Systematic Review

Risk Factors for Pancreatic Cancer in Patients with New-Onset Diabetes: A Systematic Review and Meta-Analysis

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Citation: Mellenthin, C.; Balaban, V.D.; Dugic, A.; Cullati, S. Risk Factors for Pancreatic Cancer in Patients with New-Onset Diabetes: A Systematic Review and Meta-Analysis. Cancers 2022, 14, 4684. https://doi.org/10.3390/cancers14194684

Academic Editors: Matthias Gaida and Philipp Mayer

Received: 13 August 2022
Accepted: 22 September 2022
Published: 26 September 2022

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Simple Summary: New onset diabetes patients are a high-risk group for pancreatic cancer. Since pancreatic cancer is responsible for less than 1% of new-onset diabetes cases, testing all of them might lead to an unfavorable risk/benefit balance. Additional risk factors can contribute to a better definition of the population that needs further screening. Currently, 22 studies examining additional risk factors have been published, but often they have a limited number of participants for the individual risk factor. By pooling their results in a meta-analysis, we could establish the magnitude of several risk factors. We found that pancreatic cancer cases were older than controls by 6.14 years (CI 3.64–8.65, 11 studies). Among new-onset diabetes patients, the highest risk of pancreatic cancer involved a family history of pancreatic cancer (3.78, CI 2.03–7.05, 4 studies), pancreatitis (5.66, CI 2.75–11.66, 9 studies), gallstones (2.5, CI 1.4–4.45, 4 studies), weight loss (2.49, CI 1.47–4.22, 4 studies), and high/rapidly increasing glycemia (2.33, CI 1.85–2.95, 4 studies) leading to more insulin use (4.91, CI 1.62–14.86, 5 studies). Risk factors or symptoms were distinct in the new-onset diabetes patient group. They are strongly connected to pancreatic cancer and are ideal for targeted screening, using a score or model as the first step.

Abstract: (1) Background: Patients with new-onset diabetes (NOD) are at risk of pancreatic ductal adenocarcinoma (PDAC), but the most relevant additional risk factors and clinical characteristics are not well established. (2) Objectives: To compare the risk for PDAC in NOD patients to persons without diabetes. Identify risk factors of PDAC among NOD patients. (3) Methods: Medline, Embase, and Google Scholar were last searched in June 2022 for observational studies on NOD patients and assessing risk factors for developing PDAC. Data were extracted, and Meta-Analysis was performed. Pooled effect sizes with 95% confidence intervals (CI) were estimated with DerSimonian & Laird random effects models. (4) Findings: Twenty-two studies were included, and 576,210 patients with NOD contributed to the analysis, of which 3560 had PDAC. PDAC cases were older than controls by 6.14 years (CI 3.64–8.65, 11 studies). The highest risk of PDAC involved a family history of PDAC (3.78, CI 2.03–7.05, 4 studies), pancreatitis (5.66, CI 2.75–11.66, 9 studies), cholecystitis (2.5, CI 1.4–4.45, 4 studies), weight loss (2.49, CI 1.47–4.22, 4 studies), and high/rapidly increasing glycemia (2.33, CI 1.85–2.95, 4 studies) leading to more insulin use (4.91, CI 1.62–14.86, 5 studies). Smoking (ES 1.20, CI 1.03–1.41, 9 studies) and alcohol (ES 1.23, CI 1.09–1.38, 9 studies) have a smaller effect. (5) Conclusion: Important risk factors for PDAC among NOD patients are age, family history, and gallstones/pancreatitis. Symptoms are weight loss and rapid increase in glycemia. The identified risk factors could be used to develop a diagnostic model to screen NOD patients.
Keywords: pancreatic cancer; new onset diabetes; cancer screening; risk factors; meta-analysis

1. Introduction

The incidence of pancreatic ductal adenocarcinoma (PDAC) doubled over the last 2 decades [1]. The cumulative lifetime risk is 0.91% [2]. Diagnosis of PDAC comes too late for curative treatment in 80% of cases. This contributes to PDAC being one of the deadliest cancers worldwide, accounting for 4.7% of all cancer-related deaths [3]. Among diagnosed patients, the 5-year survival rate does not exceed 10% [4]. In countries that have screening programs for breast and colorectal cancers, PDAC has become the second most frequent cause of cancer mortality [5].

It has been established that all cancers discovered in the first years after diabetes diagnosis were already present and caused the diabetes, and several underlying mechanisms are under research [6–12]. Diabetes or prediabetes is often the first symptom of PDAC: diabetes diagnosis happens up to 3 years before the cancer diagnosis [13]. Among pancreatic cancer patients, about 80% have a diagnosis of either hyperglycemia or diabetes. Blood glucose levels slowly increase as early as 10 years before PDAC diagnosis, in the prediabetes range [14]. This has led to the idea that NOD or even prediabetes could be a potential clue to the early diagnosis of pancreatic cancer [15].

As pancreatic cancer is responsible for less than 1% of NOD cases, using a biomarker test for every patient with NOD might lead to an unfavorable risk/benefit balance if the performance of the test is not exceptional [16] (Figure 1).

To further stratify the group that would need biomarker and then imaging testing, the use of a simple model or score is interesting. This strategy of 3 sieves would be more cost-effective and cause less harm than a strategy leaning on biomarkers and imaging alone.

Currently, 22 studies examining additional risk factors have been published, but often they have a limited number of participants for the individual risk factor. Pooling their results in a meta-analysis should increase the precision.

Based on a systematic review with meta-analysis, this paper aims to assess PDAC risk in NOD individuals and to identify risk factors among NOD patients, which are needed for a stepwise diagnostic strategy.
2. Materials and Methods

We performed a systematic literature search and last updated it in June 2022 in the three major databases, PubMed (RRID:SCR_004846), Embase (RRID:SCR_001650), and Google Scholar (RRID:SCR_008878), using the terms described in Appendix A. We did not apply any search restrictions. The study is registered in the inplasy study registry (INPLASY202220065).

We included observational studies (both cohorts and case-control studies) reporting on NOD patients and assessing additional factors regarding the risk of developing PDAC. Our objectives were to identify these risk factors that further enrich the NOD population in PDAC occurrence. Also, we aimed to analyze the risk of PDAC in NOD patients compared to non-diabetic persons.

We excluded studies with the sole focus on biomarkers or medication. We did not include case reports, small case series, reviews, opinions, or articles without an English abstract. When we found interesting conference abstracts, we searched with the author’s names for follow-up publications, and, if relevant, included those. As the data was presented in a very heterogenous way, we sometimes contacted the authors for additional data to be included in their study. However, not all authors answered (Appendix A, Table A1 of studies excluded at the full-text screening).

Two team members voted blindly during each step of the paper selection and quality assessment and made consensus decisions, resolving conflicts by discussion.

We extracted the following data from eligible studies: the name of the first author, journal and publication year, country and period, sample size, study type, patient characteristics, NOD definition, risk of PDAC in the NOD population, and additional risk factors (Figure 2).

![PRISMA flow diagram of the literature search and study selection process.](image)

**Figure 2.** PRISMA flow diagram of the literature search and study selection process.

Data Analysis

For identifying studies and excluding duplicates, we used Covidence software (Veritas Health Innovation, Melbourne, Australia; RRID:SCR_016484), following the updated PRISMA 2020 guideline [17].

Studies reporting associations were used in the meta-analysis. Using the method of DerSimonian & Laird (an estimate of heterogeneity after the Mantel-Haentzel model), we performed a random-effects meta-analysis of risk factors that were reported in at least
3 papers either with a Risk Ratio or an Odds Ratio or with raw numbers that allowed us to calculate the Odds Ratio. All Confidence Intervals (CI) are 95%. All analyses were performed with STATA, version 16.1 (StataCorp, College Station, TX, USA).

First, the authors (C.M. & V.D.B.) performed a quality assessment using 10 criteria as defined in the paper by Hoy et al. in a specific bias assessment tool for prevalence studies [18]. We judged overall bias for selected papers, following the corresponding bias flags among the 10 criteria. As the overall number of studies per risk factor was small, we did not exclude any study. To determine the risk of publication bias, we used a funnel plot and the Egger test (Appendix A, Figure A2).

We extracted data on the definition of NOD/subgroups of duration, age, sex, ethnicity, lifelong smoking, alcohol abuse, family history of PDAC, gall stones/cholecystitis, pancreatitis, a rapid increase of glycemia, weight loss, insulin use, obesity, and hyperlipidemia. When more than 2 groups were reported, we combined groups, for example, former smokers + current smokers = lifelong smokers. Or introduced the most meaningful cut-off; for example, for groups of BMI (Body Mass Index) reported, we distinguished BMI < 30 = not obese, BMI ≥ 30 obese (Details in Appendix A).

We also extracted the percentage of NOD patients that developed PDAC (in the cohort studies) and the OR for PDAC for NOD versus no diabetes in the case-control studies.

### 3. Results

#### 3.1. Studies

The search yielded 779 references, which we imported into Covidence. After removing duplicates and excluding irrelevant studies, we selected 15 studies for data extraction. Reference lists and citation searches (for studies that cited those we had already included) provided an additional 6 studies to be included in the analysis. There was one paper from other sources. Twenty-two studies were included. In total, 576,210 patients with NOD contributed to the analysis, of which 3560 had PDAC (Figure 2).

