Dietary oleic acid is inversely associated with pancreatic cancer – data from food diaries in a cohort study.

Short title. Dietary oleic acid and pancreatic cancer.

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Abbreviations; PDA=pancreatic ductal adenocarcinoma

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Abstract.

Background: Dietary oleic acid may prevent pancreatic ductal adenocarcinoma (PDA) by reducing hyperinsulinaemia which can otherwise promote DNA damage and tumour growth. Results from previous epidemiological studies investigating oleic acid are inconsistent. This study aims to clarify the relationship between dietary oleic acid intake and the risk of developing PDA using nutritional information from food diaries plus published serum biomarker data from HbA1c.

Methods: 23,658 participants, aged 40-74 years, were recruited into EPIC-Norfolk and completed 7-day food diaries which recorded; foods, brands and portion sizes to calculate nutrient intakes. Serum HbA1c was measured at recruitment in 11,147 participants (48.7% of cohort). Hazard ratios (HRs) for quintiles of dietary oleic acid intake and serum HbA1cwere estimated using Cox regression. Additional analyses were made according to whether body mass index (BMI) was greater or less than 25kg/m^2 as this influences hyperinsulinaemia

Results: 88 participants (55% women) developed PDA after a mean follow-up of 8.4 years (SD=3.9) (mean age at diagnosis=72.6 years, SD=8.8). A decreased risk of PDA was associated with increased dietary oleic acid intake (highest vs lowest quintile, HR=0.29, 95% CI=0.10-0.81, P trend across quintiles=0.011), with statistical significance maintained when BMI>25kg/m^2 but not if BMI<25kg/m^2. An elevated serum HbA1c was associated with increased risk of disease (highest vs lowest quintiles, HR=6.32, 95% CI=1.38-28.89, P for trend=0.004).

Conclusions: The data supports a protective role of oleic acid against development of PDA in those with higher BMIs possibly through influencing hyperinsulinaemia. Oleic acid intake should be accurately measured in future aetiological studies.

Key words: Pancreatic cancer; Oleic acid; Glycosylated Haemoglobin; Food diaries.

Introduction

Worldwide, pancreatic ductal adenocarcinoma (PDA) causes more than a quarter of a million deaths each year and is the 8th commonest cause of cancer death.[1] Less than 3% of patients survive more than 5 years with only minimal improvements in survival over recent decades.[2, 3] An improved understanding of the aetiology of pancreatic cancer would inform recommendations to reduce the risk of disease in the population. Positive risk factors for PDA include: a family history of this cancer,[4] cigarette smoking[5] and chronic pancreatitis.[6] Epidemiological studies also report an increased risk with elevated serum glucose,[7, 8] type 2 diabetes[9] and an increased body mass index[10] with hyperinsulinaemia a potential underlying mechanism for these associations. Hyperinsulinaemia may induce carcinogenesis via several mechanisms including oxidative stress[11] inducing damage to DNA,[12] directly stimulating cancer cell growth,[13, 14] and promoting tumour invasion.[15] Hyperinsulinaemia may be particularly relevant to pancreatic carcinogenesis as insulin is secreted by the pancreas and therefore present locally at high concentrations.[16]

Reducing insulin levels through lifestyle measures including dietary ones could lower the risk of developing PDA. The nutrient oleic acid is a n-9 monounsaturated fatty acid that is naturally found in greater quantities than any other fatty acid. It is present in both animal and vegetable oils, especially olive and rapeseed oils. Oleic acid can reduce insulin secretion and increase sensitivity[17-19] with actions in skeletal muscle cells effected through mitochondrial beta-oxidation mediated by PPAR alpha and protein kinase A-dependent mechanisms.[20] Oleic acid also influences the effects of the inflammatory cytokine TNF-alpha on insulin production.[17] Furthermore, increasing body mass index (BMI) is directly related to increased insulin secretion and insulin resistance,[21] with increased BMI recognised as a positive risk factor for developing PDA.[22-24] A mechanistic role for oleic acid

would be supported if its effects are more profound in those with increased body mass index.

