Investigating physical activity in the etiology of pancreatic cancer – the age at which this is measured is important and is independent of body mass index.

Nurulamin M. Noor, BMBS[1], Paul J.R. Banim, MD[2], Robert N. Luben, PhD[3], Kay-Tee Khaw, PhD[3], Andrew R. Hart, MBChB[4].

[1] Department of Medicine, University of Cambridge, Cambridge, United Kingdom.

[2] Department of Gastroenterology, James Paget University Hospital, Great Yarmouth, United Kingdom.

[3] Institute of Public Health, University of Cambridge, Cambridge, United Kingdom.

[4] Department of Medicine, Norwich Medical School, University of East Anglia, Norwich, United Kingdom.

Conflict of interest: None declared.

Source of funding: EPIC-Norfolk is supported by research program grant funding from Cancer Research, United Kingdom and the Medical Research Council, United Kingdom.

Abstract

Objectives: There are plausible biological mechanisms for how increased physical activity (PA) may prevent pancreatic cancer, although findings from epidemiological studies are inconsistent. We investigated whether the risk is dependent on the age at which PA is measured, and if independent of body mass index (BMI).

Methods: 23 639 participants, aged 40-74 years, were recruited into the EPIC-Norfolk cohort study between 1993 and 1997 and completed validated questionnaires on PA. The cohort was monitored for pancreatic cancer development and hazard ratios (HRs) were estimated, adjusted for covariates.

Results: Within 17 years, 88 participants developed pancreatic cancer (55% female). There was no association between PA and risk in the cohort (HR trend=1.06, 95% CI=0.86-1.29). However, in participants younger than 60 years, higher PA was associated with decreased risk (highest vs. lowest category HR=0.27, 95% CI=0.07-0.99). Higher PA was not inversely associated when older than 60 years (HR trend=1.23, 95% CI=0.96-1.57). Including BMI in all models, produced similar estimates.

Conclusions: The reasons why PA in younger, but not older people, may prevent pancreatic cancer needs to be investigated. PA may operate through mechanisms independent of BMI. If this association is causal, one in six cases might be prevented by encouraging more PA.

Key words: physical activity, pancreatic cancer, cohort study.

Introduction

Pancreatic cancer causes over a quarter of a million deaths each year worldwide,[1] and has the worst survival rate of any malignancy.[2,3] Only 3% of patients live for more than five years after diagnosis, with little improvement over recent decades.[2,3] The incidence varies between countries,[1,4] suggesting that lifestyle factors may play an important part in its etiology. Positive risk factors include: cigarette smoking,[5] type 2 diabetes mellitus,[6,7] and excess body weight,[8,9] although the precise etiology is unknown.

There are plausible biological mechanisms for how a decreased physical activity (PA) may promote pancreatic carcinogenesis. Increased insulin resistance and the resulting hyperinsulinaemia, are associated with several risk factors for cancer including: decreased PA,[10] type 2 diabetes,[11] and excess body weight.[12] Hyperinsulinaemia, stimulates mitogenesis of beta cells in the pancreatic islets of Langerhans,[13,14,15] with the excess insulin promoting increased expression of several cellular signaling pathways in pancreatic cells, including transforming growth factor beta (TGF-β).[16] This enhanced transmission of signals from within cell membranes to the nucleus, may promote carcinogenesis.[16] An increased PA is associated with improved insulin sensitivity,[17] which lowers insulin secretion, thereby potentially inhibiting the carcinogenic processes.

The mechanisms for how PA may protect against cancer, need to be supported by epidemiological data demonstrating that people with high levels of PA have a reduced risk of developing pancreatic cancer. The association

between *total* PA and the development of pancreatic cancer has been reported in a meta-analysis of five prospective studies (RR=0.62, 95% CI=0.35-1.09, P=0.09) with similar results after adjustment for BMI (RR=0.81, 95% CI=0.55-1.20).[18] However, only one of these studies, from Finland, reported a statistically significant inverse association (HR=0.42, 95% CI=0.22-0.83).[19] None stratified their results according to age at recruitment when PA was measured, with all studies including participants older than 60 years.[20,21,22,23] The age at which PA is measured may be crucial in etiological studies, as younger participants are more likely to be both employed and healthier, hence pursue more PA. Greater PA at younger ages may reduce the risk of pancreatic cancer developing later. Furthermore, the range of PA may be less in older people and hence harder to detect associations in epidemiological studies. This lack of age-dependent measurement of PA may explain the null findings in many previous studies, which included older participants. Furthermore, clarifying whether PA has a potential protective effect independent of BMI is important. Those pursuing more PA may have a lower BMI and it could be the latter, which is truly associated with a reduced risk of pancreatic cancer. To date, not all cohort studies have adjusted for BMI, so whether PA has an independent effect, is currently uncertain.