The study designs were heterogeneous, including retrospective cohorts (some with prospective analysis) (n = 13), case-control studies (n = 8), and one small prospectively recruited screening study, with recruitment at a diabetes clinic [19] (Table 1).

### Table 1. Studies, designs, and populations (References in brackets).

| Author, Journal, Year | City or Region, Country, Database Name (When Available), Period (Years) | Study Design, Study Population, Sampling Method | Patient Characteristics in NOD (Mean Age, Obesity, Smoking) | NOD Definition |
|-----------------------|------------------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------|---------------|
| Gupta et al., Clin Gastroenterol Hepatol, 2006 [20] | USA, VA National Patient Care database 1998–2004 | Retrospective cohort, veterans, all without previous diagnosis of PDAC or DM were included, 36,631 developed NOD, of which 149 had PDAC | US veterans > 40 years, in NOD cohort 97% male, average age 64 years | 1 year |
| Boursi et al., Gastroenterology, 2017 [21] | UK, THIN database 1995–2013 | Retrospective cohort, all patients with incident DM were included: 109,385 patients with NOD, of which 390 had PDAC | All < 35 years were excluded <3 years | <3 years |
| Lee et al., Journal of Clinical Gastroenterology 2012 [22] | Seoul, Korea, 2003–2009 | Retrospective case-control Cases: 151 NOD with PDAC, Controls: 302 NOD, no cancer 1:2 matched, randomly selected | Mean age 61 years (cases) and 56 years (controls) 58% male in cases, 66% in controls | <2 years |
| Ben et al., European Journal of Cancer 2011 [23] | Shanghai, China, Hospital Data 2000–2009 | Retrospective case-control Cases: 1458 PDAC, of which 307 NOD Controls: 1:1 matched for time of admission, age, sex, sociodemographic variables, 1528 of which 88 NOD | Mean age 62 years 67% male | <2 years |
| Liao et al., Journal of Gastroenterology and Hepatology 2012 [24] | Taiwan, National Health Insurance 1998–2007 | Retrospective cohort, entire population, nested case-control: Cases: all DM, of which 6911 had NOD, and 19 PDAC Controls: No DM, 1:4 matched for age and sex, randomly selected | Mean age of 55.9 years 54% male, Obesity 2.43% | <2 years |
| Author, Journal, Year | City or Region, Country, Database Name (When Available), Period (Years) | Study Design, Study Population, Sampling Method | Patient Characteristics in NOD (Mean Age, Obesity, Smoking) | NOD Definition |
|----------------------|-------------------------------------------------------------------------|-------------------------------------------------|--------------------------------------------------------|---------------|
| Tseng et al., Pancreas 2013 [25] | Taiwan, National Health Insurance 2005–2006 | Retrospective cohort, general population, random sample including 29,236 NOD and of those 32 PDAC | 48.5% male Groups 1, 3 or >3 years | **Tseng et al., Pancreas 2013 [25]**
| Lipworth et al., Diabetes/Metabolism Research and Reviews 2011 [26] | Milan, Italy 1983–1992; 1991–2008 | Combined data from two prospective case-control studies, hospital population, convenience sample, including 51 PDAC/NOD cases and 39 NOD controls | Median age 55 years (controls), 63 years (cases) 63% resp. 53% male Subgroup | **Lipworth et al., Diabetes/Metabolism Research and Reviews 2011 [26]**
| Lu et al., British Journal of Cancer 2015 [27] | UK, THIN Database 1996–2010 | Two retrospective cohorts from the general population | Mean age ~70 years (age groups) 58% male, 35% obesity, 23% current smokers Groups 1, 2, 5, and >5 years | **Lu et al., British Journal of Cancer 2015 [27]**
| Müller et al., Pancreatology 2019 [28] | Great Britain, Clinical Practice Research Datalink (CPRD) 2004–2013 | Combined data from 15 case-control studies Cases: PDAC Controls: hospital/hospital visitors/populationNOD subgroup; including 525 NOD/PDAC cases | Mean age 62.2 years, all < 40 years excluded by design 94% male, 74% white 46.8% obesity, 57% smoking Groups 1, 2, 3, 4 years | **Müller et al., Pancreatology 2019 [28]**
| Munigala et al., Clinical and Translational Gastroenterology 2015 [29] | St Louis, USA, Veterans’ Health Administration national medical care data sets 1996–2007 USA | Two retrospective cohorts, female nurses and male physicians, without previous diagnosis of PDAC or DM. Within the patients with NOD, 67 PDAC cases were observed. Combined data from 15 case-control studies | Mean age 69 years White 93.3%, Black 3.5% Obesity 43% Ever-smokers 56% | **Munigala et al., Clinical and Translational Gastroenterology 2015 [29]**
| Yuan et al., JAMA Oncology, 2020 [30] | Nurses’ Health Study (NHS), baseline 1978, Health Professionals Follow-Up Study (HPFS), baseline 1988 | Combined data from 15 case-control studies | Mean age < 4 years | **Yuan et al., JAMA Oncology, 2020 [30]**
| Bosetti et al., Annals of Oncology 2014 [31] | International, USA, Canada, Greece, Central Europe, Italy, Australia, 1983–2012 | Combined data from 15 case-control studies | Not published for NOD subgroup Groups < 1 years, 1–2, 2–5, >5 | **Bosetti et al., Annals of Oncology 2014 [31]**
| Illés et al., Pancreatology, 2016 [19] | Szeged, Hungary 2012–2014 | Prospectively recruited, 108 patients with NOD, of which 3 had PDAC | Mean age 58 years 42.6% male, mean BMI 30.5, 29% ever smoker <3 years | **Illés et al., Pancreatology, 2016 [19]**
| Chari et al., Gastroenterology 2005 [32] | Rochester, USA 1950–1994 | Combined data from 15 case-control studies | Mean age 66 years White 93.3%, Black 3.5% Obesity 43% Ever-smokers 56% | **Chari et al., Gastroenterology 2005 [32]**
| Hart et al., Pancreas 2011 [33] | Rochester, USA 1981–2007 | Combined data from 15 case-control studies | Mean age 76 years cases, 72 years controls, 37% male cases, 56% controls <3 years | **Hart et al., Pancreas 2011 [33]**
| Huang et al., Clinical Gastroenterology and Hepatology, 2020 [34] | Kaiser Permanente Southern California, USA (KPSC, Insurance) 2006–2016 | Combined data from 15 case-control studies | Mean age 66 years White 93.3%, Black 3.5% Obesity 43% Ever-smokers 56% | **Huang et al., Clinical Gastroenterology and Hepatology, 2020 [34]**
| Sharma et al., Gastroenterology 2018 [35] | Rochester, USA, Rochester Epidemiology Project (REP) 2000–2015 | Combined data from 15 case-control studies, with 64 PDAC/NOD and 192 NOD Controls in the discovery set, and a cohort of 1096 NOD, including 9 PDAC in the validation set | All < 50 years were excluded Mean age 65.6 years, 50% male | **Sharma et al., Gastroenterology 2018 [35]**
### Table 1. Cont.

| Author, Journal, Year | City or Region, Country, Database Name (When Available), Period (Years) | Study Design, Study Population, Sampling Method | Patient Characteristics in NOD (Mean Age, Obesity, Smoking) | NOD Definition |
|-----------------------|------------------------------------------------------------------------|-------------------------------------------------|---------------------------------------------------------------|----------------|
| Chen et al., Digestive Diseases and Sciences 2021 [36] | Kaiser Permanente Southern California, USA (KPSC, Insurance) 2010–2014 | Retrospective cohort of all patients without previous diagnosis of PDAC, meeting NOD criteria during the enrollment period, 13,947 NOD including 99 PDAC | All < 50 years were excluded No PDAC: 64.1 years, 48% male, 91 kg, PDAC: 69.2 years, 57% male, 84.4 kg | <3 years |
| Molina-Montes et al., Gut, 2021 [37] | PanGenEU, Europe, 28 centers from Spain, Italy, UK, Ireland, Germany, Sweden 2007–2014 | Retrospective case-control, we used only data from the subgroup with NOD, with general population as control. Data on long-standing diabetes was ignored. It included 200 cases of PDAC/NOD. | 63.4% male, mean age ~65 years (age groups), 30.5% obese | <2 years |
| Khan, Pancreatology, 2021 [38] | TrinetX—Validation of ENDPAC | Retrospective cohort of 15,539 NOD patients, of which 48 had PDAC | <50 years excluded by design PDAC 68 years, 54% male, 81% white, 39% smokers No PDAC, 67 years, 50% male, 76% white, 21% smokers | <3 years |
| Khan, Pancreas, 2021 [39] | TrinetX—validation of Boursi | Retrospective cohort of 27,863 NOD patients, of which 52 had PDAC | <35 years excluded by design PDAC 74 years, No PDAC 64 years | <3 years |
| Ullah, BMC Cancer, 2021 [40] | EL-PaC-Epidem London, UK 2008–2020 | Case-Control study, 965 PDAC, 3963 Non-malignant pancreatic disease, 4355 Controls | Mean age 55.1, 51% male, 54.4% white | Groups 1,2,3 years |

### 3.2. Risk Factors for PDAC in NOD Patients

The strongest demographic risk factor was older age. The overall mean age difference in the studies was more than 6 years (pooled age mean difference 6.14 years, $I^2 = 96\%$, 11 studies), which seemed to be even more pronounced in European studies. Sex was not a statistically significant risk factor: the overall effect size (ES, either from odds ratio or incidence rate ratio) in overall studies was 1.07 for the male gender ($CI\ 0.96–1.18$, $I^2 = 28.6\%$, 18 studies). Race was analyzed in only a few studies, which showed that whites had a slightly higher risk for PDAC ($CI\ 1.25–1.71$, $I^2 = 0.0\%$, 5 studies) (Figure 3).

