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Original Article

Pancreatic Cancer: State of the Art and Current Situation in the Islamic Republic of Iran

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ABSTRACT

Compared to western countries, pancreatic cancer has a relatively low incidence in Iran. It is rarely diagnosed before the fifth decade in Iran and most of the patients are older than 60 at the time of diagnosis like to the western countries, where pancreatic cancer is a disease of advanced age. The incidence of the disease in some young patients suggests a possible role of genetic defects, which is probably due to high consanguineous marriages in Iran. Despite many efforts in improving diagnosis and treatment of pancreatic cancer, this disease has still dismal prognosis. The analysis of the spatial spread of the pancreatic cancer in Mazandaran and Golestan, two provinces in the Caspian Sea region in the north of Iran, which comprise a low incidence of pancreatic cancer, showed that the disease, unlike other gastrointestinal tract cancers, does not exhibit high incidence clusters in the region. Our knowledge about the molecular and cellular pathology of the pancreatic cancer has progressed, and many agents including anti-EGFR, anti-VEGF, and immunotherapeutic agents have been applied for the treatment of the disease. However, surgery remains the only curative approach and further research is paramount to identify novel diagnostic and predictive biomarkers for early diagnosis and treatment stratification. Pancreatic cancer requires an interdisciplinary approach which involves surgery, pathology, radiology, gastroenterology, oncology, and palliative care provided in dedicated, specialized centers.

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INTRODUCTION

Pancreatic cancer – histological classification

Ductal pancreatic adenocarcinoma is the most common malignant pancreatic neoplasm, accounting for more than 90% of malignant solid pancreatic tumors. In addition, cystadenocarcinomas, acinar cell cancer, adenosquamous carcinomas, mucinous carcinomas and giant cell tumors are observed. Similar to colorectal cancers, pancreatic adenocarcinomas appear to develop in an adenoma-carcinoma sequence from preneoplastic lesions, so called pancreatic intraepithelial neoplasias or PanINs (1).

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Epidemiology

Pancreatic carcinoma causes more than 250,000 deaths annually worldwide. It is the 13th most common cancer, but the 8th most frequent cause of cancer death in the world (2). It is the 4th leading cause of cancer death in the USA (3) and the 6th leading cause of cancer death in Europe (4).

To date, there is no data on the prevalence and survival rates of patients suffering from pancreatic cancer in the Islamic Republic of Iran. However, there are data on pancreatic cancer incidence in Iran in the years 2003 to 2005. These data were collected by the National Cancer Registry (NCR) of the Islamic Republic of Iran and kindly provided for us for this review. The NCR collects its information in collaboration with 41 universities from all over the country. The universities report new cases of pathologically confirmed pancreatic cancer. Pathology is performed according to the NCR guidelines in approved laboratories. In the year 2005, there were 779 approved laboratories.

Overall, coverage of new cancer cases has changed dramatically within the recent years in Iran. In 1986, only 18% of the expected number of new cases was reported. This figure has changed to 70% and 81% in years 2004 and 2005, respectively. Of note, in 2005, five provinces (Ardabil, Golestan, Lorestan, Kerman and Isfahan) collected their data by a population based method. They received data from diagnostic centers (e.g., pathology laboratories and imaging centers), treatment centers and via the death registry system. In 2003, pancreatic cancer incidence rate per 100,000 population was 0.40% in females and 0.46% in males (2). In 2004, the respective figure was 0.42% in females and 0.46% in males. In 2005, the pancreatic cancer incidence rate was 0.39% in females and 0.56% in males. Therefore, similar to western countries, pancreatic cancer in Iran occurs slightly more commonly in men than in women (5). Pancreatic cancer is mostly a disease of elderly population. In western countries, the incidence of this disease peaks between 60-80 years of age (6). Figure 1 demonstrates age specific pancreatic cancer incidence in 2003, 2004, 2005,

