

## CLINICAL STUDY

## Is physical activity a protective factor against pancreatic cancer?

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**Abstract:** *Objectives:* The objective of the study was to analyze an association between selected factors and pancreatic cancer, assuming that knowing the etiology would help influence the incidence of this severe type of cancer through primary prevention. In addition to age, gender, BMI and education, the analysis aimed at assessing occupational and leisure-time physical activities with respect to pancreatic cancer.

*Background:* In numerous studies, physical activity is reported to be a protective factor against pancreatic cancer.

*Methods:* A case-control study was carried out in three centers in the Czech Republic in 2006–2009.

*Results:* The study comprised a total of 529 individuals, of which 309 were patients with pancreatic cancer and 220 were controls. Leisure-time physical activity showed a statistically significant inverse association with a crude odds ratio of 0.65 (95% CI 0.45–0.93), even after adjustment for other studied factors (OR =0.63, 95% CI 0.43–0.92). Conversely, for occupational physical activity, a positive association was only suggested.

*Conclusions:* Leisure-time physical activity is a protective factor against the development of pancreatic cancer. Occupational physical activity was not confirmed as a protective factor against pancreatic cancer (Tab. 4, Fig. 1, Ref. 22). Text in PDF [www.elis.sk](http://www.elis.sk).

Key words: pancreatic cancer, physical activity, risk.

**Abbreviations:** odds ratio – OR, confidence interval – CI, body mass index – BMI, relative risk – RR.

Pancreatic cancer is one of the most severe and most rapidly spreading cancers. Worldwide, more than 270,000 new cases are reported and more than 260,000 people die of the disease each year, with there being no significant differences in incidence between males and females (1.05 : 1)(1). The Czech Republic is among countries with high incidence and mortality rates. In 2009, the absolute number of new cases in this country was 1,968 (976 males and 992 females), and 1,687 persons (873 males and 814 females) died of the disease (2). As in other countries, in the Czech Republic there are no differences between male and female incidence rates. When comparing the incidence and mortality rates with those in other countries, the rates in Czech Republic (9/7/100,000, 808/100,000, respectively; world standard) rank second as to inci-

dence (just after Armenia), and third as to mortality (after Hungary and Israel) (2, 3). The severity of pancreatic cancer may be illustrated by survival rates which are among the worst, as well as by increasing trends with a two-fold increase in incidence between 1977 and the present time (2). The median survival for pancreatic cancer is only 3–6 months (4). About 95 % of patients die within one year, mostly within 4–8 months of diagnosis. The 5-year survival is less than 1 %. In only a small proportion of patients, i.e. in those undergoing radical surgery (about 10–20 % of all cases), the 5-year survival ranges from 3.4 % to 10 %, with a mean of 17–20 months (2, 5–7). Another problem is the early detection of this severe cancer, with only 5 % of cases being detected in stage I and vast majority of cases (more than 50 %) being detected as late as in stage IV (2).

The initial symptoms of the disease are mostly non-specific, leading to late diagnosis in most pancreatic cancer cases and thus to high mortality rates and rather poor survival. One of the first symptoms is pain which gradually becomes more intense and is often followed by manifestations of organ involvement. Other symptoms include jaundice, loss of appetite, weight loss and development of diabetes. The main problems with this type of cancer associated with limited options for prevention are the lack of screening programs allowing early detection of the disease and limited knowledge of its etiology.

Risk factors usually associated with pancreatic cancer may be either non-modifiable, such as age, gender, hereditary factors or urbanization, and modifiable, such as smoking, nutritional factors, especially excess energy intake and resulting obesity, alcohol consumption, occupational factors (asbestos, pesticides etc.)

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or health status, mainly chronic pancreatitis, cholelithiasis and diabetes mellitus. Factors with a very strong association include smoking, with a relative risk (RR) ranging from 2 to 6, some occupational factors, with RR of approximately 11 for work with herbicides, and especially chronic pancreatitis, with RR as high as 24, or diabetes mellitus, with RR as high as 6. Apart from factors increasing the risk for the development of pancreatic cancer, there are protective factors. In addition to nutritional factors, these include sufficient physical activity, which potentially lowers the risk by as much as 25 % (8).

The objective of this study was to analyze the association between selected factors and pancreatic cancer, assuming that knowing the etiology would help influence the incidence of this severe type of cancer through primary prevention. In addition to age, gender, body mass index (BMI) and education, the analysis aimed at assessing occupational and leisure-time physical activities with respect to pancreatic cancer.

