RESEARCH ARTICLE

Incidence and Trends of Malignant and Benign Pancreatic Lesions in Yazd, Iran between 2001 and 2011

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Abstract

Background: Despite recent valuable steps in initiating a cancer registry in Iran, data depicting prevalence, incidence, and clinical picture of pancreatic tumors in the country are exceedinglyly sparse. With the aim of filling this knowledge gap, we reviewed cases in the pathology archive of Shahid Sadoughi hospital (Yazd, Iran), between 2001 and 2011. Materials and Methods: Medical records of 177 patients are reported in the present study. In cases for which paraffin-embedded blocks were available, the specimens were evaluated by two independent pathologists blinded to the primary diagnosis. We extrapolated the frequency of malignant lesions in our study to the population of Yazd province, derived from national census data, to generate cancer incidence rates. Results: Final diagnosis of malignancy was made in 117 cases (66.1%), and the remainder (60 lesions, 33.9%) were classified as benign. Adenecarcinoma and neuroendocrine tumors were the two most common histological types of malignancy identified in 88 (75.2%) and 11 (9.4%) specimens, respectively. Crude annual incidence of pancreatic cancer was 0.55 per 100,000 person in 2001 and increased to 1.68 in 2011. Age standardized incidence rates in 2001 and 2011 were 0.75 and 2.68, respectively. A significant increasing trend in cancer incidence was observed during the 11 years of the study period (r=+0.856, p=0.009). Sex-stratified analysis, confirmed the observed trend in men (r=+0.728, p=0.034), but not women (r=+0.635, p=0.083). Conclusions: Over the past decade, incidence of pancreas malignancies has risen steadily in Yazd, Iran. Nevertheless, these figures are still substantially lower than those prevalent in developed nations.

Keywords: Pancreas - malignancy - incidence data - Yazd, Iran

Introduction

Pancreatic cancer is one of the common malignancies with high mortality rate (Jemal et al., 2008). It is the tenth most common cancer among both men and women; however it is ranked fourth with regard to cancer mortality (Jemal et al., 2009). It is estimated that about 30000 patients die each year due to pancreatic cancer in the United States. Reports indicate that prevalence and incidence of cancer of the pancreas has remained constant over the past years (Siegel et al., 2011). In 2005-2006 calendar year, an age-standardized incidence rate of 0.39 per 100000 in women and 0.45 per 100000 in men have been recorded in Iran. in the same year, a total of 475 deaths in the country have been attributed to pancreatic cancer (Mousavi et al., 2009).

Pancreatic cancer occurs more frequently in the elderly population and previous research has nominated age as an important risk factor in the etiology of pancreatic malignancies (Vincent et al., 2011). Another contributing factor, cigarette smoking has proven epidemiological correlation with development of pancreatic cancer (Momi

et al., 2012). Other significant underlying factors include positive family history (Schenk et al., 2001), type 2 diabetes mellitus, (Huxley et al., 2005) and an abundance of single genetic mutations, genetic loci, and hereditary syndromes (Iacobuzio-Donahue, 2012; Klein, 2012; McWilliams et al., 2011). Hereditary conditions including among others familial breast cancer with BRCA2 mutation (Lucas et al., 2013), Peutz-Jeghers syndrome (van Lier et al., 2010), and Hereditary Nonpolyposis Colorectal Cancer (HNCC) (Holmes and Bordeianou, 2011) have been causally implicated in malignant tumors of the pancreas. Genetic predisposition is believed to account for 10% of all cases of the disease (Kimmey et al., 2002).

Clinical presentation of the tumor varies depending on the anatomical region of the pancreas that it originates from. A large proportion of masses appear in head of pancreas and therefore frequently cause cholestatic jaundice, unspecific abdominal pain, along with nausea and vomiting (Hidalgo, 2010).

