

Pancreatic Cancer in Israel: The Epidemiology, Possibilities of Prevention, Early Detection and Screening

Paul Rozen MB BS^{1,5}, Irena Liphshitz MSc², Guy Rosner MD¹, Micha Barchana MD MPH^{2,6}, Jesse Lachter MD³, Sara Pel BA MPH¹, Tami Shohat MD MPH⁴, Erwin Santo MD¹, and the Israeli Pancreatic Cancer Consortium*

¹Department of Gastroenterology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

²Israel National Cancer Registry, Ministry of Health, Jerusalem, Jerusalem

³Department of Gastroenterology, Rambam Medical Campus and Technion-Israel Institute of Technology, Haifa, Israel

⁴Israel Center for Disease Control, Tel Hashomer, Israel

⁵Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

⁶School of Public Health, Haifa University, Haifa, Israel

ABSTRACT: Pancreatic cancer is not a common malignancy in Israel, but it is the third most common cause of cancer mortality, attributable to a lack of screening tests, inaccessibility of the pancreas, and late cancer stage at diagnosis. We reviewed the epidemiology, known risk factors and screening methods available in Israel and describe the Israeli national consortium that was established to identify persons at risk and decide on screening methods to detect and treat their early-stage pancreatic cancer. In collaboration with the Israel National Cancer Registry, we evaluated the incidence and trends of the disease in the Jewish and non-Jewish populations. The consortium reviewed known lifestyle risk habits, genetic causes, and screening methodologies used and available in Israel. Overall, there are about 600 new patients per year, with the highest incidence occurring in Jewish men of European birth (age-standardized rate 8.11/10⁵ for 2003–06). The 5 year survival is about 5%. The consortium concluded that screening will be based on endoscopic ultrasonography. Pancreatic cancer patients and families at risk will be enrolled, demographic and lifestyle data collected and a cancer pedigree generated. Risk factors will be identified and genetic tests performed as required. This concerted national program to identify persons at risk, recommend which environmental risk factors to avoid and treat, and perform endoscopic ultrasound and genetic screening where appropriate, might reduce the incidence of invasive pancreatic cancer and/or improve its prognosis.

IMAJ 2009; 11: 710–713

KEY WORDS: cancer, consortium, endoscopic ultrasonography, genetics, Israel, pancreas, prevention, screening

in Israeli Jewish men and women and 10th and 19th in Arab men and women. In contrast, it ranks 6th in the United States and 13th worldwide [1-3]. But pancreatic cancer ranks third in cancer mortality in Israel, fourth in the U.S. and eighth worldwide [1-3].

Compared to the breast, uterus, prostate, stomach and large bowel, the pancreas is an inaccessible organ without an established method for screening and early detection. Thus, pancreatic cancer is only diagnosed when presenting with symptoms. Symptomatic patients almost inevitably have locally spread disease, which makes surgical and oncological cure uncommon. The 5 year survival for the disease in Israel, the U.S. and worldwide is about 3–5% [1-3]. In the U.S. there is now a trend for increasing survival [2].

To improve this dismal prognosis, attempts are being made in the U.S. and Europe to identify risk factors and screening methodologies. To facilitate this, familial pancreatic cancer registries and multidisciplinary collaborative groups have been established as "consortiums" to establish such guidelines for early detection [4-8].

Such a consortium has now been established in Israel. To facilitate its work we: a) analyzed pancreatic cancer epidemiology in Israel, b) reviewed techniques available for early diagnosis, and c) reviewed known risk factors that could be prevented or identify persons at increased risk for the disease.

EPIDEMIOLOGY OF PANCREATIC CANCER IN ISRAEL

The data source was the Israel National Cancer Registry. Its description and methods used are described in full elsewhere [1,9]. During 2006, a total of 609 new pancreatic cancer patients were reported to the INCR; only 23 of them were Arab citizens.