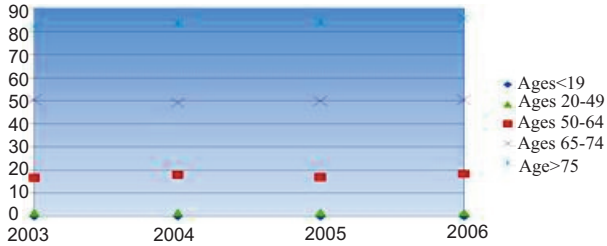

Figure 1: Age-adjusted SEER Incidence Rates by Age at Diagnosis/Death of Pancreatic Cancer in the United States of America

and 2006 in the United States of America (7).

In Germany, the mean age of patients with pancreatic cancer is 67 years in males and 74 years in females. Figure 2 shows the age-specific incidence rate of pancreatic cancer in

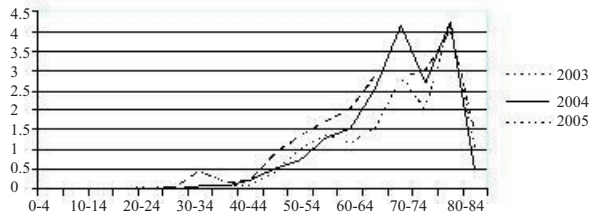

Figure 1: Age-adjusted SEER Incidence Rates by Age at Diagnosis/Death of Pancreatic Cancer in the United States of America

2003, 2004, and 2005 in Iran.

This figure shows that the overall picture in the Islamic Republic of Iran is similar to that in western countries with one notable difference: the mean age of pancreatic cancer patients in 2006 was 60.7 years in males and 60.9 years in females. Therefore, pancreatic cancer is still the disease of elderly people in Iran, but patients are comparatively younger at the time of diagnosis than in western countries. This may suggest that some genetic and/or environmental factors could contribute at least in part to the development of

pancreatic cancer in Iran. One should consider that approximately 10% of pancreatic cancers may be attributed to genetic factors (8-10) and there are two major groups of patients with genetic abnormalities; a larger group are families with multiple individuals diagnosed with pancreas cancer and with no so far identifiable genetic defect; and a smaller group are patients with well-known genetic syndromes such as Peutz-Jeghers syndrome, hereditary pancreatitis, familial atypical multiple mole melanoma, familial adenomatous polyposis, hereditary breast-ovary cancer, and hereditary non-polyposis colon cancer (11). In many areas of Iran, especially in rural regions, consanguineous marriage is still common (12,13). This may cause aggregation of genetic defects leading to pancreatic cancer.

The incidence of pancreatic cancer is not homogeneous in all over the country. In 2004, the highest pancreatic cancer incidence in females was registered in the provinces of Hormozgan (1.20%), Chaharmahal and Bakhtiari (1.06%), and Kohkiloueh and Boyerahmad (0.93%). In males, the highest pancreatic cancer incidence was detected in the provinces of Zanjan (0.97%), Kermanshah (0.84%), and Isfahan (0.76%). In 2005, the highest incidence rate in females was found in the provinces of North Khorasan (2.26%), Chaharmahal and Bakhtiari (1.24%), and in males in the provinces of Semnan (1.17%), Markazi (1.12%), Ilam (1.03%), and Kohkiloueh and Boyerahmad (1.01%) (2). Considering the fact that most of these provinces constitute a relatively small population, a slight over-reporting may contribute to the reported higher rates of pancreatic cancer in these provinces. However, these provinces may benefit from a better quality of cancer registry and this may also contribute to the results. On the other hand, one cannot completely reject the possible role of environmental and/or genetic factors in development of pancreatic cancer in these provinces. Most of these provinces including Khorasan, Hormozgan, Chaharmahal and Bakhtiari, Ilam, and Kohkiloueh and Boyerahmad are among the provinces with high rate of consanguineous marriage in Iran (12,13). Other environmental factors may also be associated with the higher rate of pancreatic cancer in these provinces as Chaharmahal and Bakhtiari and Kohkiloueh and Boyerahmad are two provinces close to each other in the surrounds of Zagros mountain range. People living in these two provinces have many cultural characteristics and behavioral habits in common.