To support an aetiological role for oleic acid in preventing PDA, epidemiological studies are required investigating dietary oleic acid intake and the risk of developing PDA. However, two US (United States) cohort studies reported no associations.[25, 26] Case-control studies reported both inverse[27]and positive associations.[28] The inconsistencies in these results may be due to inaccuracies in measuring diet which may make any true differences difficult to detect although the methods of recording dietary intake vary. All previous aetiological studies have used food frequency questionnaires (FFQs), where subjects recorded the frequency of consumption of standard portion sizes of selected listed food items. FFQs are quicker to complete than 7-day food diaries (7-DFDs) but are less accurate.[29] The baseline measurement of nutrient intake has been demonstrated to be an accurate at ranking an individual over a five year period.[30]

The aim of this work was to conduct, for the first time, a prospective cohort study of dietary oleic acid intake in the aetiology of pancreatic cancer using nutritional data derived from 7-day food diaries (7-DFDs). We sought to provide mechanistic data using glycosylated haemoglobin (HbA1c) a marker of insulin resistance. Oleic acid in reducing insulin resistance would lead to decreased levels of HbA1c and an associated reduction in the risk of PDA. Consistent dietary and biomarker results would support a role for a decreased oleic acid intake along with hyperinsulinaemia in the aetiology of PDA and suggest dietary measures to reduce cancer risk.

Materials and Methods

The cohort was 23 658 men and women, aged 40 to 74 years, who were recruited into the European Prospective Investigation of Cancer-Norfolk Study (EPIC-Norfolk) and completed 7-day food diaries, between the years 1993 and 1997.

Participants were resident in the county of Norfolk, United Kingdom, registered in 35 general practices in rural, suburban and inner city areas. The Norwich District Health Authority Ethics Committee approved the study. All participants gave signed consent for their medical notes to be reviewed in the future. At recruitment, participants completed detailed questionnaires on their: demography, previous medical history, medication, habitual diet and smoking. Participants attended a baseline health check, supervised by a nurse,[31] who explained the completion of the 7-day food diary (7-DFD), the first day of which was recorded with the nurse, as a 24 hour recall of the participant's previous day's dietary intake. The remaining six days were completed by participants themselves at home, who recorded their entire dietary intake, including: food types, portion sizes, brands, cooking methods and recipes in eight separate meal times each day. The names of commercially prepared foods or packaging from products consumed were recorded in the diary to allow more accurate nutritional assessments. Portion sizes were estimated by participants by either weighing their food or comparing it with supplied photographs of varying portion sizes. After completion the 7-DFDs were returned to the study headquarters where they were coded by a nutritionist, with the data inputted into a specially designed computer programme called DINER (Data In to Nutrients for Epidemiological Research). Each entry in the diary was matched to one of 11 000 food items and 55 000 portion sizes within DINER, by selecting the food item which best described it. Where descriptions were lacking the item was assigned the average composition for that food type. DINER facilitated the translation from participant reported free text of food to structured data which could then be electronically converted into nutrient values or food groups(11). The DINER nutrient database is based on foods in the United Kingdom Food Composition Database, the nutrient database of the Royal Society of Chemistry and from food manufacturers' databases. Each 7-DFD took approximately 4 hours to code with an average of 220 individual food and drink items reported by participants in their diaries. An example of the detail of this method was that 337

specific types and brands of breakfast cereals were included in DINER. The computer program checked for potential errors in the coded diaries such as unexpectedly large portion sizes or duplication and any anomalies were checked by the nutritionists. A total of 11 112 of the total cohort (47.0%), that were recruited after November 1995, underwent venepuncture for a sample of EDTA-anticoagulated blood which was used to measure HbA_{1c}. The blood was stored at 4–7°C until it was transported for HbA_{1c} assay by high-performance liquid chromatography on a Bio-Rad Diamat.

Following recruitment, the cohort was monitored for 17 years, up to June 2010, to identify those initially well participants who later developed incident pancreatic cancer. Cases were identified by matching the EPIC-Norfolk database with: firstly the Norfolk Health Authority records of hospital admissions and secondly the Eastern Cancer Registry and Information Centre (ECRIC). The notes of all potential cases were reviewed by a medical gastroenterologist (PJRB) to verify the diagnoses and the clinical staging as classified by the American Joint Committee on Cancer.[32] Information was also obtained on the confirmatory investigations, treatment received and survival time following diagnosis. Cases were excluded if there was diagnostic uncertainty, participants had pancreatic cancer prior to enrolment or if the diagnosis was made within 12 months of entering the study.

