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Title: **Clinical and Pathological Features of Familial Pancreatic cancer**

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**ABSTRACT**

***BACKGROUND:*** Inherited predisposition to pancreatic cancer (PC) contributes significantly to its incidence, and an opportunity for the development of early detection strategies. The genetic basis of predisposition remains unexplained in a high proportion of familial PC (FPC).

***PATIENTS AND METHODS:*** Clinico-pathologic features and outcome were assessed in a cohort of 766 patients with a diagnosis of PC. Patients were defined as FPC if they had one or more first-degree relatives (FDR) with PC, and the remaining patients were classified as sporadic PC (SPC).

***RESULTS:*** The prevalence of FPC was 8.9% (68/766). There was no difference in the mean age at PC diagnosis between FPC and SPC patients (65.8 vs 66.0 years, $P = 0.90$). In FPC families with an affected parent-child pair, 71% were diagnosed on average 12.3 years younger in the subsequent generation. FPC patients had more FDRs with an extra-pancreatic malignancy (EPM) (42.6% vs 21.2, $P < 0.0001$) in particular melanoma and endometrial cancer, but not a personal history of EPM (14.7% vs 10.3%, $P = 0.26$). SPC patients were more likely to be active smokers, have higher cumulative tobacco exposure and have fewer multi-focal precursor lesions than FPC patients, but these were not associated with differences in survival. Long-standing diabetes mellitus (> 2 years) was associated with poor survival in both groups.

***CONCLUSION:*** FPC represents 9% of all PC cases, and risk of malignancy in kindreds does not appear to be confined to the pancreas. FPC patients have more precursor lesions and fewer active smokers but other clinico-pathologic factors and outcome are similar to SPC patients. Some FPC kindreds may show anticipation with over two-thirds of children from affected parent-child pairs diagnosed significantly younger. A better understanding of the clinical features of PC will facilitate efforts to uncover susceptibility genes and the development of early detection strategies.

## INTRODUCTION

Pancreatic cancer (PC) is a lethal disease with a 5 year survival of less than 5%.[1] The majority of patients present with locally advanced, or metastatic disease that is not amenable to surgical resection, which currently offers the only chance of cure. Of the 10-20% of patients who undergo resection the majority (≈80%) still succumb to PC with a median survival of less than 2 years.[2] Long-term survival is rare but most often occurs in those who undergo resection for small non-metastatic tumors with negative margins and clear lymph nodes.[3,4] PC evolves through non-invasive precursor lesions, the majority from microscopic ductal lesions known as pancreatic intraepithelial neoplasia (PanIN), with a small percentage from cystic lesions: intraductal papillary mucinous neoplasms (IPMN) or mucinous cystic neoplasms.[5,6] Recent studies also estimate that a period of 10 to 20 years is required from the time of an initiating mutation, to the establishment of advanced disease, suggesting a prolonged period where intervention may be possible.[7]

Strategies that facilitate the early detection of PC or its precursors during this broad window are extremely attractive. Screening of the general population is not feasible due to the low incidence of PC and the lack of a robust screening test. As a consequence, the focus has shifted to individuals considered to be at high-risk. Established risk factors for PC constitute both environmental and inherited influences and include age, ABO blood group, cigarette smoking, diabetes mellitus, obesity and a family history of PC.[8] Inherited predisposition to PC manifests in 3 different settings identified to date [9]: 1. Hereditary tumor predisposition syndromes which account for 15-20% of the burden of inherited disease and include: Hereditary Breast Ovarian Cancer (HBOC), Peutz-Jegher syndrome (PJS), Familial Atypical Multiple Mole Melanoma (FAMMM), Li Fraumeni syndrome, Hereditary Non-Polyposis Colo-rectal Cancer (HNPCC) and Familial Adenomatous

Polyposis (FAP) [10], 2. Hereditary Pancreatitis, and 3. Familial PC (FPC). FPC is defined as a kindred with at least two first-degree relatives with PC which do not fulfill the diagnostic criteria for an inherited cancer syndrome. [11] The underlying genetic basis of PC predisposition has been identified in less than 25% of such families, [12-15] with 50-80% of families demonstrating an autosomal dominant inheritance pattern.[16,17]

## PATIENTS AND METHODS

### Patient and Data acquisition

Detailed clinico-pathologic, treatment and outcome data for a cohort of 766 patients with a histopathologic diagnosis of PC was accrued from twelve hospitals associated with the Australian Pancreatic Cancer Genome Initiative between 1994 and 2012 (APGI; www.pancreaticcancer.net.au) (Table 1). Patients were defined as FPC if they had one or more first-degree relatives with a confirmed diagnosis of PC, and the remaining patients were classified as sporadic PC (SPC). No patient had a known predisposing genetic mutation or hereditary tumor syndrome at enrolment. Ethical approval for the acquisition of data and biological material was obtained from the Human Research Ethics Committee at each participating institution.