INCR = Israel National Cancer Registry

* Listed at the end of the article

Throughout the world, the incidence of pancreatic cancer is highest in countries with a westernized lifestyle, including Israel. Even so, pancreatic cancer is not a common malignancy, being the 12th and 15th most common malignancy

Table 1. Pancreatic cancer in Israeli Jews and Arabs by gender and continent of birth (Jews), age-standardized incidence rates/10⁵ for 5 year periods, 1980–2006, and the changing rate ratio of cancer with time

	Jewish males: ASR					Jewish females: ASR					Arabs ASR	
	European born	Non-European born	Rate ratio	P	All males	European born	Non-European born	Rate ratio	P	All females	Males	Females
1980–84	9.45	7.37	1.4	< 0.01	8.83	5.92	4.92	1.3	< 0.01	5.62	3.59	1.41
1985–89	9.81	7.06	1.3	< 0.01	8.62	6.64	5.44	1.2	< 0.01	6.06	3.87	2.87
1990–94	8.47	6.84	1.3	< 0.01	7.75	5.90	4.87	1.3	< 0.01	5.63	4.11	2.86
1995–98	8.73	5.81	1.5	< 0.01	7.44	5.94	4.54	1.3	< 0.01	5.50	5.86	2.70
1999–2002	9.24	8.11	1.2	< 0.01	8.88	6.81	5.06	1.2	< 0.01	6.11	6.91	3.05
2003–06	8.11	7.45	1.1	0.04	7.98	5.70	5.62	1.1	0.02	5.94	5.61	3.41
Rate ratio												
80–89 vs. 99–06	1.11	0.94			1.04	0.98	0.96			0.95	0.69	0.68
P value	< 0.01	NS			NS	NS	NS			NS	< 0.01	< 0.01

ASR = age-standardized incidence

INCIDENCE RATES AND TRENDS 1980–2006

Table 1 shows that the incidence rates were significantly higher in European-born Jews of both genders and in both the European and non-European-born males. Among Jewish male immigrants who arrived after 1990, the incidence is insignificantly higher than among other Israelis (not shown). For the same period, the incidence in the Arab population was lower than in the Jewish population and was also higher in men [Table 1].

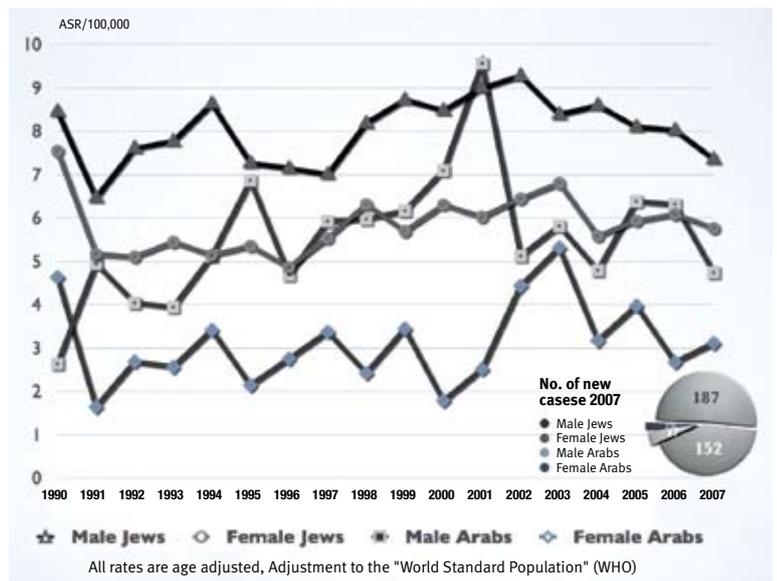
Trend analysis demonstrated a recent significant decreased incidence of pancreatic cancer occurring in Jewish males of European origin, but a significant rising trend, until recently, in the Arab population [Table 1, Figure 1].

RISK FACTORS FOR PANCREATIC CANCER

Epidemiological studies have identified environmental and familial risk factors for the disease [4-6,10]. These include: male gender, aging, obesity, diabetes (type 2 or hyperglycemia occurring as a paraneoplastic phenomenon), tobacco smoking, high consumption of fried/grilled/processed meats, and chronic pancreatitis. Many of these environmental risk factors are common to the etiology of cardiovascular disease and other frequently occurring malignancies. Although it is usual to recommend avoiding or treating these risk factors, there is no perspective study to show that this reduced the incidence of pancreatic cancer. However, the recent reduction in incidence in both Israel and the U.S. could be explained by the efforts, during that last three decades, to prevent cardiovascular disease and cancer [1,2,11].