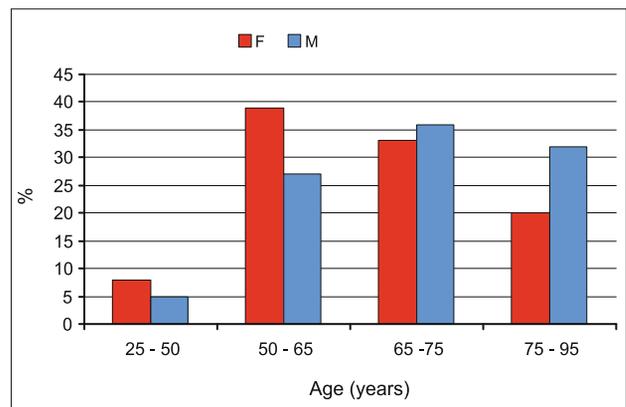
## Methods

This case-control study was carried out in 2006–2009 in three centers – Olomouc, Ostrava and Ceske Budejovice. The study comprised a total of 529 individuals, of which 309 were patients with pancreatic cancer and 220 were controls. The numbers of pancreatic cancer patients and controls in individual centers are shown in Table 1.

The group comprised 303 males and 226 females. Cases were selected in hospitals located in individual centers (University Hospital Olomouc, University Hospital Ostrava and Ceske Budejovice Hospital) among patients newly diagnosed with pancreatic cancer who lived in the particular region. Controls were recruited in collaboration with selected general practitioners to form a population control group. To avoid bias, controls and cases were from the same region. Age, gender and health status were considered. Due to difficulties with recruiting population controls, their number was lower (71 %) than the number of pancreatic cancer patients. This difference was particularly significant in the Ceske Budejovice region, with controls accounting for only 58 % of the number of cases (Tab. 1). Information was obtained directly from the participants questioned by trained interviewers using a standardized questionnaire. The questionnaire contained questions on lifestyle, including both occupational and leisure-time physical activities, education as a socio-economic factor, and health status. Data for calculating BMI were ascertained for ages 20 and 40, for 2 years prior to the development of the disease (or 2 years prior to the interview in controls), and for the time of the interview. For the analysis itself, current BMI values were used. Physical activity was divided into parts related to either occupation or leisure time. Oc-

**Table 1. Cases and controls in individual centers.**

Center	Cases	Controls	Total	Cases: controls
Olomouc	72	60	132	1 : 0.83
Ostrava	64	60	124	1: 0.94
České Budejovice	173	100	273	1: 0.58
Total	309	220	529	1: 0.71



**Fig. 1. Age distribution of individuals with pancreatic cancer and control subjects.**

cupational physical activity was defined as physical activity lasting at least one hour a week over 1 year or lasting 3 hours weekly for a period of 4 months. The intensity of activity was classified as low, moderate or high based on whether it induced no increase in pulse rate, increased pulse rate and mild sweating, or very high pulse rate and severe sweating, respectively. Leisure-time physical activity was defined as at least 26 hours of physical activity per year, which is 30 minutes weekly over 1 year or 2 hours per week for 3 months. Once again, the intensity of physical activity was assessed using the above criteria. The intensity of physical activity was self-reported by the participants.

The study was approved by the ethics committee of the Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc. Prior to their enrollment in the study, all participants gave informed consent.

Since the participants chose not to answer some questions, the answer rates for individual characteristics may vary.

To determine the prevalence of the above factors in cases and controls, the crude odds ratio (OR) with a 95% confidence interval (CI) and logistic regression were used. To determine statistical significance, a 5% significance level was used. Statistical analyses were carried out using the Stata v. 10 software.

## Results

The analysis revealed a statistically significant difference in age depending on gender, with the mean age at disease onset being significantly higher in females (68.9 years) than in males (65.4 years). Figure 1 shows the age distribution at diagnosis of pancreatic cancer.

There was no statistically significant difference in the prevalence between males and females despite the ratio of 1.4 : 1 and thus slightly higher prevalence in males. Current BMI values showed a statistically significant difference in males, with male cases having lower BMI values than male controls ( $p < 0.001$ ). Similarly, female cases had lower current BMI than female controls ( $p < 0.048$ ) which may be explained by the studied type of cancer (Tab. 2). The association between overweight and obesity

**Table 2. BMI values in cases and controls according to gender in the pancreatic cancer study.**

BMI (kg/m <sup>2</sup> ) Time	Males – arithmetic mean (SD)			Females – arithmetic mean (SD)		
	cases (N=180)	controls (N=123)	p-value	cases (N=129)	controls (N=97)	p-value
Current	24.68 (3.74)	27.89 (4.34)	0.000	25.91 (5.03)	27.25 (4.81)	0.048
Two years ago	27.05 (4.16)	27.96 (4.35)	0.071	28.08 (4.79)	27.32 (4.72)	0.240
At 20 years	24.09 (2.73)	23.57 (2.78)	0.107	22.47 (3.21)	21.77 (2.38)	0.073
At 40 years	26.51 (3.53)	26.00 (3.40)	0.216	25.48 (3.77)	24.49 (3.40)	0.044

