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PANCREATIC CANCER: EPIDEMIOLOGY AND RISK FACTORS

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Although the pancreatic cancer has a relatively small incidence compared to the incidence of others types of cancers, it is a major public health problem due to the extreme mortality rate as results from epidemiological data carried-out on all continents and in both sexes and at all ages. This could be explained by the long asymptomatic evolution, and conseqently the late diagnosis, in advanced stages when the terapeutical aproach has a low rate of succes. Although the real causeof pancreatic cancer remains unknown, there are many factors that have been associated with increased risk of pancreatic cancer and the most common are: diabetes, smoking, obesity, alcoholism and chronic pancreatitis. The asociation between pancreatic cancer and diabetes could be asociated with mitogenic function of insulin. However, a higher association between diabetes and pancreatic cancer seems to be bidirectiona: patients with diabetes mellitus being at risk of developing pancreatic cancer but also hyperglycemia is increased in patients with pancreatic cancer, without being known as diabetics.

Keywords: diabetes/cancer; epidemiology; mortality; pancreatic cancer; cancer in Romania.

INTRODUCTION

Pancreatic cancer (PC) incidence is relatively low compared to the other types of cancer in 2012 being 2.4% worldwide[1], and PC is a major public health problem of extreme gravity due to high mortality, with one of the highest rates mortality among other cancer types. According to IARC-Globocan in 2012 were diagnosed worldwide a total of 337 872 cases of PC and were recorded a total of 330.39 deaths due to PC. The risk of cancer of the pancreas range from 2.0 (Herault, France) to 20.8 (central Louisiana, USA) at 100,000 individuals[2,3]. Pancreatic cancer has one of the highest rates of mortality, survival at 5 years regardless of disease stage is approximately 4.7% (period 1975–2006)[4] with a growing survival rate at 5 years from 3% 1975 to 7.6% in 2006[2, 4].

In 2011, in the study Quaresma M[5] the survival of pancreatic cancer from 1 to 5 and 10 years 2005–2006 was 17.4%, 3% and 1.2% compared to 10.6%, 2.3% and 1.2% in 1971–1972[5]. In Quaresma M study, the survival rate of patients with various cancers to 10 years ranged from 1.1% for pancreatic cancer (both men and women) and 98.2% for testicular cancer and survival rate for all cancers and 10 years was 49.8%[5]. PC had the lowest survival rate of all cancers at both 1 year and 5 and 10 years[5].

Depending on the stage of the tumor, inoperable patients presenting advanced disease have a survival rate of 6–11 months, and patients presenting with metastasis at diagnosis have a survival rate of only 2–6 months[6–8].

Youths have the largest survival, in the Cancer Research UK survival rate in the age group 15–49 years is 14% in men[9–10] and 24% in women[9–10] and in the age group of 80–99 years survival is 2%[9–10] in the same in men and women[9–10].

Pancreatic cancer occurs more frequently after age 40 years, cases under 40 years being rare, with an average age of occurrence between 60–80 years[3, 11], and with a slight predominance of males and higher frequency in African-American[2]. The risk of developing PC during the life of both women and men is about 1.5%[4].

Numerous studies have highlighted the importance of the anatomical PC location of the tumor in the pancreas as a determinant of

survival[12–16], late presentation of patients with PC located at body or tail being considered a possible factor for increased mortality and decreased survival[12–16]. In Artinyan A[16] study of the 33 752 patients with pancreatic adenocarcinoma 18,666 (56%) had localized pancreatic tumors of head, 5982 (18%) at body or tail and 9104 (26%) in other areas[16]. The PC location in the BT area gave a higher additional risk of 11% mortality compared to the cephalic region (OR 1.11, 95% CI 1.00–1.23, p = 0.05) with a higher degree of metastasis (67% *versus* 36%, p < 0.001) and a lower rate of surgery (16% *versus* 30%, p < 0.001) BT pancreatic tumors compared with those located in the cephalic region[16].

CLASIFICATION OF PCs

Pancreatic cancer can affect both exocrine and endocrine pancreas (Table 1). 99% of pancreatic cancers are exocrine tumors and 90% of these are ductal pancreatic adenocarcinoma – (PADK). Depending on the anatomical location of tumor, PC can be located at: head, body, tail, intraductal[18].

