Risk factors and possibility of prevention in pancreatic cancer

Factori de risc şi posibilităţi de prevenţie în cancerul pancreatic

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Abstract

Pancreatic cancer is an uncommon tumor but is characterized by extremely aggressive behaviour, has a high fatality rate with on overall 5 years survival rate under 4 %. Beside age, race and genetic factors (germline mutations, genetic polymorphisms), several lifestyle and environmental factors have been reported to contribute to the development of this disease. The etiology of pancreatic cancer remains partial unknowed, in consequency the prevention is difficult to accomplish. There are no entirely effective screening strategies currently available. For high-risk individuals, with a strong family history of pancreatic cancer or genetic syndrome, screening techniques such as magnetic resonance or endoscopic ultrasound guided fine-needle aspiration is the only approach to detect precancerous or early cancerous changes.

Keywords: *pancreatic cancer, prevention, screening.*

Rezumat

Cancerul pancreatic este o afecţiune mai puţin frecventă decât alte neoplazii, dar are o evoluţie gravă, o rată mare de mortalitate şi o rată de supravieţuire la 5 ani de la diagnostic mai mică de 4%. Pe lângă vârstă, rasă, factori genetici (mutaţii ale unor gene, polimorfism genetic), o serie de factori ai mediului ambiental şi ai stilului de viaţă pot contribui la apariţia bolii. Etiologia cancerului pancreatic nu este în întregime elucidată, în consecinţă, prevenţia este dificil de realizat. Nu există o metodă de screening cu aplicabilitate în populaţia generală. Pentru persoanele la risc foarte înalt, cei cu antecedente familiale de cancer pancreatic sau cu sindroame genetice, screeningul, folosind metode performante cum sunt rezonanţa magnetică sau endoscopia cu ultrasunete ghidată şi cu aspiraţie de fragmente tumorale, reprezintă o modalitate foarte promiţătoare pentru detectarea leziunilor precanceroase sau a cancerelor timpurii.

Cuvinte-cheie: *cancer pancreatic, prevenţie, screening.*

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Pancreatic cancer (PC) is one of the most lethal of all human cancer, being the 4th cause of cancer mortality in the United States, 5th in Japan and the 6th in Europe and New Zealand [1].

Because of high fatality rates, the trend in incidence and mortality follows a very similar pattern, the incidence rate is being almost equal to mortality rate.

The incidence of the disease is high in industrialized nations such as USA, Western Europe, New Zealand. In these areas the rate have been stabilized over the past 2 decades, but continue to increase in countries where rates were relatively low 3-4 decades ago, such as Japan. The lowest incidence has been noted in Africa (Malawi) [2].

Cancer of the pancreas is a silent disease remaining asymptomatic until late in the natural history of the disease [3].

Current clinical detection methodologies are inadequate to detect disease in early phase (preinvasive or early invasive) when it is curable [4].

Although the survival rates increase in the last time, they remain short, approximately 24 % within one year of diagnosis and under 4 % five years after diagnosis [5, 6].

The prognosis for persons diagnosed with PC is poor, partly due to non-specific symptoms in the beginning stages of the disease, partly because there is not a screening test that can be used in general population being in the same time cost-effective [6 - 8].

The incidence of PC worldwide appears to correlate with increasing age, it is slightly more common among men, Afro-americans and Ashkenazy jewish people [5].

Pancreatic cancer susceptibility is associated with a combination of environmental, lifestyle and genetic factors [8]. An overall estimation indicates that 40 % of PC are sporadic in nature, 30 % related to smoking, 20 % may be associated with dietary factors, 5-10% are associated with genetic disorders and less than 5% are related to chronic pancreatitis [6]. Most of the knowledge regarding etiology of this disease comes from conventional epidemiological studies. Cigarette smoking is the most prominent and consistent lifestyle risk factor in PC, the relative risk of smoker being in case-control or cohort studies at least 2 [9] and attributable risk in population, 25% [1]. The risk increases as the level of cigarette smoking increases, current smoker with over a 40 pack-year history of smoking have up a 5-6 fold increase risk of the disease [7].

Dietary factors are less important for PC than in other digestive tract tumors. Numerous case-control studies and several cohort studies have been conducted to examine this association, the finding is inconclusive and the role of diet remains elusive. Generally, high consumption of meat, animal protein and fat is associated with increased risk, whereas vegetables and fruits are linked to a reduced risk [10 - 12]. Alcohol consumption, coffee, tea and other drinks are not associated with an increased risk for PC [12, 13].

Occupational exposure to some carcinogens (formaldehyde, pesticides, organochlorines) may contribute to induce PC, although case-control studies have not consistently confirmed these association [1].