Concerning other risk factors, smoking was a just barely statistically significant risk factor ($ES\ 1.20$, $CI\ 1.03–1.41$, $I^2 = 44.0\%$, 9 studies); the same was true for alcohol ($ES\ 1.23$, $CI\ 1.09–1.38$, $I^2 = 5.9\%$, 9 studies). Pancreatitis ($ES\ 5.66$, $CI\ 2.75–11.66$, $I^2 = 85.5\%$, 9 studies) and gall stones/cholecystitis ($ES\ 2.5$, $CI\ 1.4–4.45$, $I^2 = 87.0\%$, 4 studies) showed an increased risk. Positive family history of pancreatic cancer was a very strong risk factor, with an effect size of 3.78 ($CI\ 2.03–7.05$, $I^2 = 68.6\%$, 4 studies). Obesity (defined as BMI $\geq 30$) was not associated with more pancreatic cancer cases within the studied populations of NOD ($ES\ 0.67$, $CI\ 0.45–1$, $I^2 = 84.3\%$, 5 studies).

Weight loss was a significant symptom, with an effect size of 4 ($CI\ 3.1–4.9$, $I^2 = 89.3\%$, 4 studies). A rapid increase in glycaemia was significant in 7 studies [22,27,28,35,36,41,42], but it was reported with such heterogeneity that a meta-analysis was impossible for all studies ($ES\ 2.33$, $CI\ 1.85–2.95$, $I^2 = 6.7\%$, 4 studies). The rapid increase in glycaemia could lead to more insulin use ($ES\ 4.91\ CI\ 1.62–14.86\ I^2 = 91.9\%$, 5 studies) in pancreatic cancer patients. A few studies showed a negative association with high blood lipids [19,25,26,38,42] (Figure 4).
Concerning other risk factors, smoking was just barely statistically significant (ES 1.20, CI 1.03–1.41, I² = 44.0%, 9 studies); the same was true for alcohol (ES 1.23, CI 1.06–1.41, I² = 58.3%, 5 studies).

**Sex**

| Name     | ES (95% CI) | Weight |
|----------|-------------|--------|
| Gupta    | 1.10 (0.41, 2.97) | 1.05   |
| Liao     | 1.06 (0.63, 1.80)  | 3.37   |
| Tseng    | 1.06 (0.72, 1.57)  | 5.56   |
| Müller   | 1.01 (0.85, 1.20)  | 14.61  |
| Yuan     | 0.99 (0.77, 1.29)  | 3.13   |
| Ilies    | 0.67 (0.08, 7.58)  | 0.18   |
| Chari    | 2.01 (0.75, 5.38)  | 1.08   |
| Huang    | 0.95 (0.76, 1.19)  | 11.29  |
| Sharma   | 0.83 (0.47, 1.46)  | 2.95   |
| Chen     | 1.45 (0.97, 2.16)  | 5.33   |
| Bourai   | 1.00 (0.82, 1.22)  | 12.76  |
| KhanV    | 1.18 (0.67, 2.06)  | 2.94   |
| Subtotal (I-squared = 0.0%, p = 0.858) | 1.03 (0.93, 1.13) | 64.26 |

**Case-control**

| Name     | WMD (95% CI) | Weight |
|----------|--------------|--------|
| Lea      | 0.69 (0.46, 1.04) | 5.28  |
| Ben      | 1.04 (0.89, 1.21) | 15.81 |
| Bosetti  | 1.44 (0.99, 2.09) | 5.94  |
| Hart     | 0.48 (0.18, 1.27) | 1.12  |
| Molina   | 2.89 (1.27, 6.57) | 1.21  |
| Ullah    | 1.38 (0.96, 2.00) | 6.08  |
| Subtotal (I-squared = 70.3%, p = 0.004) | 1.13 (0.83, 1.53) | 35.74 |
| Overall (I-squared = 28.6%, p = 0.125) | 1.07 (0.96, 1.18) | 100.00 |

**Note:** Weights are from random effects analysis.

**Age**

| Name     | WMD (95% CI) | Weight |
|----------|--------------|--------|
| North America |              |        |
| Gupta    | 2.70 (1.01, 4.39) | 10.04 |
| Chari    | 6.30 (2.53, 10.07) | 8.50 |
| Hart     | 4.70 (0.89, 8.51)  | 8.46 |
| Sharma   | 6.80 (4.11, 9.49)  | 9.39 |
| Chen     | 5.10 (3.44, 6.76)  | 10.06 |
| Subtotal (I-squared = 53.2%, p = 0.073) | 4.85 (3.24, 6.47) | 46.46 |
| Asia     |              |        |
| Lee      | 5.50 (3.50, 7.50)  | 9.87  |
| Ben      | 0.70 (0.04, 1.36)  | 10.45 |
| Subtotal (I-squared = 95.0%, p = 0.000) | 3.00 (-1.70, 7.70) | 20.32 |
| Europe   |              |        |
| Ilies    | 12.00 (3.80, 20.20) | 4.95 |
| Bourai   | 8.00 (7.24, 8.76)  | 10.43 |
| Ullah    | 9.56 (7.19, 11.93) | 9.82 |
| Subtotal (I-squared = 14.9%, p = 0.308) | 8.37 (7.25, 9.48) | 24.99 |
| International |          |        |
| KhanN    | 10.00 (5.92, 14.08) | 8.23 |
| Subtotal (I-squared = .%, p = .) | 10.00 (5.92, 14.08) | 8.23 |
| Overall (I-squared = 96.0%, p = 0.000) | 6.14 (3.64, 8.65) | 100.00 |

**Note:** Weights are from random effects analysis.

**White Race**

| Name     | ES (95% CI) | Weight |
|----------|-------------|--------|
| Gupta    | 1.19 (0.86, 1.66) | 23.05 |
| Bosetti  | 1.40 (0.79, 2.49)  | 7.45  |
| Huang    | 1.49 (1.19, 1.87)  | 49.13 |
| Chen     | 1.95 (1.31, 2.99)  | 15.70 |
| KhanV    | 1.37 (0.66, 2.93)  | 4.67  |
| Overall (I-squared = 0.0%, p = 0.467) | 1.46 (1.25, 1.71) | 100.00 |

**Note:** Weights are from random effects analysis.

Figure 3. Meta-analysis of demographic risk factors.
3.3. Association between NOD and PDAC

All studies identified a strong association between NOD and PDAC. The overall effect size was 3.35 (CI 2.75–4.09, I² = 83.3%), with a clear tendency of the ES to be higher when the interval since NOD diagnosis was shorter: in the first year after diabetes diagnosis, it was 5.52 (CI 3.61–8.46, I² = 85.6%).

3.4. Proportion of NOD Caused by PDAC

As we assumed that all PDAC was present before the diabetes diagnosis and the cause of NOD, we calculated the cumulative percentage of observed PDAC diagnosis. It ranged from 0.13% in the Taiwanese registry study by Tseng et al. [25] to 2.7% in the prospectively recruited screening study by Illés et al. [19]. Studies excluding people under 50 found 0.74% (CI 0.63–0.85%) of PDAC cases among NOD patients. The overall cumulative percentage of PDAC in NOD patients was 0.36% (CI 0.3–0.42, I² = 86.3%, 14 studies) (Figure 5).
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![Figure 5. Meta analysis of OR of PDAC in NOD as opposed to no diabetes in patients grouped by the allowed duration of NOD as defined in the study or by the corresponding subgroup. The proportion of NOD with pancreatic adenocarcinoma as a probable reason for diabetes in the cohort studies in subgroups of applied age restriction. When only NOD older than 50 were included, it was highest.](image)

4. Discussion

Limitations and Strengths of the Study

Despite our systematic approach, we could have overlooked critical studies through our choice of search terms. We minimized this by using several formulations and searching references regarding the included papers. The most significant limitations of our findings are biases in the included studies and the disparity of representation of geographical regions. Many studies are from the USA, Europe, and Asia, and one is from Australia, but we could not identify any South American or African studies.

In extracting the data, we were limited by the heterogeneity of the included studies. To have enough data to analyze, we included studies with slightly different definitions. Definitions of how we extracted the data are in Appendix A. The results of our meta-analyses still show considerable heterogeneity, partially explained by the difference in inclusion criteria (for example, age), ethnicity, and definition of new-onset diabetes, all of
which we also examined as risk factors or subgroups. Some risk factors might also interact with each other.

A strength of our review is that it gives a complete, systematic overview of the current body of evidence regarding additional risk factors for PDAC in NOD populations. Our paper is, to our knowledge, also the first to conduct a meta-analysis on the risk factors.

5. Conclusions

5.1. Interpretation of Findings

The association between diabetes and PDAC has long been recognized. Several papers have shown that the risk is highest directly after diagnosis and then decreases over subsequent years [41]. The association might be confounded by commonly shared risk factors such as obesity or chronic pancreatitis. The actual frequency of pancreatic cancer in the population of NOD is still unclear, as most studies are retrospective, and the percentage in the only prospective study is much higher. Currently, four prospective studies are recruiting patients and might bring more clarity [42–45].