All cases underwent central pathology review by at least one specialist pancreatic histopathologist (A.J.G, A.C, J.G.K) blinded to the diagnosis and clinical outcome to verify the diagnosis of pancreatic ductal adenocarcinoma and to define histopathologic features in a standardized manner using a synoptic report developed for the purpose[18]. Tumors were staged according to the AJCC Cancer Staging Manual 7$^{th}$ edition 2009[19].

Clinico-pathologic information was acquired initially retrospectively, but became prospective in 2006. Prospectively recruited PC cases underwent a structured interview by a trained interviewer using a previously validated questionnaire.[20] Detailed baseline information was acquired including demographic data, cigarette smoking and alcohol consumption, personal and family history of malignancy and medical comorbidities including diabetes mellitus and pancreatitis. Cigarette smoking was stratified into 3 groups: active, reformed and non-smokers. Active smoking was defined as ongoing use at time of diagnosis of PC or ceased within 6 months of PC diagnosis. Reformed smokers as having

smoked more than 100 cigarettes in their lifetime but ceased more than 6 months prior to PC diagnosis and were further stratified based on duration of abstinence (6 months - 10 years and >10 years). Non-smokers had never smoked or smoked fewer than 100 cigarettes. Cigarette smoking was quantified using pack-years with 1 pack-year representing smoking 20 cigarettes per day for 1 year. Alcohol consumption was classified into 3 groups on the basis of average consumption of all alcohol types for 12 months prior to PC diagnosis: mild, moderate, heavy. Alcohol consumption was quantified by the number of standard drinks per day, with 1 standard drink representing 10g of ethanol. Mild alcohol consumption represents 0-2, moderate 3-4 and heavy ≥5 standard drinks per day. Diabetes mellitus (DM) was based on physician diagnosis or treatment with insulin or oral hypoglycemics. The duration of diabetes prior to PC diagnosis, where available was stratified into 2 groups: ≤ 2 years and > 2 years. In both prospective and retrospective cases, additional clinical data was obtained from hospital notes, physician records and family members if required. The date and cause of death was obtained from cancer registries and treating clinicians.

**Statistical Analysis**

Disease-specific survival was used as the primary end point and was calculated from date of histopathologic diagnosis to date of death or last clinical follow-up. Patients with an R2 resection (macroscopically positive resection margins) were excluded from the survival analysis performed for resected patients. Patients who were alive at the census date (1$^{st}$ June 2013) were censored. Univariate Kaplan-Meier analysis of patient, tumor and treatment variables compared median survival using the log-rank test. Clinico-pathologic variables analyzed with a significant *P* value and those reported to be significant were entered into a Cox Proportional Hazard multivariate analysis and models resolved using backward elimination of redundant variables. Chi-square and Fisher exact tests were used

to compare categorical variables and the students t-test to compare continuous variables. Reported *P* values are two-sided and variables with a $P < 0.05$ were considered statistically significant. Statistical analysis was performed using Statview 5.0 software (Abacus Systems, Berkeley, CA, USA).

## RESULTS

### Patient Cohort

The cohort consisted of 766 consecutive patients who had a pathologic diagnosis of PC of which 698 were classified as sporadic (SPC) and 68 satisfied the criteria for FPC. The majority of patients (77.9%) underwent pancreatic resection with curative intent. The clinico-pathological characteristics are summarised in Supplementary Tables 1 and 2. In the FPC subset, 57 patients (83.8%) underwent pancreatic resection and 11 had a diagnostic biopsy only. The majority (77.9%) of FPC families had two affected FDRs and 8.8% had three affected FDRs. The remaining FPC families had combinations of affected first- and second-degree relatives (SDR) as described in Table 1.