Pancreatic malignancies continue to be amongst the cancers with highest mortality rates in spite of the advances made in cancer diagnosis and treatment (Jemal

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et al., 2005). Various therapeutic strategies (i.e. surgery, chemo- and radiotherapy, or a combination of these) have largely failed to improve patients' prognosis and long-term survival (Vincent et al., 2011). Median survival for patients with locally advanced disease is 9-15 months; this rate dwindles to 3-6 months if there is evidence for distant metastases (Vincent et al., 2011). The overall 5-year survival rate of pancreatic cancer is believed to be less than 5% (Li et al., 2004).

To our knowledge, despite recent valuable steps in initiating a cancer registry in Iran, yet, evidence depicting prevalence, incidence, and clinical picture of pancreatic tumors in the country is overwhelmingly sparse. Therefore, this study was conducted in an attempt to fill this knowledge gap. For this purpose, we reviewed the archives of pathology department of Shahid Sadoughi hospital, a large university-affiliated referral center (Yazd, Iran) between 2001 and 2011 to retrospectively elucidate the profile of pancreas tumors in the region.

Materials and Methods

In this retrospective study, between 2001 and 2011, medical records of all patients with a pancreas specimen in the pathology department were reviewed. A total of 177 cases with available pathology blocks were found eligible and enrolled in the current study. In order to prevent breaches of patient's privacy, clinical history and laboratory evaluations were recorded with no name or telephone number. The study protocol was in accordance to Declaration of Helsinki for investigation with human subjects and was approved by the ethics committee of Yazd University of Medical Sciences.

Clinical presentations of patients with pancreas lesions including jaundice, itching, hypoglycemia, fever, changes in stool or urine color, weight loss, nausea and vomiting and abdominal pain were extracted and recorded. Additionally, wherever available, results of radiographic or ultrasonographic evaluations were also documented. Unfortunately, we encountered a high rate of missing data regarding these assessments. Therefore, no statistical analysis was conducted for these findings.

The paraffin-embedded blocks available in the pathology department of Shahid Sadoughi hospital were stained using Hemotoxylin and Eosin (H&E) technique and were re-evaluated independently by two pathologists blinded to the natural history and clinical presentation of the case. Each pathologist was then asked to classify histological variants based on the World Health Organization's International Histological Classification of Tumours (Klöppel, 1996). Excellent agreement was observed between the two pathologists. Few discrepant diagnoses were discussed and agreement was reached via consensus.

Statistical analysis

Statistical analyses were done using SPSS software version 20.0 (IBM Inc, New York, US). Categorical variables are presented as percentage and continuous variables are shown as mean and standard deviation. Chi-square test was used to compare the frequency of clinical sign and symptoms between patients with benign and malignant lesions.

The pathology department of Sadoughi hospital serves as the pathology referral center in Yazd province and pathologic specimens from medical centers within the area are sent to this department for second opinion and registration in cancer registry. Based on this fact, we extrapolated the frequency of malignant lesions in our study to population of Yazd province. Annual population of Yazd between 2001 and 2011 were extracted from the results of national censuses available at the website of Statistical Center of Iran.

With population data available, crude and age-specific incidence of pancreatic cancer is calculated and reported for each year.

World Health Organization (WHO) standard world population distribution was used to assess the age adjusted and standardized incidence ratio (Ahmad et al., 2001). In order to evaluate whether a significant change has been observed in the annual incidence of pancreatic cancer over the past ten years, Pearson product-moment correlation coefficient, and chi square tests were employed, where appropriate. In all tests, p value of less than 0.05 was considered necessary to reject the null hypothesis.

Results

In this retrospective study, a total of 177 patients were enrolled. Demographic characteristics of patients along with anatomical site of lesions are presented in Table 1. Women comprised 50.8% of the participants, and the mean age at diagnosis was 58.33±17.64. Pancreatic lesions were most frequently (24.5%) detected in eights decade of life (71-80 years). Final diagnosis of malignancy was made in 117 lesions (66.1%), and the remainder (60 lesions, 33.9%) were classified as benign. The most common anatomical sites of lesions were head of the pancreas (48 lesions, 27.1%), followed by Ampulla of Vater (42 lesions, 23.7%).

