RISK FACTORS IN PANCREATIC CANCER

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ABSTRACT

PREVIOUS STUDIES HAVE SHOWN A VARIETY OF RISK FACTORS THAT MAY BE INVOLVED IN THE AETIOLOGY OF PANCREATIC NEOPLASIA. WE EXAMINED RISK FACTORS FOR PANCREATIC CANCER IN A CASE–CONTROL STUDY CONDUCTED IN FUNDENI CLINICAL INSTITUTE BETWEEN SEPTEMBER 2016 AND SEPTEMBER 2018, THAT INCLUDED 74 INCIDENT CASES AND 74 CONTROLS ADMITTED FOR NON-NEOPLASTIC DISEASES, FREQUENCY-MATCHED TO CASES BY SEX AND AGE. LOGISTIC REGRESSION MODELS WERE USED FOR MULTIVARIATE OR SUCH AS SEX, AGE, DIABETES, VIRAL HEPATITIS, SMOKING AND ALCOHOL CONSUMPTION STATUS, AND OTHER PERSONAL AND FAMILIAL HISTORY. OUR FINDINGS SUPPORT PREVIOUS STUDIES INDICATING THAT DIABETES IS A RISK FACTOR FOR PANCREATIC CANCER (OR 4.8, P<0.05). CHOLECYSTECTOMY ALSO APPEARED TO BE A RISK FACTOR, SUBJECTS WITH A CHOLECYSTECTOMY AT LEAST 20 YEARS PRIOR TO THE DIAGNOSIS OF PANCREATIC CANCER EXPERIENCED AN INCREASED RISK, WHICH WAS MARGINALLY SIGNIFICANT. IN CONTRAST, SIGNIFICANT 2- FOLD (P<0.05) REDUCED RISK WAS ASSOCIATED WITH ALLERGIES. IN ADDITION, WE OBSERVED SIGNIFICANTLY INCREASED RISKS FOR SUBJECTS WHO SMOKED OR ARE CURRENTLY SMOKING. THIS STUDY DEMONSTRATES THE ROLE AS RISK FACTORS OF SOME ENVIRONMENTAL FACTORS, PERSONAL AND FAMILIAL HISTORY, BUT THESE ASSOCIATIONS, HOWEVER, MAY BE DUE TO CHANCE SINCE THE NUMBER OF INDIVIDUALS INCLUDED IN THE STUDY IS REDUCED.

KEY WORDS: PANCREAS, CANCER, RISK FACTORS, DIABETES, ALCOHOL DRINKING, SMOKING, MEDICAL CONDITION

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Introduction: Pancreatic cancer is the 4th leading cause of cancer-related death for both men and women, and it is the 11th most commonly diagnosed cancer in men and the 8th in women world-wide. In Romania epidemiological data are not very accurate because they are from regional registries, because a national programme for patients with oncologic disease is lacking and the incidence seems to be 7.9/100,000 habitants.

A study published in 2014, conducted in USA, which took into consideration demographic changes showed that mortality caused by pancreatic cancer will continue to rise, exceeding mortality caused by colorectal cancer, reaching the second place by 2030,[5] therefore pancreatic cancer becomes one of the most lethal neoplastic diseases. This fact is due to the location of the pancreas that is not very accessible for screening, so the diagnosis is delayed and also because of rapid progress, and resistance to chemotherapy and radiotherapy, 5 year- survival rate after diagnosis being under 6%.[6]

There are several studies approaching the risk factors in the evolution of pancreatic cancer, but except for smoking, most results are contradictory.

The unfavourable prognosis and high mortality in a relatively short term and the incidence that is continuously increasing, and the high variability between countries and even regions, suggest the impact of genetic factors, lifestyle and medical history in the aetiology of pancreatic neoplasia. Identifying these factors may help preventing and making an early diagnosis of this disease, as currently the diagnosis is made frequently in advanced stages, just 20% of the cases having the possibility of surgical resection.

