67) | <0.001 | 6.57 (4.18-10.32) | <0.001 | 4.74 (3.01-7.47) | <0.001 | 8.69 (5.31-14.21) | <0.001 | 5.17 (3.13-8.55) | <0.001 |
| Year 5 | 0.30 | 0.93 | 1.07 | 4.20 | 3.12 (1.91-5.10) | <0.001 | 1.85 (1.12-3.05) | 0.017 | 3.59 (1.87-6.91) | <0.001 | 2.65 (1.37-5.11) | 0.004 | 14.16 (9.30-21.56) | <0.001 | 8.95 (5.81-13.78) | <0.001 |
| Year 6 | 0.32 | 1.07 | 0.98 | 1.17 | 3.35 (2.02-5.58) | <0.001 | 1.70 (1.01-2.84) | 0.045 | 3.08 (1.46-6.46) | 0.003 | 2.14 (1.02-4.51) | 0.045 | 3.67 (1.52-8.82) | 0.004 | 1.92 (0.80-4.65) | 0.147 |
| Year 7 | 0.33 | 1.42 | 1.14 | 1.45 | 4.34 (2.65-7.11) | <0.001 | 2.25 (1.36-3.71) | 0.002 | 3.52 (1.68-7.39) | 0.001 | 2.49 (1.18-5.24) | 0.016 | 4.45 (1.85-10.70) | 0.001 | 2.39 (0.99-5.77) | 0.054 |
| Year 8 | 0.35 | 1.46 | 1.16 | 1.80 | 4.18 (2.42-7.21) | <0.001 | 2.16 (1.24-3.76) | 0.006 | 3.33 (1.50-7.43) | 0.003 | 2.37 (1.06-5.30) | 0.035 | 5.20 (2.17-12.46) | 0.002 | 2.71 (1.12-6.57) | 0.027 |
| Year 9 | 0.34 | 1.01 | 0.93 | 2.27 | 3.02 (1.44-6.34) | 0.004 | 1.49 (0.70-3.15) | 0.298 | 2.78 (1.04-7.42) | 0.041 | 1.99 (0.75-5.32) | 0.17 | 6.75 (2.80-16.23) | <0.001 | 3.42 (1.41-8.28) | 0.006 |
| Year 10 | 0.35 | 1.37 | 2.01 | 2.33 | 3.87 (1.84-8.13) | <0.001 | 2.04 (0.97-4.32) | 0.062 | 5.68 (2.70-11.94) | <0.001 | 4.23 (2.01-8.90) | <0.001 | 6.61 (2.48-17.64) | <0.001 | 3.63 (1.36-9.73) | 0.01 |

\* versus controls (remaining patients in the database without AP or CP), adjusted for age (age at the time of entry into the study), gender, race, smoking, alcohol, gallstones, and diabetes. AP- acute pancreatitis, CP- chronic pancreatitis; APCP- acute pancreatitis with pre-existing chronic pancreatitis; HR- Hazard ratio, PDAC- pancreatic cancer.

**Table S3. Incidence of pancreatic cancer by year and acute pancreatitis etiology**

AP- acute pancreatitis, CI- confidence interval, HR- Hazard ratio, PDAC- pancreatic cancer.

\* versus controls (remaining patients in the database without AP or CP), adjusted for age (age at the time of entry into the study), gender, race, smoking, alcohol, and diabetes.