It is essential to look specifically at the group of NOD patients, as they differ from the general population. For instance, NOD patients tend to be more obese than the general population, as obesity is a very important risk factor for diabetes mellitus. Within the population of NOD patients, obesity is not associated with more PDAC cases, as our analysis shows. In fact, the mean BMI of pancreatic cancer cases was lower than that of NOD controls. This might be even more pronounced through tumor-induced recent weight loss. It was surprising to find at most a weak association of smoking and alcohol abuse in this meta-analysis. Possibly these risk factors are more important for non-diabetic PDAC patients, or their importance has generally been overestimated.

Risk factors or symptoms that are distinct in the NOD patient group and are strongly connected to pancreatic cancer are ideal for targeted testing. They can be used for statistical model fitting. Our analysis showed that age, family history of PDAC, pancreatitis/cholecystitis, weight loss, and rapid increase in glycemia/necessity of insulin are robust candidates. A tendency to lower lipids, unusual in newly diagnosed diabetes patients, is also interesting. Unfortunately, some of the strongest risk factors are rather rare, which negatively impacts the sensitivity of such models. The correct balance between the frequency and magnitude of those risk factors remains to be found.

5.2. Importance of the Presented Work and Future Directions for Early Diagnosis Programs

Screening programs aim to diagnose cancer in the asymptomatic, early stages amenable to curative treatment. Scrutiny regarding balancing benefits and burdens, cost, survival extension, and quality-life years gain is essential. As pancreatic cancer has a low incidence in the total population, this is a challenge. The main risk of pancreatic cancer screening is a too-high rate of false-positive results, leading to unnecessary further investigations. Including the identified additional risk factors or symptoms can help define the target population.

A stepwise approach of first identifying a group with increased risk of pancreatic cancer within the NOD population through a scoring or diagnostic model and then further reducing the number of patients needing imaging by a biomarker test has been proposed by Pannala et al. [15]. Several studies have proposed scores to identify the best group for testing [19,22,35,36]. A scoring system has advantages, as it is objective and can be validated. Nevertheless, it also has disadvantages, such as being time-consuming for the family physician or challenging to apply when data is missing. The complexity of a scoring model should consider the balance between the accuracy of prediction and the simplicity of daily use. Considering the slightly different associations of risk factors in different regions (for example, the USA, Europe, Asia), such scoring might differ depending on the location. These regional differences are related not only to the characteristics of PDAC patients but also to NOD. Diabetes is closely related to diet and obesity, which are subject to socio-cultural and genetic influences. In the USA, the average age for diabetes diagnosis is lower than it is in Europe. In Asia, patients with a much lower BMI than that in western
countries suffer from an increased risk for diabetes [46]. In conclusion, before using a score as a diagnostic model in a new population, it will need adaptation, or at least calibration and validation.

Author Contributions: C.M. and V.D.B. contributed equally to this review. Conceptualization, V.D.B. and C.M.; methodology, V.D.B. and C.M.; validation, V.D.B., C.M., A.D., and S.C.; formal analysis, V.D.B. and C.M.; investigation, V.D.B. and C.M.; resources, C.M.; data curation, C.M.; writing—original draft preparation, V.D.B. and C.M.; writing—review and editing, A.D. and S.C.; visualization, V.D.B. and C.M.; supervision, S.C.; project administration, C.M.; funding acquisition, C.M. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the HFR Research Grant-2108.

Data Availability Statement: For access to data, contact the corresponding author.

Acknowledgments: We thank the HFR Research Foundation for their financial support, and Leo Bühler for his advice and encouragement.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

Appendix A

Appendix A.1. Search Terms

Pubmed search of:
(((“carcinoma, pancreatic ductal”[MeSH Terms] OR (“pancreatic neoplasms”[MeSH Terms] OR “pancreatic”[All Fields] AND “neoplasms”[All Fields]) OR “pancreatic neoplasms”[All Fields] OR (“pancreatic”[All Fields] AND “cancer”[All Fields]) OR “pancreatic cancer”[All Fields])) AND (“probability”[MeSH Terms] OR “risk factors”[MeSH Terms] OR “diagnostic techniques and procedures”[MeSH Terms]) AND “diabetes mellitus, type 2”[MeSH Terms]) AND hasabstract[text].

Embase search of:
Pancreas carcinoma AND non-insulin-dependent diabetes mellitus AND high-risk population
OR
Pancreas carcinoma AND non-insulin-dependent diabetes mellitus AND risk assessment.

Google scholar search of:
All in the title: diabetes risk OR diagnosis “pancreatic cancer”.

After the selection of relevant articles, we also checked their references for additional possible matches with our research topic, which had been missed in the initial search, and checked for publications that cite those we previously included. Additional papers that were already known to the authors or came to their knowledge from other sources were also included.

Appendix A.2. Effect Size of PDAC in NOD Patients versus No Diabetes Patients

Each study had a different definition of NOD. Some used a definition of 1 year, others 2, 3, or 4 years after diabetes diagnosis (Table 1). Other studies had several subgroups for the duration of diabetes. This variability of definitions influenced the results considerably. For that reason, we did a subgroup analysis, either with the subgroups as published or with the definition used in the study. This has the disadvantage that a study without subgroups and using a 3-year definition will have in that group patients with diabetes onset less than a year ago—that is not reported separately so we cannot know that.

Appendix A.3. Parameters for Meta-Analysis, Remarks about the Reported Risk Factors/Symptoms

There was considerable heterogeneity between the studies and the published values. To include as many different studies as possible, we did a meta-analysis of the reported effect size. Where a crude Odds Ratio was reported, we took this. When possible, we
calculated an Odds Ratio from the published case frequency numbers. In a small number of studies, only a Relative Risk or Incidence Ratio was published, and there were no case numbers to calculate an Odds Ratio. In this case, we used the published Effect size.

**Smoking**

3 studies of the 6 with data on smoking reported 3 categories: never smokers, ex-smokers, and current smokers; the others only 2 categories, exposed or not exposed. We put all patients that were ever exposed to smoking into one group.

**Alcohol abuse**

The reporting on alcohol consumption was also heterogeneous, with 2, 3, or 4 different exposure groups. To group participants according to their alcohol status, we used the cut-off of 20 g/day of risky consumption (independent of gender) and sorted the published groups accordingly.

**Obesity**

Whenever several groups of body mass index were reported, we introduced dichotomous sorting with the limit of body mass index equal to or above 30 as the definition of “obesity”.

**Pancreatitis**

Some studies reported on “chronic pancreatitis” and others on status “post pancreatitis”, but as there were few studies, and acute pancreatitis can lead to chronic pancreatitis, we analyzed them together.

**Gall stones/Cholecystitis**

Some studies reported on Gall stones, others on Cholecystitis. We grouped those together under “Gall stones”, as Cholecystitis without Gall stones is very rare.

**Rapid increase/High Glycemia**

Here the heterogeneity was huge, as some papers reported means and differences in means, others a slope, and third a proportion. Some referred to HbA1c, others to fasting glucose. To be able to meta-analyze it at all, we used all papers that reported numbers of patients, though some reported the numbers with a rapid increase [27,28], while others reported those with high fasting glucose (>160 mg/dL) at diagnosis [35,36].

**Insulin use**

Medication was not the focus of our review, and studies that looked solely at medication were excluded, so we have not included all studies that look at the association of insulin use.

**Appendix A.4. Bias Assessment**

**External validity**

The most relevant concern was selection bias. Some studies [19,23,26] sampled selectively from hospital populations that were probably not representative of the general population. Other studies [27,29] examined military veterans, a rather specific cohort comprising predominantly males and not representative of the overall population.

The choice of controls was also prone to some bias, as in some studies [26,28], convenience samples were used. The controls in Ben et al. [23] consisted of a hospital population. Moreover, they excluded all malignant diseases and all patients with diagnoses related to alcohol, tobacco, and drugs, which introduces considerable bias in assessing risk factors.

**Internal validity**

The registry studies, which did not collect data directly from the patients, are at risk of misclassifications. Generally, the retrospective assessment of records is problematic because missed diagnoses regarding PDAC and diabetes might lead a study to underestimate the connection between those two diseases (Figure A1).
**Figure A1.** Bias assessment of publications. Risk of Bias Assessment.

**External validity**
- Was the study’s target population a close representation of the national population in relation to relevant variables?
- Was the sampling frame a true or close representation of the target population?
- Was some form of random selection used to select the sample/the control, or was a census undertaken?

**Internal validity**
- Were data collected directly from the subjects (as opposed to a proxy)?
- Was an acceptable case definition used in the study?
- Was the study instrument that measured the parameter of interest shown to have validity and reliability?
- Was the same mode of data collection used for all subjects?
- Was the length of the longest duration for the parameter of interest (NOD) appropriate?
- Were the numerator(s) and denominator(s) for the parameter of interest appropriate?

**Overall risk of bias**
For assessing the overall risk of bias, we considered patient selection as the most crucial factor, which dominated our decision.