### Clinico-pathologic variables and outcome

Patients from families meeting the criteria for FPC represented 8.9% of all cases. There was no difference in outcome between SPC and FPC patients (Figure 1A and 1B) with median survival in resected patients of 19.8 and 17.4 months respectively ($P$ = 0.1468). In addition, resected FPC and SPC patients showed no difference in the distribution of prognostic clinico-pathological variables (Table 2 and Supplementary Table 1). In both groups, patients with tumors located in the head of the pancreas and who received adjuvant chemotherapy had a better survival. The limited number of patients and end-points in the FPC group likely affected the statistical significance of other clinico-pathological variables such as size and nodal status.

There was no significant difference between FPC and SPC patients in gender distribution and the mean age at diagnosis (65.8 vs 66.0 years, $P$ = 0.8952). Furthermore there was no difference in the proportion of patients diagnosed at an early age (< 50 years). (Table 2) Of the 68 FPC patients, 40 were members of an affected parent-child pair. In 28 of

these the age at diagnosis was confirmed in the affected parent and child. In 20 of the 28 (71.4%) the age of the child was more than 5 years younger at diagnosis than the affected parent. In the 28 parent-child pairs the mean age at diagnosis in parents was 72.9 years and 60.6 years in affected offspring ($P < 0.0001$). The parent of origin did not appear to affect the age at diagnosis in the successive generation with children diagnosed 12.3 years earlier if the father was affected and 12.2 years for an affected mother ($P = 0.9675$).

Resected FPC patients had more precursor lesions, specifically PanIN-2 and -3 distinct from the carcinoma in the resected specimen than SPC (36.8% vs 23.9%, $P = 0.0320$)(Table 2). In FPC the most severe lesion was PanIN-3 in 52.4% and PanIN-2 in 47.6%, and in SPC 65.9% and 34.1% respectively. The presence of foci of PanIN-2 and -3 did not affect post-resection survival in the FPC or SPC groups (Figure 1C and D).

**Previous extra-pancreatic malignancy**

There were 11 previously diagnosed extra-pancreatic malignancies (EPM) in 10 patients in the FPC group and 76 EPM in 72 patients in the SPC group. One patient in the SPC group had a prior PC diagnosed 5 years earlier. There was no difference in the proportion of FPC or SPC patients with a previously diagnosed malignancy (14.7% vs 10.3%, $P = 0.2636$). In the FPC group, 1 patient (1.5%) had two previous malignancies along with 4 patients (0.6%) in the SPC group**.** The distribution of prior EPMs were similar in both groups with breast, colo-rectal, prostate and melanoma being the most common. (Supplementary Table 3) A history of prior EPM had no impact on survival in either resected FPC (16.7 vs 19.8 months, $P = 0.5699$) nor SPC (16.1 vs 17.8 months, $P = 0.9408$) patients.

**Family history of extra-pancreatic malignancy**

FPC patients were significantly more likely than SPC patients to have at least one FDR with an extra-pancreatic malignancy (44.1% vs 21.2%, *P* < 0.0001). Furthermore FPC patients were significantly more likely than SPC to have multiple FDRs with an EPM (mean 1.52 vs 1.26 FDRs, *P* = 0.0372)(Table 1). The most common malignancies in both FPC and SPC were breast, colorectal, melanoma, lung and prostate. The distribution of malignancies in FDRs was similar in both groups except that FPC kindreds were significantly more likely to develop melanoma (8.8% vs 0.6%, *P* < 0.0001) and endometrial cancer (2.9% vs 0.6%, *P* = 0.0345). There was a trend to higher rates of breast cancer in FPC kindreds (10.3% vs 4.9%, *P* = 0.0579)(Table 1).

**Environmental risk factors**

The prevalence of diabetes mellitus (DM) in FPC and SPC was 27.9% (19/68) and 28.9% (202/698) respectively (*P* = 0.8623). There was no difference between FPC and SPC patients with regard to mean duration of DM prior to the diagnosis of PC (mean 6.1 vs 5.0 years, *P* = 0.6112) or the proportion diagnosed within 2 years of PC (58.3% vs 53.0%, *P* = 0.7346). There was no correlation between the presence of DM, or duration, with age at PC diagnosis in resected FPC and SPC patients. (Supplementary Table 5) DM duration greater than 2 years was associated with a poor post-resection survival in both FPC and SPC groups (Supplementary Figure 1B – D). Multivariate analysis showed that positive lymph nodes, involved margins, size ≥ 20mm, adjuvant chemotherapy, post-resection CA19.9 >120 U/ml and DM greater than 2 years duration were independent prognostic factors (Table 3 and Supplementary Tables 1, 4,5 and 6). Multivariate analysis was not performed in FPC and SPC groups individually due to limited numbers in the FPC cohort.