Prognosis of pancreatic cancer

There are no early symptoms or sensitive and specific markers that allow early diagnosis of pancreatic cancer. Furthermore, pancreatic cancer is characterized by early metastasis. The majority of pancreatic cancers are detected at a late stage without a chance of curative surgery. In addition, pancreatic cancer is largely chemo- and radiotherapy resistant. Therefore, the mortality rate of this tumor is essentially identical to its incidence. Overall one-year and five-year survival rates for pancreatic cancer in the USA and in Europe are about 25% and 5%, respectively (4,7) demonstrating that long term survival of patients with pancreatic cancer is still exceptional. Thus, pancreatic cancer has a dismal prognosis. Therefore, despite its comparatively low incidence, it ranks high with respect to cancer deaths in western statistics. A similar situation can be observed in the Islamic Republic of Iran. Although pancreatic cancer incidence rate was 20th among other cancers in females and 19th in males in 2003, it was 12th and 13th frequent cause of cancer death in 23 provinces studied in females and in males, respectively. Accordingly, in 2004, pancreatic cancer incidence was 20th among other cancers in females and in males; but it was 14th and 13th

leading cause of cancer deaths in 27 studied provinces in females and males, respectively. Overall, pancreatic cancer was 13th cause of deaths due to cancers in 2003 and 2004. The corresponding data for 2005 are not yet available. Of note, the data on cancer deaths in 2003 did not take into account cancers of the small intestine, testis, ovary, adrenal, endocrine glands, bone and joints. Cancer mortality was assessed only in 23 provinces. However, the data for 2004 did comprise the aforementioned cancers and cancer mortality was evaluated in all but one province demonstrating a marked improvement in the cancer registry.

Risk factors for pancreatic cancer and potential preventive measures

There is a higher risk of pancreatic cancer for the first degree relatives of patients with pancreatic carcinoma, or for those suffering from Peutz-Jeghers-syndrome, hereditary pancreatitis, chronic pancreatitis and type 2 diabetes. Currently, no diagnostic tests can be recommended for monitoring patients who are at a higher risk for pancreatic cancer (11). There is no diet that has been proven to be effective in preventing pancreatic cancer. The effect of certain dietary factors on pancreatic cancer development is summarized in table 1.

Table 1: Impact of nutrition on pancreatic cancer risk.

Factor	Risk increased	Risk reduced	definitive relationship
Smoking tobacco	Yes (28,29)		
Drinking alcohol*	Yes (30-32)		
Obesity	Yes (33,34)		
Smoked/grilled meat	(yes) (35,36)		
Physical activity/reducing weight		Yes (37,38)	
Drug prophylaxis (anti oxidants, NSAIDs)	aspirin in females? (39,40)	No	
Fiber			(x) (41)
Fruit, vegetables,		(yes) (42-44)	
Vitamin C containing food		(yes) (42)	
Fat	(yes) (35,45)		
Low cholesterol food		(no)	
Red meat		(no)	
White meat			(x) (46,47)
Fish			(x) (47)
Sugar			(x) (48)
Milk		(no) (49)	
Coffee			X (50,51)
Tea			X (green tea) (50)

Table legend: ( ) likely relationship ( ) insufficient data * more than 30g/d in male