**Appendix A.5. Publication Bias**
To test for publication bias (done only for effects reported in at least 10 studies), we calculated a funnel plot for the effect size of PDAC in the NOD population (11 studies with 26 OR (different age groups) reported this), the age difference (reported by 10 studies), and for the effect size of sex as a risk factor within the NOD subgroup (reported by 18 studies). There was no suspicion of relevant publication bias (Figure A2).
Internal validity

- Were data collected directly from the subjects (as opposed to a proxy)?
- Was an acceptable case definition used in the study?
- Was the study instrument that measured the parameter of interest shown to have validity and reliability?
- Was the same mode of data collection used for all subjects?
- Was the length of the longest duration for the parameter of interest (NOD) appropriate?
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Figure A2. Funnel plots and Eggers test.

| First Author, Year | Journal Title | Reason for Exclusion | Notes |
|--------------------|---------------|----------------------|-------|
| Ballotari, 2017    | Diabetes and risk of cancer incidence: Results from a population-based cohort study in northern Italy. | Wrong population | |
| Zhang, 2018        | Clinical features and risk factors for cancer in patients with type 2 diabetes in Qingdao, China. | Conference abstract/letter/review | |
| Arthur, 2019       | Adiposity, history of diabetes, and risk of pancreatic cancer in postmenopausal women. | Wrong population | |
| Gullo, 1999        | Diabetes and the risk of pancreatic cancer. | Wrong outcomes | No other risk factors are looked at. |
| Jamal, 2009        | Diabetes mellitus as a risk factor for gastrointestinal cancer among American veterans. | Wrong population | Not about pancreatic cancer: Conference abstract, uploaded the corresponding article. |
| Gul, 2010          | Ca 19-9 levels in type 2 diabetes mellitus patients. | Wrong outcomes | |
| Brodovicz, 2011    | Synergistic effect of type 2 diabetes (T2D) and history of pancreatitis on pancreatic cancer risk: A retrospective cohort study from the general practice research database (GPRD). | Conference abstract | Abstract, unable to find paper |
| Hense, 2011        | Cancer incidence in type 2 diabetes patients—First results from a feasibility study of the ISC cohort. | Wrong population | Could not find a sub-analysis on PDAC, only overall risk for cancer according to diabetes duration |
Table A1. Cont.

| First Author, Year | Journal | Title | Reason for Exclusion | Notes |
|--------------------|---------|-------|----------------------|-------|
| 9. Geng, 2012      | World J of Gastroenterology | ABO blood type, diabetes, and risk of gastrointestinal cancer in Northern China. | Wrong patient population | Paper that followed had wrong patient population |
| 10. Henry, 2012    | Cancer Research | History of diabetes mellitus as a risk factor for pancreatic cancer: The Iowa Women’s Health study. | Conference abstract | Letter about an article, imported it into full-text review. |
| 11. Andersen, 2012 | Diabetes/Metabolism Research and Reviews | The practical importance of recognizing pancreaticogenic or type 3c diabetes. | Conference abstract | Abstract, unable to find paper |
| 12. Honjo, 2012    | Epidemiology/Genetics | Japanese subjects with type 2 diabetes with special reference to pancreatic cancer. | Conference abstract | Abstract, unable to find paper |
| 13. Elena, 2013    | Cancer Causes and Control | Diabetes and risk of pancreatic cancer: A pooled analysis from the pancreatic cancer cohort consortium. | Wrong population |  |
| 14. Suceveanu, 2015 | Pancreatology | Independent risk factors for pancreatic adenocarcinoma (PAC) in the Romanian Black Sea coast area. | Conference abstract |  |
| 15. Mansoor, 2016  | Gastroenterology | Risk factors for pancreatic cancer in new-onset diabetes mellitus: A population-based study. | Conference abstract |  |
| 16. DeJong, 2016   | Gastroenterology | Glucagon/insulin ratio as a potential biomarker for pancreatic cancer. | Wrong population |  |
| 17. Lu, 2016       | British J of Cancer | Reply to Comment on “New-onset type 2 diabetes, elevated HbA1c, antidiabetic medications, and risk of pancreatic cancer”. | Letter | Answer to a comment over the paper |
| 18. Dugrani, 2016  | Pancreatology | Diabetes associated with pancreatic ductal adenocarcinoma is just diabetes: Results of a prospective observational study in surgical patients. | Wrong population |  |
| 19. Attner, 2012   | Cancer Causes & Control | Cancer among patients with diabetes, obesity and abnormal blood lipids: a population-based register study in Sweden. | Wrong population | The population are cancer cases, not NOD, and diabetes is the outcome. |
| 20. Mizuno, 2013   | J of Gastroenterology | Risk factors and early signs of pancreatic cancer in diabetes: screening strategy based on diabetes onset age. | Wrong patient population |  |
| 21. Zhang, 2012    | BMC Public health | Increased risk of cancer in patients with type 2 diabetes mellitus: a retrospective cohort study in China. | Wrong population |  |
| 22. Magliano, 2012 | European J of Endocrinology | Incidence and predictors of all-cause and site-specific cancer in type 2 diabetes: the Fremantle Diabetes Study. | Wrong population |  |
| 23. Lai, 2013      | The J of Clinical Endocrinology and Metabolism | The association between self-reported diabetes and cancer incidence in the NIH-AARP Diet and Health Study. | Wrong population |  |
| 24. Tseng, 2013    | Acta Diabetologica | Diabetes, insulin use, smoking, and pancreatic cancer mortality in Taiwan. | Wrong population |  |
| 25. Ahn, 2013      | The Korean J of Gastroenterology | [New-onset diabetes as an early sign of pancreatic cancer]. | Article in Korean google translate shows that it is a review. |  |
| 26. Valent, 2015   | J of Diabetes and Its Complications | Diabetes mellitus and cancer of the digestive organs: an Italian population-based cohort study. | Wrong population |  |
| 27. Kolb, 2009     | Cancer Biology & Therapy | Glucagon/insulin ratio as a potential biomarker for pancreatic cancer in patients with new-onset diabetes mellitus. | Wrong population |  |
| 28. Ogunleye, 2009 | British J of Cancer | A cohort study of the risk of cancer associated with type 2 diabetes. | Wrong population |  |
| 29. Hemminki, 2010 | The Oncologist | Risk of cancer following hospitalization for type 2 diabetes. | Wrong population | No NOD |
| 30. Ber, 2012      | Diabetes/Metabolism Research and Reviews | Clinical profiles and long-term outcomes of patients with pancreatic ductal adenocarcinoma and diabetes mellitus. | Conference abstract | Abstract, unable to find paper |
| 31. LaVecchia, 1994 | British J of Cancer | A case-control study of diabetes mellitus and cancer risk. | Wrong population | No real NOD, only < 5 y. |
| 32. Hjalgrim, 1997 | J of Internal Medicine | Cancer and diabetes—A follow-up study of two population-based cohorts of diabetic patients. | Wrong population | nothing about NOD; nothing about PC |
| 33. He, 2017       | Oncotarget | Serum metabolomics differentiating pancreatic cancer from new-onset diabetes. | Wrong outcomes | Biomarker study |
| 34. Pan, 2018      | American J of Epidemiology | Type 2 Diabetes and Risk of Incident Cancer in China: A Prospective Study among 0.5 Million Chinese Adults. | Wrong population | No PDAC group |
| 35. Dakner, 2018   | Diabetes/Metabolism Research and Reviews | Newly diagnosed type 2 diabetes may serve as a potential marker for pancreatic cancer. | Wrong population | No NOD |
| 36. de jong, 2018  | Cancer Epidemiology | Gastrointestinal cancer incidence in type 2 diabetes mellitus: results from a large population-based cohort study in the UK. | Wrong population | No NOD |
Table A1. Cont.