**Table 3. Association between physical activity and other selected factors and the risk for developing pancreatic cancer expressed by crude OR.**

Risk factor	Category	Number total	Pancreatic cancer		Crude OR	95% CI
			cases	controls		
Age	≤49	37	20	17	1*	
	50 – 64.9	177	102	75	1.16	0.57–2.36
	65 – 74.9	182	111	71	1.33	0.65–2.71
	≥75	133	76	57	1.13	0.55–2.36
Gender	male	303	180	123	1*	
	female	226	130	97	0.95	0.65–1.30
Smoking	no	241	137	104	1*	
	yes	280	166	114	1.11	0.78–1.57
BMI	≥ 18.5<25 kg/m <sup>2</sup>	160	98	62	1*	
	≥25<30 kg/m <sup>2</sup>	212	121	91	0.84	0.55–1.28
	≥ 30 kg/m <sup>2</sup>	144	80	64	0.79	0.50–1.25
Education	primary	96	65	31	1*	
	vocational	185	122	63	0.92	0.55–1.56
	secondary	163	81	82	0.47	0.28–0.80
	tertiary	82	38	44	0.41	0.22–0.76
Occupational physical activity	no	185	96	89	1*	
	yes	319	190	129	1.37	0.95–1.97
Leisure-time physical activity	no	279	173	106	1*	
	yes	210	108	102	0.65	0.45–0.93
Occupational physical activity - intensity	low	43	26	17	1*	
	moderate	121	76	45	1.10	0.54–2.26
	high	29	19	10	1.24	0.47–3.31
Leisure-time physical activity - intensity	low	47	21	26	1*	
	moderate and high	126	62	54	0.70	0.36–1.39

1\*basic category

was analyzed using both the crude and adjusted ORs (OR = 0.84 and 0.79, respectively, and 0.93 and 0.79, respectively after adjustment). However, no statistically significant association was found (Tabs 3 and 4). Although smoking is considered a causative risk factor for the development of pancreatic cancer, the study failed to confirm the association (crude OR = 1.11) and this factor was not included in the logistic regression model. When analyzing whether education is related to the development of pancreatic cancer, an inverse association was found in individuals with higher education, with crude ORs of 0.47 (95% CI 0.28–0.80) for secondary education and 0.41 (95% CI 0.22–0.76) for tertiary education. When compared with primary education, higher education proved to be a protective factor, as confirmed by adjusting for other studied factors, with values of 0.47 and 0.45, respectively. Unlike the occupational physical activity, in which a positive association was suggested and the bias was likely due to other occupation-related factors, the leisure-time physical activity showed a statistically significant inverse association and a 35 % decrease in the risk (crude OR = 0.65, 95% CI 0.45–0.93). Even after adjustment for other studied factors (OR = 0.63; 95 % IS 0.43–0.92) the result stayed statistically significant. When calculating the crude OR for occupational physical activity, its intensity (low, moderate or high)

was taken into consideration. To assess leisure-time physical activity, however, the moderate and high categories of intensity were merged into a single one due to a low number of participants, with no statistical significance. The assessment of leisure-time physical activity in pancreatic cancer patients and controls showed that individuals with pancreatic cancer undertake less physical activity in their leisure time and the difference was statistically significant ( $p = 0.019$ ). The results are summarized in Tables 3 and 4.

## Discussion

Pancreatic cancer is a disease that most frequently develops at the age of 45–80 years, with the peak incidence in the Czech Republic in the age group of 65–74 years for males and in the age group of 75–79 years for females. In the study group, the mean age was 65.4 years for males and 68.9 years for females, with the difference between genders being statistically significant. Although the mean ages in both males and females were lower than the national peak rates for the incidence of pancreatic cancer, there is an apparent gender difference in age at the onset of this cancer, with females being older than males at the time of diagnosis (2). In the presented study, slightly more males than females were affected by