Genetic risk factors are believed responsible for 5–10% of pancreatic cancer cases [Table 2]. They include both genetic disorders where pancreatic involvement is not the usual target

Figure 1. Pancreatic cancer incidence and time trends, in Jews and Arabs, 1990–2007. Note the recent significant decreased incidence in European-born male Jews and a decrease in the significantly rising incidence in Arabs. Figure provided by Dr. Barchana, INCR.



organ and also pancreas-specific genetic mutations causing cancer [4,6,12-16].

EARLY DETECTION

Review of the literature and recommendations of similar international groups concluded that there are no sensitive non-invasive screening modalities or early diagnostic tests. These include: blood tests, standard and high resolution

Table 2. Genetic syndromes with increased risk for pancreatic cancer

Genetic syndrome	Gene(s)	Chromosome site	Pancreatic cancer risk (RR)
Hereditary breast/ovarian cancer	BRCA2 BRCA1	13q12 17q21	3.51 fold 2.26 fold
FAMM melanoma syndrome	CDKN2A	9p21	13-22 fold
Peutz-Jeghers syndrome	STK11	19p13.3	132 fold
Lynch syndrome	Mismatch repair genes (<i>MLH1, MSH2</i>)	2p22, 3p21	RR increased
Hereditary pancreatitis	<i>PRSS1, SPINK1</i>	7q35, 5q31	50 fold
Cystic fibrosis (heterozygotes)	CFTR	7q35	3.5 fold
Ataxia telangiectasia	ATM		RR increased
Fanconi anemia	FANCC	9q22	RR increased
Familial pancreatic cancer	Unknown	Unknown	Suspected autosomal dominant inheritance
Familial pancreatic cancer	PALB2	16p12	High penetrance
Pancreatic cancer in ≥ three first-degree relatives			RR = 32
Pancreatic cancer in two first-degree relatives			RR = 6.4
Pancreatic cancer in one first-degree relative			RR = 4.5

RR = relative risk; derived from references 4,6,12-16

pancreas-dedicated abdominal computed tomography, and ultrasonography [5,17]. Advanced imaging techniques using magnetic resonance might be useful but are not readily available in Israel [17].

Endoscopic ultrasound sonography is the most sensitive screening test available. It can identify early pancreatic changes caused by an IPMN (pre-malignant intraductal papillary mucinous neoplasm), mucinous cysts, or malignant lesions (small masses and PanIN lesions, i.e., preneoplastic pancreatic intraepithelial neoplasia), or early features of chronic pancreatitis. With this procedure biopsies/cytology/cancer markers can be obtained [5,6,16].

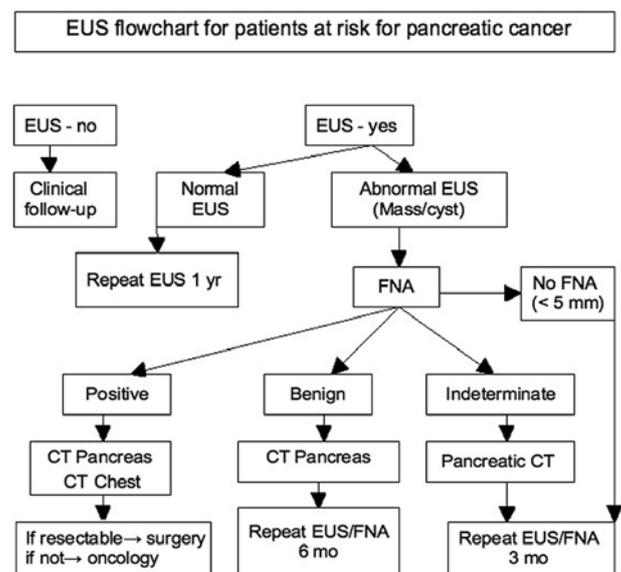
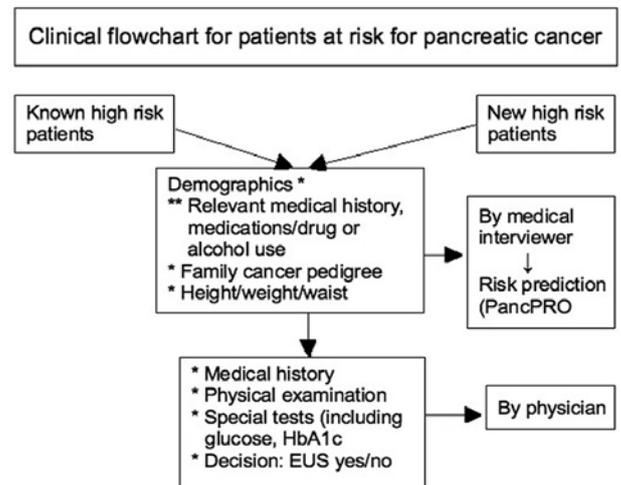
ISRAELI CONSORTIUM FOR PANCREATIC CANCER PREVENTION