| First Author, Year | Journal | Title | Reason for Exclusion | Notes |
|--------------------|---------|-------|----------------------|-------|
| 37 Dong, 2018      | Digestion | Predictive Factors for Differentiating Pancreatic Cancer-Associated Diabetes Mellitus from Common Type 2 Diabetes Mellitus for the Early Detection of Pancreatic Cancer. | Wrong population | Controls have long-standing diabetes. |
| 38 Maitra, 2018    | Pancreas | A Prospective Study to Establish a New-Onset Diabetes Cohort: From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. | Conference abstract/letter/review | This is a study protocol, not a study. The study is ongoing. |
| 39 Ewald, 2012     | Diabetes/ Metabolism Research and Reviews | Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c). | Wrong population | |
| 40 Fest, 2019      | J of Internal Medicine | The Potential of Glycemic Control and Body Weight Change as Early Markers for Pancreatic Cancer in Patients with Long-standing Diabetes Mellitus: A Case-Control Study. | Wrong population | |
| 41 Müller, 2018    | Pancreas | Diabetes type II, other medical conditions and pancreatic cancer risk: A prospective study in the Netherlands. | Wrong population | |
| 42 Eijgenraam, 2013| British J of Cancer | Investigating the synergistic interaction of diabetes, tobacco smoking, alcohol consumption, and hypercholesterolemia on the risk of pancreatic cancer: A case-control study in Italy. | Wrong population | |
| 43 LaTorre, 2014   | BioMed Research International | Comparison of incidence rates of acute pancreatitis and pancreatic cancer among the general population and type 2 diabetes mellitus patients between different databases in the safeguard project. | Conference abstract | No NOD is excluded. |
| 44 Maschke, 2014   | Gastroenterology | Benefits of screening for pancreatic cancer in new-onset diabetes mellitus. | Conference abstract | Publication was by Fest, 2019. |
| 45 Illés, 2014     | Pancreatology | Hospitalization and mortality for pancreatic cancer and diabetes: A cohort from a tertiary hospital. | Conference abstract | Publication was not found. |
| 46 Freitas, 2014   | Endocrine Reviews | Diabetes and cancer risk in a population-based study with 20 years of follow-up: The Rotterdam Study. | Conference abstract | Publication was by Brodovicz. |
| 47 DeBrujin, 2014  | Diabetologia | Electronic health data as source of clinical evaluation and pancreatic cancer (PC) diagnosis (DX) in patients with type 2 diabetes (T2DM). | Conference abstract | |
| 48 Ritchey, 2014   | Pharmacoepidemiology and Drug Safety | Screening for pancreatic cancer in new-onset diabetes mellitus is beneficial? | Conference abstract | No NOD |
| 49 Czako, 2014     | Pancreas | Middle-aged men with type 2 diabetes as potential candidates for pancreatic cancer screening: A 10-year nationwide population-based cohort study. | Wrong population | |
| 50 Koo, 2019       | Acta Diabetologica | Overall obesity, abdominal adiposity, diabetes, and cigarette smoking in relation to the risk of pancreatic cancer in two Swedish population-based cohorts. | Wrong population | No NOD |
| 51 Larsson, 2005   | Nature Publishing Group | Diabetes: risk factor for developing pancreatic cancer or manifestation of the disease? | Review | Review of long-standing diabetes studies. |
| 52 Fisher, 2001    | World J of surgery | Pancreatic cancer-associated diabetes mellitus: prevalence and temporal association with diagnosis of cancer. | Wrong population | Their population is PDAC, not NOD. |
| 53 Chari, 2008     | Gastroenterology | Type 2 diabetes mellitus is associated with increased risk of pancreatic cancer: A veteran administration registry study. | Wrong population | No NOD |
| 54 Makhoul, 2016   | SAGE Open Medicine | ABO Blood Group and Diabetes Mellitus Influence the Risk for Pancreatic Cancer in a Population from China. | Wrong population | No NOD |
| 55 Li, 2018        | International Medical J of Experimental and Clinical Research | HBAlc Levels, Body Weight Change, and Risk of Pancreatic Cancer Among Patients With Long-Standing Diabetes Mellitus: A Case-Control Study. | Conference abstract | Conference abstract, study published by Müller, 2018. |
| 56 Müller, 2017    | Pharmacoepidemiology and Drug Safety | Diabetes Mellitus Is a Risk Factor for Pancreatic Cancer: A Case Control Study in Half a Million Veterans: 168. | Conference abstract | Study published by Khurana, 2007. It is about medication. |
| 57 Khurana, 2004   | American J of Gastroenterology | History of diabetes mellitus, cholecystectomy, and gallstone disease and risk of pancreatic cancer 1045 Higher Pancreatic Cancer Risk Following New Onset of Diabetes Mellitus in Non-Obese Patients with Chronic Pancreatitis. | Conference abstract | Conference abstract, Study: Henry, 2012 conference abstract, paper is Munigala, 2015. |
| 58 Prizment, 2011  | ACR | Body mass index, physical activity and the risk of pancreatic cancer in relation to smoking status and history of diabetes: A large-scale population-based cohort study in Japan—The JPHC study. | Wrong population | No NOD |
### Table A1. Cont.

| First Author, Year | Journal | Title | Reason for Exclusion | Notes |
|--------------------|---------|-------|-----------------------|-------|
| 61                 | Lo, 2013 | *International Journal of Cancer* | Modest increase in risk of specific types of cancer types in type 2 diabetes mellitus patients. | Wrong population |
| 62                 | Luo, 2013 | *Cancer Causes and Control* | Diabetes mellitus as a risk factor for gastrointestinal cancers among postmenopausal women. | Wrong population |
| 63                 | Lin, 2014 | *British Journal of Cancer* | Independent and joint effect of type 2 diabetes and gastric and hepatobiliary diseases on the risk of pancreatic cancer risk: 10-year follow-up of population-based cohort. | Wrong population |
| 64                 | Liu, 2015 | *International Journal of Cancer* | Cancer risk in patients with type 2 diabetes mellitus and their relatives. | Wrong outcomes |
| 65                 | Christensen, 2016 | *Journal of Diabetes and its Complications* | Venous thromboembolism and risk of cancer in patients with diabetes mellitus. | Wrong population |
| 66                 | Koo, 2019 | *The Incremental Risk of Pancreatic Cancer According to Fasting Glucose Levels: Nationwide Population-Based Cohort Study.* | | No NOD |
| 67                 | Fritz, 2020 | *Int J Epidemiol* | The triglyceride-glucose index as a measure of insulin resistance and risk of obesity-related cancers. | Wrong population |
| 68                 | Wlodarczyk, 2018 | *Journal of Gastroenterology* | The differential effect of diabetes status on the risk of developing pancreatic cancer. A case-control study in two centers in the UK. Diabetes mellitus, glycated hemoglobin and C-peptide levels in relation to pancreatic cancer risk. | Wrong population |
| 69                 | Carey, 2013 | *Gastroenterology* | Diabetes mellitus, glycated hemoglobin and C-peptide levels in relation to pancreatic cancer risk: A study within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. | Wrong population |
| 70                 | Grote, 2011 | *Diabetologia* | Diabetes mellitus, other medical conditions, and familial history of cancer as risk factors for pancreatic cancer. | Wrong population |
| 71                 | Silverman, 1999 | *The Role of Insulin-like Growth Factor (IGF) Axis in Diabetes mellitus as a risk factor for gastrointestinal cancer.* | | Wrong outcomes |
| 72                 | He, 2018 | *Current Medical Research and Opinion* | Retrospective database analysis of cancer risk in patients with type 2 diabetes mellitus in China. | Wrong population |
| 73                 | Brodovicz, 2012 | *Diabetes, Obesity & Metabolism* | Impact of diabetes duration and chronic pancreatitis on the association between type 2 diabetes and pancreatic cancer risk. | Wrong study design |
| 74                 | Johnson, 2011 | *Diabetologia* | Time-varying incidence of cancer after the onset of type 2 diabetes: evidence of potential detection bias. Nationwide Trends in Pancreatitis and Pancreatic Cancer Risk Among Patients with Newly Diagnosed Type 2 Diabetes Receiving Dipeptidyl Peptidase-4 Inhibitors. | Wrong outcomes |
| 75                 | Lee, 2019 | *Diabetes Care* | Cancer risk in Chinese diabetes patients: A retrospective cohort study based on management data. | Wrong population |
| 76                 | Fang, 2018 | *Endocrine Connections* | Diabetes mellitus, other medical conditions, and familial history of cancer as risk factors for pancreatic cancer. | Wrong outcomes |
| 77                 | Oberaigner, 2014 | *BMC Public Health* | Increased cancer incidence risk in type 2 diabetes mellitus: Results from a cohort study in Tyrol/Austria. | Wrong outcomes |
| 78                 | Antolino, 2020 | *European Journal of Surgical Oncology* | Is TPS3 Arg72Pro a risk factor for pancreatic cancer in diabetic patients? | Conference abstract |
| 79                 | Yuan, 2020 | *Diabetes* | Is Type 2 Diabetes Causally Associated with Cancer Risk? Evidence From a Two-Sample Mendelian Randomization Study. Diabetes duration and weight loss are associated with onset age and remote metastasis of pancreatic cancer in patients with diabetes mellitus. | Wrong population |
| 80                 | Ma, 2022 | *J of Diabetes* | Modifiable and non-modifiable risk factors for pancreatic cancer. | Wrong population |
| 81                 | Roxana, 2019 | *Journal of Gastrointestinal and Liver Diseases* | Diverse transitions in diabetes status during the clinical course of patients with resectable pancreatic cancer. | Wrong study design |
| 82                 | Shinyoji, 2020 | *Japanese Journal of Clinical Oncology* | Less aggressive treatment and worse overall survival in cancer patients with diabetes: a large population-based analysis. | Wrong population |
| 83                 | Van de Pall-Franse, 2007 | *International Journal of Cancer* | Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. | Wrong population |
| 84                 | Everhart, 1995 | *JAMA* | Prevalence and clinical profile of pancreatic cancer-associated diabetes mellitus. | Wrong population |
| 85                 | Huxley, 2005 | *British Journal of Cancer* | Diabetes mellitus and pancreatic cancer in a population-based case-control study in the San Francisco Bay Area, California. | Wrong outcome |
| 86                 | Pannala, 2008 | *Gastroenterology* | Diabetes mellitus and pancreatic cancer: Case-control study. Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus, and choleslithiasis as risk factors for pancreatic carcinoma. Screening for pancreatic neoplasia in high-risk individuals: The Johns Hopkins Experience. | No risk factors on top of NOD |
| 87                 | Wang, 2006 | *Cancer Epidemiology, Biomarkers and Prevention* | Diabetes mellitus and pancreatic cancer in a population-based case-control study in the San Francisco Bay Area, California. | Wrong outcome |
| 88                 | Hassan, 2007 | *American Journal of Gastroenterology* | Risk factors for pancreatic cancer: Case-control study. Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus, and choleslithiasis as risk factors for pancreatic carcinoma. | Wrong population |
| 89                 | Kalapothaki, 1993 | *Cancer Causes Control* | Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus, and choleslithiasis as risk factors for pancreatic carcinoma. Screening for pancreatic neoplasia in high-risk individuals: The Johns Hopkins Experience. | No risk factors on top of NOD |
| 90                 | Canto, 2002 | *Gastroenterology* | Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus, and choleslithiasis as risk factors for pancreatic carcinoma. Screening for pancreatic neoplasia in high-risk individuals: The Johns Hopkins Experience. | No full text |
Table A1. Cont.

