Pancreatology xxx (2015) 1–5

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original article

Early onset pancreatic cancer: Risk factors, presentation and outcome

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Pancreatic cancer
Early onset
Smoking
Family history
Metastasis
Survival

ABSTRACT

Background: About 10% of pancreatic cancer patients are aged ≤50 at diagnosis and defined as Early Onset Pancreatic Cancer (EOPC). There is limited information regarding risk factors for EOPC occurrence and their outcome.
Aim: To investigate risk factors, presentation features and outcome of EOPC patients.
Methods: Consecutive, histologically confirmed, pancreatic cancer patients enrolled. Data regarding environmental and genetic risk factors, clinical and pathological information, treatment and survival were recorded. EOPC patients (aged ≤50 at diagnosis) were compared to older subjects.
Results: Twenty-five of 293 patients (8.5%) had EOPC. There was no difference regarding sex distribution, medical conditions and alcohol intake between EOPC and older subjects. EOPC patients were more frequently current smokers (56% vs 28% $p = 0.001$) and started smoking at a significantly lower mean age (19.8 years, 95%CI 16.7–22.9) as compared to older patients (26.1, 95%CI 24.2–28) ($p = 0.001$). Current smoking (OR 7.5; 95%CI 1.8–30; $p = 0.004$) and age at smoking initiation (OR 0.8 for every increasing year; 95%CI 0.7–0.9; $p = 0.01$) were significant and independent risk factors for diagnosis of EOPC. There were no differences regarding genetic syndromes and pancreatic cancer family history. EOCP presented less frequently with jaundice (16% vs 44%, $p = 0.006$) and had a higher rate of unresectable disease, albeit not significantly (84% vs 68%, $p = 0.1$). EOPC patients were more frequently fit for surgery or chemotherapy than their counterpart, resulting in similar stage-specific survival probability.
Conclusion: EOPC seems related to active and early smoking but not to familial syndromes. Young patients display aggressive disease but not worse outcome.

Introduction

Pancreatic Ductal Adenocarcinoma (PDAC) is the most common and lethal type of neoplasia occurring in the pancreas. Its incidence has progressively increased in Western countries, possibly due to changes in lifestyle [1]. The prognosis of PDAC is dismal, due to delayed diagnosis, biological aggressiveness and poor response to medical treatment [1,2]. PDAC is therefore the 12th most common cancer type by incidence for both sexes, the 7th cause of cancer-related death for men and 8th for women [2]. The median onset age of PDAC is between 65 and 75 [1–4], however, the diagnosis of PDAC might occur a decade or more before this age. Previous studies have defined as affected by "Early Onset Pancreatic Cancer" (EOPC), patients with tumour occurring within 50 years of age, with the rate of EOPC ranging between 5 and 10% of all PDAC cases in different series [5–7]. EOPC is considered to be more frequent in individuals with inherited genetic syndromes associated with an increased risk for PDAC, such as Hereditary Pancreatitis [8], Familial Atypical Multiple Mole Melanoma [9], Peutz Jeghers Syndrome [10] and Breast Ovarian Cancer Syndromes

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http://dx.doi.org/10.1016/j.pan.2015.01.013

(BRCA1/2) [11]. The age of onset of PDAC is also lower in subjects with Familial Pancreatic Cancer (FPC), a dominant autosomic disorder for which no specific genetic defect has been identified [12]. In such familial syndromes, a progressive anticipation of onset age among generations has been reported and the age of onset is further anticipated in smokers [13].

Raimondi et al., indirectly suggested a relationship between heavy smoking and early onset of pancreatic cancer in European countries [14]. Others have investigated the histological and molecular features of EOPC and reported a high rate of mucinous or adenosquamous variants and a low rate of KRAS mutations [15,16].

One might, therefore, hypothesize that EOPC patients are characterized by a high rate of family history of neoplasms and by peculiar exposures. However, there are no studies specifically investigating other risk factors, such as alcohol, for EOPC in patients without "genetic syndromes". It is also unknown whether other medical conditions already reported as associated with the risk of developing pancreatic cancer, such as chronic pancreatitis, peptic ulcer and cholecystectomy, might be relevant for EOPC. Furthermore, while for other cancer types such as colorectal cancer [17], it has been reported that early onset cases display distinct, more aggressive features at diagnosis, but do not show a worse stage-specific survival as compared with patients with later-onset cancer, knowledge about presentation and survival of EOPC is limited.

This study is therefore aimed at investigating risk factors for the occurrence of EOPC, its features at presentation and the outcome of EOPC patients in terms of received treatments and survival.