All types of chronic pancreatitis are substantial risk for the development of PC, patients with alcoholic and non-alcoholic chronic pancreatitis have a 10-20 fold increase in the risk and patients with hereditary pancreatitis have a 50 fold higher risk, as compared with patients without pancreatitis [7].

Another medical condition that has been related with PC is diabetes mellitus. Meta-analysis of 36 studies concluded that patients with diabetes mellitus at 20 years durations have a 2 fold increased risk for developing PC [14].

Both case-control and cohort studies suggest that family history of some disease is an important indicator of PC risk [6 - 8]. Several genetic syndromes have been associated with familial aggregation of this cancer. Exemples

include mutation in ataxia-telangiectazia (ATM); hereditary non-polyposis colorectal cancer syndrome (hMLH1); Peutz-Jenghers syndrome (STK11/LKB1); familial atipical multiple mole melanoma syndrome [16]. Certain germ line mutations such as BRCA2, BRCA1, PRSS1, as well as susceptibility gene polimorphisms, are known to rise the risk for PC [1].

There are some specific features of PC which induce obstacles in PC research:

- pancreatic cancer occurs in general population with low freqnency and because of that it is often difficult for investigators to have enought cases for statistically significant findings;
- has a high fatality rate;
- the patients are diagnosed late in the disease process. Late diagnosis reduces the time when patient is available for study, including the studies regarding molecular mechanism of disease.

Despite numerous epidemiological studies risk factors that may contribute to the development of PC, the etiology of the disease remains incomplete known. In consequence, the prevention of PC is difficult to accomplish.

Four levels of prevention are identified, corresponding to different phase in development of the disease:

Primordial prevention. The aim of this prevention is to avoid the emergence and establishment of the social, economic and cultural pattern of living, that are known to contribute to an elevated risk for disease.

Primordial prevention of PC should include smoking cessation programmes and healthy nutrition programmes.

Primary prevention. The purpose of primary prevention is to limit the incidence of the disease by controlling causes and risk factors.

Because there are not effective screening tests for PC, the prevention of this malignancy includes identification and reduction of modifiable risk factors. Avoidance of tabacco use, the consumption of appropriate diet and limiting exposure to occupational and other environmental carcinogens become very important.

The reduction of dietary risk factors (animal protein, red meat, fat, carbohydrate or sugar); increased consumption of fruits and vegetables contenting folate and lycopene (citric fruits, tomates) or contenting protease inhibitors (beans, lentils, peas) are neccerary [15, 16].

The role of N-nitroso compounds, formed even by cooking or formed endogenously from drinking water or dietary sources of nitrite and nitrate in developing of PC has been documented, so, the reduction of mutagenic compounds avoiding frying or grilling meat is recommended.

Supplemental antioxidants do not appear to decrease the risk for PC. Two antioxidants, alpha-tocopherol and beta-carotene have been evaluated in a prospective study of male smokers, these antioxidants did not reduced the frequency of PC over a period of 8 year of observation [1].

An increased intake of calories causes obesity that can increase the risk for PC, so exercise which help to maintain normal body weight has been associated, in some studies, with reduced risk [8].

Smoking is the most consistent lifestyle risk factors for PC, so the priority should be given to efforts to control smoking. Reducing the prevalence of smoking is the single most effective measure to prevent PC [13]. Using a computer model to estimate the impact of smoking cessation on the frequency of PC in Europe Union, Mulder [9], estimated that suddenly cessation of smoking can reduce the number of new patients with 15 %. The most realistic goal is the reduction of smoking prevalence. A decrease of smoking prevalence with ~ 45 % in males and with ~30% in females, leads to a reduction of almost 30.000 male and 10.000 female patients with PC by the year 2015.

Regular use of aspirin and other nonsteroid anti-inflammatory drugs, that directly targets enzyme COX-2 has been associated

Table I. Eligibility and Exclusion Criteria for Screening Patients at High Risk for Pancreatic Cancer [7]

Eligibility Criteria
Correlation with one of the following high-risk groups: • Patient has 2 or more relatives with pancreatic cancer and has a first-degree relationship with at least one of the relatives with pancreatic cancer. • If only 2 family members are affected, then both must have had pancreatic cancer and a first-degree relationship with the individual screened. • If there are more than 2 affected individuals on the same side of the family, at least 1 of the individuals must have a first-degree relationship with the member being screened. • Patient is at least 40 years of age or 10 years younger than the youngest affected individual. Peutz-Jeghers syndrome patients age>30 years. Hereditary pancreatitis patients. Patients with familial atypical multiple mole melanoma (FAMMM) syndrome. Patients with $BRCA_2$ mutation and at least 1 first or second – degree relative with documented pancreatic cancer. Willingness to undergo EUS with possible FNA. Willingness to undergo surgical evaluation for abnormal EUS/FNA finding. Willingness to undergo radiographic evaluation if screening findings are abnormal.
Exclusion Criteria
Medical contraindications to undergoing endoscopy or obstruction of the gastrointestinal tract that precludes passage of the endoscope. Personal history of pancreatic adenocarcinoma. Previous partial or complete resection of the pancreas for adenocarcinoma. Prior partial or total gastrectomy with Billroth II or Roux-en Y anastomosis. Coexisting cancer in other organs or AIDS/HIV. Life expectancy <5 years. Previous CT scan or ultrasound of the abdomen within the last 3 years.

