Population-based epidemiology, risk factors and screening of intraductal papillary mucinous neoplasm patients

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Abstract

Intraductal papillary mucinous neoplasm (IPMN) was first recognized in the 1980s with increasing publications over the last decade as the incidence increased sharply, especially at tertiary-care referral centers. Population-based studies have estimated the age and sex-adjusted cumulative incidence of IPMN to be 2.04 per 100,000 person-years (95% confidence interval: 1.28-2.80). It is now understood that IPMN can be classified anywhere along the spectrum of the adenoma to carcinoma sequence and often harbors mutations in genes such as KRAS early in the disease process. Many patients are diagnosed incidentally after imaging of the abdomen for other diagnostic purposes. Patients that present with a history of symptoms such as pancreatitis and abdominal pain are at high risk of harboring a malignancy. Clinico-pathologic features such as involvement of the main pancreatic duct, presence of mural nodules, and side branch disease >3.0 cm in size may indicate that there is an underlying invasive component to the IPMN. In addition, the incidence of extra-pancreatic neoplasms is higher in patients with IPMN, with reported rates of 25% to 50%. There are no current screening recommendations to detect and diagnose IPMN but once the diagnosis is made, screening for extrapancreatic neoplasms such as colon polyps and colorectal cancer should be considered. Surgical resection is the recommend treatment for patients with high-risk features while close observation can be offered to patients without worrisome signs and symptoms of carcinoma.

Key words: Intraductal papillary mucinous neoplasm; Incidence; Prevalence; Risk factors; Screening

INTRODUCTION

The first report of intraductal papillary mucinous neoplasm (IPMN) was made in 1982 by Ohashi et al who described ‘mucin-producing’ pancreatic neoplasms in four patients. In an effort to identify the presence of IPMN prior to 1982, a single hospital-based study was undertaken...
by Tollefson and colleagues\textsuperscript{[12]} at Mayo Clinic. They evaluated slides from 84 of 4000 patients with pancreatic cancer who were treated from 1960 to 1980. All patients had a histology report with terms such as “mucinous”, “cystic”, or “papillary”. The diagnosis of IPMN was made in 21 of these 84 patients, implicating that IPMN was present prior to 1982, but went unrecognized.

Intraductal papillary mucinous neoplasm was not established as a distinct entity until more than a decade after its identification. Prior to that, a number of terms (e.g. mucinous ductal ectasia, intraductal papillary mucinous tumor (IPMT), mucin-secreting neoplasm, etc.) were used to describe these lesions in the literature, leading to extensive variability in terminology when reporting the disease. This issue was partially resolved in 1996, when the World Health Organization (WHO) classified cystic mucin-producing tumors and fully resolved in 2000 when a revision differentiated between IPMN and mucinous cystic neoplasm (MCN). Strict diagnostic criteria were proposed for each disease type. There are three types of IPMN (main duct, branch duct, and mixed), and the WHO has recommended classifying these lesions histopathologically as benign, borderline, or invasive carcinoma.

Further clarification for the diagnosis, management, and prognosis of the disease was achieved in 2004 after consensus conferences were held by experts at Johns Hopkins University\textsuperscript{[3]} and by members of the International Association of Pancreatology who convened in Sendai, Japan\textsuperscript{[4]}. The criteria established at these conferences have dictated the contemporary definition, evaluation, and management of IPMN.

**POPULATION-BASED EPIDEMIOLOGY**

Over the last two decades, there has been an increase in the number of publications related to IPMN. Many of these reports suggest that the frequency of IPMN is increasing, an observation that coincides with the increasing use and availability of computed tomography (CT) and other abdominal imaging modalities\textsuperscript{[5-7]}. The vast majority of these studies have dealt with the diagnosis and operative outcome of affected patients rather than the epidemiology or natural history\textsuperscript{[8,9,10]}. Given that there are no ‘screening’ protocols for IPMN to-date (not deemed necessary because of its rarity), available data on incidence and prevalence is primarily based on extrapolation from single tertiary health care center reports. The underlying assumption is that all patients with IPMN in that population were treated at the designated hospital. Therefore, there is an obvious risk of under-estimating the incidence or prevalence of IPMN since only patients who are symptomatic or receive an incidental diagnosis receive clinical attention.

Cognizant of the above issues, we reported the first and only population-based study of the incidence and prevalence of IPMN\textsuperscript{[11]}. The study population encompassed Olmsted County, Minnesota, which is served by a unified healthcare system. The goal was to take advantage of the Rochester Epidemiology Project (REP)\textsuperscript{[12]}, a unique medical records-linkage system that encompasses the care delivered to residents of Olmsted County, Minnesota. The REP combines clinical documentation of patients seen at Mayo Clinic with those obtained by other providers in the county. The REP is therefore able to provide incidence data for almost any condition and can also support population-based analytic studies of diseases and outcomes.