Table 1

The classification of tumors of the pancreas
(Adapted from [17] to [28])

Pancreatic tumor histologic type		
EXOCRINE	Epithelial	**Benign** Serous cystadenoma Mucinous cystadenoma Intraductal papillary-mucinous adenoma Mature teratoma Borderline (uncertain malignant potential) Mucinous cystic neoplasm with moderate dysplasia Intraductal papillary-mucinous neoplasm with moderate dysplasia Solid-pseudopapillary neoplasm
		Malignant *Ductal adenocarcinoma* Mucinous noncystic carcinoma Signet ring cell carcinoma Adenosquamous carcinoma Undifferentiated (anaplastic) carcinoma Undifferentiated carcinoma with osteoclast-like giant cells Mixed ductal-endocrine carcinoma *Serous cystadenocarcinoma* *Mucinous cystadenocarcinoma* – non-invasive – invasive *Intraductal papillary-mucinous carcinoma* – non-invasive – invasive (papillary-mucinous carcinoma) *Acinar cell carcinoma* Acinar cell cystadenocarcinoma Mixed acinar-endocrine carcinoma *Pancreatoblastoma* *Solid-pseudopapillary carcinoma*
	Mesenchymal	lymphangioma: pancreatic lymphangioma lipoma: pancreatic lipoma pancreatoblastoma teratoma: pancreatic teratoma lymphoma: pancreatic lymphoma schwannoma neurofibroma sarcoma
ENDOCRINE		Insulinoma Gastrinoma Glucagonoma VIP-oma Somatostatinoma Pancreatic polypeptidoma Carcinoid Miscellaneo

RISK FACTORS FOR PANCREATIC CANCER

The main cause of pancreatic neoplasm remains unknown, but several factors show a modest association with its occurrence (Table 2) Among the most important risk factors we can include:

1. Diabetes mellitus – Diabetes has a high (40%) prevalence in pancreatic cancer and frequently is new onset[55]. A lot of studies higlighted the risc of cancer in diabetes particularly pancreatic cancer and diabetes have a unique relationship because diabetes has become a pandemic, and pancreatic cancer is one of the most lethal forms of malignancy known[56]. In a study of Chari S.T.[57] of 2122 diabetic subjects, 18 (0.85%) were diagnosed with pancreatic cancer within 3 years of meeting criteria for diabetes[57], therefore approximately 1% of diabetes subjects aged ≥ 50 years will be diagnosed with pancreatic cancer within 3 years of first meeting criteria for diabetes[57], therefore we can say pancreatic cancer

is a powerful diabetogenic state and it and appears to be associated with conventional risk factors for DM[58].

2. Cigarette smoking has a relative risk of 2.2 higher comparative with non-smokers[32] and the risk increases with increasing amount of pack year smoked but smoking cessation can reduce risk[29, 32, 33]. Exposure to environmental tobacco is not increasing pancreatic cancer risk[34]. Tobacco smoke contains more than 7,000 chemicals and at least 69 can cause cancer or are suspected to cause cancer including the folowingă[35]: Arsenic[35], Benzene[35], Beryllium (a toxic metal)[35], 1,3–Butadiene (a hazardous gas)[35] Cadmium (a toxic metal)[35], Chromium (a metallic element)[35], Ethylene oxide, Nickel (a metallic element)[35], Polonium-210 (a radioactive chemical element)[35], Vinyl chloride[35], Formaldehyde[35], Benzo[α]pyrene[35], Toluene[35].

Table 2

Factors associated with increased risk of pancreatic cancer (Adapted from [2,29–31])

Factors associated with increased risk of pancreatic cancer	
Avancing age: older people	Low socioeconomic status
Cigarette smoking	Alcohol consumption
Native female Hawaiians Ashkenazic Jewish heritage African American males	Ionising radiation: Thorium-232 and its decay products X-radiation Gamma-radiation
Pancreatitis	Gallstones/Peptic ulcer
Genetic conditions Hereditary pancreatitis PRSSI (7q35) Hereditary nonpolyposis colorectal cancer (Lynch II variant) hMSH2, hMLH1, and others Hereditary breast and ovarian cancer BRCA2 (13q12q13) Familial atypical multiple mole melanoma (FAMMM) syndrome p16 (9p21) Peutz-Jeghers syndrome STK11/LKB1 (19p13) Ataxia-telangiectasia ATM (11q22-23)	Occupational exposure to carcinogens: PCBs, polychlorinated biphenyls; DDT, dichlorodiphenyl trichloroethane; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone Infections: hepatitis B, C Helicobacter Pylori (H.Pylori) Porphyromonas gingivalis/periodontal disease
Familial pancreatic cancer.	
Obesity (abdominal fatness)	Increased height
Diabetes mellitus	Diet: red meat,low fiber, higher fat
Low level of physical activity	A blood group
High-fat and cholesterol diet	Idiopathic deep-vein thrombosis
Cholecystectomy (increased cholecystokinin levels)	Dermatomyositis and polymyositis

3. Pancreatitis. A metanalysis of Duell[53] compared previous (> 2 years) pancreatitis in younger pancreatic cancer cases (< 65 years) with the older cases (≥ 65 years) and showed that in younger group pancreatic cancer has stronger associations comparative with older (OR: 3.91, 95% CI: 2.53–6.04)[53] *vs.* (OR: 1.68, 95% CI: 1.02–2.76;[53] P value for interaction: 0.006)[53]. Chronic pancreatitis is associated with a 15-fold increase in the risk for pancreatic cancer[29] and more than 53-fold in people with hereditary pancreatitis[54].