A case-cohort analysis was performed between cases and a random sample of 3 970 food diaries from controls that had had their food diaries coded. A case-cohort analysis compares those in a cohort who develop disease against controls selected from the parent cohort without using matching criteria. This method of analysis was used as not all of the diaries of the 23 658 participants are coded. Baseline characteristics were compared between participants with and without incident pancreatic cancer using a t-test for normally distributed continuous variables and a chi-squared test for categorical ones. Oleic acid intakes and serum HbA1c were divided into quintiles across the distribution of the whole cohort. The primary

outcomes were Hazard ratios, estimated using Cox proportional hazard regression models, with 95% confidence intervals, of developing pancreatic cancer for each quintile of oleic acid intake, using the lowest one as the reference. All analyses were adjusted for the co-variates of age at recruitment and gender, with additional models including cigarette smoking status (never, previous or current) and type 2 diabetes at baseline (yes/no) and total energy intake. No adjustments were made for body mass index as it is related to energy intake and may act via the same mechanistic pathway; i.e. via hyperinsulinaemia. To provide mechanistic information that oleic acid may prevent PDA through reducing hyperinsulinaemia, analyses were conducted in participants with a BMI greater than and less than 25kg/m^2. Support for such a mechanism would be suggested by inverse associations with oleic acid this group but not in those less likely to have increased insulin i.e. those with a BMI<25kg/m^2. No adjustment was made for serum HbA1c as it too is likely to be part of the same causal pathway. For all analyses a further calculation was made excluding those diagnosed within 5 years of recruitment to reduce the risk of a protopathic bias (undiagnosed disease influencing results) and ensure that the data was truly prospective, i.e. before the development of symptoms and subsequent diagnosis of cancer.

Results

In the cohort of 23 658 participants (55% were female) who attended the baseline health check and completed a 7-day food diary, 88 (0.37%) participants developed pancreatic cancer during the 17 year follow up period of which 48 cases (55% of cases) were female. The mean time between recruitment and diagnosis was 8.4 years (SD=3.9 years). At diagnosis 14.9% had disease localised to the pancreas, 30.1% locally advanced disease, 46.6% had metastatic disease with no staging available on 8.0%. Histological confirmation was available in 35%. The treatments received were: surgery (8%), chemotherapy (35%) and solely palliative measures (57%). The median survival after diagnosis was 4.0 months (range 0.5-25 months).

For patients where histology was not sought, a diagnosis of pancreatic cancer was made via at least two radiological modalities which demonstrated typical findings of the disease. The clinical characteristics of the patients with and without histology were similar; namely local or metastatic spread (78% vs 74%, p=0.65) and median survival (3 vs 4 months, p=0.73). The characteristics of the subcohort of controls used in this analysis were almost identical to the demographics of other controls in the whole cohort, whose food diary data was not available (age at recruitment 59.3 yrs in subcohort vs 59.0 yrs in whole cohort and gender was 43.8% men in subcohort vs 45.5% men in whole cohort). The average daily intake of oleic acid was significantly lower in cases (16.9 grams per day) compared to controls (18.7 grams per day) (table 1). Serum HbA1c was higher in cases (39.1 mmol/mol) compared to controls (34.6 mmol/mol).

In the analysis of dietary oleic acid intake there were statistically significant inverse association for the risk of developing pancreatic cancer for each of the three higher quintiles of intake (highest vs lowest quintile HR=0.29 (95% CI=0.10-0.81). Importantly, there was also a significant trend across categories (HR=0.72, 95% CI 0.56-0.93, p=0.011) (Table 2). After excluding participants diagnosed within 5 years of enrolment, all four higher quintiles of intake had significant inverse associations (highest vs lowest quintile HR=0.16 (95% CI=0.05-0.52)) with a significant trend across quintiles (HR=0.65 95% 0.48-0.86, p=0.003) (table 2). Excluding participants with known diabetes at recruitment did not alter the magnitude of the associations. In the model containing only age and gender the results were similar, but with smaller effect sizes. Analysing dietary oleic acid intake by BMI, identified those with a BMI greater than 25kg/m^2 (whose participants are more likely to have a hyperinsulinaemic state), had a significant trend across quintiles HR=0.67 (95% CI 0.47-0.95, p=0.022). In those with a BMI<25kg/m^2 no effects were seen although the hazard ratios for an increased oleic acid intake suggested a negative association (trend across quintiles HR=0.78 95% CI 0.54-1.13, p=0.19).The small numbers of participants with prevalent

diabetes (125 participants including 4 cases) prevented undertaking a meaningful sensitivity analysis according to diabetes status at baseline.