Fruit and vegetable consumption may be of particular interest for the Iranian population. Although the evaluation of a potentially protective effect of these nutrients in pancreatic cancer is difficult, and the results of different studies have been contradictory, (see Table1), consumption of fruit and vegetables may reduce the pancreatic cancer risk. One should consider that most of the studies showing a protective effect of fruits and vegetables are case-controls studies, where there is a possibility of recall bias. On the other hand, results of cohort studies are not conclusive (5). Because of the high consumption of fruits and vegetables in Iran, conducting a cohort study on the effects of these agents on incidence of pancreatic cancer may facilitate solving this controversy. Interestingly, Iranians drink less alcoholic beverages. Therefore one could assume that these drinks or chronic pancreatitis due to alcohol abuse may not contribute to pancreatic cancer in Iran. Tobacco products such as cigars and chewing

tobacco (smokeless tobacco) cause a moderate increase in pancreatic cancer risk, which is of borderline significance (14). It is assumed that much of the increase in the incidence of pancreas cancer during the second half of the 20th century resulted from increasing exposure to tobacco. There is some evidence that upon reduction of exposure to tobacco at the beginning of 21st century in the USA, the cancer related mortality is beginning to decline. The same trend is predicted for Europe (15). Smoking is less common in the Iranian population (16). This may in part contribute to the relatively lower incidence of pancreatic cancer in Iran compared to western countries. Unfortunately, exposure of Iranians to tobacco is slightly increasing (16). This may result in a significant increase in the incidence of pancreatic cancer in Iran in the coming years.

Diagnosis of pancreatic cancer

According to the most recent interdisciplinary guidelines, a newly acquired asymptomatic icterus as well as acute pancreatitis of unknown etiology in patients of ≥50 years of age should lead to diagnostic testing for pancreatic cancer (11). Abdominal ultrasound is the first diagnostic tool to establish whether a suspected tumor is present. If pancreatitis of unknown etiology is present, endoscopic ultrasound (EUS) should be performed. Multidetector computed tomography (MD-CT) with a biphasic contrast injection protocol or magnetic resonance tomography (MRT) with MRCP or ERCP are also suitable for diagnosis of pancreatic carcinoma. However, ERCP alone is not sufficient, because it shows only ductal irregularities, but not the lesion itself. MD-CT and endoscopic ultrasound are also the preferred diagnostic tools for the preoperative assessment of resectability. If MD-CT is not performed, abdominal ultrasound and a chest x-ray are mandatory for correct tumor staging. Positron emission tomography with fluorodeoxyglucose does currently not play a role in the preoperative or general assessment of patients with pancreatic cancer (11). Restaging during the palliative treatment should be done by abdominal ultrasound or MD-CT. CA 19-9-testing is not recommended to establish a primary diagnosis of pancreatic cancer and should only be used for follow up; e.g., after resection of a pancreatic carcinoma.

Cytological and histological examination

Currently, brush cytology from the bile duct or the pancreatic duct is not recommended due to low sensitivity. Any suspicious and potentially resectable pancreatic lesion should be resected. An exemption could be small branch duct IPMN lesions. Recent evidence suggests that some branch duct IPMNs are less aggressive than main-duct IPMNs. Branch duct IPMNs with a tumor diameter ≥30 mm, mural nodules and dilated main pancreatic duct have a high malignant potential and must be resected (17-19). However, patients with branch duct IPMN <30 mm, no mural nodules and without dilation of the pancreatic duct can be put under active surveillance with endoscopic ultrasound performed every 6 months and MRCP performed every 12 months. During follow-up of branch duct IPMNs, one must remember that also ductal carcinoma of the pancreas develops at a higher rate in patients with IPMN (19). EUS-guided biopsy is only recommended, if the outcome of this diagnostic test will potentially change the therapeutic procedure. However, a tumor biopsy is mandatory prior to palliative treatment. Here, the primary tumor or a metastasis can be used for biopsy (11).

Treatment of pancreatic cancer

Surgical treatment of pancreatic cancer: The only curative treatment for pancreatic cancer is surgery. The ultimate goal is the resection of a pancreatic carcinoma with tumor-free resection

margins (R0).

