The impact of diabetes mellitus on survival following resection and adjuvant chemotherapy for pancreatic cancer

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Background: Diabetes mellitus is frequently observed in pancreatic cancer patients and is both a risk factor and an early manifestation of the disease.

Methods: We analysed the prognostic impact of diabetes on the outcome of pancreatic cancer following resection and adjuvant chemotherapy using individual patient data from three European Study Group for Pancreatic Cancer randomised controlled trials. Analyses were carried out to assess the association between clinical characteristics and the presence of preoperative diabetes, as well as the effect of diabetic status on overall survival.

Results: In total, 1105 patients were included in the analysis, of whom 257 (23%) had confirmed diabetes and 848 (77%) did not. Median (95% confidence interval (CI)) unadjusted overall survival in non-diabetic patients was 22.3 (20.8–24.1) months compared with 18.8 (16.9–22.1) months for diabetic patients (P = 0.24). Diabetic patients were older, had increased weight and more co-morbidities. Following adjustment, multivariable analysis demonstrated that diabetic patients had an increased risk of death (hazard ratio: 1.19 (95% CI 1.01, 1.40), P = 0.034). Maximum tumour size of diabetic patients was larger at randomisation (33.6 vs 29.7 mm, P = 0.026).

Conclusions: Diabetes mellitus was associated with increased tumour size and reduced survival following pancreatic cancer resection and adjuvant chemotherapy.

Pancreatic cancer is currently the fourth most common cause of cancer-related mortality in developed countries (Siegel et al, 2015) and is predicted to be the second leading cause within the next decade (Rahib et al, 2014). Most patients are diagnosed at an advanced stage with distant metastasis and/or locally advanced unresectable tumours (Hidalgo et al, 2015). Together with limited and often ineffective treatment options, this results in an overall low 5-year survival rate of <7%. Surgery, the only chance for cure, can be offered to only 15–20% of patients resulting in ~20% 5-year survival rates (Kleeff et al, 2016).

Risk factors that have been identified for pancreatic cancer include tobacco smoking, diabetes mellitus and others

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Several studies have established that diabetes mellitus has a higher prevalence in patients with pancreatic cancer than other cancers or control subjects especially in patients with a more recent diagnosis (Chari et al., 2008; Pannala et al., 2008; Aggarwal et al., 2013). Systematic reviews and meta-analyses have confirmed that diabetes is a risk factor for pancreatic cancer with risk ratios of around 1.8–2.1 (Huxley et al., 2005; Ansary-Moghaddam et al., 2006; Stevens et al., 2007; Ben et al., 2011). The risk is higher with recent onset diabetes (Calle et al., 1998; Huxley et al., 2005; Ben et al., 2011), possibly as an early manifestation of pancreatic cancer. In contrast to an earlier report (Guillo et al., 1994), long-standing diabetes mellitus (>5 years) has also been shown to have an increased risk ratio of pancreatic cancer of 1.5–2.0 (Everhart and Wright, 1995; Huxley et al., 2005; Li et al., 2011). There is still an excess risk of pancreatic cancer even with a long-standing diagnosis of diabetes of 20 years or more, but at a lower level with an odds ratio (OR) of 1.3 (Bozetti et al., 2014). There is some evidence that diabetes mellitus may resolve after pancreatic cancer resection in a proportion of new onset cases, whereas it remains unchanged in patients with long-standing diabetes (Perment et al., 1993; Pannala et al., 2008), which appears to be specific for pancreatic cancer, as resection for chronic pancreatitis does not improve pre-existing diabetes (Litwin et al., 2008). Although diabetes mellitus increases the risk of pancreatic cancer, there is also evidence that pancreatic cancer itself induces diabetes (type 3c). Potential mechanisms include the release of adrenomedullin, a potential mediator of beta cell dysfunction (Aggarwal et al., 2012) or by beta cell apoptosis induced by pancreatic stellate cells (Kikuta et al., 2013). Thus, diabetes is both causal and consequential to pancreatic cancer, the latter offering a window for screening, early tumour detection and therapy (Jenkinson et al., 2015).

