PANCREAS NEWS

Screening Tests for Pancreatic Cancer:
Searching for the Early Symptoms or the Population at Risk

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In the past four decades, the incidence of pancreatic cancer has increased steadily in most of the world and now this type of tumor ranks as the fifth or sixth most frequent cause of death due to cancer in many western countries [1]. For example, in 2000, worldwide figures for pancreatic cancer were projected at 216,400 new cases and 213,500 deaths [2]; the data coming from the United States in 2004, estimated that 31,860 patients would be diagnosed with pancreatic cancer and 31,270 would die of the disease [3]. The 5-year survival rate estimated by the Surveillance Epidemiology and End Results program is 4% and this figure is the lowest for all types of cancer [4]. Late diagnosis and the subsequently low resection rate is the major reason for the poor survival of these patients.

Despite technological advances, the diagnosis of pancreatic cancer continues to be made very late and the prognosis remains extremely poor. This delay in diagnosis is, for the most part, due to the fact that abdominal pain and jaundice, which are the main symptoms of pancreatic cancer, appear late when the tumor is already in an advanced stage [5]. Moreover, if we consider that the many epidemiological studies performed so far have failed to identify significant risk factors for pancreatic cancer which might facilitate its early diagnosis or prevention [6], the resulting picture is extremely poor.

At present, the only source of hope of reaching a more rapid diagnosis of this type of cancer would seem to come from the clinical history and, in particular, from the presence of earlier symptoms which could induce patients to seek medical advice at a time when the tumor might be smaller and treatment more feasible. Surprisingly, despite the large number of studies on pancreatic cancer, very little is known on this topic. Early studies reported the existence of early symptoms such as sudden onset of diabetes mellitus, weight loss tiredness and malaise, change in bowel habits, and upper abdominal discomfort of pancreatic cancer; however, either the time of onset [7] or the symptoms themselves [8] were not specified.

Three years ago, a study carried-out in Italy involving a large series of patients with pancreatic cancer was published. Its objective was to investigate whether symptoms exist before the pain and/or jaundice that could suggest the possibility of pancreatic cancer and thus help earlier recognition of the tumor [9]. The authors found that of the 305 pancreatic cancer patients, 49.5% had some disturbances shortly before diagnosis, 35.4% had problems 6 months or less before diagnosis (pain or jaundice) and 14.1% had problems more than 6 months before diagnosis. Among the latter, 14 (4.6% of all patients) had had anorexia and/or early satiety and/or asthenia (7-20 months before pain or jaundice), 11 (3.6%) had disgust for coffee and/or smoking and/or wine (7-20 months before), 14 (4.6%) had diabetes (7-24 months before), and four (1.3%) had acute pancreatitis (8-26 months before). Among the

controls, the only reports of these symptoms were two (0.7%) cases of asthenia (4 and 6 years earlier), 22 (7.2%) cases of diabetes (of which only two were diagnosed 7-24 months before the interview), and one (0.33%) case of acute pancreatitis (10 years earlier). Apart from acute pancreatitis, all the differences between patients and controls were statistically significant. In approximately 15% of the patients, disturbances which, although not specific, could have raised suspicion of the possibility of pancreatic cancer had existed for more than 6 months before pain or jaundice. However, in this study, no information on the so-called early symptoms and the possible survival rate was reported.

A possible aid is that of the study coming from the U.S. [10]. In this population-based study, data coming from 120 consecutive patients with pancreatic cancer and control participants of the San Francisco Bay Area enrolled between 1994 and 2001 were collected and analyzed.

Patients with pancreatic cancer 21-85 years of age were identified by the Northern California Cancer Center's rapid case ascertainment within 1 month of diagnosis in hospitals in 6 Bay Area counties. To confirm diagnoses, the Surveillance Epidemiology and End Results abstracts were obtained from the Northern California Cancer Center which identified all pancreatic cancer cases in the Bay Area about 18 to 24 months after diagnosis.

Control participants were identified by using random digit dial and Health Care Financing Administration files to supplement the recruitment of those equal to or greater than 65 years of age. All control participants were matched to patients with pancreatic cancer according to sex and age within 5 years.

In addition to interviews administered in person, a questionnaire was designed to collect clinical data pertaining to the 5 years before diagnosis or interview. It included signs and symptoms of pancreatic cancer previously reported in the literature, and the diagnostic tests and procedures conducted in order to evaluate the cause of the reported symptoms. The rule used to set the symptom-specific minimum duration for controls was one half the median duration reported by patients for each symptom, except for fatigue and altered sleep.

The clinical questionnaire was carried out as a telephone interview to 180 age- and sex-matched population-based control participants. Most signs and symptoms occurred within 3 years before diagnosis with pancreatic cancer in the cases and interview in the controls; many signs and symptoms were more likely to have been reported by patients as compared to control participants and included appetite loss, pale stools, abdominal pain, jaundice, unusual bloating, unusual belching, weight loss, dark urine, constipation, diarrhea, itching, fatigue, altered ability to sleep, and unusual heartburn.

As expected, the tumor extent was significantly associated with symptoms of bile duct obstruction and abdominal pain, and surgical resection was associated with symptoms of bile duct obstruction, abdominal pain, and unusual bloating. In hierarchical modeling which used factors identified in the initial analyses of symptoms taken singly, the model that best differentiated resected tumors from non-resected tumors based on the model score chi-square statistic included tumor extent, jaundice, and dark urine.

Diabetes mellitus was diagnosed in 18 of 120 patients with pancreatic cancer (15%); in 4 of these patients (3%), diabetes was diagnosed within the 3 years before their pancreatic cancer diagnosis. Of the 4 patients with recent diabetes, 1 patient had a tumor confined to the pancreas, 2 patients had tumors with regional spread, and 1 patient had a tumor with distant metastasis; none of these 4 patients had undergone surgical resection, thus confirming the results of a previous Italian study [11]. This study further confirm that pancreatic cancer is typically diagnosed at a relatively advanced stage. Most patients are diagnosed when pancreatic cancer becomes symptomatic; abdominal pain and jaundice as primary symptoms often appear late when the tumor is advanced; some of the common presenting symptoms such as dyspepsia and

weight loss have an insidious onset and are easily mistaken for other diseases or functional disorders.

A prompt diagnosis of pancreatic cancer comes from a careful clinical history and appropriate tests and our hope is that, in the near future, we will able to identify a larger risk population than that known at present, such as members of families with a history of pancreatic cancer, as well as those of families with distinct hereditary cancer syndromes such as Peutz-Jeghers syndrome, hereditary pancreatitis, familial atypical multiple mole melanoma syndrome, hereditary breast and ovarian cancer syndrome and hereditary non-polyposis colorectal cancer.

The identification of germline mutations in genes predisposing to pancreatic cancer, together with the analysis of exogenous risk factors, could be used for a more precise risk assessment for the development of this neoplasm. This may allow the application of non-invasive or invasive screening methods for the identification of early pancreatic cancer or, even better, its precursor lesions in high-risk individuals, providing the option of timely curative pancreatectomy.

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