A history of chronic pancreatitis was present at similar rates in both FPC and SPC (8.8% vs 5.3%, P = 0.2283) and was not associated with an earlier age of diagnosis. There was

no difference in post-resection survival between those with a history of pancreatitis and those without (median survival 18.1 vs 17.9 months, *P* = 0.3481). SPC patients were significantly more likely than FPC patients to be active smokers at the time of diagnosis (28.2% vs 8.8%, *P* = 0.0003). Furthermore SPC patients (active and reformed) had higher levels of smoke exposure with a mean of 34.9 pack-years of smoking versus 25.7 in FPC patients (*P* = 0.0479)(Table 3). Active smokers were diagnosed on average 9.8 years and 5.2 years younger in resected FPC (57.3 vs 67.1 years, *P* = 0.0144) and SPC (62.4 years vs 67.6 years, *P* < 0.0001) patients, respectively compared to never smokers and reformed smokers for greater than 10 years. Resected SPC reformed smokers of less than 6 months were diagnosed 3.7 years earlier than never smokers and reformed > 10 years (63.9 vs 67.6 years, P = 0.0237), but this was not significant in the FPC group. There was no difference in age at diagnosis between FPC and SPC active smokers (57.3 years vs 63.0 years, *P* = 0.2342) or never smokers and reformed > 10 years (67.1 vs 67.6, *P* = 0.7536). There was no difference in survival after resection between the 3 smoking classes (Supplementary Figure 1 E and 2A – B).

The majority of patients with both FPC and SPC had a low alcohol intake (nil or less than 2 SD per day) in the 12 months prior to diagnosis (85.3% vs 77.5%, *P* = 0.3000), and only 7.4% and 10.2% were heavy drinkers respectively (*P* = 0.4216). There was no correlation between alcohol intake and age at diagnosis in FPC. There was a trend for SPC patients who drank at least 5 standard drinks per day to be diagnosed 2.9 years younger than non-drinkers (63.7 years vs 66.6 years, *P* = 0.0630)(Supplementary Figure 2C – E).

## DISCUSSION

The prevalence of familial PC in this cohort was 8.9%. There was no difference in age at diagnosis between FPC and SPC patients, but 71% of FPC families showed probable anticipation. FPC patients were more likely to have multifocal precursor lesions but fewer active smokers and lower smoke exposure. FPC patients were more likely to have one or more kindreds with an extra-pancreatic malignancy (EPM), but not more likely to have a personal history of an EPM.

A prevalence of FPC of 8.9% is consistent with previous case-control and cohort studies, [21-24], although the requirement of histological confirmation in relatives lowers the rate of familial aggregation.[25,26] Previous reports of younger age at diagnosis in FPC are inconclusive [16,27] although some suggest earlier onset by 5 years and a higher proportion (≈16%) of young-onset disease. [28-30] We found no difference in the age of diagnosis between FPC and SPC patients overall (mean 65.8 vs 66.0 years), or the proportion with young-onset (<50 years) disease (9.6% vs 8.6%). However, active smokers were diagnosed 9.8 years (FPC) and 5.2 years (SPC) earlier than never smokers, and those who ceased greater than 10 years previously. In 71% of affected parent-child pairs the child was diagnosed, on average 12.3 years younger. This finding is unlikely to be due to environmental risk factors as the majority were non-smokers. Anticipation has been reported in 32-85% of FPC families with successive generations developing PC 10-20 years earlier. [17,28,31] Age at diagnosis, anticipation and smoking has important implications for risk management and screening program development.[32]