The survival of diabetic cancer patients compared with normoglycemic individuals across all cancer types seems to be less with risk ratios of around 1.4 (van de Poll-Franse et al., 2007; Barone et al., 2008), but not for pancreatic cancer, possibly because of the limited cohort size (Park et al., 2006). Analysis of diabetes as covariate on survival outcome in advanced pancreatic cancer is difficult due to the large number of variables and the very short survival. Preoperative diabetes found in 275 (56.3%) of 488 patients with pancreatic cancer that had resection also did not influence survival although tumour size was significantly larger (mean = 36 mm) compared with the non-diabetics (mean = 33 mm) (Hart et al., 2014). In another study, 93 (45.4%) of 209 patients with pancreatic cancer and preoperative diabetes had a median survival of 15 months, which was less compared with 17 months in non-diabetics with a hazard ratio (HR) of 1.55 (Chu et al., 2010). The risk of survival was even less in new onset diabetics (<2 years duration) compared with the long-standing diabetics with a HR of 1.75 (Chu et al., 2010). Diabetics also had a larger tumour size (mean = 38 mm) compared with non-diabetics (mean = 32 mm).

Thus, the prognostic effect of diabetes mellitus in patients with pancreatic cancer is uncertain. The purpose of this study was to analyse the prognostic effect of clinically revealed diabetes on long-term survival in pancreatic cancer patients following resection and adjuvant chemotherapy from three randomised controlled trials of the European Study Group for Pancreatic Cancer (ESPAC) trials, namely ESPAC-1Plus, ESPAC-1 and ESPAC-3 (Neoptolemos et al., 2001, 2004, 2009, 2010).

RESULTS

Clinical and pathological variables. A total of 1105 patients were included in the analysis, 164 (15%) patients from the ESPAC-1 studies and 941 (85%) patients from the ESPAC-3 study. There were 25 (15%) and 232 (25%) diabetics, respectively, from these studies. Together there were 257 (23%) patients with clinically revealed diabetes mellitus and 848 (77%) who were non-diabetic at the point of randomisation. Patient characteristics at baseline and univariate analyses are presented to identify patient characteristics associated with diabetes (Table 1). Patients with diabetes were significantly older with a median (interquartile range) age of 65 (57–71) vs 63 (56–69) years for non-diabetics (P = 0.04), and had an increased median (interquartile range) weight at presentation of 72 (62, 80) vs 66 (58, 75) kg for non-diabetics (P < 0.001). Diabetic patients were also more likely to have concurrent medical conditions other than diabetes (64% vs 42%; P < 0.001). About 146 of 257 (57%) diabetic patients completed all six cycles of adjuvant therapy, which was not significantly different from the 458 of 848 (54%) non-diabetic
## Table 1. Baseline characteristics and univariate analysis