In the biomarker analysis of HbA1c, 35 cases of PDA had donated serum (39.8% of the total cases). All higher quintiles of HbA1c were associated with at least a doubling of the risk of developing PDA, with the highest quintile reaching statistically significance (HR=6.32, 95% CI=1.38-28.89), with a trend across quintiles (HR=1.52, 95% CI 1.15-2.03,p=0.003)(table 2). For cases diagnosed after 5 years of recruitment (n=26), the magnitude of the effect sizes were increased (highest vs lowest quintile, HR=8.79 95% 1.09-71.04), with a trend across quintiles HR=1.63 (95%CI 1.14-2.33, p=0.006). Excluding participants with diabetes at recruitment did not significantly alter the HbA1c results (highest vs lowest quintile HR=6.20, 95% CI=1.35-28.40, p=0.004).

Discussion

The main finding of this study was that an increased dietary oleic acid intake was inversely associated with the development of PDA. Evidence for a causal protective effect of oleic acid is suggested by the plausible biological mechanisms, large effect sizes, a biological gradient, adjustment for covariates and temporal collection of the nutrient data. The highest intake of oleic acid was associated with an 84% reduction in risk after excluding those diagnosed within 5 years. To achieve the highest quintile of intake, participants would have consumed at least 23.7 grams per day of oleic acid which equates to 34 grams (two tablespoons) of olive oil per day.

Oleic acid increases insulin sensitivity in animal models,[17] patients with type 2 diabetes,[18] adult populations[19] and in studies of volunteers randomised to diets rich in oleic acid.[33] Excess insulin may promote carcinogenesis by increasing pro-inflammatory cytokine production, including interleukin-6, tumour necrosis factor-α and C-reactive protein.[34] These stimulate the formation of reactive oxygen species which can induce mutations in key oncogenes and tumour suppressor genes.[12]

Furthermore, insulin directly induces tumour growth, in a dose-dependent effect on pancreatic cancer cell lines in-vitro.[35] Excess insulin is particularly relevant to PDA as there is a 20-fold higher concentration of insulin in the pancreas than in the systemic circulation and hence its local mitotic effect could be profound.[16] Oleic acid may lower insulin levels which reduces the risk of developing PDA. This is supported by our findings, firstly; that increased dietary oleic acid had a stronger association in participants with a higher BMI (which is associated with hyperinsulinaemia) and secondly; there was an 8-fold increased risk with elevated serum HbA1c (a marker of hyperinsulinaemia) including in those without diabetes at enrolment. The lack of a statistical effect of oleic acid intake in those with a BMI<25 could be explained by two potential mechanism. Firstly; a reduction in case numbers (dropping from 88 to 41) preventing the detection of an association (type 2 error). Secondly; that oleic acid has less of an impact on those with a low BMI as this population will have lower insulin levels and hence not benefit from further insulin modification.

Two previous cohort studies have also reported positive associations of HbA1C with pancreatic cancer.[36, 37] The stronger associations with PDA noted after excluding those diagnosed within 5 years of enrolment suggest that pancreatic carcinogenesis occurs over a prolonged period which could reflect the evolution of pancreatic intraepithelial neoplasia (PanINs).

To confirm that dietary oleic acid has a causal role in preventing pancreatic cancer supportive data from many epidemiological studies is required, ideally from prospective cohort investigations or randomised controlled trials of oleic acid supplementation in the general population. To the best of our knowledge, there are just two prospective cohort investigations, although these used nutritional information reported in food frequency questionnaires rather than more accurate7-DFDs. The US Nurses' Health Study and the NIH-AARP study both reported no differences between the highest and lowest quintiles of oleic acid intake and no trends across categories.[25, 26] A case-control study from Canada of 462 cases of pancreatic cancer