with reduced risk of PC. Experimental studies in hamsters reveal a possible role of non-steroid anti-inflammatory drugs in reducing the risk of PC, epidemiological studies examining similar association in human population become important [17]. As regards the aspirin use, further investigations, eventually randomized-controlled clinical trials are needed to demonstrate its protective role [18].

Secondary prevention aims are to cure patients and to reduce the consequences of disease through early diagnosis and prompt and effective interventions. It is directed at the period between onset of disease and the normal time of diagnosis. Pancreatic cancer being a silent disease, screening is the only practical approach to detect early modifications at the phase in which surgical intervention and adjuvant therapy will have a chance of cure.

Screening needs to be done in asymptomatic individuals from general population, but such screening tests for PC does not exist.

Current efforts to detect PC in a curative phase are focused on screening individuals at very high risk for development of this disease [7]. They include kindreds with two or more first-degree relatives affected with PC and those with known heredity pancreatic syndromes [19].

When pancreatic cancer is suspected the most common imaging modalities used for diagnostic are: transcutaneous ultrasound (TCUS); computer tomography (CT); magnetic resonance imaging (MRI); endoscopic ultrasound (EUS); endoscopic retrograde cholangiopancreatography (ERCP) and most recently EUS-guided fine needle aspiration (EUS-FNA). The EUS-guided FNA had a sensitivity of 94 % and accuracy of 92 % for detecting malignant disease in patients