| Category                  | Level                  | Non-diabetic, number (%) | All diabetic, number (%) | Total, number (%) | P-value | No insulin, number (%) | Insulin, number (%) | P-value |
|---------------------------|------------------------|---------------------------|--------------------------|-------------------|---------|------------------------|---------------------|---------|
|                           |                        |                           |                          |                   |         |                        |                     |         |
| Total                     | All                    | 848 (77%)                 | 257 (23%)                | 1105              |         | 111                    | 144                 |         |
|                           | Trial                  |                           |                          |                   |         |                        |                     |         |
|                           | ESPAC-1 trials         | 139 (85%)                 | 25 (15%)                 | 164               | 0.011   | 12 (52%)               | 11 (48%)            | 0.512   |
|                           | ESPAC-3 trial          | 646 (71%)                 | 32 (29%)                 | 968               | 0.002   | 69 (50%)               | 93 (50%)            | 0.913   |
|                           | Gender                 |                           |                          |                   |         |                        |                     |         |
|                           | Female                 | 387 (80%)                 | 94 (20%)                 | 481               | 0.001   | 40 (43%)               | 54 (57%)            | 0.983   |
|                           | Male                   | 461 (74%)                 | 163 (26%)                | 624               | 0.013   | 71 (44%)               | 90 (56%)            | 0.913   |
|                           | Weight, kg             | Median (IQR)              | 66 (58, 75)              | 72 (68, 80)       | <0.001  | 72 (64, 80)            | 72 (60, 80)         | 0.583   |
|                           | Age, years             | Median (IQR)              | 63 (56, 69)              | 65 (57, 71)       | 0.04    | 67 (59, 71)            | 63 (57, 70)         | 0.015   |
| Smoking status            | Never                  | 326 (79%)                 | 88 (21%)                 | 414               | 0.303   | 43 (49%)               | 44 (51%)            | 0.483   |
|                           | Past                   | 327 (74%)                 | 113 (26%)                | 440               |         | 46 (41%)               | 66 (59%)            |         |
|                           | Present                | 145 (76%)                 | 47 (24%)                 | 192               | 0.095   | 20 (43%)               | 27 (57%)            |         |
| WHO performance status    | 0                      | 286 (76%)                 | 90 (24%)                 | 376               |         | 39 (43%)               | 51 (57%)            |         |
|                           | 1                      | 419 (77%)                 | 127 (23%)                | 546               | 0.031   | 55 (43%)               | 72 (57%)            | 0.889   |
|                           | 2                      | 92 (75%)                  | 31 (25%)                 | 123               | 0.895   | 12 (39%)               | 19 (61%)            |         |
| Resection margin status   | Negative               | 571 (78%)                 | 165 (22%)                | 736               | 0.391   | 74 (45%)               | 90 (55%)            |         |
|                           | Positive               | 277 (75%)                 | 92 (25%)                 | 369               |         | 37 (41%)               | 54 (59%)            |         |
| Tumour stage              | 1                      | 64 (68%)                  | 30 (32%)                 | 94                |         | 13 (43%)               | 17 (57%)            |         |
|                           | 2                      | 187 (72%)                 | 71 (28%)                 | 258               |         | 32 (45%)               | 39 (55%)            |         |
|                           | 3                      | 425 (79%)                 | 114 (21%)                | 539               | 0.016   | 46 (40%)               | 68 (60%)            |         |
|                           | 4                      | 22 (63%)                  | 13 (27%)                 | 35                |         | 6 (46%)                | 7 (54%)             | 0.922   |
| Lymph node involvement    | Negative               | 258 (74%)                 | 91 (26%)                 | 349               |         | 42 (46%)               | 49 (54%)            |         |
|                           | Positive               | 588 (78%)                 | 164 (22%)                | 752               | 0.138   | 69 (43%)               | 93 (57%)            |         |
| Local invasion at surgery | No                     | 504 (77%)                 | 149 (23%)                | 653               | 0.666   | 64 (43%)               | 84 (57%)            | 0.911   |
|                           | Yes                    | 330 (76%)                 | 105 (24%)                | 435               |         | 47 (45%)               | 58 (55%)            |         |
| Maximum tumour size       | Mean (s.d.)            | 29.67 (14.53)             | 33.59 (20.64)            | 30.59 (16.25)     | 0.026   | 302.68 (15.24)         | 34.32 (24.10)       | 0.507   |
| Tumour differentiation    | Moderate               | 517 (78%)                 | 147 (22%)                | 664               | 0.505   | 60 (41%)               | 87 (59%)            |         |
|                           | Poor                   | 202 (76%)                 | 64 (24%)                 | 266               |         | 29 (46%)               | 34 (54%)            |         |
|                           | Well                   | 118 (74%)                 | 42 (26%)                 | 160               |         | 21 (50%)               | 21 (50%)            |         |
| Concurrent medical condition | No                  | 474 (84%)                 | 89 (16%)                 | 563 (53%)         | <0.001  | 43 (48%)               | 46 (52%)            |         |
|                           | Yes                    | 341 (68%)                 | 159 (32%)                | 500 (47%)         |         | 63 (37%)               | 96 (63%)            |         |
| Operation                 | Distal panc.           | 42 (73%)                  | 23 (27%)                 | 85                |         | 14 (61%)               | 9 (39%)             |         |
|                           | Py. Pres.              | 267 (78%)                 | 74 (22%)                 | 341               |         | 32 (44%)               | 41 (56%)            |         |
|                           | Total pancreatectomy   | 11 (26%)                  | 31 (74%)                 | 42                | 0.001   | 5 (16%)                | 26 (84%)            |         |
|                           | Whipple’s              | 503 (80%)                 | 129 (20%)                | 632               |         | 60 (47%)               | 68 (53%)            | 0.005   |
| Post-operative Complications | No                  | 635 (77%)                 | 194 (23%)                | 829               | 0.453   | 86 (45%)               | 106 (55%)           |         |
|                           | Yes                    | 204 (77%)                 | 62 (23%)                 | 266               | 1       | 25 (40%)               | 37 (60%)            |         |
| Treatment                 | S-Fluorouracil         | 501 (78%)                 | 141 (22%)                | 642               | 0.259   | 60 (43%)               | 79 (57%)            |         |
|                           | Gemcitabine            | 347 (75%)                 | 116 (25%)                | 463               |         | 51 (44%)               | 65 (56%)            | 0.999   |
Diabetes and pancreatic cancer survival