Tumors in the head of the pancreas can be treated with pylorus maintaining or partial duodenopancreatectomy with gastrectomy. An extended lymph node dissection according to standard procedures has no advantage. A pancreatic carcinoma can be R0 resectable even if neighboring organs are infiltrated including the portal vein and the superior mesenteric vein. However, R0-resection is almost never possible if the coeliac trunk and the superior mesenteric artery are infiltrated. In case of organ metastasis or distant lymph node metastasis, resection of the primary tumor does not improve the prognosis (11). A patient should not be excluded from resection of the pancreatic carcinoma because of age. However, comorbidity can be a reason not to perform resection.

Systemic treatment of pancreatic cancer

Palliative treatment: Standard treatment for locally advanced, inoperable (LAPC) and metastatic pancreatic cancer (mPC) is chemotherapy with gemcitabine (20). Using this chemotherapeutic agent, median survival rates of about 6 months for mPC and 9-10 months for LAPC can be achieved. Recent data suggest that for patients with LAPC, radiochemotherapy could be an option in case the tumor is controlled by initial chemotherapy (21). Patients with mPC may benefit from a combination of gemcitabine with erlotinib, a tyrosine kinase inhibitor that targets the epidermal growth factor receptor. This combination is particularly effective when patients develop a marked skin rash within the first weeks of treatment. In this case, median survival of more than 10 months has been reported (22). Other chemotherapeutic combinations or other combinations with targeted therapies could not demonstrate superior overall survival compared to gemcitabine (23). If the first line therapy fails, second line treatment should be initiated, particularly if the patient presents with good performance status. Best evidence so far exists for the combination of 5-FU and oxaliplatin (24).

Adjuvant/additive treatment

After R0- or R1 resection of pancreatic cancer, adjuvant/additive chemotherapy should be performed in patients with Eastern Cooperative Oncology Group (ECOG) performance status 0-2 regardless of age. For ECOG stage 3, the decision for adjuvant chemotherapy should be taken individually. Standard of care is gemcitabine given for 6 months (25). Treatment with 5-FU is also an option (26). Adjuvant therapy improves the disease free survival and overall survival of patients after surgery for pancreatic cancer. Therapy should be started within 6 weeks postoperatively. Following R0-resection, there is currently no indication for an adjuvant or additive radiochemotherapy except in clinical trials.

Treatment of pancreatic cancer in Iran

Little is known about the current state of different therapeutic approaches to pancreatic cancer in Iran. Up to now, the NCR does not collect the data on the treatment options offered to the patients in different hospitals or the number of hospitals providing chemotherapy for patients with pancreatic cancer. Currently, there is no specialized center for treatment of pancreatic cancer in Iran. The comparatively low incidence of pancreatic cancer in Iran and pancreatic cancer being only the 13th cause of cancer deaths are likely to be the main reasons for this shortcoming. However, taking into account that ageing and cigarette smoking are two major risk factors for pancreatic cancer and considering the fact that Iran is facing a phase of increase in both of these risk factors, a significant increase in the incidence of pancreatic cancer in Iran in near future is predictable. In order to overcome the burden of

pancreatic cancer in future, planning national based integrated and multidisciplinary programs in the fields of both cancer registry and cancer diagnosis and treatment could be a good way forward to meet these challenges.