Materials and methods

Study design and population

A retrospective analysis of consecutive cases of patients with incident (diagnosed within 6 months before the interview), histologically confirmed, PDAC, prospectively seen between January 2006 and January 2013 at the S. Andrea Hospital, University of Rome, was performed. Patients were interviewed by trained medical doctors who filled in a specific questionnaire to collect data on demographics, possible environmental and genetic risk factors (such as smoking history, alcohol use, body mass index, medical history, family history of cancer) and on clinical symptoms leading to the diagnosis of PDAC.

To avoid possible bias due to cancer symptoms or subsequent cancer therapies (either surgical or medical), patients were interrogated about risk factors present 12 months before diagnosis or presentation symptoms. No proxies were interviewed. All patients gave written informed consent. Data about tumour stage at diagnosis and histological grading were also collected. Patients received appropriate medical treatments and their outcome was recorded in a dedicated database. The study received approval from the local Hospital Review Board.

Risk factor assessment and exposure definitions

Ever smokers were defined as subjects reporting >6 months of smoking or >100 cigarettes smoked during their lifetime. The following data about smoking were recorded for each patient: age at smoking initiation, mean daily number of smoked cigarettes and total years of smoking. For former smokers, the number of years since quitting smoking was also recorded.

Ever-alcohol drinkers were defined if they drank at least a mean of 12.5 g of alcohol per day for at least 1 year, or a lower amount for >1 year. One glass of wine, one pint (or can) of beer and one shot of hard liquor were all considered equal to one alcohol unit (~12.5 g of alcohol). The number of mean alcohol units per day drunk by patients was recorded [18,19].

Subjects were asked about the first- and second-degree relatives' cancer history. When available, data on the number of family members with cancer, type(s) of cancer and age at cancer diagnosis were recorded. As far as regards symptoms, cachexia was defined as weight loss >5% [20].

For the present study, patients with EOPC were defined as aged ≤50 at the time of diagnosis of PDAC. Patients with EOPC were compared to those aged >50, that were defined as "Normal Onset Pancreatic Cancer" (NOPC) patients and served as control group.

Statistical analysis

Differences between EOPC and NOPC in terms of risk factors, neoplasm features and outcome were analysed. Fisher test for comparison of proportions for categorical variables and Student's t-test or Mann–Whitney test for continuous variables were employed. Multiple logistic regression analysis was employed to investigate factors associated with risk of EOPC. Survival probability was calculated with the Kaplan–Meier curve and Cox analysis was employed to calculate hazard ratios (HR). Tests of statistical significance and confidence intervals were two-sided; a $p < 0.05$ was considered to be statistically significant. A dedicated software (MedCalc, Mariakerke, Belgium) was used throughout the study.

Results

General features and incidence of early onset pancreatic cancer

Twohundred-93 patients with PDAC were enrolled. A histological or cytological diagnosis was obtained in all cases either from the primary pancreatic lesion or from metastases. Of the 293 patients, 158 (54%) were male, with a median age of 68 years (95%CI 66–69) at diagnosis. Ninty-one (31%) patients had potentially resectable disease at diagnosis, 88 (30%) locally advanced disease and 114 (39%) distant metastasis. Twenty-five (8.5%) patients were diagnosed at age ≤50 years and defined as Early Onset Pancreatic Cancer.

Factors associated with early onset pancreatic cancer

Patients' history and environmental risk factors

Gender distribution was not significantly different between EOPC and NOPC patients, but a higher rate of male patients was observed in younger patients (68% vs 48%; $p = 0.2$). As far as regards previous medical history (see Table 1), there were no differences in terms of previous history of cholecystectomy, chronic pancreatitis or peptic ulcer. The analysis of potential risk factors is reported in Table 2.

EOPC patients were more frequently current smokers (56% vs 28% $p = 0.001$) 12 months before diagnosis. There was no difference regarding prevalence of ever smokers (72% vs 61% $p = 0.4$) between EOPC and NOPC patients. EOPC patients, however, started smoking at a significantly lower mean age (20 years, 95%CI 17–23) as compared with NOPC (26, 95%CI 24–28) ($p = 0.0012$). The mean number of smoked cigarettes per day was not different between EOPC (23; 95%CI 18–28) and NOPC patients (23; 95%CI 20–25) ($p = 0.96$).

As far as regards the 100 NOPC patients classified as "former-smokers", the mean interval of time from quitting smoking to the diagnosis of PDAC was 20 years (95%CI 18–24).

The percentage of ever-alcohol drinkers (36% of EOPC vs 42.5% of NOPC $p = 0.6$) was similar amongst the two groups. The mean number of alcohol units drunk per day was not different between

Please cite this article in press as: Piciucchi M, et al., Early onset pancreatic cancer: Risk factors, presentation and outcome, Pancreatology (2015), http://dx.doi.org/10.1016/j.pan.2015.01.013