Table 1. Baseline Characteristics of Patients and Pancreatic Lesions

Patients	Malignant (n=117)	Benign (n=60)
Gender, n (%): Female	57 (48.7)	33 (55.0)
Male	60 (51.3)	27 (45.0)
Age strata, n (%): 0-10	0 (0)	1 (1.7)
11-20	5 (4.3)	1 (1.7)
21-30	3 (2.6)	5 (8.3)
31-40	4 (3.4)	6 (10.0)
41-50	15 (12.8)	11 (18.3)
51-60	23 (19.7)	11 (18.3)
61-70	30 (25.6)	7 (11.7)
71-80	31 (26.5)	13 (21.7)
81-90	6 (5.1)	5 (8.3)
Lesions: Anatomical origin of lesions, n (%)		
Head	30 (25.6)	18 (30.0)
Body	8 (6.8)	7 (11.7)
Tail	6 (5.2)	5 (8.3)
Ampulla of Vater	34 (29.1)	8 (13.3)
Head and Ampulla of Vater	21 (17.9)	5 (8.4)
Unknown	18 (15.4)	17 (28.3)

Benign lesions

Most frequent types of benign lesions were chronic pancreatitis (21 lesions, 35%), acute pancreatitis (16 lesion, 26.7%), and adenomas (8 lesions, 13.3%) (Table 2). Frequency of clinical sign and symptoms for benign pancreas lesions are presented in Table 3. The most common reported clinical presentation was pain (78.3%), followed by nausea and vomiting (48.3%) and jaundice (45%). When compared between benign and malignant lesions, patients with benign lesions were significantly more likely to experience nausea and vomiting (p=0.004). Frequency of other clinical presentations were comparable between the two groups. In abdominal radiography of patients with benign pancreatic disease, solid and cystic lesions were identified in 10(35.7%) and 10(35.7%) cases, respectively. Similarly, ultrasonographic evaluation confirmed the previous findings and detected solid and cystic parts in 10(31.3%) and 10(31.3%) patients, respectively.

Malignant lesions

Pathologic re-evaluation of available specimens showed that adenecarcinoma and neuroendocrine tumors are the two most common histological types of malignancy identified in 88 (75.2%) and 11 (9.4%) patients, respectively. Ampulla of Vater (29.1%) followed by pancreas head (25.6%) were the most frequent anatomical origins of malignant lesions. Subjects with

malignant tumors commonly presented with unspecific abdominal pain and jaundice (Table 3). Data regarding radiographic and ultrasound evaluation of patients with malignancies were missing in nearly half the patients but according to available data, palin abdominal film found solid component in 30(57.7%) patients. In a similar fashion, ultrasound detected solid component in the same number of cases; 30 (47.6%).

Incidence and trends of pancreatic cancer. Age-specific and age-adjusted incidence of pancreatic cancer is illustrated in Figure 1. The highest age-specific incidence rate was observed from 71-80 years (109.66 per 100000 person-years).

Crude annual and age-standardized incidence of pancreatic cancer between 2001 and 2011 is depicted in Figure 2. A significant increasing trend in cancer incidence was observed during the 11 years study period (r=+0.856, p=0.009). When sex-specific analyses were performed, increasing trend was observed in men (r=+0.728, p=0.034) but not in women (r=+0.635, p=0.083). Sex-specific incidence rates for pancreatic cancer between 2001 and 2011 are illustrated in Figure 3. During the study period, the highest sex-specific incidence rate was 2.25 per 100000 person-years for men (2010), and 1.49 per 100000 person-years for women.