4. Alcohol consumption can increase de the risk of cancer through several mechanisms: metabolizing ethanol to acetaldehyde which can damage DNA[44]; generating reactive oxygen species[44]; interference with a variety of nutrients including vitamin A, vitamin B complex-folate, vitamin C, vitamin D, vitamin E, and carotenoids[44]; a variety of carcinogenic contaminants that are introduced during fermentation and production, such as nitrosamines, asbestos fibers, phenols, and hydrocarbons[44]. Alcohol overconsumption affect the liver leading to alcoholic liver disease which include: fatty liver[45], alcoholic hepatitis[45], and chronic hepatitis[45] with hepatic fibrosis or cirrhosis[45]. Cirrhosis is a risk factor for pancreatic cancer. Moderate drinking is up to 1 drink per day for women and up to 2 drinks per day for men and it is not associated with risk of pancreatic cancer[46–48].

5. Diet. Pancreatic cancer risk was associated with a high intake of calorically dense and highly procesed food, additives and a high intake of fat especially saturated fat, salt and red meat (50 g per day of processed meat and and 120 g fresh red meat in men consumption was associated with a statistically significant 19% respectively 29% increased risk of pancreatic cancer)[36–37]. Many components in cooked food can be deleterious such acrylamyde found in potatoes cooked above 120 degree Celsius (acrylamide is formed by asparagine contained in potatoes which heated-especially frying, baking, or broiling at high temperatures in presence of some sugars)[38–41], heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) found in cooked pork, fish, or poultry meat at high temperatures in open fire. HCAs and PAHs is formed by interaction between creatine, aminoacids and sugars when meat is cooked at high temperatures[42–43]. A healthy life-style including a balanced diet high in fiber, fruits and vegetables has a protective effect.

6. Excess weight (overweight and obesity) is associated with pancreatic cancer risk[49–51]. Pancreatic cancer increases by 11% per 10 cm waist circumference[52] and by 10% per 5–unit BMI increase[52]. A meta-analysis of Berrington de Gonzalez showed a relative risk of 1.19 (95% CI:1.10–1.29) for obese people (BMI = 30 kg/m^2) compared to people with a normal body weight (22 kg/m^2)[52].

THE PLACE OF PANCREATIC CANCER IN VARIOUS STATISTICS

In the Table 3 are given the distribution of the pancreatic cancer indicating the incidence and mortality by PCs in various regions of the world.

Although a great progress has been made in the early detection of various cancers and in their treatment, reflected in their increased incidence and decreased mortality, however a large diference can be found between various countries according to their economical and social status. The incidence and mortality of pancreatic cancer in Roumania versus other European countries are given in Table 4.

There are many risk factors for cancers. In the Table 5 are presented several risk factors for pancreatic cancer according with 2014 WHO statistics colected from various continents including the European region and also Romania.

Table 3

Pancreatic cancer distribution by region and sex in 2012 – Adapted from Globocan [1]