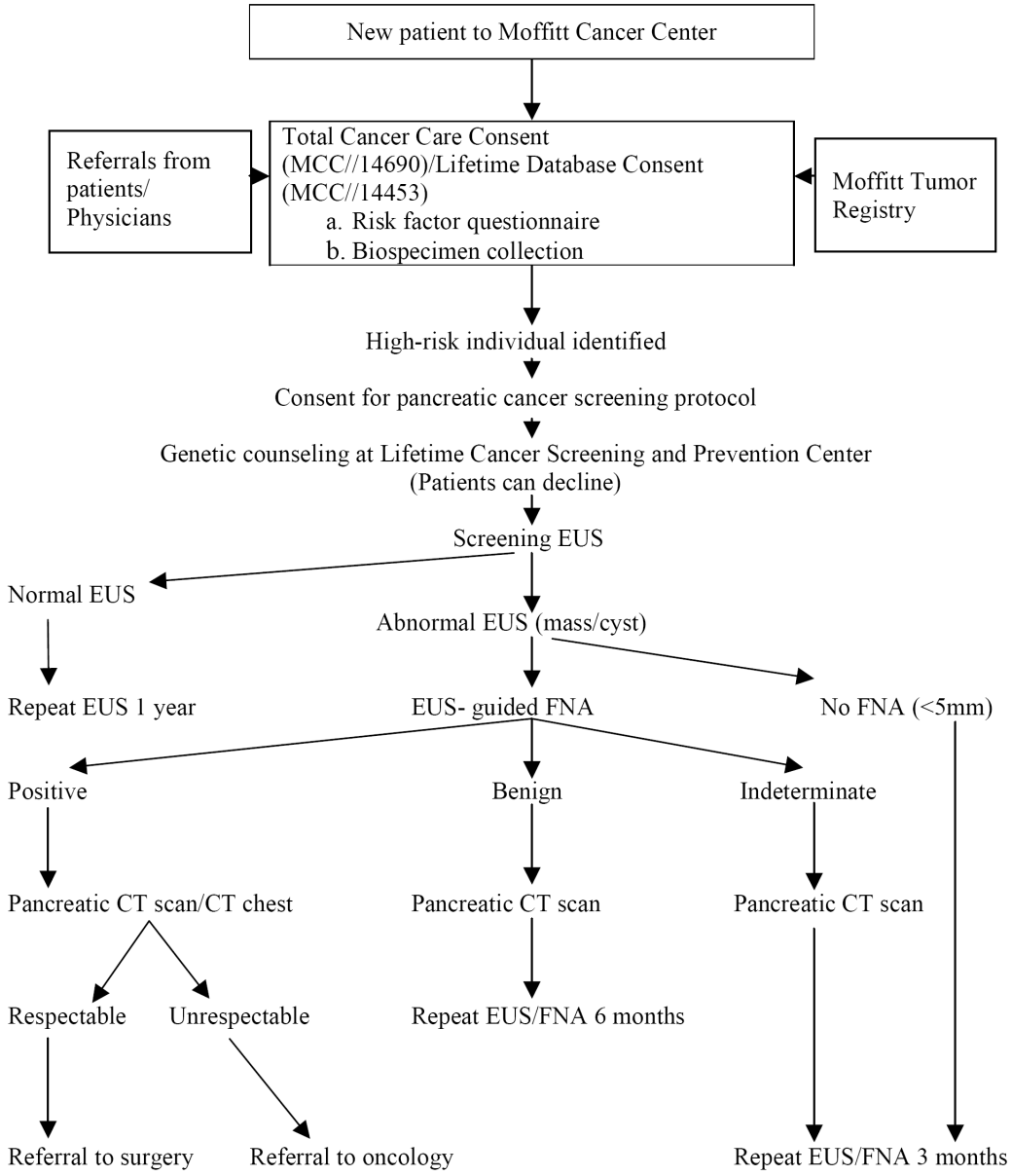

Figure 1. Protocol for high-risk assessment, screening, and early detection of pancreatic cancer at Moffitt Cancer Center [7]

with negative ERCP tissue sampling and 90 % sensitivity and 84 % accuracy in patients with negative CT-guided biopsy [7, 20].

A programme for screening patients at high-risk for the development of PC was established in USA at the Moffitt Cancer Center [7]. After completing a self-reported risk factor questionnaire, the potential high-risk individuals were selected for screening by eligibility and exclusion criteria (*Table I*).

Genetic counseling, as part of selection for screening, includes a detailed review o patient's family history, to determine if a cancer indeed runs in the family. Patients must be

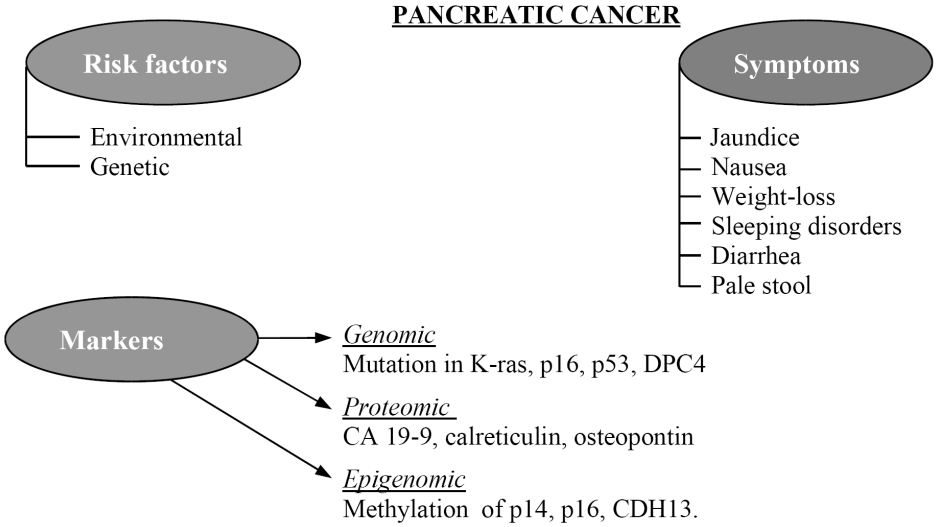

Figure 2. Risk factors and symptoms for pancreatic cancer [8]

asked for their permission to be included in screening programme, to store their blood and clinical data. The programme of Moffitt Cancer Center was based on EUS as the screening procedure and was conducted under a special protocol (*Figure 1*).

Today the screening for PC is limited to high-risk patients which represent only 10% of patients with PC.

Recent development in determining proteomic profiles during different stages of PC and methylation markers are promising for early detection of the disease.

Identification of circulating tumor antigens and related antibodies, as well as the detection of antibodies to calreticulin also have potential in identifying disease early (*Figure 2*).

Unfortunately none of these markers have been proven to be highly sensitive or specific to PC and therefore their detection is not suitable for screening [7, 19, 21].

Tertiary prevention. Tertiary prevention is aimed at reducing the progress or complications of a disease and is an important aspect of therapeutic and rehabilitation medicine.

Tertiary prevention of PC includes surgical treatment, adjuvant or palliative therapy, and control of the patients after treatment.

The first evaluation of the screening, associated in case of discovering the modifications, by specifically therapy, indicated an increase of median survival rate from three months to nine months, and an amelioration of the survival rate at five years, up to 12 % [6, 7].

Following efforts are needed to discover effective test to identify patients with non-hereditary risk factors and also to develop less invasive and more cost-effective screening modalities.

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