| First Author, Year | Journal | Title | Reason for Exclusion | Notes |
|--------------------|---------|-------|-----------------------|-------|
| 91 Chow, 1995       | J of National Cancer Institute | Risk of pancreatic cancer following diabetes mellitus: a nationwide cohort study in Sweden. | Wrong population | NOD excluded |
| 92 Gullo, 1994      | NEJM    | Diabetes and the risk of pancreatic cancer. Italian Pancreatic Cancer Study Group. | Wrong population | NOD excluded |
| 93 Bonelli, 2003    | Pancreas | Exocrine pancreatic cancer, cigarette smoking, and diabetes mellitus: A case-control study in northern Italy. | Wrong outcome | No risk factors on top of NOD |
| 94 Kim, 2014        | Mol. Cancer | Serum CA 19-9 as a screening test for pancreatic cancer in new-onset diabetic patients. | No full text | Probably conference abstract |
| 95 Cui, 2012        | Endocrine-Related Cancer | Diabetes and pancreatic cancer. | Wrong population | NOD excluded |
| 96 Atchinson, 2011  | International J of Cancer UK | Risk of cancer in a large cohort of U.S. veterans with diabetes. | Wrong population | No NOD |
| 97 Norell, 1996     | British J of Cancer | Diabetes, gallstone disease, and pancreatic cancer. | Wrong population | No NOD |
| 98 Olson, 2016      | Pancreas | Diabetes, fatigue, and depression preceding pancreatic cancer. | Wrong outcomes | No risk factors on top of NOD |
| 99 Stapley, 2012    | British J of Cancer | The risk of pancreatic cancer in symptomatic patients in primary care: a large case-control study using electronic records. | Wrong population | No NOD |
| 100 Maier, 2018     | Pancreas | The potential of glycemic control and body weight change as early markers for pancreatic cancer in patients with long-standing diabetes mellitus: A case-control study. | Wrong population | NOD excluded |
| 101 Aggarwal, 2012  | Pancreatology | New-onset diabetes in pancreatic cancer: a study in the primary care setting. | Wrong population | Seemed to be the same study as Chari 2013 |
| 102 Chen, 2011      | Diabetes Care | Risk of malignant neoplasm of the pancreas in relation to diabetes: A population-based study in Taiwan. | Wrong population | No NOD |
| 103 Rousseau, 2006  | International J of Cancer | Diabetes mellitus and cancer risk in a population-based case-control study among men from Montreal, Canada. | Wrong population | No NOD |
| 104 Bao, 2011       | Biochim Biophys Acta | The complexities of obesity, diabetes, and the development and progression of pancreatic cancer. | Wrong population | No NOD |
| 105 Wu, 2020        | JAMA    | Association of Glycated Hemoglobin Levels with Risk of Pancreatic Cancer. | Basic research | NOD excluded |
| 106 Setiawan, 2019  | National Cancer Institute | Pancreatic Cancer Following Incident Diabetes in African Americans and Latinos: The Multiethnic Cohort. | Wrong outcome | We tried to include it twice but found no data we could analyze, and authors did not respond |
| 107 Keum, 2018      | Cancer Causes Control | Long-term patterns of fasting blood glucose levels and pancreatic cancer incidence. | Wrong outcomes | No risk factors on top of NOD |

Explanation: “Wrong population” usually means that the study population are not NOD patients (most of the time, all diabetes patients instead), and no subgroup with NOD patients are examined for additional risk factors. “Wrong outcomes” usually means that no further risk factors are examined within the group of NOD.

References
1. Hu, J.-X.; Zhao, C.-F.; Chen, W.-B.; Liu, Q.-C.; Li, Q.-W.; Lin, Y.-Y.; Gao, F. Pancreatic Cancer: A Review of Epidemiology, Trend, and Risk Factors. World J. Gastroenterol. 2021, 27, 4298–4321. [CrossRef] [PubMed]
2. Dyba, T.; Randi, G.; Bray, F.; Martos, C.; Giusti, F.; Nicholson, N.; Gavin, A.; Flego, M.; Neamtiu, L.; Dimitrova, N.; et al. The European Cancer Burden in 2020: Incidence and Mortality Estimates for 40 Countries and 25 Major Cancers. Eur. J. Cancer 2021, 157, 308–347. [CrossRef] [PubMed]
3. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J. Clin. 2021, 71, 209–249. [CrossRef]
4. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer Statistics, 2021. CA Cancer J. Clin. 2021, 71, 7–33. [CrossRef] [PubMed]
5. World Health Organisation Cancer Fact Sheet Switzerland. Available online: https://gco.iarc.fr/today/data/factsheets/populations/756-switzerland-fact-sheets.pdf (accessed on 3 March 2022).
6. Jeong, H.R.; An, S.S.A. Causative Factors for Formation of Toxic Islet Amyloid Polypeptide Oligomer in Type 2 Diabetes Mellitus. Clin. Interv. Aging 2015, 10, 1873–1879. [CrossRef] [PubMed]
7. Wang, F.; Herrington, M.; Larsson, J.; Permert, J. The Relationship between Diabetes and Pancreatic Cancer. Mol. Cancer 2003, 2, 4. [CrossRef]
8. Permert, J.; Larsson, J.; Westermark, G.T.; Herrington, M.K.; Christmanson, L.; Pour, P.M.; Westermark, P.; Adrian, T.E. Islet Amyloid Polypeptide in Patients with Pancreatic Cancer and Diabetes. N. Engl. J. Med. 1994, 330, 313–318. [CrossRef]
9. Ding, X.; Flatt, P.R.; Permert, J.; Adrian, T.E. Pancreatic Cancer Cells Selectively Stimulate Islet β Cells to Secrete Amylin. Gastroenterology 1998, 114, 130–138. [CrossRef]
Cancers 2022, 14, 4684

10. Javeed, N.; Sagar, G.; Dutta, S.K.; Smyrk, T.C.; Lau, J.S.; Bhattacharya, S.; Truty, M.; Petersen, G.M.; Kaufman, R.J.; Chari, S.T.; et al. Pancreatic Cancer-Derived Exosomes Cause Paraneoplastic β-Cell Dysfunction. *Clin. Cancer Res.* 2015, 21, 1722. [CrossRef]

11. Aggarwal, G.; Ramachandran, V.; Javeed, N.; Arumugam, T.; Dutta, S.; Klee, G.G.; Klee, E.W.; Smyrk, T.C.; Bamlet, W.; Han, J.J.; et al. Adrenomedullin Is Up-Regulated in Patients with Pancreatic Cancer and Causes Insulin Resistance in β Cells and Mice. *Gastroenterology* 2012, 143, 1510–1517.e1. [CrossRef]

12. Syrigos, K.N.; Konstantoulakis, M.M.; Fyssas, I.; Katsilambros, N.; Golematis, B.C. Autoantibodies against Insulin and β-Islet Cells in Pancreatic Adenocarcinoma: A Possible Explanation for Diabetes Mellitus. *Int. J. Cancer* 1996, 66, 624–626. [CrossRef]

13. Chari, S.T.; Leibson, C.L.; Rabe, K.G.; Timmons, L.J.; Ransom, J.; de Andrade, M.; Petersen, G.M. Pancreatic Cancer–Associated Diabetes Mellitus: Prevalence and Temporal Association with Diagnosis of Cancer. *Gastroenterology* 2008, 134, 95–101. [PubMed]

14. Pannala, R.; Leibson, C.L.; Rabe, K.G.; Timmons, L.J.; Ransom, J.; de Andrade, M.; Petersen, G.M.; Chari, S.T. Temporal Association of Changes in Fasting Blood Glucose and Body Mass Index with Diagnosis of Pancreatic Cancer. *Am. J. Gastroenterol.* 2009, 104, 2318–2325. [CrossRef] [PubMed]

15. Pannala, R.; Basu, A.; Petersen, G.M.; Chari, S.T. New-Onset Diabetes: A Potential Clue to the Early Diagnosis of Pancreatic Cancer. *Lancet Oncol.* 2009, 10, 88–95. [CrossRef] [PubMed]

16. Zwahlen Nicola and Egger Matthias, M.L. Population-Based Screening—The Difficulty of How to Do More Good than Harm and How to Achieve It. *Swiss. Med. Wkly.* 2010, 140, w13061. [CrossRef]

17. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *Syst. Rev.* 2021, 10, 89. [CrossRef]

18. Hoy, D.; Brooks, P.; Woolf, A.; Blyth, F.; March, L.; Bain, C.; Baker, P.; Smith, E.; Buchbinder, R. Assessing Risk of Bias in Prevalence Studies: Modification of an Existing Tool and Evidence of Interrater Agreement. *J. Clin. Epidemiol.* 2012, 65, 934–939. [CrossRef]

19. Illés, D.; Terzín, V.; Holzinger, G.; Kosár, K.; Rőka, R.; Zsóri, G.; Abrahám, G.; Czakó, L. New-Onset Type 2 Diabetes Mellitus–A High-Risk Group Suitable for the Screening of Pancreatic Cancer? *Pancreatology* 2016, 16, 266–271. [CrossRef]