Diabetic patients

| Category Level | Non-diabetic, number (%) | Insulin, number (%) |
|----------------|--------------------------|--------------------|
| Tumour location |                         |                    |
| Body           | 24 (77%)                 | 7 (23%)            |
| Other          | 6 (86%)                  | 1 (14%)            |
| Tail           | 22 (81%)                 | 5 (19%)            |
| Uncinate       | 19 (95%)                 | 1 (5%)             |

| Completed therapy | No 390 (78%) | 111 (22%) |
|-------------------|--------------|-----------|
| Yes               | 458 (76%)    | 146 (24%) |

| Time to start of therapy | Median (IQR) |
|--------------------------|--------------|
|                         | 7.86 (6.57, 9.71) |

| Abbreviations: Distal panc. = distal pancreatectomy; ESPAC = European Study Group for Pancreatic Cancer; GBCA = Gallbladder Cancer; IQR = interquartile range; Pyl. Pres. = pylorus preserving duodenopancreatectomy; WHO = World Health Organization. |

X̂²LR(1DF) = 1.39 (P = 0.238). Multivariable model analysis for overall survival identified World Health Organization performance status and smoking status as independent prognostic clinical indicators and resection margin status, tumour differentiation and lymph node involvement as independent prognostic pathological indicators (Table 3). Following adjustment of other terms, diabetic status was significantly associated with survival, with diabetic patients having an increased risk of death (HR: 1.19 (95% CI: 1.01, 1.40), P = 0.034). The fitted effect of diabetic status is given in Figure 1. Assessment of Schoenfeld residuals did not identify any prognostic factors, which may be associated with non-proportional hazards.

Of the 257 patients who were diabetic, insulin status was missing in two patients. One hundred and forty four (56%) of these 255 patients were insulin dependent and the remainder (n = 111) were non-insulin dependent received either oral antidiabetics or were controlled by diet alone. At least 13 patients were receiving oral antidiabetic therapy (seven taking metformin), but specific information was not available for the remaining 98 non-insulin-dependent diabetics. The median (95% CI) overall survival estimates was 18.0 (16.5, 21.1) months for patients who used insulin and 20.5 (16.0, 26.6) months for patients who did not use insulin. The unadjusted overall survival by diabetic status was not significant (X̂²LR(1DF) = 0.03, P = 0.857). The unadjusted overall survival for diabetics in those using insulin vs metformin or other oral diabetic medication was not significant (X̂²LR(2DF) = 0.80, P = 0.371). The median (95% CI) overall survival estimates was 18.0 (16.5, 21.1) months for patients who used insulin (n = 144) and 22.2 (20.7, 23.9) months for patients who were not diabetic or who were non-insulin dependent (n = 959) (X̂²LR(1DF) = 0.4, P = 0.527).