Table 2. Histological Diagnoses of being and Malignant Lesions

		n (%)
Benign Lesions	Chronic pancreatitis	21 (35.0)
	Acute pancreatitis	16 (26.6)
	Adenomatous change	8 (13.3)
	Pseudo cyst	9 (15.0)
	Mucinous cyst	3 (6.7)
	Simple cyst	1 (1.7)
	Serous cyst	1 (1.7)
Malignant Lesions	Adenocarcinoma	88 (75.2)
	Neuroendocrine tumors	11 (9.4)
	Pseudo papillary tumors	6 (5.1)
	Small cell carcinoma	5 (4.3)
	Lymphoma	3 (2.6)
	Signet ring	2 (1.7)
	Mucinous carcinoma	2 (1.7)

Table 3. Frequency of Clinical Sign and Symptoms in Benign and Malignant Lesions

	Malignant (n=117) n (%)	Benign (n=60) n (%)	P Value
Abdominal pain	81 (69.2)	47 (78.3)	0.2
Jaundice	67 (57.3)	27 (45.0)	0.122
Nausea and vomiting	31 (26.5)	29 (48.3)	0.004
Weight Loss*	34 (29.1)	12 (20.0)	0.193
Anorexia	52 (44.4)	23 (38.0)	0.436
Itching	36 (30.8)	11 (18.3)	0.076
Stool and/or urine discoloration,	31 (26.5)	10 (16.7)	0.142
Fever	21 (17.9)	10 (16.7)	0.832
New onset diabetes	8 (6.8)	3 (5.0)	0.704

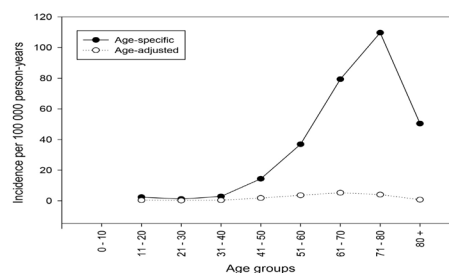*Unexplained weight loss more than 2.3 kg per month

Figure 1. Age-specific and Age-adjusted Incidence Rate of Pancreatic Cancer
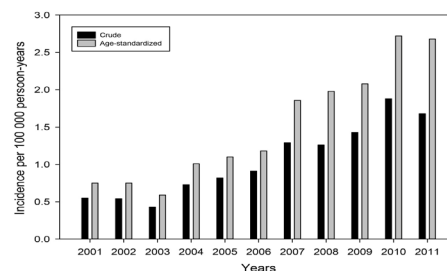

Figure 2. Crude Annual and Standardized Incidence Rate of Pancreatic Cancer in Yazd, Iran between 2001 and 2011
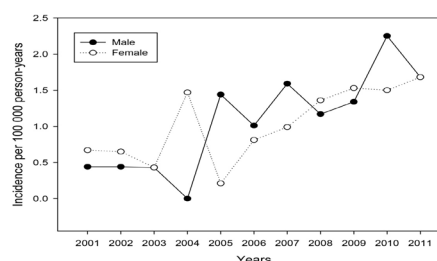

Figure 3. Sex-specific Incidence Rate of Pancreatic Cancer. Male to female ratio in 2001 was 0.65 and in the two last years (2010 and 2011) were 1.5 and 1, respectively

Discussion

In an attempt to fill the available knowledge gap in cancer epidemiology in Iran, we reported cancer incidence in Yazd between 2001 and 2011. Based on our observations, annual incidence of pancreas malignancies have gradually and consistently increased over the past decade.

We also demonstrated that pancreatic cancer is particularly more frequent in eighth decade of life. Our results showed a noticeable difference between age-specific and age-adjusted incidence rates in the mentioned age group, which is most likely due to population structure of Iran. Age composition of Iran's population has changed dramatically over the latter half of the twentieth century and as a result, a large proportion of Iranian population are under 35 years old .