20. Gupta, S.; Vittinghoff, E.; Bertenthal, D.; Corley, D.; Shen, H.; Walter, L.C.; McQuaid, K. New-Onset Diabetes and Pancreatic Cancer. *Clin. Gastroenterol. Hepatol.* 2006, 4, 1366–1372. [CrossRef]

21. Boursi, B.; Finkelman, B.; Giantonio, B.J.; Haynes, K.; Rustgi, A.K.; Rhim, A.D.; Mantmari, R.; Yang, Y.X. A Clinical Prediction Model to Assess Risk for Pancreatic Cancer among Patients with New-Onset Diabetes. *Gastroenterology* 2017. [CrossRef]

22. Lee, J.H.; Kim, S.-A.; Park, H.Y.; Lee, K.H.; Lee, K.T.; Lee, J.K.; Bae, J.C.; Kim, K.W. New-Onset Diabetes Patients Need Pancreatic Cancer Screening? *J. Clin. Gastroenterol.* 2012, 46, e58–e61. [CrossRef] [PubMed]

23. Ben, Q.; Cai, Q.; Li, Z.; Yuan, Y.; Ning, X.; Deng, S.; Wang, K. The Relationship between New-Onset Diabetes Mellitus and Pancreatic Cancer Risk: A Case–Control Study. *Eur. J. Cancer* 2011, 47, 248–254. [CrossRef] [PubMed]

24. Liao, K.; Lai, S.; Li, C.; Chen, W. Diabetes Mellitus Correlates with Increased Risk of Pancreatic Cancer: A Population-based Cohort Study in Taiwan. *J. Gastroenterol. Hepatol.* 2012, 27, 709–713. [CrossRef] [PubMed]

25. Tseng, C.-H. New-Onset Diabetes with a History of Dyslipidemia Predicts Pancreatic Cancer. *Pancancer* 2013, 42, 42–48. [CrossRef]

26. Lipworth, L.; Zucchetto, A.; Bosetti, C.; Franceschi, S.; Talamin, R.; Serraino, D.; McLaughlin, J.K.; la Vecchia, C.; Negri, E. Diabetes Mellitus, Other Medical Conditions and Pancreatic Cancer: A Case-Control Study. *Diabetes Metab. Res. Rev.* 2011, 27, 255–261. [CrossRef]

27. Lu, Y.; Garcia Rodriguez, L.A.; Malgerud, L.; González-Pérez, A.; Martín-Pérez, M.; Lagergren, J.; Bexelius, T.S. New-Onset Type 2 Diabetes, Elevated HbA1c, Anti-Diabetic Medications, and Risk of Pancreatic Cancer. *Br. J. Cancer* 2015, 113, 1607–1614. [CrossRef]

28. Mueller, A.M.; Meier, C.R.; Jick, S.S.; Schneider, C. Weight Change and Blood Glucose Concentration as Markers for Pancreatic Cancer in Subjects with New-Onset Diabetes Mellitus: A Matched Case-Control Study. *Pancareology* 2019, 19, 578–586. [CrossRef]

29. Munigala, S.; Singh, A.; Gelrud, A.; Aggarwal, B. Predictors for Pancreatic Cancer Diagnosis Following New-Onset Diabetes Mellitus. *Clin. Transl. Gastroenterol.* 2015, 6, e118. [CrossRef]

30. Yuan, C.; Babic, A.; Khalaf, N.; Nowak, J.A.; Brais, L.K.; Rubinson, D.A.; Ng, K.; Aguirre, A.J.; Pandharipande, P.V.; Fuchs, C.S.; et al. Diabetes Mellitus, Other Medical Conditions and Pancreatic Cancer Risk. *JAMA Oncol.* 2020, 6, e202948. [CrossRef]

31. Bosetti, C.; Rosato, V.; Li, D.; Silverman, D.; Petersen, G.M.; Bracci, P.M.; Neale, R.E.; Muscat, J.; Anderson, K.; Gallinger, S.; et al. Diabetes, Antidiabetic Medications, and Pancreatic Cancer Risk: An Analysis from the International Pancreatic Cancer Case-Control Consortium. *Ann. Oncol.* 2014, 25, 2065–2072. [CrossRef]

32. Chari, S.T.; Leibson, C.L.; Rabe, K.G.; Ransom, J.; de Andrade, M.; Petersen, G.M. Probability of Pancreatic Cancer Following Diabetes: A Population-Based Study. *Gastroenterology* 2005, 129, 504–511. [CrossRef] [PubMed]

33. Hart, P.A.; Kamada, P.; Rabe, K.G.; Srinivasan, S.; Basu, A.; Aggarwal, G.; Chari, S.T. Weight Loss Precedes Cancer-Specific Symptoms in Pancreatic Cancer-Associated Diabetes Mellitus. *Pancreas* 2011, 40, 768–772. [CrossRef] [PubMed]

34. Huang, B.Z.; Pandol, S.J.; Jean, C.Y.; Chari, S.T.; Sugar, C.A.; Chao, C.R.; Zhang, Z.-F.; Wu, B.U.; Setiawan, V.W. New-Onset Diabetes, Longitudinal Trends in Metabolic Markers, and Risk of Pancreatic Cancer in a Heterogeneous Population. *Clin. Gastroenterol. Hepatol.* 2020, 18, 1812–1821.e7. [CrossRef]

35. Sharma, A.; Kandakunta, H.; Nagpal, S.J.S.; Feng, Z.; Hoos, W.; Petersen, G.M.; Chari, S.T. Model to Determine Risk of Pancreatic Cancer in Patients With New-Onset Diabetes. *Gastroenterology* 2018, 155, 730–739.e3. [CrossRef]
36. Chen, W.; Butler, R.K.; Lustigova, E.; Chari, S.T.; Wu, B.U. Validation of the Enriching New-Onset Diabetes for Pancreatic Cancer Model in a Diverse and Integrated Healthcare Setting. *Dig. Dis. Sci.* 2021, 66, 78–87. [CrossRef]

37. Molina-Montes, E.; Coscia, C.; Gómez-Rubio, P.; Fernández, A.; Boenink, R.; Rava, M.; Márquez, M.; Molero, X.; Löhrl, M.; Sharp, L.; et al. Deciphering the Complex Interplay between Pancreatic Cancer, Diabetes Mellitus Subtypes and Obesity/BMI through Causal Inference and Mediation Analyses. *Gut* 2021, 70, 319–329. [CrossRef] [PubMed]

38. Khan, S.; Safarudin, R.F.; Kupec, J.T. Validation of the ENDPAC Model: Identifying New-Onset Diabetics at Risk of Pancreatic Cancer. *Pancreatology* 2021, 21, 550–555. [CrossRef]

39. Khan, S.; al Heraki, S.; Kupec, J.T. Noninvasive Models Screen New-Onset Diabetics at Low Risk of Early-Onset Pancreatic Cancer. *Pancreas* 2021, 50, 1326–1330. [CrossRef]

40. Dayem Ullah, A.Z.M.; Stasinos, K.; Chelala, C.; Kocher, H.M. Temporality of Clinical Factors Associated with Pancreatic Cancer: A Case-Control Study Using Linked Electronic Health Records. *BMC Cancer* 2021, 21, 1279. [CrossRef]

41. Everhart, J.; Wright, D. Diabetes Mellitus as a Risk Factor for Pancreatic Cancer: A Meta-Analysis. *JAMA* 1995, 273, 1605–1609. [CrossRef]

42. Pereira, S.P.; Oldfield, L.; Ney, A.; Hart, P.A.; Keane, M.G.; Pandol, S.J.; Li, D.; Greenhalf, W.; Jeon, C.Y.; Koay, E.J.; et al. Early Detection of Pancreatic Cancer. *Lancet Gastroenterol. Hepatol.* 2020, 5, 698–710. [CrossRef]

43. Illés, D.; Ivány, E.; Holzinger, G.; Kosár, K.; Adam, M.G.; Kamlage, B.; Zsöri, G.; Tajti, M.; Szévís, M.M.; Horváth, V.; et al. New Onset of DiabetEs in Association with Pancreatic Ductal Adenocarcinoma (NODES Trial): Protocol of a Prospective, Multicentre Observational Trial. *BMJ Open* 2020, 10, e037267. [CrossRef] [PubMed]

44. Chari, S.T.; Maitra, A.; Matrisian, L.M.; Shrader, E.E.; Wu, B.U.; Kambadakone, A.; Zhao, Y.-Q.; Kenner, B.; Rinaudo, J.A.S.; Srivastava, S.; et al. Early Detection Initiative: A Randomized Controlled Trial of Algorithm-Based Screening in Patients with New Onset Hyperglycemia and Diabetes for Early Detection of Pancreatic Ductal Adenocarcinoma. *Contemp. Clin. Trials* 2022, 113, 106659. [CrossRef] [PubMed]

45. Maitra, A.; Sharma, A.; Brand, R.E.; van den Eeden, S.K.; Fisher, W.E.; Hart, P.A.; Hughes, S.J.; Mather, K.J.; Pandol, S.J.; Park, W.G.; et al. A Prospective Study to Establish a New-Onset Diabetes Cohort: From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. *Pancreas* 2018, 47, 1244–1248. [CrossRef] [PubMed]

46. Ma, R.C.W.; Chan, J.C.N. Type 2 Diabetes in East Asians: Similarities and Differences with Populations in Europe and the United States. *Ann. N. Y. Acad. Sci.* 2013, 1281, 64–91. [CrossRef]