In insulin-dependent diabetic patients, the median (95% CI) overall survival estimates with a maximum tumour diameter >30 mm was 17.0 (15.2–22.7) months compared with 18.5 (15.9–26.1) months for patients with a maximum tumour diameter ≤30 mm (HR (95% CI): 0.96 (0.65, 1.4); P = 0.823). In non-insulin-dependent diabetic patients, the median (95% CI) overall survival estimates with a maximum tumour diameter >30 mm was 14.6 (9.51–21.9) months compared with 32.0 (22.11–41.4) months for patients with a maximum tumour diameter ≤30 mm (HR (95% CI): 1.99 (1.30, 3.03); P < 0.001). The overall survival difference was significant (X̂²LR(2DF) = 10.37, P = 0.016) (Figure 2).

A multivariable analysis was carried out on factors independently associated with overall survival specifically in the 257 diabetic patients. Due to the interaction between insulin status
and MTS, we included the latter as a nested effect within insulin status, allowing for separate HRs for insulin-dependent and non-dependent groups. This showed that lymph node metastasis remained an independent prognostic factor (Table 4). There was also a significant effect of MTS for non-insulin-dependent patients but not for patients who were insulin dependent. Landmark

| Term                               | Level       | Est (s.e.) | Hazard ratio (95% confidence interval) | P-value |
|------------------------------------|-------------|------------|----------------------------------------|---------|
| Resection margin status            | Negative    | 0.26 (0.073) | 1.3 (1.125, 1.496) | <0.001  |
| Tumour differentiation             | Well        | 0.27 (0.107) | 1.31 (1.058, 1.61) | 0.013   |
|                                    | Moderate    | 0.55 (0.119) | 1.74 (1.379, 2.197) | <0.001  |
|                                    | Poor        | 0.55 (0.119) | 1.74 (1.379, 2.197) | <0.001  |
| Lymph node status                  | Negative    | 0.62 (0.081) | 1.85 (1.577, 2.171) | <0.001  |
| WHO Performance status             | 0           | 0.17 (0.077) | 1.19 (1.022, 1.384) | 0.025   |
|                                    | 1           | 0.38 (0.118) | 1.46 (1.159, 1.837) | 0.001   |
|                                    | 2           | 0.38 (0.118) | 1.46 (1.159, 1.837) | 0.001   |
| Smoking status                     | Never       | 0.03 (0.079) | 1.03 (0.883, 1.204) | 0.698   |
|                                    | Past        | 0.23 (0.099) | 1.25 (1.031, 1.522) | 0.023   |
|                                    | Present     | 0.23 (0.099) | 1.25 (1.031, 1.522) | 0.023   |
| Diabetic status                    | No          | 0.18 (0.083) | 1.19 (1.014, 1.402) | 0.034   |

Abbreviations: Est = estimated; WHO = World Health Organization.

Figure 1. Fitted effect of diabetic status on overall survival in 1105 pancreatic cancer patients following resection and adjuvant chemotherapy. Yes = diabetic patients; No = non-diabetic patients.
analyses, removing patients who died within the first 30, 60 and 90 days, respectively, showed that the magnitude and direction of all treatment effects remained consistent showing that the effects reported are not overly effected by early deaths. Details are included in Supplementary Table 1. Further to this, assessment of Schoenfeld residuals did not identify any prognostic factors, which may be associated with non-proportional hazards.

**DISCUSSION**

The present study shows that diabetes mellitus is associated with increased tumour size and a small but significant increased overall risk of death with a HR of 1.19. There was a significant effect of MTS on survival for non-insulin-dependent but not for insulin-dependent diabetic patients. Two specific smaller studies also showed increased tumour size with diabetes with only one of these found a worse prognosis for diabetic patients following tumour resection (Chu et al, 2010; Hart et al, 2014). A meta-analysis of retrospective studies demonstrated worse prognosis in diabetic patients following resection with a HR of 1.32 (Walter et al, 2014).