**Table 4. Association between physical activity and pancreatic cancer risk in the logistic regression model.**

Risk factor	Category	Total number	Pancreatic cancer		Adjusted OR	95% CI	p-value
			cases	controls			
Age	≤49	37	20	17	1*		
	50 – 64.9	177	102	75	0.82	0.37–1.82	0.637
	65 – 74.9	182	111	71	1.08	0.49–2.38	0.854
	≥75	133	76	57	0.77	0.34–1.74	0.537
Gender	male	303	180	123	1*		
	female	226	129	97	0.88	0.58–1.32	0.524
BMI	≥ 18.5 < 25 kg/m <sup>2</sup>	160	98	62	1*		
	≥ 25 < 30 kg/m <sup>2</sup>	212	121	91	0.93	0.58–1.47	0.751
	≥ 30 kg/m <sup>2</sup>	144	80	64	0.79	0.47–1.32	0.368
Education	primary	96	65	31	1*		
	vocational	185	122	63	0.90	0.50–1.64	0.736
	secondary	163	81	82	0.47	0.26–0.85	0.012
	tertiary	82	38	44	0.45	0.22–0.90	0.023
Occupational physical activity	no	185	96	89	1*		
	yes	319	190	129	1.27	0.85–1.91	0.247
Leisure-time physical activity	no	279	173	106	1*		
	yes	210	108	102	0.63	0.43–0.92	0.018

1\*basic category

pancreatic cancer. According to Olson, this may be due to smoking habits (9). The presented study, however, failed to confirm the association between smoking and higher risk for pancreatic cancer. Similarly, pancreatic cancer was not statistically significantly more frequent in males in the study group. Since pancreatic cancer is strongly age-dependent, the population aging trend will result in an increase in the incidence of pancreatic cancer in the following decades, mainly in countries with longer life expectancy (10).

Obesity is one of the few risk factors considered to be associated with this type of cancer. Numerous epidemiological studies and meta-analyses have confirmed that the risk mostly ranges from weak to strong association, namely between 1.1 and 2.8 (9, 11, 12). Plausible mechanisms of the impact of obesity include inflammatory and hormonal effects of adipose tissue, energy imbalance, and increased exposure to carcinogenic substances due to increased food consumption and lower physical activity (11). Maintaining normal body weight is an adequate means of decreasing pancreatic cancer morbidity and mortality (14). The earlier the overweight or obesity develops, the higher the risk. Rosato et al. found that individuals who were overweight at the age of 30 had an OR of 1.27 (95% CI, 0.91–1.78) (15). This study, however, failed to show the positive association between overweight or obesity and higher risk for pancreatic cancer. Increased body weight between early adulthood and old age is also associated with a higher risk for the development of pancreatic cancer (9, 13). Although such an increase was observed in this study, there were no differences between the cases and controls.

Education and housing are considered to be factors allowing the assessment of the socio-economic status. Especially the level of education significantly influences the socio-economic status of both individuals and entire families as well as their hierarchy of values and behavior. After completion of studies, the level of education no longer changes and it therefore cannot be affected by potential deterioration of health in adulthood (16–18). Results of the study showed protective effects in individuals with second-

ary or tertiary education, with the risk being decreased by more than 50 %.

The association between the physical activity and the risk for developing pancreatic cancer is not consistently reported in studies. The analysis included both occupational physical activity and leisure-time physical activity, suggesting in the former a positive association but statistically non-significant results affected by confounding occupational factors, rather than by physical activity. Epidemiological studies on the relationship between physical activity and pancreatic cancer risk mostly found an inverse association and risk decrease by 12–37 % (8). In case of occupational activity, this protective effect was not confirmed by the presented study. However, the results may be distorted by lower education, occupational exposure, smoking and other factors such as age and gender. Leisure-time physical activity proved to be a significant protective factor, with a risk decrease of 72 %. At the same time, 64 % of responders (both cases and controls) described their activity as moderate. According to the Second Expert Report published by the World Cancer Research Fund in 2007, excess body weight increases the risk for developing pancreatic cancer and, therefore, the risk may be decreased by maintaining the weight. Although the results are not consistent, some studies showed an inverse association between physical activity and pancreatic cancer (19, 20). Physical activity has been proved to have beneficial effects on metabolic processes as it decreases glucose levels, increases utilization of glucose in the organism, affects lipid profile, positively influences blood pressure and reduces the amount of body fat. Regular physical activity is the most important factor in preventing the development of obesity and diabetes in individuals with impaired glucose tolerance. The effect of physical activity is complex, affecting the development of obesity, insulin resistance and diabetes mellitus, i.e. the potential risk factors for pancreatic cancer (20). Physical activity on its own or in combination with dietary modifications decreases the incidence of obesity, which in turn affects the incidence of type 2 diabetes and thus also the

incidence of pancreatic cancer. Michaud et al. pointed to the protective effect of physical activity against pancreatic cancer with weight reduction, particularly in obese persons (21). Physical activity also decreases DNA damage by increasing the effectiveness of antioxidant enzymes, affects carcinogenesis through glutathione S-transferase, influences cell proliferation and apoptosis, reduces inflammation by strengthening the immune system and suppresses angiogenesis (22). Through physiologically plausible mechanisms, physical activity may contribute to prevention of the development of this type of cancer (19).

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