In our study, the multi-linked REP database was queried for all in- and out-patient visits, autopsy reports, and nursing home care using the relevant International Classification of Diseases (ICD) codes. Patients with a clinical diagnosis of IPMN made on imaging, endoscopy (including endoscopic ultrasound and/or endoscopic retrograde pancreateography), or pathological assessment were included. Pathological slides of all identified cases were examined by two expert pathologists. Incident cases were identified between January 1, 1984, and December 31, 2005, among residents of Olmsted County aged 20 years or older.

**INCIDENCE AND PREVALENCE**

The age and sex-adjusted cumulative incidence of IPMN in Olmsted County was 2.04 per 100,000 person-years [95% confidence interval (CI): 1.28-2.80]. The incidence seemed to increase with time (0.3 per 100,000 during 1984-1985 to 4.5 per 100,000 person-years during the period of 2001-2005), but the number of annual cases remained low. The point prevalence, on December 31, 2005, was 25.96 cases per 100,000 persons (95% CI: 14.5-37.3); however, this increased to 99 cases per 100,000 (95% CI: 54-143) in those older than 60 years. The median age at the time of diagnosis was 73.1 years (range 41-92 years), and the majority of patients were asymptomatic and received the diagnosis incidentally.

While the data suggests an increase in the incidence of IPMN over time, it is important to distinguish between a rising diagnosis and treatment of the condition with an accumulation of cases at specialist centers, as opposed to a true rise in incidence\textsuperscript{[13]}. Our data suggests a low incidence in the county which appears to be on the rise. The data, however, does not depict an ‘epidemic’. Further epidemiologic studies may help resolve the true change in pathological behavior.

Recently, Simons and colleagues\textsuperscript{[14]} investigated national resection rates and survival for malignant IPMN between 1988 and 2005 using the nationwide database, Surveillance Epidemiology and End Results (SEER). The United States Census data were utilized to investigate age-adjusted statistics. A total of 1834 patients were identified with malignant IPMN from the database. Of those patients, 54% did not undergo surgery, and the remaining patients had operative resection. The age-adjusted incidence for malignant IPMN varied over the study period, ranging from 0.48 per 100,000 in 1988 to 0.29 per 100,000 in 2003; whereas, the number of patients undergoing resection rose significantly (P = 0.001) from 5.8% in 1998 to 14.8% in 2003, the highest rate of resection being 16% in 2001. The median survival of resected and non-resected patients
was 16 and 3 mo respectively. The authors concluded that detection of malignant IPMN is decreasing but earlier detection is contributing to increasing resection rates.

In another epidemiologic study using the California Cancer Registry, a segment of SEER, from 2000-2007, Le et al. reported over 15,000 cases of pancreatic cancer. Of those cases, 880 patients were diagnosed with mucinous tumors, but only 43 were diagnosed with IPMN. The hazard ratio of IPMN in this population was 0.19 (0.10-0.35). Le concluded that IPMN is rare, and if resected, had a statistically better prognosis than pancreatic adenocarcinoma. Incidence or prevalence data were not reported.

Yoon and colleagues investigated the frequency of cystic pancreatic neoplasms by exploring patient records from 20 university-teaching hospitals between 1993 and 2005. All diagnoses were confirmed surgically or were biopsy-proven. They found IPMN to be the most commonly reported cystic neoplasm, 436 of 1064 patients. Contrary to our findings, only 32% of their patients were asymptomatic and only 13% were diagnosed incidentally. One of their expected findings was that asymptomatic patients had a lower risk of harboring malignancy.

Most of the epidemiologic studies outlined above share the limitations of population-based analyses including the lack of independent histologic review of specimens, variable sources of reporting and diagnostic methods, and broad staging criteria (that is, SEER summary staging instead of American Joint Committee on Cancer staging methods). However, it appears that the incidence of IPMN is rare with estimates between 0.48-2.04 per 100,000 persons. There is no conclusive evidence that IPMN is rapidly increasing in the general population but reported data does suggest an increase of patients seen at tertiary health care centers with the disease.

**RISK FACTORS**

Reports on risk factors for IPMN are also rare in the literature. Potential risk factors include chronic pancreatitis. In an attempt to see if patients with chronic pancreatitis were at risk for IPMN, Talamini and colleagues reported a long-term study of patients diagnosed with chronic pancreatitis between 1981 and 1998. A total of 476 patients were identified, 93 of whom had chronic obstructive pancreatitis and 46 had biopsy-proven IPMN. The two groups were compared with respect to age, gender, smoking and alcohol history. The group of patients with IPMN had significantly fewer smokers and consumed less alcohol. They concluded that the IPMN was the cause of chronic pancreatitis in these patients rather than an effect.