Taken together, there is now solid evidence that the diabetic state at the time of resection influences outcome. There are several concepts on how diabetes mellitus might impact on prognosis of pancreatic cancer patients. Patients with long-standing type II diabetes exhibit insulin resistance and hypersecretion of insulin (Fisher et al, 1996; Li, 2012). In addition, elevated insulin levels result in increased bioavailability of IGFs and pancreatic cancer cells highly express high-affinity insulin and IGF receptors (Li, 2012). Insulin has been shown to act as a mitogen for pancreatic cancer cells (Fisher et al, 1996; Ding et al, 2000), and IGF-1 besides its mitogenic effects, induces angiogenesis and increases invasion and blocks apoptosis of pancreatic cancer cells, thereby promoting tumour growth (Li, 2012). In line with this hypothesis, this and two other mentioned studies (Chu et al, 2010; Hart et al, 2014) have shown that diabetic patients have larger tumours at the time of resection. The present study has also demonstrated that the effects of diabetes on outcome were independent from tumour size, suggesting that other mechanisms are responsible for the worse prognosis of diabetic patients. It is conceivable that in the adjuvant setting, hyperinsulinemia supports growth of occult pancreatic cancer cells, resulting in worsened prognosis. This might further be augmented by related obesity, leading to enhanced oxidative stress and inflammatory responses (Li, 2012). Indeed, the median weight of diabetic patients was significantly higher than of non-diabetic patients in the present analysis.

| Term                        | Level       | Est (s.e.) | Hazard ratio (95% confidence interval) | P-value |
|-----------------------------|-------------|------------|---------------------------------------|---------|
| Lymph node status           | Negative    | 0.86 (0.165) | 2.37 (1.714, 3.272) | <0.001  |
| Insulin dependent           | No          | 1.86 (0.818) | 6.45 (1.298, 32.014) | 0.023   |
| Non-insulin dependent       | Yes         | 0.51 (0.212) | 1.67 (1.103, 2.533) | 0.015   |
| Insulin dependent           | Maximum tumour size | -0.06 (0.097) | 0.94 (0.78, 1.142) | 0.553   |

Abbreviation: Est = estimated.

*Maximum tumour size is included in the model using a log(x+1) transformation.
The association between diabetes and tumour size has been substantiated from three large trials. Here, we show in addition, that in the group of diabetic patients, tumour size was an important prognostic indicator in non-insulin-dependent, but not in insulin-dependent patients. This suggests that in non-insulin-dependent diabetes mellitus, tumour size has a predominant effect on prognosis, whereas insulin-dependent diabetes mellitus has a stronger, likely systemic effect on survival. There is evidence that therapies that increase insulin levels such as exogenous insulin or sulfonylurea could increase cancer risk. Therapies that decrease insulin levels by decreasing insulin resistance such as metformin, which also inhibits mTOR activity (Gong et al., 2014), would decrease the risk. Long duration (>15 years) of oral antidiabetics is associated with a decreased pancreatic cancer risk (OR 0.31), whereas insulin use (<5 years) is associated with increased cancer risk (OR 5.6) (Bosetti et al., 2014). A case-control study has shown that diabetic patients on metformin had a significantly reduced risk of pancreatic cancer compared with patients not on metformin. In contrast, patients on insulin or insulin secretagogues had a significantly higher risk (Li et al., 2009), while a meta-analysis showed a reduced pancreatic cancer risk for patients on metformin but not sulfonylurea (Soranna et al., 2012). Another recent meta-analysis could not verify these associations between metformin or insulin and pancreatic cancer risk (Singh et al., 2013).