In our study, comparison of frequency of signs and symptoms between benign and malignant lesions suggested that subjects with non-cancerous pathologies are significantly more likely to present with nausea and vomiting. Vomiting in benign lesions such as acute pancreatitis is usually accompanied with abdominal pain and is a results of debilitating pain (Banks and Freeman, 2006). However, when this symptom is seen in patients with malignant lesions it can be a consequence of gastric outlet obstruction, an indicator of advanced disease (Vincent et al., 2011). Eight patients (6.8%) in malignant group (mean age 66.6±9.34), and three (5%) in benign group (mean age 61.2±8.78) presented with new onset diabetes mellitus. It is proposed that new onset of diabetes in the elderly should raise suspicion of pancreatic tumors (Pannala et al., 2009).

In concert with a number of previous reports, our findings indicated that adenecarcinoma is by far the most common cancer subtype in pancreatic lesions (Carriaga and Henson, 2006; Winter et al., 2006). Moreover, it has been proven that the most common anatomical site of malignant tumor was found to be pancreas head (Hidalgo, 2010). Similar results were obtained in our study as well.

To the best of our knowledge, few studies to date have investigated incidence of pancreatic cancer in Iran. Jamali et al. (2011) using the data of National Cancer Registry (NCR), estimated incidence rate of pancreatic cancer between 2003 and 2005. The authors revealed that the highest incidence rate in this period was 0.56 per 100000 person-years observed in male patients in 2005. The mean age of diagnosis was 60.7 in men and 60.9 in women. Similarly, we observed that malignant lesions are frequently diagnosed in the elderly; 31 (26.5%) cases aging between 71 and 80 year old (age-specific incidence ratio of 109.66 and age-adjusted incidence ratio of 4.06). Mousavi et al (2009) using the same database, reported slightly different incidence rates: 0.46 in males and 0.33 in females in 2005. Our observation revealed that the total incidence of pancreatic cancer was 0.82 (1.44 in male and 0.21 in female) in the same year in Yazd province, which is higher than the national incidence. Pancreatic cancer is slightly more frequent in men and based on this fact it has been suggested that male gender confers susceptibility for this type of malignancy (Li et al., 2004).

However, we observed mixed year to year sex ratios in our incidence rates from 2001-2011. Male:female ratio was 0.65:1 in 2001, 1.5:1 in 2010 and 1:1 in 2011. Recent trend analysis also indicate that by increasing the incidence of this cancer in women the ratio is approaching to 1:1 (Jemal et al., 2008).

Compared with developing countries, incidence of pancreas malignancies is significantly higher in developed nations. In 2002, incidence of pancreatic cancer in developed world has been estimated to be about 7-9 per 100000 person years in men and 4.5-6 per 100000 person years in women (Parkin et al., 2005). The data available in cancer registry of Great Britain in 2008 documented a crude incidence of 13.1 in England, 14.2 in Wales, 13.2 in Scotland and 12.5 in Northern Ireland (per 100000 person-years).

Higher incidence rates in developed world compared with developing countries is likely due to better diagnostic strategies, imaging techniques, and resource allocations; nonetheless differential distribution of risk factors also contributes to this discrepancy (Parkin et al., 2005). Similarly, the gradual increasing trend in pancreatic cancer diagnosis in Iran over the past decade should be seen, to the most part, in light of advances in cancer diagnosis and care, employment of state of the art imaging modalities (e.g. computed tomography, Endoscopic Retrograde Cholangiopancreatography, and Magnetic Resonance Imaging), and population awareness (Palesh et al., 2007).

Proportion of elderly population (individuals 65 years and older) have increased from 3.39% in 1991 to 5.72% in 2011. Since most pancreatic cancers are diagnosed in eighth decade of life, this population increment might have contributed to increased cancer rates, albeit to a lesser extent.

In conclusion, our findings complement the existing knowledge with respect to cancer epidemiology. Over the past decade, incidence of pancreas malignancies has risen steadily in Yazd, Iran. Nevertheless, these figures are yet substantially lower than those obtained in developed nations.

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