We examined the newly developed literature-derived risk factors for pancreatic cancer in a case–control study conducted in Romania between September 2016 and September 2018. This included 74 incident cases and 74 controls admitted to the Fundeni Clinical Institute in Bucharest for non-pancreatic neoplastic diseases, frequency-matched to cases by sex and age. Logistic regression models were used for multivariate OR such as sex, age, diabetes, viral hepatitis, smoking and alcohol consumption status, and other personal and familial history. The control series was drawn from medical stuff and patients admitted in the hospital, without pancreatic neoplasia. The information about the detailed medical conditions, family history of cancer, diabetes, smoking habits, alcohol consumption, coffee drinking, ordinary occupation were drawn either by a questionnaire and by blood or faeces analysis (for infection with hepatitis B or C, blood group respectively Helicobacter Pylori infection). Prior to the interview, written informed consent to participate in the study was obtained from each person. Subjects were queried about their height and weight, at diagnosis, one or 5 years prior diagnosis, and also from 10 to 10 years from the beginning of the adult life, which was used to compute body mass index. We queried subjects to obtain detailed information on the following medical conditions and interventions: diabetes mellitus (type, treatment, onset of diagnosis), cholecystectomy, pancreatitis, gastrectomy, allergies. Subjects were asked questions regarding their age at onset and duration of each medical condition. Regarding diabetes we obtained detailed information on the use of insulin and other drugs to treat diabetes mellitus. Only one case and one control reported a hospitalization of pancreatitis and none had hepatitis C infection prohibiting any detailed analysis of the potential

[5] StatesLola Rahib, Benjamin D. Smith, Rhonda Aizenberg, Allison B. Rosenzweig, Julie M. Fleshman and Lynn M. Matrisian Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver, and Pancreas Cancers in the United States American Association for Cancer Research, 2014,july
[6] Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60:277–300

risk factor. With regard to family history of cancer, subjects were asked whether any first degree blood relative ever had cancer, and if so, to specify the type of neoplasm.

In the pancreatic cancer group the average age at diagnosis was 65.29 years, ranging from 45 to 86 years old. The female to male sex ratio was 1.17:1. While using t-test, the interval confidence of 95% for age and sex, significant differences (P >0.5) were not noticed.

Tobacco consumption is the most well-established risk factor in pancreatic cancer, in a meta-analysis that included 47 case-control and 35 cohort studies, the calculated risks were estimated for current and former smokers to be 1.7 and 1.2.[7] In our study, in the pancreatic cancer group 40.54 % were ex-smokers, and 18.19% were still smoking, and in the control group 28% were smokers, and 14% were ex-smokers, so the risk was 3 times higher for current and former smokers for pancreatic cancer (p<0.05) than for those who had never smoked.

Alcohol consumption seemed not to be a significant risk factor (p >0.5 OD 1.3) although there was a higher incidence in the pancreatic cancer group: 70%, respectively 50%.

Regarding coffee consumption, there wasn`t a significant difference between the groups, although there seemed to lower the risk for pancreatic cancer, but insignificant (OR 0.7, 95% Cl 0.28-1.8, p>0.05)

Although there are several studies and even a meta-analysis regarding principal jobs and occupational exposure associated with pancreatic cancer, there is no consensus; in our study, 43.24% subjects were exposed to different substances like pesticides, solvents, chloride and diesel, and just 10.81% in the control group, resulting a significant risk for those exposed (OR 6.28, 95%Cl 1.87-21,3, P<0.01).

Regarding allergies, there was seen a significant difference between the two groups, with a frequency of 43.24% in the control group and 18.91% in the pancreatic neoplasia group, subjects with a history of allergic condition having a significantly reduced risk (OR 0.3 95%Cl 0.1-0.87, P<0.05)

A significantly positive risk for pancreatic cancer was seen in patients with diabetes (OD 5.44; 95% Cl 1.38-21.33; p <0.05). Diabetes was frequently type 2 (97%). The onset of diabetes was seen on average with 6.63 years prior to the diagnosis of pancreatic cancer, 2 months the earliest, and 16 years the latest. A higher prevalence for subjects with onset of diabetes within 2 years of diagnosis of cancer was seen (fig. 1). Patients recently diagnosed with type II (<2 years) needed insulin therapy in the beginning in 80% of cases, and those diagnosed later (>2 years) 50% needed changing of oral anti-diabetes with insulin therapy at 1 year prior to pancreatic cancer being diagnosed. The median age for the diagnosis of pancreatic cancer in patients with diabetes was 64.73 years similar to those without neoplasia.