A previous study has shown that the effect on survival was especially pronounced for recent onset diabetes (Chu et al., 2010). Tumours that induce diabetes might constitute a more aggressive subtype. Alternatively, symptoms of diabetes may mask symptoms of a developing tumour and contribute to delayed diagnosis. Our data on this aspect are conflicting, in as much as tumours of diabetic patients were significantly larger, but had significantly less lymph node involvement and did not display differences in tumour differentiation. Furthermore, diabetic patients might have been treated less aggressively than non-diabetic patients, as it has been shown for other tumour entities (van de Poll-Franse et al., 2007), although there was no difference in surgery and adjuvant therapy (including completion of therapy) in our series. On the other hand, it is also conceivable that cancer-induced diabetes results in earlier diagnosis, and thus in potentially better outcome. It could be speculated that all of these effects might have a role and that our data reflect the sum of these effects.

This study relied on clinical data collected in prospectively randomised controlled trials of patients with histological proven ductal adenocarcinoma involving a total of 1105 patients of whom 257 (23%) were diabetic (Neoptolemos et al., 2001, 2004, 2009, 2010). Diabetes mellitus status was determined by the principal investigator at each of the referring sites according to the best available clinical evidence and guidelines at that time and site. This is a limitation of the present study, as no clear definition or test was utilised. Diagnosis reflected actual clinical care at the different sites and under-diagnosis is a likely issue, as routine use of specific tests (e.g. glucose tolerance test) was not mandatory within the ESPAC-study protocols. Thus, it is possible that some of the patients were actually diabetic, but had not been formally assessed prior to therapy.

In conclusion, diabetic patients who undergo resection for pancreatic cancer and adjuvant therapy present with larger tumours and have a small but significantly higher risk of death than non-diabetic patients. There seem to be important differences in patients with pancreatic cancer between those with insulin- and non-insulin-dependent diabetes mellitus and from previous studies between those with new onset and established diabetes mellitus. Understanding the biological mechanisms behind these observations may offer new opportunities for diagnosis and therapy.
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Chu CK, Mazo AE, Goodman M, Egnatchevli V, Sarmiento JM, Staley CA, Galloway JR, Adsay NV, Jacobs S, Kooby DA (2010) Preoperative diabetes mellitus and long-term survival after resection of pancreatic adenocarcinoma. *Ann Surg Oncol* 17(2): 502–513.

Cox DR (1972) Regression models and life-tables. *J R Stat Soc Series B (Methodological)* 34(2): 187–220.

Ding XZ, Fehsenfeld DM, Murphy LO, Perment J, Adrian TE (2000) Physiological concentrations of insulin augment pancreatic cancer cell proliferation and glucose utilization by activating MAP kinase, PI3 kinase and enhancing GLUT-1 expression. *Pancreas* 21(3): 310–320.

Everhart J, Wright D (1995) Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. *JAMA* 273(20): 1605–1609.

Fisher WE, Boros LG, Schirmer WJ (1996) Insulin promotes pancreatic cancer: evidence for endocrine influence on exocrine pancreatic tumors. *J Surg Res* 63(1): 310–313.

Gong J, Robbins LA, Ludgea A, Waldron RT, Jeon CY, Pandol SJ (2014) Diabetes, pancreatic cancer, and metformin therapy. *Front Physiol* 5: 426.

Gullo L, Pezzilli R, Morselli-Labate AM. Italian Pancreatic Cancer Study G (1994) Diabetes and the risk of pancreatic cancer. *N Engl J Med* 331(2): 81–84.

Hart PA, Law RJ, Frank RD, Bamlet WR, Burch PA, Petersen GM, Rabe KG, Chari ST (2014) Impact of diabetes mellitus on clinical outcomes in patients undergoing surgical resection for pancreatic cancer: a retrospective, cohort study. *Am J Gastroenterol* 109(9): 1484–1492.

Hidalgo M, Cascini S, Kleeff J, Labianca R, Lohr JM, Neoptolemos J, Real FX, Van Laethem JL, Heinemann V (2015) Addressing the challenges of pancreatic cancer: future directions for improving outcomes. *Pancreatology* 15(1): 8–18.

Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M (2005) Type-2 diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer* 92(11): 2076–2083.

