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

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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 HbA1c were estimated using Cox regression. Additional analyses were made according to whether body mass index (BMI) was greater or less than 25 kg/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>25 kg/m^2 but not if BMI<25 kg/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.

1. 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

Abbreviations: PDA, pancreatic ductal adenocarcinoma.

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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.

2. Materials and methods

The cohort was 23 658 men and women, aged 40–74 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 h 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 h 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 3970 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 25 kg/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

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