CONCLUSION

In this paper, we aimed at providing a comprehensive overview on pancreatic cancer in the Islamic Republic of Iran as well as a short review on evidence-based current diagnosis and treatment of this disease. Compared to western countries, pancreatic cancer has a relatively low incidence in Iran but is similarly associated with a dismal prognosis. The risk factors of the disease are not extensively studied in Iran. However, as Figure 1 shows, similar to the western countries pancreatic cancer is a disease of advanced age, rarely diagnosed before the fifth decade in Iran and most of the patients are older than 60 at the time of diagnosis. The analysis of the spatial spread of the pancreatic cancer in Mazandaran and Golestan, two provinces in the Caspian Sea region in the north of Iran, which comprise a low incidence of pancreatic cancer, showed that the disease, unlike other gastrointestinal tract cancers, does not exhibit high incidence clusters in the region (27). Although the significance of hereditary pancreatic cancer is not clearly discussed in Iran, the incidence of the disease in some young patients suggests a possible role of genetic defects in some patients with pancreatic cancer in Iran. The relatively high prevalence of consanguineous marriages in Iran may suggest a possible role for aggregated genetic defects in these young patients. In the recent years, as our knowledge about the molecular and cellular pathology of the pancreatic cancer has progressed, and many agents including anti-EGFR, anti-VEGF, and immunotherapeutic agents have been applied for the treatment of the disease, there is increasing hope to improve survival of patients with pancreatic cancer. However, surgery remains the only curative approach and further research is paramount to identify novel diagnostic and predictive biomarkers for early diagnosis and treatment stratification. Improvement in care for patients with pancreatic cancer is not only dependent on new treatment modalities, but also on a change in the overall approach to cancer diagnosis and treatment. Pancreatic cancer requires an interdisciplinary approach which involves surgery, pathology, radiology, gastroenterology, oncology, and palliative care provided in dedicated, specialized centers.

REFERENCES

1. Hruban RH, Adsay NV, Albores-Saavedra J, Compton C, Garrett ES, Goodman SN, et al. Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions. *Am J Surg Pathol* 2001; 25: 579-86.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; 55: 74-108.
3. Cancer Facts and Figures. American Cancer Society Inc 2007. Atlanta: American Cancer Society, 2007.
4. Bray F, Sankila R, Ferlay J, Parkin DM. Estimates of cancer incidence and mortality in Europe in 1995. *Eur J Cancer* 2002; 38: 99-166.
5. Lowenfels AB, Maisonneuve P. Epidemiology and risk factors for pancreatic cancer. *Best Pract Res Clin Gastroenterol* 2006; 20: 197-209.
6. Yeo TP, Hruban RH, Leach SD, et al. Pancreatic cancer. *Curr Probl Cancer* 2002; 26: 176-275.
7. Horner MJ, Ries LAG, Krapcho M, et al. Seer Cancer Statistics review 1975-2006 National Cancer Institute. http://seercancergov/csr/1975_2006/ 2009.
8. Hahn SA, Greenhalf B, Ellis I, Sinal-Frey M, Rieder H, Korte B, et al. BRCA2 germline mutations in familial pancreatic carcinoma. *J Natl Cancer Inst* 2003; 95: 214-21.
9. Hruban RH, Goggins M, Kern SE. Molecular genetics and related developments in pancreatic cancer. *Curr Opin in Gastroenterol* 1999; 15: 404-9.
10. Ferrone CR, Levine DA, Tang LH, Allen PJ, Jarnagin W, Brennan MF, et al. BRCA Germline Mutations in Jewish Patients With Pancreatic Adenocarcinoma. *J Clin Oncol* 2009;27:433-8.
11. Adler G, Seufferlein T, Bischoff SC, Brambs HJ, Feuerbach S, Grabenbuuer G, et al. S3-Guidelines "Exocrine pancreatic cancer" 2007. *Z Gastroenterol* 2007; 45: 487-523.
12. Abbasi-Shavazi MJ, Mcdonald P, Hosseini-Chavoshi M. Modernization or Cultural Maintenance: The Practice of Consanguineous Marriage in Iran. *J Bios Scien* 2008; 40: 911-33.
13. Saadat M. Consanguineous marriages in Iranian folktales.