Cholecistectomy represents a significant risk factor for panceatic cancer (OR 6.05; 95% 1.2-30.42 p<0.05), 24% of cases been cholecistectomised within 20 years before the pancreatic cancer diagnosis.

Little or no excess risk was associated with having or having had viral hepatits B (OR 1.3; 95% Cl 0.28 – 6.61 p >0.5) or gastrectomy (OR 2.05 95% Cl 0.17-23.72, p>0.5)

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[7] Iodice S Gandini S Maisonneuve P et al. Tabacco and the risk of pancreatic cancer: a review and meta-analysis. LanfebecksArch Surg 2008;393:535-545

CONCLUSIONS

Our findings indicate that diabetes mellitus is a risk factor for pancreatic cancer. The association between diabetes mellitus and pancreatic cancer has been evaluated in multiple studies and several meta-analyses [8,9,10] with most indicating a positive relation. The question arising from this is whether diabetes is an etiological factor or a consequence of pancreatic neoplasia during a pre-diagnosis stage. In our study, the diabetes occurred frequently around the time of cancer diagnosis, and needed insulin therapy and the diabetes diagnosed about 2 years earlier imposed changing the therapy to insulin, this fact therefore suggesting that it may rather be a consequence than an etiological factor.

Another finding of our study was the positive association between cholecystectomy and pancreatic cancer risk. This finding was seen also in several studies[11], but cholecystectomy's principal risk factor is obesity, and the latter also represents a risk factor for pancreatic cancer, all these suggesting the necessity of studies aiming at clarifying if it really represents a risk factor per se or is secondary to obesity.

In our study there was not seen significant risk associated with having had gastrectomy or viral hepatitis B, although most reviews reported a positive association, with relative risk ranging from 1.2 to 3.8 according to HBV carrier status.[12,13,14] This difference may occur because of the reduced number of subjects included in the study and the high incidence of hepatitis B in Romania (17.93 cases at 100,000 habitants)[15].

History of allergies is the only factor that seems to have a protective effect for pancreatic cancer, this was also reported in some studies.

Tobacco is the most well established risk factor for pancreatic cancer, and this was also confirmed in our study.

Even if there are several studies on risk factors, the majority of patients are diagnosed in advanced stages, when they present metastases or are no longer candidates for curative resection. With continuously increasing incidence we need to make multicentre studies, which will include more subjects in order to identify the main risk factors and high-risk individuals and then offer them a personalised screening program.

[8]Everhart J wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. The Journal of the American Medical Association 1995; 273:1605-09

[9] Huxeley R Ansary-Moghaddam A Berrington de Gonzalez A et al. Type II diabetes and pancreatic cancer a meta-analysis of 36 studies. British Journal of Cancer 2005; 92:2076-2083

[10]Pisani P. Hyper-insunaemia and cancer, meta-analyses of epidemiological studies. Arch Physiol Biochem 2008;113:63-70

[11] Ling G zeng Z Wang X Wu Z et al. Cholecystectomy and risk of pancreatic cancer: a meta-analysis of observational studies. Cancer causes Control 2012;23:59-67

[12] Wang Y Yang S Song F et al. Hepatitis B virus status and the risk of pancreatic caner: a meta-analysis. European Journal of Cancer Prevention 2013;22:328-324

[13] Fiorino S Chili E Bacchi-Reggiani L et al. Association between hepatitis B or hepatitis C virus infection and risk of pancreatic adenocarcinoma development: a systematic review and meta analysis. Pancreatology 2013;13:147-160

[14] Xu JH Fu JJ Wang XL et al. Hepatitis B or C viral infection and risk of pancreatic cancer: a meta-analysis of observational studies. World Journal Gastroenterology 2013;19:4234-4241

[15] European Centre for Disease Prevention and Control (ECDEC) Annual epidemiological report Food and waterborne diseases and zoonoses 2014