We found FPC (42.6%) twice as likely as SPC patients (21.2%) to have at least one FDR with an extra-pancreatic malignancy. In particular, melanoma, endometrial and breast

cancer. In the majority of inherited cancer syndromes, the risk of malignancy is not confined to a single organ. In addition to pancreas, breast and ovarian malignancies *BRCA2* mutation carriers are at increased risk of cancers of the prostate, gallbladder, bile duct, stomach and melanoma. [33,34] A personal history of extra-pancreatic malignancy was present in nearly 15% of FPC patients, which was not significantly higher than SPC patients at 10%. This is consistent with previous reports of a 13 - 16% incidence of previous EPM in SPC. [35,36] Approximately 8.0% of cancer patients in the United States and Australia will develop a second invasive malignancy in the same organ and an estimated 6% risk of developing a second malignancy in a different organ.[35,37,38] The occurrence of multiple primary malignancies in PC patients and FPC kindreds is suggestive of an underlying genetic predisposition, with variable penetrance, interaction with other modifier alleles, and gene-environment factors.[39]

SPC patients were more likely to be active smokers at time of PC diagnosis and had higher exposure to cigarette smoke than FPC patients. There was no difference in other risk factors such as alcohol consumption, DM and chronic pancreatitis. Recent data also support the notion that patients who smoke and have a family history of malignancy in a FDR require a reduced dose of tobacco exposure for the development of PC.[40] A higher proportion of multifocal precursor lesions in FPC patients is consistent with previous findings.[41,42] Importantly this did not affect outcome after localized resection.

Consistent with previous studies, there was no difference in survival between resected FPC and SPC patients. [27,43,44] Importantly we found that long-standing DM (> 2 years) was an independent prognostic variable in all patients who underwent resection. Its role as a prognostic marker is less well established, [45,46] and previous studies have yielded conflicting results.[47-50]

In conclusion, in our cohort FPC represents nearly 9% of all PC patients. FPC is likely to be a heterogeneous syndrome with phenotype determined by the underlying genetic mechanism and modified by environmental risk factors, although some familial clustering is likely to occur due to phenocopies from common environmental exposures.[51] Robust clinical characterization of FPC is indispensible for ongoing efforts to identify susceptibility genes, particularly in the age of massively parallel genomic sequencing.

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**Table 1: Distribution of relatives with PC and extra-pancreatic malignancy (EPM) in the FPC and SPC groups**

| Variable | FPC *N* = 68 (%) | SPC *N* = 698 (%) | *P* value |
|---|---|---|---|
| **FDR with PC** | | | |
| 2 FDR | 6 (8.8) | - | |
| 1 FDR | 53 (77.9) | - | |
| 1 FDR and 1 SDR | 8 (11.8) | - | |
| 1 FDR and 2 SDR | 1 (1.5) | - | |
| **FDR with EPM** | | | |
| **Number of FDR with an EPM** | | | |
| 1 | 20/68 (29.4) | 115/698 (16.5) | |
| 2 | 4/68 (5.9) | 27/698 (3.9) | |
| 3 | 4/68 (5.9) | 6/698 (0.9) | |
| 4 | 1/68 (1.5) | 0 | |
| Mean | 1.52 | 1.26 | 0.0372 |
| Total FDRs with an EPM | 44 | 187 | |
| **EPM Site** | | | |
| - breast | 7/68 (10.3) | 34/698 (4.9) | 0.0579 |
| - colo-rectal | 7/68 (10.3) | 44/698 (6.3) | 0.2077 |
| - prostate | 3/68 (4.4) | 16/698 (2.3) | 0.2834 |
| - endometrial | 2/68 (2.9) | 4/698 (0.6) | 0.0345 |
| - ovarian | 1/68 (1.5) | 6/698 (0.9) | 0.6133 |
| - melanoma | 6/68 (8.8) | 4/698 (0.6) | <0.0001 |
| - gastric | 3/68 (4.4) | 12/698 (1.7) | 0.1261 |
| - lung | 4/68 (5.9) | 26/698 (3.7) | 0.3813 |
| - Unknown primary | 3/68 (4.4) | 15/698 (2.1) | 0.2397 |
| - Head and neck | 0/68 | 5/698 (0.7) | 0.4838 |
| - brain | 2/68 (2.9) | 5/698 (0.7) | 0.1219 |
| - hepatocellular | 2/68 (2.9) | 3/698 (0.4) | 0.0652 |
| - renal tract | 1/68 (1.5) | 2/698 (0.3) | 0.2437 |
| - lymphoma | 1/68 (1.5) | 1/698 (0.1) | 0.1698 |
| - oesophageal | 1/68 (1.5) | 4/698 (0.6) | 0.3803 |
| - myeloma/leukaemia | 0/68 | 3/698 (0.4) | >0.9999 |
| - sarcoma | 0/68 | 2/698 (0.3) | >0.9999 |
| - gallbladder | 0/68 | 1/698 (0.1) | >0.9999 |
| - testicular | 1/68 (1.5) | 0/698 | 0.0888 |
| **TOTAL with EPM in ≥1 FDR** | **29/68 (42.6)** | **148/698 (21.2)** | **<0.0001** |