Region		1	2	3	4	5	6	7	8	9
World	**Male**	**178161**	**52.7**	**2.4**	**173827**	**52.6**	**3.7**	**114434**	**54.1**	**0.7**
	Female	**159711**	**47.3**	**2.4**	**156564**	**47.4**	**4.4**	**97110**	**45.9**	**0.6**
	Total	**337872**	**100**	**2.4**	**330391**	100	**4**	**211544**	100	**0.7**
Asia	Male	80704	56.3	2.2	76698	56.1	2.9	55797	57.2	0.9
	Female	62659	43.7	2	60553	43.9	3.3	41744	42.8	0.6
	Total	143363	100	2.1	137251	100	3.1	97541	100	0.7
Africa	Male	6625	54.7	1.8	6424	54.9	2.3	4780	55	0.8
	Female	5476	45.3	1.1	5280	45.1	1.7	3924	45	0.3
	Total	12101	100	1.4	11704	100	2	8704	100	0.5
North America	Male	23949	50.6	2.6	23165	50.6	6.4	14316	51.9	0.5
	Female	23422	49.4	2.7	22651	49.4	6.9	13292	48.1	0.5
	Total	47371	100	2.7	45816	100	6.6	27608	100	0.5
South America	Male	9544	47.1	2.4	9910	47.9	4.3	6823	47.8	0.8
	Female	10738	52.9	2.6	10788	52.1	5.2	7441	52.2	0.7
	Total	20282	100	2.5	20698	100	4.7	14264	100	0.7
Oceania	Male	1854	53.4	2.2	1597	51	4.9	993	53.9	0.4
	Female	1615	46.6	2.3	1534	49	5.7	851	46.1	0.4
	Total	3469	100	2.2	3131	100	5.2	1844	100	0.4
Europe	Male	51962	50	2.9	52631	50.3	5.4	29222	51.9	0.6
	Female	51833	50	3.2	51923	49.7	6.7	27114	48.1	0.6
	Total	**103845**	100	**3**	**104554**	100	**6**	**56336**	100	**0.6**
Romania	Male	1692	54.9	3.9	1546	55.6	5.4	862	56.7	1
	Female	1390	45.1	3.9	1236	44.4	6.4	657	43.3	0.7
	Total	**3082**	100	**3.9**	**2782**	100	**5.8**	**1519**	100	**0.9**
MDC*	**Total**	**187465**	**–**	**3.1**	**184429**	**–**	**6.4**	**107118**	**–**	**0.6**
LDC**	**Total**	**150407**	**–**	**1.9**	**145962**	**–**	**2.7**	**104426**	**–**	**0.7**

1 = Incidence No. (for all ages); 2 = male; 3 = female; 4 = Mortality No. 5 = male; 6 = female; 7 = 5-year Prevalence No. (adult only); 8 = male; 9 = female.

* MDC = More developed country
** LDC = Less developed country

Table 4

Pancreatic cancer distribution by European country region and sex in 2012 – Adapted from Globocan [1]

Country		1	2	3	4	5	6	7	8	9
Romania	Male	1692	54.9	3.9	1546	55.6	5.4	862	56.7	1
	Female	1390	45.1	3.9	1236	44.4	6.4	657	43.3	0.7
	Total	**3082**	100	**3.9**	**2782**	100	**5.8**	**1519**	100	**0.9**
France	Male	4555	49.8	2.3	4909	51.2	5.4	3256	50.2	0.6
	Female	4594	50.2	3	4679	48.8	7.3	3226	49.8	0.7
	Total	9149	100	2.6	9588	100	6.2	6482	100	0.6
Germany	Male	7972	48.5	2.9	7900	48.8	6.7	4765	50.8	0.6
	Female	8479	51.5	3.8	8288	51.2	8.3	4622	49.2	0.7
	Total	16451	100	3.3	16188	100	7.4	9387	100	0.7
Russia	Male	7206	49.7	3.3	8168	49.9	5.2	3890	52.4	0.9
	Female	7306	50.3	3	8203	50.1	5.9	3530	47.6	0.5
	Total	14512	100	3.2	16371	100	5.5	7420	100	0.7
UK	Male	4211	48.1	2.5	4095	48.7	4.9	1742	49.5	0.4
	Female	4536	51.9	2.8	4311	51.3	5.8	1780	50.5	0.4
	Total	8747	100	2.7	8406	100	5.3	3522	100	0.4
Sweden	Male	483	50.1	1.7	756	46.1	6.6	227	51.5	0.3
	Female	481	49.9	2.1	884	53.9	8.4	214	48.5	0.3
	Total	964	100	1.9	1640	100	7.4	441	100	0.3
Turkey	Male	2015	63.5	2.3	1944	63.4	3.3	1428	64.3	0.9
	Female	1159	36.5	1.9	1120	36.6	3.4	793	35.7	0.5
	Total	3174	100	2.1	3064	100	3.3	2221	100	0.7
Italy	Male	4946	50.1	2.6	5074	47.7	5.3	3051	47.6	0.6
	Female	5742	49.9	3.5	5563	42.2	7.4	3363	52.4	0.7
	Total	**10688**	100	**3**	**10637**	100	**6.3**	**6414**	100	**0.6**
Spain	Male	3335	52.4	2.6	3003	52.5	4.7	1849	53.8	0.6
	Female	3032	47.6	3.5	2717	47.5	6.9	1588	46.2	0.6
	Total	**6367**	100	**3**	**5720**	100	**5.5**	**3437**	100	**0.6**
Bulgary	Male	686	55.5	4.2	599	56.9	5.7	353	57.4	1.1
	Female	550	44.5	3.5	453	43.1	6	262	42.6	0.6
	Total	**1236**	100	**3.9**	**1052**	100	**5.8**	**615**	100	**0.8**
Hungary	Male	906	48.8	3.4	888	48.6	5.3	473	50.9	0.8
	Female	950	41.2	4	940	41.4	7	456	49.1	0.8
	Total	**1856**	100	**3.7**	**1828**	100	**6**	**929**	100	**0.8**
Serbia	Male	669	53.3	3	695	52.4	4.6	418	54.9	0.8
	Female	585	46.7	3	632	47.6	5.8	344	45.1	0.6
	Total	**1254**	100	**3**	**1327**	100	**5.1**	**762**	100	**0.7**
Poland	Male	2549	50.9	3.3	2459	50.7	4.6	1319	53.6	0.8
	Female	2455	49.1	3.3	2387	49.3	5.7	1141	46.4	0.6
	Total	**5004**	100	**3.3**	**4846**	100	**5.1**	**2460**	100	**0.7**
Switzerland	Male	548	46.8	2.3	491	45.5	5.4	336	48.7	0.5
	Female	624	53.2	3.4	589	54.5	8	354	51.3	0.6
	Total	**1172**	100	**2.8**	**1080**	100	**6.6**	**690**	100	**0.5**
Ukraine	Male	2546	53.8	3.7	2377	57	4.9	1392	56.9	1
	Female	2182	46.2	3	1791	43	4.6	1052	43.1	0.5
	Total	**4728**	100	**5.9**	**4168**	100	**4.8**	**2444**	100	**0.7**
Finland	Male	555	48.2	3.7	504	47.9	8.3	266	50.1	0.6
	Female	596	51.8	4.5	548	52.1	10.3	265	49.9	0.7
	Total	**1151**	100	**4**	**1052**	100	**9.2**	**531**	100	**0.6**
Greece	Male	829	53.9	3.6	863	52.9	5	490	54.9	0.9
	Female	710	46.1	4	767	47.1	6.7	403	45.1	0.8
	Total	**1539**	100	**3.8**	**1630**	100	**5.7**	**893**	100	**0.9**
Austria	Male	785	49.5	3.5	728	49	6.6	484	51.4	0.8
	Female	800	50.5	4.2	758	51	8.1	457	48.6	0.9
	Total	**1585**	100	**3.9**	**1486**	100	**7.3**	**941**	100	**0.8**