Jenkinson C, Elliott V, Oldfield L, Jenkins RE, O‟Brien DP, Apostolidou S, Gerty-Maharaj A, Fourkala EO, Jacobs I, Menon U, Cox TF, Campbell F, Pereira SP, Tuveson DA, Park PK, Greenhalf W, Sutton RP, Timms JF, Neoptolemos J, Costello E (2015) Decreased serum thrombospondin-1 levels in pancreatic cancer patients up to 24 months prior to clinical diagnosis with diabetes mellitus. *Clin Cancer Res.*

Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53(282): 457–481.

Kikut K, Masamune A, Hamada S, Takikawa T, Nakano E, Shimosegawa T (2013) Pancreatic stellate cells reduce insulin expression and induce apoptosis in pancreatic beta-cells. *Biochem Biophys Res Commun* 433(3): 292–297.

Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin AV, Neale RE, Kikuta K, Masamune A, Hamada S, Takikawa T, Nakano E, Shimosegawa T, Neoptolemos JP, Dunn JA, Stocken DD, Almond J, Link K, Herreras-Cruz L, Dervenis C, Lacaife F, Falconi M, Pederzoli P, Pop A, Spooner D, Kerr DJ, Buchler MW. European Study Group for Pancreatic Cancer (2004) A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 350(12): 1200–1210.

Neoptolemos JP, Stocken DD, Todor Smith C, Bassi C, Ghaneh P, Owen E, Moore M, Padbury R, Doi R, Smith D, Buchler MW (2009) Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. *Br J Cancer* 100(2): 246–250.

Pannala R, Leirness JB, Bamlet WR, Basu A, Petersen GM, Chari ST (2008) Prevalence and clinical profile of pancreatic-cancer-associated diabetes mellitus. *Gastroenterology* 134(4): 981–987.

Park SM, Lim MK, Shin SA, Yun YH (2006) Impact of prediagnosis smoking, alcohol, obesity, and insulin resistance on survival in male cancer patients: National Health Insurance Corporation Study. *J Clin Oncol* 24(31): 5017–5024.

Perment J, Ihse I, Jorfeldt L, von Schenck H, Arquint HJ, Larsson J (1993) Improved glucose metabolism after subtotal pancreatectomy for pancreatic cancer. *Br J Surg* 80(8): 1047–1050.

Peto R, Peto J (1972) Asymptotically efficient rank invariant test procedures. *J R Stat Soc Series A* 135(2): 185–207.

R-Development-Core-Team (2011) R: a language and environment for statistical computing. Vol. 2.11.1. Vienna, Austria. Available at: http://www.R-project.org/.

Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM (2014) Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 74(11): 2913–2921.

Schepmeier M, Smith TL (1996) A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 17(4): 343–346.

Schoenfeld D (1982) Partial residuals for the proportional hazards regression model. *Biometrika* 69(1): 239–241.

Siegel RL, Miller KD, Jemal A (2015) Cancer statistics, 2015. *CA Cancer J Clin* 65(1): 5–29.

Singh S, Singh PP, Singh AG, Murad MH, McWilliams RR, Chari ST (2013) Anti-diabetic medications and risk of pancreatic cancer in patients with diabetes mellitus: a systematic review and meta-analysis. *Am J Gastroenterol* 108(4): 510–519; quiz 520.

Soranna D, Scotti L, Zambon A, Bosetti C, Grassi G, Catapano A, La Vecchia C, Mancia G, Corrao G (2012) Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: a meta-analysis. *Oncologist* 17(6): 813–822.

Stevens RJ, Roddam AW, Beral V (2007) Pancreatic cancer in type 1 and young-onset diabetes: systematic review and meta-analysis. *Br J Cancer* 96(3): 507–509.

van de Poll-Franse LV, Houterman S, Janssen-Heijnen ML, Dercks MW, Coebergh JW, Haak HR (2007) Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population based analysis. *Int J Cancer* 120(9): 1986–1992.

Walter U, Kobelt T, Rahbari NN, Weitz J, Welsch T (2014) Impact of preoperative diabetes on long-term survival after curative resection of pancreatic adenocarcinoma: a systematic review and meta-analysis. *Ann Surg Oncol* 21(4): 1082–1089.

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