**Table 2: Comparison of clinico-pathological variables in resected PC patients**

| Variable | FPC (%) | SPC (%) | *P* value |
|---|---|---|---|
| Mean age at diagnosis | 65.8 | 66.0 | 0.8952 |
| Age < 50 | 4/57 (7.0) | 44/540 (8.1) | 0.7653 |
| Location – body/tail | 10/57 (17.5) | 97/540 (18.0) | 0.9326 |
| LN involved | 38/57 (66.7) | 356/540 (65.9) | 0.9106 |
| Differentiation poor | 19/56 (33.9) | 146/537 (27.2) | 0.2841 |
| Tumor size >20mm | 50/57 (87.7) | 427/540 (79.1) | 0.6547 |
| Margins involed | 18/57 (31.6) | 199/540 (36.9) | 0.4312 |
| Perineural invasion | 43/53 (81.1) | 397/522 (76.0) | 0.4059 |
| Vascular invasion | 26/47 (55.3) | 265/506 (52.4) | 0.6987 |
| Multifocal disease<br>- PanIN2 or PanIN3 | 21/57 (36.8) | 129/540 (23.9) | 0.0320 |
| **Pre-2004** | | | |
| Any adjuvant chemotherapy | 7/15 (46.7) | 68/290 (23.4) | 0.0417 |
| Adjuvant chemotherapy ≥3 cycles | 5/15 (33.3) | 34/290 (11.7) | 0.0145 |
| **Post-2004** | | | |
| Any adjuvant chemotherapy | 31/42 (73.8) | 155/246 (63.0) | 0.1761 |
| Adjuvant chemotherapy ≥3 cycles | 29/42 (69.0) | 136/246 (55.3) | 0.0956 |

## Table 3: Risk factors for PC

| Variable | FPC | SPC | *P* value |
|---|---|---|---|
| **Diabetes Mellitus** | 19/68 (27.9) | 202/698 (28.9) | 0.8623 |
| Missing date of diagnosis | 6/19 (31.6) | 98/202 (48.5) | |
| DM ≤ 2 years | 7/19 (36.8) | 47/202 (23.3) | 0.5551 |
| DM > 2 years | 6/19 (31.6) | 57/202 (28.2) | 0.9327 |
| **Chronic Pancreatitis** | 6/68 (8.8) | 37/698 (5.3) | 0.2283 |
| **Alcohol** | | | |
| Missing alcohol data | 0 | 18/698 (2.6) | |
| Nil or Low Alcohol Intake (≤ 2 SD) | 58/68 (85.3) | 541/698 (77.5) | 0.3000 |
| Mod Alcohol Intake (3-4 SD) | 5/68 (7.4) | 68/698 (9.7) | 0.4831 |
| Heavy Alcohol Intake (≥ 5 SD) | 5/68 (7.4) | 71/698 (10.2) | 0.4216 |
| **Cigarette Smoking** | | | |
| Missing date ceased | 2/21 (9.5) | 31/165 (18.8) | |
| Never Smoked | 41/68 (60.3) | 318/698 (45.6) | 0.0315 |
| Reformed Smoker | 21/68 (30.9) | 165/698 (23.6) | 0.3314 |
| - reformed ≤ 10 years | 5/21 (23.8) | 50/165 (30.3) | 0.9702 |
| - reformed > 10 years | 14/21 (66.7) | 84/165 (50.9) | 0.0627 |
| Active Smoker | 6/68 (8.8) | 197/698 (28.2) | 0.0003 |
| **Mean smoke exposure (pack-years)** | 25.7 | 34.9 | 0.0479 |

**Figure Legend:**

**Figure 1:** Kaplan-Meier survival curves for: A. Survival post-resection for FPC and SPC patients, B. Survival in non-resected FPC and SPC patients, C. Survival in FPC patients who underwent localized resection, with and without PanIN 2 and/or 3, D. Survival in SPC who underwent localized resection, with and without PanIN 2 and/or 3.

**Figure 1:**