|  |  |  |  |
| --- | --- | --- | --- |
| **Follow-up** | **AP group** | **Non-gallstone AP** | **Gallstone AP** |
| **No of PDAC** | **Incidence**  | **No of PDAC** | **Incidence**  | **Adjusted HR\*****(95% CI)** | **P-value** | **No of PDAC** | **Incidence**  | **Adjusted HR\*****(95% CI)** | **P-value** |
| Year 3 | 27 | 1.12 | 17 | 1.09 | 3.02 (1.87-4.87) | <0.001 | 10 | 1.05 | 2.56 (1.37-4.76) | 0.003 |
| Year 4 | 28 | 1.40 | 17 | 1.31 | 3.72 (2.30-6.01) | <0.001 | 11 | 1.37 | 3.44 (1.90-6.23) | <0.001 |
| Year 5 | 14 | 0.80 | 10 | 0.93 | 2.57 (1.38-4.80) | 0.003 | 6 | 0.91 | 2.27 (1.02-5.07) | 0.045 |
| Year 6 | 14 | 1.06 | 7 | 0.81 | 1.97 (0.93-4.14) | 0.075 | 8 | 1.48 | 3.44 (1.72-6.90) | <0.001 |
| Year 7 | 14 | 1.33 | 8 | 1.15 | 2.75 (1.37-5.52) | 0.004 | 8 | 1.85 | 4.13 (2.06-8.28) | <0.001 |
| Year 8 | 10 | 1.21 | 5 | 0.91 | 1.98 (0.82-4.77) | 0.129 | 8 | 2.35 | 5.00 (2.50-10.01) | <0.001 |
| Year 9 | 5 | 0.78 | 3 | 0.70 | 1.61 (0.52-5.01) | 0.41 | 4 | 1.53 | 3.46 (1.30-9.22) | 0.013 |
| Year 10 | 6 | 1.27 | 6 | 1.88 | 4.13 (1.85-9.23) | <0.001 | 1 | 0.52 | 1.10 (0.16-7.81) | 0.925 |

**Table S4. Post-AP risk of PDAC in smokers and alcohol drinkers**

**S4A. Current Smokers vs Non-smokers**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Non-smokers** | **Current Smokers** | UnadjustedHR(95% CI) | AdjustedHR(95% CI) |
| **Controls** | **0.25%** | **0.28%** | 1.20(1.15-1.24)P<0.001 | 1.43(1.38-1.48)P<0.001 |
| **AP group** | **0.45%** | **0.38%** | 0.87(0.57-1.31) P=0.50 | 1.20(0.76-1.88)P=0.44 |
|  |  |  |  |  |  |  |
| Unadjusted HRHR (95% CI) | 3.32(2.46-4.48) | 3.09(2.46-3.90) |  |  |  |  |
|  | P<0.001 | P<0.001 |  |  |  |  |
| Adjusted HR\* (95% CI) | 1.73(1.28-2.35) | 1.94 (1.53-2.45) |  |  |  |  |
|  | P<0.001 | P<0.001 |  |  |  |  |

AP- acute pancreatitis; CI- confidence intervals, HR- hazard ratio.

\*all adjusted HR’s were computed after adjusting for age, race, gender, diabetes mellitus and gallstone disease. For controls and AP group, HR’s were computed for current smokers using non-smokers as reference group. For non-smokers, current smokers, non-alcoholics and alcoholics, HR’s were computed for AP group using controls as a reference category.

**S4B. Alcoholics versus non-alcoholics**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Non-Alcoholic** | **Alcoholics** |  | UnadjustedHR(95% CI) | AdjustedHR(95% CI) |
| **Controls** | **0.22%** | **0.28%** |  | 1.14(1.09-1.18)P<0.001 | 1.22(1.17-1.28)P<0.001 |
|  |
| **AP Group** | **0.42%** | **0.35%** |  | 0.84(0.56-1.24)P=0.38 | 1.15(0.73-1.80)P=0.56 |
|  |  |  |  |  |  |  |
| Unadjusted HRHR (95% CI) | 3.59(2.84-4.53) | 3.43(2.67-4.42) |  |  |  |  |
|  | P<0.001 | P<0.001 |  |  |  |  |
| Adjusted HR\* (95% CI) | 1.61(1.27-2.04) | 2.27(1.76-2.93) |  |  |  |  |
|  | P<0.001 | P<0.001 |  |  |  |  |

AP- acute pancreatitis; CI- confidence intervals, HR- hazard ratio.