1 = Incidence No. (for all ages); 2 = male; 3 = female; 4 = Mortality No. 5 = male; 6 = female; 7 = 5-year Prevalence No. (adult only); 8 = male; 9 = female.

Table 5

Different parameters adapted from *World Health Statistics* 2014 – World Health Organization [59]

Region	1		2		3		4	5	
	M	F	M	F	M	F		F	M
Africa	8.3	9.2	38.1	35.5	5.3	11.1	6	22	7
America	11.5	9.9	26.3	19.7	23.5	29.7	8.4	26	16
South East Asia	9.9	9.8	25.4	24.2	1.7	3.7	3.5	34	4
European region	9.6	8	33.1	25.6	20.4	23.1	10.9	38	19
Romania	10.0	8.9	39	32.9	16.3	19	14.4	38	18
Eastern Mediterranean	11	11.6	30.7	29.1	13.0	24.5	0.7	38	4
Western Pacific	9.2	8.6	28.7	23.7	5.1	6.8	6.8	38	3
GLOBAL	9.8	9.2	29.2	24.8	10	14	6.2	47	8

1 = Prevalence of raised fasting blood glucosef (≥ 25 years) (%);
2 = Prevalence of raised blood pressure g (≥ 25 years) (%);
3 = Adults aged ≥ 20 years who are obese h (%);
4 = Alcohol consumption among adults aged ≥ 15 years (litres of pure alcohol per person per year);
5 = Prevalence of smoking any tobacco product among adults aged ≥ 15 years (%).

CONCLUSIONS

Pancreatic cancer have a lower incidence compared to other forms of cancer but with an increased mortality remains a major public health problem.

Although in their aparition are incriminated several risk factors such as diabetes, obesity, smoking, pancreatitis and diet, pancreatic cancer etiology remains unknown.

Pancreatic cancer and diabetes are in a close correlation and is evidenced in many studies. An explenation may be an increased mitogenic function of insulin in patients treated with insulin or having an oral treatment with sulphonilureas or other drogs stimulating insulin secretion.

Finding a therapeutic solution able to decrease the high rate mortality of PCs, one of the objectives to be observed in the future. Until then, the pancreatic cancer remains a very agressive form with one of the highest mortality.

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