At the founding meeting in August 2009, called by the Pancreas Subcommittee of the Israel Gastroenterology Society, it was concluded that, as in America and Europe, there was a need to establish a consortium with the aim of evaluating the feasibility of prevention, early diagnosis and treatment of pancreatic cancer in high risk patients with preneoplastic lesions and/or at least two first-degree relatives with pancreatic and/or another cancer [4,5,7,8,16].

The consortium decided that EUS would be their standard test for pancreatic cancer [18]. They adopted the following

standard protocol as used in an American multicenter study for examination, documentation and follow-up of these lesions and/or patients at high risk for the disease [7]. Similar protocols are used in Europe [8,16]. These are summarized as follows and by the flowcharts.

Identifying individuals and families at risk would be carried out at both the local and national level. At each collaborating center, cancer pedigrees of pancreatic cancer patients and their relatives will be recorded and defined syndromes identified [Table 2], which will enable their risk assessment for disease [13]. They will be invited for genetic consultation and DNA analysis where appropriate. If a specific genetic analysis is not available in Israel, then assistance will be requested from an international collaborating group.



EUS = endoscopic ultrasound sonography

Preventive advice on lifestyle habits will be given to patients and family members at risk for pancreatic cancer [10]. In addition, public lectures will be given locally to encourage relatives to come for evaluation. At the national level, there will be collaboration with the Israel Center for Disease Control and the INCR. They will also help identify families at risk by linkage of the INCR database with the national population database. Families will not be approached directly, but the last treating physician will be asked to invite the family to one of the collaborating centers for screening.

The protocol will initially be performed over a 2 year period, after which conclusions will be drawn on feasibility, compliance, performance results, and whether changes need to be made according to international and local experience. All the above activities, including tests, will be performed after obtaining agreement of the local and national ethics committees and informed consent from patients. The protocol has been approved by the Tel Aviv Medical Center's ethics committee and is awaiting approval from the other collaborating centers.

The strength of this protocol is the concerted effort to identify the small number of asymptomatic persons at increased risk for pancreatic cancer and implement the preventive and screening tests in this group. This is similar to the policy for persons at increased risk for colon or breast cancers. The limitations include user-dependent EUS diagnosis and repeated performance of an invasive endoscopic procedure with or without biopsy and/or cytology. The reports of mortality following EUS have been attributed, in the main, to the procedure learning curve and the instruments available at that time [19]. Recent outcome evaluations showed that morbidity from the procedures is similar to that of all screening-surveillance procedures, such as colonoscopy [20]. For these reasons, the consortium membership has been limited to experienced and established EUS centers.

In conclusion, pancreatic cancer is not a common malignancy, but it has a very poor prognosis when identified clinically. We will examine the feasibility of a concerted national program to identify persons at risk, perform EUS and/or genetic screening where appropriate, and provide recommendations to treat and avoid environmental risk factors. This might reduce the incidence of invasive pancreatic cancer and/or improve its prognosis.

Acknowledgments:

We thank the Israel Cancer Society for supporting the study (Dr. Santo), Sestopali Gastrointestinal Cancer Prevention Fund and Katzman Family Foundation for supporting administrative and publication costs (Dr. Rozen), and Ms. Sally Zimmerman for secretarial assistance and Ms. Ziona Samuel for her help.