The aim of this epidemiological investigation was to conduct a prospective cohort study to determine if there is an inverse association between increasing levels of *total PA* and pancreatic cancer. For the first time, to the best of our knowledge, the age at which PA is measured will be studied to see if there is a differential effect. Furthermore, we would investigate such

associations adjusting for BMI, to provide information on the potential mechanism. Demonstrating inverse associations would support measuring PA in etiological studies of pancreatic cancer according to age, and offer an approach to preventing this highly lethal cancer.

Methods

A total of 23 639 men and women aged between 40-74 years old were recruited into the European Prospective Investigation of Cancer (EPIC-Norfolk) Study between the years 1993 to 1997.[24] Potential participants were identified from 35 general practices in the county of Norfolk, United Kingdom. Participants completed a self-administered questionnaire recording information on their *total PA* in a typical week over the past year: PA was assessed: firstly at work (classed into categories of either; sedentary, standing, physical work or heavy manual), secondly at home (housework, gardening, do-it-yourself work) and thirdly at recreation (walking, cycling, jogging etc.). The PA questionnaire recorded details of the intensity and duration of these activities, and also the number of flights of stairs climbed each day. From these questions, a global total PA index was derived, divided into four categories, namely: *inactive*, *moderately inactive*, *moderately active*, and *active* (Table 1). Within each category, the summation of occupational, home and recreational PA levels were similar. This PA index had been validated against physiological markers of exercise, namely cardiorespiratory fitness (as measured by sub-maximal oxygen consumption whilst cycling) and four-day energy expenditure (as determined by four day heart rate monitoring).[25] At recruitment, participants also completed questionnaires on

their demographics, medical history and their diet from seven-day food diaries. In the food diaries, participants recorded their entire food intake for a week including: food type, brands, recipes and portion sizes. All attended a health check which measured their height and weight measurements in light clothing, to calculate their BMI (kg/m^2). The Norwich District Health Authority Ethics Committee approved the study and all volunteers gave signed consent for their medical notes to be reviewed.

After recruitment, the cohort was followed up to 2010, to identify those participants who developed incident pancreatic cancer. Cancer cases were identified by matching the EPIC-Norfolk database with the Norfolk Health Authority records of hospital admissions as well as the Eastern Region Cancer Registry. A medical gastroenterologist reviewed the medical notes of all potential cases to verify the diagnoses and to document the confirmatory investigations. Cases were excluded where there was: diagnostic uncertainty after review of notes, in those diagnosed with pancreatic cancer prior to recruitment or if the diagnosis was made less than 12 months after enrollment. The latter helped ensure that data on PA was recorded prospectively before symptoms developed.

In the analysis, Cox regression estimated the hazard ratios (HR), plus 95% confidence intervals (95% CIs), for developing pancreatic cancer for each of the four categories of PA (Intercooled STATA, SE version 11.0). The lowest level of physical activity (*inactive*) was the reference value and in the first analysis, age at recruitment and gender were included in the model. In a

second analysis, additional covariates which influence the etiology of pancreatic cancer namely: cigarette smoking (*never, former, current smoker*), and type 2 diabetes (*yes, no*) were included.[11,18,26] These analyses were performed in a sub-cohort of 4 058, which consisted of a random sample of 3970 non-cases plus the 88 identified cases. This approach was used so that nutrient information from participants with fully coded seven-day food diaries could be included in several analyses of PA. Currently all the nutrient information from the whole cohort is unavailable. Each of these analyses were performed firstly in all ages at recruitment, secondly participants younger than 60 years and thirdly those older than 60 years. The age of 60 years was chosen as it is an estimated age after which participants may start retiring from their occupation and are more likely to develop medical illnesses, both of which may result in less PA. The HRs were adjusted for information from the food diaries, namely total energy intake, which is associated with PA, and total dietary antioxidant intake, for which we have previously reported inverse associations with the risk of pancreatic cancer.[27] Finally, further analyses were performed to assess if the effects of PA were independent of BMI (categories of kg/m^2, <25, 25-<30, 30-<35 and >35). The population attributable fraction was calculated, namely the proportion of cases that could be prevented, assuming a causal association, if participants in the lowest three categories of PA increased their PA to that in the *active* one.

Results

In the cohort of 23 639 participants, a random sample of 4058 were identified for whom we had information on PA and coded food diaries, including 88 (2.17%) of whom developed pancreatic cancer (55% female, mean age at recruitment 64 years, SD=7.8 years). Pancreatic cancer was diagnosed after a mean follow-up time since recruitment of 8.6 years (SD=3.8 years). Most patients had metastatic spread at diagnosis (81%, American Joint Committee on Cancer, stage 4[28]) and only 7% had cancer localized to the pancreas and less than 2 centimeters in dimension (stages 0, 1A or 1B). The treatments used were: surgery (8%), chemotherapy (35%) and palliative measures (57%). There was histological confirmation in 31 cases (35%), and in the remainder, the diagnosis was confirmed from firstly, at least two radiological modalities and secondly symptoms suggestive of pancreatic cancer. The clinical characteristics of patients with and without histology were similar namely: cancer staging and median survival of four months in both groups.