Community Genetics 2007; 10: 38-40.
14.Alguacil J, Silverman DT. Smokeless and other noncigarette tobacco use and pancreatic cancer: A case-control study based on direct interviews. *Cancer Epidemiol Biomarkers Prev* 2004; 13: 55-8.
15.Levi F, Lucchini F, Negri E, La Vecchia C. Pancreatic cancer mortality in Europe: The leveling of an epidemic. *Pancreas* 2003;27:139-42.
16.Fotouhi A, Khabazkhoob M, Hashemi H, Mohammad K. The Prevalence of Cigarette Smoking in Residents of Tehran. *Arch Iran Med* 2009; 12: 358-64.
17.Sugiyama M, Suzuki Y, Abe N, Mori T, Atomi Y. Management of intraductal papillary mucinous neoplasm of the pancreas. *J Gastroenterol* 2008; 43: 181-5.
18.Takeshita K, Kutomi K, Takada K, Haruyama T, Fukushima J, Aida R, et al. Differential diagnosis of benign or malignant intraductal papillary mucinous neoplasm of the pancreas by multidetector row helical computed tomography: Evaluation of predictive, factors by logistic regression analysis. *J Compu Assis Tomog* 2008;32:191-7.
19.Uehara H, Nakaizumi A, Ishikawa O, Lishi H, Tatsumi K, Takakura, R, et al. Development of ductal carcinoma of the pancreas during follow-up of branch duct intraductal papillary mucinous neoplasm of the pancreas. *Gut* 2008; 57: 1561-5.
20.Burris HA, 3rd, Moore MJ, Andersen J, Green MR, Rothenbevg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; 15: 2403-13.
21.Huguet F, Andre T, Hammel P, Artru P, Balosso J, Selle F, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol* 2007; 25: 326-31.
22.Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; 25: 1960-6.
23.Seufferlein T, von Wichert G, Adler G. Palliative treatment of pancreatic cancer. *Dtsch Med Wochenschr* 2007;132:813-7.
24.Pelzer U, Stieler J, Roll L, Hilbig A, Dorken B, Riess H, et al. Second-Line Therapy in Refractory Pancreatic Cancer. Results of a Phase II Study. *Onkologie* 2009; 32: 99-102.
25.Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 2007; 297: 267-77.
26.Neoptolemos JP, Stocken DD, Friess H, Stocken DD, Friess H, Bassi C, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; 350: 1200-10.
27.Mohebbi M, Mahmoodi M, Wolfe R, Nourijelyani K, Mohammad K, Zeraati H, et al. Geographical spread of gastrointestinal tract cancer incidence in the Caspian Sea region of Iran: spatial analysis of cancer registry data. *BMC Cancer* 2008; 8: 137.
28.Sponsiello-Wang Z, Weitkunat R, Lee PN. Meta-analysis of the relationship between European and North American smokeless tobacco and pancreatic cancer. *Am J Epidemiol* 2008; 167: S1-S147.
29.Capurso G, Schunemann H, Delle Fave G. Passive smoking and the use of noncigarette tobacco products in association with risk for pancreatic cancer - A case-control study. *Cancer* 2008; 112 :671-2.
30.Heinen MM, Verhage BAJ, Ambergen TAW, Goldbohm RA, van den Brandt PA. Alcohol Consumption and Risk of Pancreatic Cancer in the Netherlands Cohort Study. *Am J Epidemiol* 2009; 169: 1233-42.
31.Genkinger JM, Spiegelman D, Anderson KE, Bergkvist L, Bernstein L. Alcohol Intake and Pancreatic Cancer Risk: A Pooled Analysis of Fourteen Cohort Studies. *Cancer Epidemiol Biomarkers & Prev* 2009; 18: 765-76.
32.Zolotarevsky E, Brand R, Lee SY, Sherman S, Whitcomb A, Sasson A, et al. Dose-dependent effects of alcohol and tobacco on age of presentation in pancreatic cancer (PC): A multicenter, international study. *Gastroenterology* 2008;134:A696-A7.
33.Luo J, Margolis KL, Adami HO, Lacroix A, Ye W. Obesity and risk of pancreatic cancer among postmenopausal women: the Women's Health Initiative (United States). *Br J Cancer* 2008; 99: 527-31.
34.Fleming JB, Gonzalez RJ, Petzel MQB, Lin E, Morris JS, Gomez H. Influence of Obesity on Cancer-Related Outcomes After Pancreatectomy to Treat Pancreatic Adenocarcinoma. *Arch Surg* 2009; 144: 216-21.
35.Nothlings U, Wilkens LR, Murphy SP, Hankin JH, Henderson BE, Kolonel LN, et al. Meat and fat intake as risk factors for pancreatic cancer: the multiethnic cohort study. *J Natl Cancer Inst* 2005; 97: 1458-65.
36.Heinen MM, Verhage BA, Goldbohm RA, van den Brandt PA. Meat and fat intake and pancreatic cancer risk in the Netherlands Cohort Study. *Int J Cancer* 2009;125:1118-26.
37.Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS, et al. Physical activity, obesity, height, and the risk of pancreatic cancer. *JAMA* 2001; 286: 921-9.
38.Zhang J, Dhakal IB, Gross MD, Lang NP, Kadlubar FF, Harnak LJ, et al. Physical activity, diet, and pancreatic cancer: a population-based, case-control study in Minnesota. *Nutr Cancer* 2009; 61: 457-65.
39.Jacobs EJ, Connell CJ, Rodriguez C, Patel AV, Calle EE, Thun MJ, et al. Aspirin use and pancreatic cancer mortality in a large United States cohort. *Journal of the National Cancer Institute* 2004; 96: 524-8.
40.Schernhammer ES, Kang JH, Chan AT, Michaud DS, Skinner HG, Giovannucci E, et al. A prospective study of aspirin use and the risk of pancreatic cancer in women. *Journal of the National Cancer Institute* 2004; 96: 22-8.
41.Chan JM, Wang F, Holly EA. Whole grains and risk of pancreatic cancer in a large population-based case-control study in the San Francisco Bay Area, California. *Am J Epidemiol* 2007;166:1174-85.
42.Bae JM, Lee EJ, Guyatt G. Citrus fruit intake and pancreatic