\*all adjusted HR’s were computed after adjusting for age, race, gender, diabetes mellitus and gallstone disease. For controls and AP group, HR’s were computed for current smokers and alcoholics using non-smokers and non-alcoholics as reference groups, respectively. For non-smokers, current smokers, non-alcoholics and alcoholics, HR’s were computed for AP group using controls as a reference category.

**Figure S1. Study cohort timeline and follow-up**

Washout period

No prior AP or PDAC

PDAC ≤2 years of study entry not evaluated

PDAC

assessment period

**Controls**  Follow-up

**AP**  Follow-up

**CP**  Follow-up

**APCP**  Follow-up

Censor at study end (December 2015), PDAC occurrence or death

T2

Start of follow-up

T0

Study entry

1st VA encounter or

Beginning of the database (September 1999)

AP- acute pancreatitis; CP- chronic pancreatitis; APCP- acute pancreatitis with pre-existing chronic pancreatitis; PDAC- pancreatic cancer; VA- Veterans affairs.

**Figure S2. Post-acute pancreatitis cumulative incidence of pancreatic cancer by smoking and alcohol status**

**Figure S2A. Smokers vs Non-Smokers**



CI- Confidence intervals, HR- Hazard ratio

NOTE: Hazard ratios presented on the figures are unadjusted hazard ratios from Cox-proportional model. Gray K-Sample Test P-value is for comparing the cumulative incidence between the groups

**Figure S2B. Alcoholics vs Non-alcoholics**



CI- Confidence intervals, HR- Hazard ratio

NOTE: Hazard ratios presented on the figures are unadjusted hazard ratios from Cox-proportional model. Gray K-Sample Test P-value is for comparing the cumulative incidence between the group

**Table S5. Sensitivity analysis of PDAC risk >2 years after AP**

|  |  |  |
| --- | --- | --- |
|  | Current Data  | Data using inpatient primary ICD 9 diagnosis codes only for defining AP  |
| Group | N | PDACN (%) | Adjusted HR(95% CI) | P-value | N | PDACN (%) | Adjusted HR (95% CI) | P-value |
| Controls | 7099764 | 16168 (0.23%) | Reference | - | 7099764 | 16168 (0.23%) | Reference | - |
| AP | 27394 | 133 (0.49%) | 1.85 (1.55-2.20) | <0.001 | 17054 | 87 (0.51%) | 1.91 (1.54-2.36) | <0.001 |
| APCP | 8156 | 92 (1.13%) | 4.29 (3.49-5.28) | <0.001 | 5821 | 76 (1.31%) | 4.89 (3.89-6.13) | <0.001 |
| CP | 12545 | 82 (0.65%) | 2.83 (2.27-3.52) | <0.001 | 12545 | 82 (0.65%) | 2.83 (2.27-3.52) | <0.001 |

**Table S6. Sensitivity analysis of PDAC risk >2 years after AP**

|  |  |  |
| --- | --- | --- |
|  | Current Data  | Data using two ICD 9 for defining PDAC and CP diagnosis |
| Group | N | PDACN (%) | Adjusted HR(95% CI) | P-value | N | PDACN (%) | Adjusted HR (95% CI) | P-value |
| Controls | 7099764 | 16168 (0.23%) | Reference | - | 7094059 | 10463 (0.15%) | Reference | - |
| AP | 27394 | 133 (0.49%) | 1.85 (1.55-2.20) | <0.001 | 26729 | 81 (0.30%) | 1.68 (1.35-2.10) | <0.001 |
| APCP | 8156 | 92 (1.13%) | 4.29 (3.49-5.28) | <0.001 | 4360 | 38 (0.87%) | 4.67 (3.39-6.44) | <0.001 |
| CP | 12545 | 82 (0.65) | 2.83 (2.27-3.52) | <0.001 | 5779 | 32 (0.55%) | 3.54 (2.50-5.01) | <0.001 |