In the descriptive analyses, participants who developed pancreatic cancer were more likely than controls to be older at recruitment. However, there were no significant differences in BMI, cigarette smoking status or the prevalence of diabetes (table 2). In all ages of recruitment, there were no significant differences in proportions of cases and non-cases in each of the four categories of PA. Data on BMI category was collected in 99.8% of non-cases and 100% of the cases and data on smoking was collected in 99.2% of non-cases and 100% of the cases.

In the multivariate analyses of all ages at recruitment, there were no associations between PA and the risk of pancreatic cancer for any individual categories, or for trends across categories (HR trend=1.06, 95% CI=0.86-1.29, P=0.60, table 3). At recruitment 52.8% of participants were younger than 60 years. In this group, more did have increased PA compared to participants older than 60 years (*active* 23.8% vs. 12.1%, P=0.07 and *moderately active* 27.3% vs. 17.5%, P=0.07). For patients recruited younger than 60 years (n=29 cases) there were inverse associations with the three higher quartiles of PA, although only the *active* category reached statistical significance (HR=0.27, 95% CI=0.07-0.99, table 4), with a non-significant trend across categories (HR trend=0.75, 95% CI=0.53-1.06, P=0.11, table 4). In participants recruited older than 60 years (n=59 cases), no association was found with PA and pancreatic cancer risk (active vs. inactive HR=1.98, 95% CI=0.94-4.16, P=0.07, HR trend=1.23, 95% CI=0.96-1.57, P<0.10, table 5). Potential reasons for this might be that; firstly that there may be residual confounders associated with PA in this age group, which have an adverse effect on risk. Secondly if the carcinogenetic process occurs over many years, PA may only influence this process in younger people. All the HRs were similar when adjusted for both total energy intake and total dietary antioxidant intake. If the association with PA is causal, and based on the HRs reported, then 47% of pancreatic cancers could be prevented in those younger than 60 years, if those in the three least active categories increased their PA to that of the *active* level. When including BMI in the models, the effect sizes for all PA categories and trends were similar for all ages of recruitment (HR trend=1.03, 95% CI=0.84-1.27, P=0.77) and in those aged younger than 60 years (highest

vs. lowest category HR=0.25, 95% CI=0.07-0.93, HR trend=0.73, 95% CI=0.51-1.04, P=0.08, table 4). Similarly, in participants recruited older than 60 years, the magnitude of associations were comparable (HR trend=1.21, 95% CI=0.94-1.55, P=0.13, table 5).

Discussion

The main finding of this study was that the associations between PA and the risk of pancreatic cancer were dependent on the age at which PA was measured. There was a large, although imprecise, inverse association in those undertaking higher levels of PA when younger than 60 years, with participants who were active (a standing job or with >1.0 hour daily recreational activity) 73% less likely to develop pancreatic cancer. Evidence for a causal association with PA is suggested by: the large effect size, suggestion of a dose response and the temporal measurement of PA. The epidemiological findings support the experimental work on possible biological mechanisms for how PA may inhibit pancreatic carcinogenesis.[16] These include, PA reducing hyperinsulinaemia, with lowering of the mitogenic effects of excess insulin which may lead to a decreased expression of several cellular signaling pathways involved in carcinogenesis. In participants, older than 60 years at recruitment, higher PA was not associated with a decreased risk. The reasons for this are unknown, but may reflect residual confounders in older people which are associated with both PA, which negate any potential beneficial effects of PA. This research will continue to investigate other exposures, including diet, and assess if these are linked with PA and may explain this finding. Additionally, if the carcinogenetic process evolves over many years, increased PA may only exert an influence on this process in younger people. Investigating whether the effect of PA is independent of BMI is important, to help elucidate the potential protective mechanisms of the former. A raised BMI, which is associated with hyperinsulinaemia, is also decreased by increased PA levels. However, our results showed the

association remained even when BMI was included in the analyses, suggesting the effect of PA indicates mechanisms independent of simply reducing BMI.

The influence of PA on risk, many years before the actual diagnosis of cancer, possibly suggests a long time period during which pancreatic carcinogenesis evolves. Ductal adenocarcinoma, the commonest pancreatic cancer, has been postulated to arise from histological abnormalities in the ducts, called pancreatic intraepithelial neoplasias (PanINs).[29] The histological changes in PanINs; include metaplasia and cellular atypia which can progress to malignant cancer over time.[29] Perhaps increasing levels of PA in younger people influence mechanisms, which inhibit the progression of such pre-cancerous lesions, thereby decreasing the risk of pancreatic cancer.