and 4721 controls, documented dietary oleic acid was associated with a non-significant reduced risk of pancreatic cancer (highest vs lowest intake OR=0.75, 95% CI=0.55-1.02). As in our work, a stronger inverse association was found in participants with an increased BMI (BMI>30kg/m^2highest quartile, odds ratio=0.36, 95% CI 0.19-0.72, P-trend=0.002) and no effect in those with a BMI<25kg/m^2.[27] The Canadian retrospective study also reported several fatty acid groups were associated with a decreased odds, including saturated and MUFAs, which could represent a correlated effect of nutrients or recall bias in cases for pre-symptomatic diet. A case-control study from San Francisco with 532 cases of PDA reported oleic acid was associated with an increased risk of disease (highest vs. lowest quartile, OR=1.4, 95% CI=1.1-1.9, P-trend=0.008).[28] The inconsistencies in these results from epidemiological studies may be due to measurement error for diet and biases inherent in retrospective work which may make any true differences difficult to detect. All these previous studies used food frequency questionnaires (FFQs) to measure habitual diet, where subjects record the frequency of consumption of standard portion sizes of selected listed food items. FFQs, although quicker to complete are less accurate than detailed seven day food diaries (7-DFDs).[29] For example, using 16 day weighed records as the standard, the correlation coefficients from 7-DFDs for fat intake were 0.63 compared with those from FFQs of 0.55 and for sugar intake the correlation coefficients were 0.77 and 0.51 respectively.[29] Our study is the first cohort investigation to use the more accurate 7-DFDs to assess oleic acid in the aetiology of pancreatic cancer.

Our work has several methodological strengths including the minimisation of biases associated with case-control investigations including selection bias and recall bias for diet. The case ascertainment was accurate as all potential case notes of PDA were reviewed by a clinical gastroenterologist to confirm the diagnosis. Follow-up bias was minimised by identifying cases from two comprehensive sources; namely hospital records and regional cancer registry data. Furthermore, twenty years

after recruitment commenced 94.6% of participants still lived in Norfolk. By analysing exposures in those diagnosed after more than 5 years of enrolment this further reduces any potential effect of recall bias or alteration of biomarkers by the pre-symptomatic cancer. Although the study was conducted in just one county in England, the cohort was generalisable in terms of: demography, incidence and the clinical characteristics of PDA.[1] The intake of dietary oleic acid in this study was similar to other work. Our top quintile range of oleic acid intake was 23.7 to 78.4 grams/day with the Canadian case-control reporting the highest quartile median intake of 28.4grams per day.[27] The San Francisco case-control study recorded the highest quartile intake of oleic acid was greater than 25grams per day.[28] Several risk factors for PDA were included in the analyses, namely smoking and diabetes. No adjustment was made for BMI as it is on the same causal pathway as oleic acid and furthermore energy intake was considered, which is positively associated with BMI. There were several methodological limitations of this study including the small numbers which reduced the precision of several estimates although the effect sizes were large enough to detect with this sample size. In the future, we will continue case ascertainment in the cohort to obtain more precision of the estimates.

Changes can occur in participants' diet between recruitment and over time and with seasonal variation, although these will occur in both those who become cases and those who become controls. This form of measurement error, regression dilution bias, will result in a spurious under-estimate of the true effect size rather than an inaccurate over-estimate. A single baseline measurement of diet has been demonstrated to rank subjects according to their nutrient intake with a decline of correlation coefficients of only 0.07 over 5 years[30] which allows a reasonable comparison to be made of nutrient intake between subjects to be made over a prolonged period. In our study, the maximum follow up interval to diagnosis was 17 years, although the mean time to diagnosis was 8.4 years with a standard deviation of 3.9 yrs. Pancreatic carcinogenesis could be influenced by environmental factors

over a prolonged period, with the precursor lesions for pancreatic cancer, “PanINs”, common in later life, although only a small percentage progress from low grade to high grade lesions associated with invasive disease.[38]

A potential weakness was that histological confirmation of pancreatic cancer was obtained in only 35% of the cases. This was due to the lack of tissue sampling techniques in the 1990’s, such as endoscopic ultrasound and fine needle aspiration, which only became available later. However, the clinical characteristics between cases with and without histology were similar so this is unlikely to have introduced significant error. A further weakness is the case-cohort method of analysis rather than a full cohort analysis, although the use of nearly four thousand non-cases in this study is expected to produce very similar results to analysis against the whole cohort of 23 658 participants. In the future, the EPIC study aims to code all participant’s diaries when the data can be reanalysed.

In conclusion, this prospective cohort study reported, for the first time, large inverse associations between oleic acid intake, in a dose-dependent manner, and the risk of pancreatic cancer. There are plausible biological mechanism for this association including oleic acid increasing insulin sensitivity, which is supported by firstly our data on the positive association with serum HbA1c and secondly, oleic acid reducing the risk in those with higher BMIs, both of which are associated with hyperinsulinaemia. Future observational studies need to confirm this association to imply causality, preferably in prospective cohort studies using dietary information derived from food diaries. If the findings are consistent, increased oleic acid consumption in the population may be an effective method to prevent this highly aggressive cancer.

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(iii) All authors have reviewed and approved the final manuscript.

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