Correspondence:

Dr. P. Rozen

Director, Sestopali Fund for Gastrointestinal Cancer Prevention, Dept. of Gastroenterology, Tel Aviv Medical Sourasky Center, 6 Weizmann Street, Tel

Aviv 64239, Israel

Phone: (972-3) 695-5833, **Fax:** (972-3) 695-9528, **email:** prozen@o12.net.il

Members of the Pancreatic Cancer Consortium:

(alphabetical), as of 15 August 2009

M. Barchana (Israel National Cancer Registry, epidemiologist); Y. Biderman & E. Meltzer (Kaplan Hospital, Rehovot, EUS); Z. Fireman (Hillel Yaffe Hospital, Hadera, EUS); J. Lachter (Rambam Medical Campus, Haifa, EUS and consortium secretary); G. Leichtman (Meir Hospital, Kfar Saba, EUS); E. Meltzer (Kaplan Hospital, Rehovot, EUS); S. Pel (Tel Aviv Sourasky Medical Center' study coordinator); G. Rosner (Tel Aviv Sourasky Medical Center, study geneticist); P. Rozen (Tel Aviv Sourasky Medical Center, consultant); E. Santo (Tel Aviv Sourasky Medical Center, EUS and consortium chairman); E. Scapa (Assaf Harofeh Hospital, Rishon Lezion, EUS), T. Shohat (Israel Center for Disease Control, epidemiologist)

References

1. Israel National Cancer Registry: (www.health.gov.il/icr) accessed 2009.
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; 59: 225-49.
3. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; 55: 74-108.
4. Petersen GM, de Andrade M, Goggins M, et al. Pancreatic cancer genetic epidemiology consortium. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 704-10.
5. Lambert R, Kurtz RC. Cancer of the exocrine pancreas. *World Gastroenterol News* 2009; 14: 5-10 (www.worldgastroenterology.org/wgn.html)
6. Shi C, Hruban RH, Klein AP. Familial pancreatic cancer. *Arch Pathol Lab Med* 2009; 133: 365-74.
7. Screening for Early Pancreatic Neoplasia (Cancer of the Pancreas Screening or CAPS4 Study), <http://clinicaltrials.gov/ct2/show/NCT00714701> Accessed August 2009.
8. The European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC), www.europac-org.eu Accessed October 2009.
9. Rozen P, Liphshitz I, Barchana M. The changing epidemiology of upper gastrointestinal cancers in Israel: clinical and screening implications. *Eur J Cancer Prev* 2009; 18: 191-8.
10. Batty GD, Kivimaki M, Morrison D, et al. Risk factors for pancreatic cancer mortality: extended follow-up of the original Whitehall Study. *Cancer Epidemiol Biomarkers Prev* 2009; 18: 673-5.
11. Hart AR, Kennedy H, Harvey I. Pancreatic cancer: a review of the evidence on causation. *Clin Gastroenterol Hepatol* 2008; 6: 275-82.
12. Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. *Cancer Res* 2004; 64: 2634-8.
13. Wang W, Chen S, Brune KA, Hruban RH, Parmigiani G, Klein AP. PancPRO: risk assessment for individuals with a family history of pancreatic cancer. *J Clin Oncol* 2007; 25: 1417-22.
14. Jacobs EJ, Rodriguez C, Newton CC, et al. Family history of various cancers and pancreatic cancer mortality in a large cohort. *Cancer Causes Control* 2009; 20: 1261-9.
15. Tischkowitz MD, Sabbaghian N, Hamel N, et al. Analysis of the gene coding for the BRCA2-interacting protein PALB2 in familial and sporadic pancreatic cancer. *Gastroenterology* 2009; 137: 1183-6.
16. Larghi A, Verna EC, Lecca PG, Costamagna G. Screening for pancreatic cancer in high-risk individuals: a call for endoscopic ultrasound. *Clin Cancer Res* 2009; 15: 1907-14.
17. Kinney TP, Freeman ML. Pancreatic imaging: current state of the art. *Gastroenterology* 2009; 136: 776-9.
18. Lachter J, Cooperman JJ, Shiller M, et al. The impact of endoscopic ultrasonography on the management of suspected pancreatic cancer – a comprehensive longitudinal continuous evaluation. *Pancreas* 2007; 35: 130-4.
19. Lachter J. Fatal complications of endoscopic ultrasonography: a look at 18 cases. *Endoscopy* 2007; 39: 747-50.
20. DeWitt J. EUS and pancreatic tumors. In: Hawes R, Fockens P, eds. *Endosonography*. London: Elsevier, 2006: 77-203.