This investigation had both methodological strengths and weaknesses. The former, are its prospective design and the use of a questionnaire measuring PA, which had been validated against physiological parameters. The measurements of PA from the questionnaire are highly correlated with objective measures of energy expenditure ($P = 0.003$) and cardiorespiratory fitness ($P=0.001$).[25] A cohort study is superior to a retrospective case-control design in that both recall and selection biases are minimized. In etiological studies it is important that PA before symptoms is recorded, as once symptoms develop, PA will be reduced. In a case-control study, patients may have difficulty in recalling their pre-symptomatic PA levels and report their current PA level. This recall bias is reduced in prospective work, where

participants are recruited when they are well and report their current levels of PA. Follow-up bias will have been low due to use of comprehensive cancer registries to identify cases and the stable geographical nature of the population in Norfolk. Twenty years after cohort recruitment commenced, 94.6% of EPIC-Norfolk participants were still resident in the county. To minimize potential confounding, the covariates of age, sex, cigarette smoking status, type 2 diabetes and BMI were all included in our analyses. Furthermore, adjusting for energy intake and antioxidant consumption did not influence the results. The findings are generalizable in that the population and clinical characteristics, namely incidence, cancer staging, treatments and survival were similar to that expected.[30] Moreover, PA in Norfolk was comparable to that in other counties in the United Kingdom, with national data reporting 60% of the population meeting recommendations for at least moderate activity (59.3% *moderately active* or *active* in our non-cases).[31] The main potential weakness of our work was that only one PA measurement was used, which could introduce measurement error, if PA changes over time. Regular, repeated recordings of PA would reduce this but we did not have access to this information. However, such measurement error would result in a spurious under-estimate, not over-estimate, of any effects of PA. Furthermore, only 35% of cases had histological confirmation of pancreatic cancer, potentially introducing misclassification bias. In the early years after recruitment, namely in the 1990s, more recently developed radiological techniques for obtaining tissue, namely endoscopic ultrasound with fine needle aspiration of tissue, were unavailable. However, this bias is unlikely as there were clinical similarities between cases with or without histology,

including cancer staging and survival. Also to reduce error, for all patients without histology, the medical notes were reviewed by a medical gastroenterologist to confirm a likely diagnosis of pancreatic cancer. Finally, the number of cases in the active group younger than 60 years was low at 3 cases, which resulted in imprecision of the effect size. Despite this, in several models the estimate was still statistically significant, with more cases in the baseline reference category and several hundred controls in the comparator groups. However, the cohort should continue to be monitored to accrue more cases to ensure the effect size is maintained.

To help confirm that increased levels of total PA, in younger people, may contribute to preventing cancer, supportive data from many epidemiological studies are required, ideally prospective ones. To the best of our knowledge, there are currently five other such studies, which have investigated *total PA*. In the largest, analyzing data from the whole EPIC cohort of 438 405 males and females from 10 European countries,[20] of which EPIC-Norfolk is a sub-cohort of 6%, there were 324 cases of pancreatic cancer. No significant associations were reported across all ages of recruitment (recruitment age range, 19-84 years),[20] although the effects of PA according to particular ages were not assessed. The Hawaii-Los Angeles Multiethnic cohort study which studied 167 430 participants, including 472 cases of pancreatic cancer, reported no association with PA (recruitment age range, 45-75 years).[21] The Finnish Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study of 29 048 males with 172 cases of pancreatic cancer, was the only study which documented a significant inverse association with PA (HR=0.42, 95%

CI=0.22-0.83).[19] A US study in the Breast Cancer Detection Demonstration Project (BCDDP) of 33 530 participants, of which 70 developed pancreatic cancer, did not report any associations (recruitment age range, 30-91 years).[23] The Japan Public Health Centre (JPHC) study of 99 670 participants with 224 cases of pancreatic cancer, again found no associations (recruitment age range, 45-75 years).[22] The null findings in most of these studies may have been due to age-dependent PA at recruitment not being measured. This is important as PA is likely to significantly change once an individual ceases work i.e. retires, as occupational activity is a major contributor to PA levels.

In summary, this prospective study reported large, although imprecise, inverse associations with higher levels of PA in those younger than 60 years and the development of pancreatic cancer. This association was independent of BMI. The lack of associations reported from other etiological studies may be due to differences in the age at which PA was recorded and future work should perhaps specifically measure this. If a causal association is confirmed by consistent findings from other epidemiological studies, then population based PA recommendations may help to prevent this highly aggressive cancer.

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Acknowledgements

The authors thank the EPIC participants who took part in the study, their General Practitioners and the staff of EPIC-Norfolk.

Contributors: All authors were involved in the physical activity study concept, design, analysis and interpretation of data, drafting and critical revision of the manuscript. ARH supervized the data analysis and writing of the manuscript.