No clinical reports have identified any lifestyle (smoking, alcohol, excessive body mass index, etc), geographic, viral, history of exposure (to radiation), or familial link to IPMN and genetic advances remain the only avenue of progress in better understanding the likely causality. The absence of evidence, of course, does not categorically eliminate these factors and one has to accept the paucity of investigations in this arena.

**SCREENING OF PATIENTS WITH INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM**

While there are no formal recommendations for population-based screening of IPMN, there is a growing body of literature reporting the increased incidence of extrapancreatic neoplasm in patients with IPMN, suggesting that patients with IPMN should be screened for other neoplasms. Sugiyama et al. investigated the incidence of non-pancreatic neoplasms in 42 patients undergoing resection for IPMN. They reported a high incidence of neoplasms (48%), particularly malignancies (36%). Colorectal adenomas, adenocarcinomas, and gastric carcinomas accounted for the majority of non-pancreatic neoplasms. In their study, the incidence of non-pancreatic neoplasms and malignancies was significantly higher in patients with IPMN than in patients with pancreatic ductal adenocarcinoma (PC) (11% vs 7%).

Similarly, Kamisawa et al. found malignancies in 35% of patients diagnosed with IPMN, particularly gastric and colonic in origin. The majority (85%) were diagnosed prior to or at the time of the diagnosis of IPMN. Interestingly, three patients with IPMN had also independent PC, and all patients diagnosed with IPMN were found to be of branch-duct type located in the head of the pancreas. Choi et al. studied 61 patients who underwent operative resection for IPMN and found extra pancreatic neoplasms and malignancies in 39% and 30% of patients, respectively. The majority were discovered preoperatively or at the time of surgery; again gastric and colorectal cancers were the most common. The incidence of extra-pancreatic neoplasms was higher in patients with IPMN than in patients with MCN or PC (39% vs 8% vs 10% respectively).

These same results were found in an epidemiologic study by Riall et al. who evaluated 19,000 patients from the SEER database with either sporadic PC (95%) or invasive IPMN (5%). In both groups, 10% of patients had one or more extra-pancreatic primary cancers in addition to their primary PC. The most common sites were colorectal (20.1%), breast (19%), prostate (16.6%), urinary system (11.1%), and lung (9.8%). In contrast to the previous studies, gastric cancer was found only in 1% of patients with invasive IPMN. A similar rate was found for esophageal cancer. Again, the majority (86%) were diagnosed prior to the diagnosis of invasive IPMN. Although the incidence of additional primary malignancies in this population-based study was not as high as previously reported in smaller studies, the findings are still significant and comparable to the incidence seen in patients with sporadic PC, warranting the surveillance of patients with IPMN. Interestingly, these patients are not only at higher risk for other primary cancers, but they are also at a greater risk for a PC even after margin negative resection for benign (non-invasive) disease.

In our recent study evaluating the presence of extra-pancreatic neoplasms in patients diagnosed with IPMN,
the proportion of patients having any diagnosed prior to or coincidentally with diagnosis of IPMN was 52%, compared with 36% in PC patients and 43% in the general referral population at Mayo Clinic in Rochester, Minnesota. Benign neoplasms, most frequent in the IPMN group, included colonic polyps (24%) and Barrett's esophagus (4%). Additionally, non-melanoma skin (7%), breast (5%), prostate (5%), colorectal cancer (4%), and carcinoid tumors (1%) were the most common malignant neoplasms observed. This study differs from all others in that it examines the frequency of extra-pancreatic neoplasms in patients with all stages of IPMN, independent of whether they were operatively resected or followed with observation and surveillance alone.

Our findings support the previous reports that patients with IPMN are at an increased risk for having extra-pancreatic neoplasms (benign and malignant), diagnosed before or coincidentally to their diagnosis of IPMN when compared to matched groups of patients with PC and general referral controls. Based on our data, we recommend that all patients with a new diagnosis of IPMN undergo a screening colonoscopy to detect adenomatous polyps or colorectal cancer. An upper endoscopy to rule out Barrett's esophagus should be considered in patients with symptoms of gastroesophageal reflux or dysphagia.

CONCLUSION

The incidence of IPMN in the population is low but the frequency of patients diagnosed with IPMN is increasing at tertiary care facilities. These patients are at an increased risk of developing benign or malignant neoplasms, especially colorectal in origin. Based on available reports, we recommend that all patients diagnosed with IPMN undergo a screening colonoscopy. A screening upper endoscopy should be reserved for patients with upper gastrointestinal symptoms.

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