cancer risk: a quantitative systematic review. *Pancreas* 2009;38:168-74.
43. Vrieling A, Verhage BA, van Duijnhoven FJ, Jenab M, Overvad K, Tjonneland A, et al. Fruit and vegetable consumption and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2009; 124: 1926-34.
44. Larsson SC, Hakansson N, Naslund I, Bergkvist L, Wolk A. Fruit and vegetable consumption in relation to pancreatic cancer risk: a prospective study. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 301-5.
45. Thiebaut AC, Jiao L, Silverman DT, Cross AJ, Thompson FE, Subar AF, et al. Dietary fatty acids and pancreatic cancer in the NIH-AARP diet and health study. *J Natl Cancer Inst* 2009; 101: 1001-11.
46. Chan JM, Wang F, Holly EA. Pancreatic cancer, animal protein and dietary fat in a population-based study, San Francisco Bay Area, California. *Cancer Causes Control* 2007; 18: 1153-67.
47. Larsson SC, Hakanson N, Permert J, Wolk A. Meat, fish, poultry and egg consumption in relation to risk of pancreatic cancer: a prospective study. *Int J Cancer* 2006; 118: 2866-70.
48. Chan JM, Wang F, Holly EA. Sweets, sweetened beverages, and risk of pancreatic cancer in a large population-based case-control study. *Cancer Causes Control* 2009; 20: 835-46.
49. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Dietary meat, dairy products, fat, and cholesterol and pancreatic cancer risk in a prospective study. *Am J Epidemiol* 2003; 157: 1115-25.
50. Luo J, Inoue M, Iwasaki M, et al. Green tea and coffee intake and risk of pancreatic cancer in a large-scale, population-based cohort study in Japan (JPHC study). *Eur J Cancer Prev* 2007; 16: 542-8.
51. Soler M, Chatenoud L, La Vecchia C, Franceschi S, Negri E. Diet, alcohol, coffee and pancreatic cancer: final results from an Italian study. *Eur J Cancer Prev* 1998; 7: 455-60.