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Pancreatic Cyst Prevalence and the Risk of Mucin-Producing Adenocarcinoma in United States Adults

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Abstract

OBJECTIVES—The presence of a pancreatic cyst often prompts concern, although the rate of malignant transformation to mucin-producing adenocarcinoma is not known. We aimed to determine the prevalence rate of mucin-producing adenocarcinoma in US adults with pancreatic cysts.

METHODS—This retrospective, population-based cross-sectional study calculated the annual number of mucin-producing adenocarcinomas using the Surveillance Epidemiology and End Results (SEER 18) database and the 2010 United States census. The overall prevalence rate of cysts in the population was found using data from large cross-sectional imaging studies of incidental cyst prevalence. Prevalence rates were then calculated by dividing the annual number of mucin-producing adenocarcinomas by the cyst prevalence rate.

RESULTS—Between 2005 and 2009, 1,137 mucin-producing adenocarcinomas were estimated to be found annually in a United States adult population of 137,154,960. The total number of pancreas cysts, given a cyst prevalence rate of 2.5%, was 3,428,874. Therefore, the prevalence of mucin-producing adenocarcinoma arising in patients with pancreatic cysts was 33.2 per 100,000 (95% CI: 21.6–44.0). The prevalence rate was 32.8 per 100,000 (95% CI: 21.6–44.0) in women and 33.5 per 100,000 (95% CI: 22.2–44.8) in men. As expected, the rate of malignant transformation increased linearly with advancing age (highest 38.6 per 100,000 in 80- to 84-year old men).

CONCLUSIONS—Malignant transformation of pancreatic cysts into mucin-producing adenocarcinoma in US adults is a very rare event. Current clinical guidelines and resource allocation for pancreatic cyst disease should be reconsidered given these findings.

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Keywords

IPMN; MCN; SEER; mortality; pancreas cysts; prevalence

INTRODUCTION

In the last past two decades, there has been a dramatic increase in the prevalence of pancreatic cysts diagnosed in US adults because of the increased frequency and better quality of cross-sectional imaging, as well as the aging of the population.[1–4] Because of the malignant transformation potential of cysts into mucin-producing adenocarcinoma, diagnostic strategies such as endoscopic ultrasound fine needle aspiration and DNA-based evaluation of cyst fluid have been used to help determine at-risk lesions.[5–7] However, despite improved recognition, more focused diagnostic strategies and increased frequency of surgical resection for proven mucin-producing pancreatic cysts, mortality rates for both pancreatic adenocarcinoma and intraductal papillary mucinous neoplasms (IPMN)-related pancreatic adenocarcinoma have not changed.[4,8–10]

One reason for the lack of improvement in pancreatic adenocarcinoma mortality is likely the lack of prospective natural history data on the rate of malignant transformation of pancreatic cysts into mucin-producing adenocarcinoma. Of particular interest is whether the increasing recognition and treatment of pancreatic cystic is clinically meaningful. While estimates (based on surgical series) of the malignant transformation rate have been estimated as high as a 25% lifetime risk in patients with branched-duct IPMN, our center's clinical experience of evaluating and following longitudinally 100–200 patients annually with pancreatic cystic disease overwhelmingly suggests that malignant transformation is unlikely.[11–15]

The aim of this study was to determine the prevalence rate of mucin-producing adenocarcinoma in US adults with pancreatic cysts. We hypothesized *a priori* that based on cancer registry and US census data, malignant transformation of pancreatic cysts into mucin-producing adenocarcinoma is a rare event.

METHODS

Study Design

As this study was based on de-identified data, institutional review board approval was not obtained. The study design was a retrospective, population-based cross-sectional study which, calculated the annual total number of a specific numerator (mucin-producing adenocarcinoma) over a denominator representing the population at risk (US adults with pancreatic cysts) to obtain a prevalence rate. Given the low prevalence of both pancreatic cysts and pancreatic malignancy in patients < 40 years old, we included only adults aged 40–84 years. The primary outcome was the prevalence rate of mucin-producing adenocarcinoma in United States adults with pancreatic cysts. Secondary outcomes included the aforementioned prevalence rate in men and women.

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Establishing the Numerator

Currently, the most comprehensive national database of mucin-producing adenocarcinoma can be obtained from national Surveillance Epidemiology and End Results (SEER-18) data.[16] The SEER-18 database reflects histologically confirmed cancer registry cases collected between the years 2005 to 2009 from 18 geographic areas within the United States.

To identify the annual number of patients with mucin-producing adenocarcinoma between the ages of 40 and 84, the annual total number of patients with pancreatic malignancy was calculated by multiplying pancreatic cancer incidence rates (prevalence rates not available) from SEER 18 (Table 1.4 (*Age-adjusted SEER incidence by primary cancer site, sex and time period*)) and United States census data from 2010.[16,17] SEER 18 data (Table 1.10 (*Age Distribution (%) of Incidence Cases by Site, 2005–2009*)) was then used to capture the prevalence of adenocarcinoma only in those patients between the ages of 40 and 84 years. The number of pancreatic malignancies attributable to adenocarcipoma (and not to islet cell neoplasms, for example) was then calculated using SEER 18 data (Table 22.2 (Cancer of the Pancreas (Invasive)).[16] To identify cases of mucin-producing adenocarcinoma, search criteria were limited to ICD-0–3 histology codes 8480 and 8482 (pancreatic mucinous adenocarcinoma) and 8481 (pancreatic mucin-producing adenocarcinoma) in SEER 18 Table 22.2.[16] This percentage was then multiplied by the annual number of pancreatic adenocarcinoma to determine the number of annual mucin-producing pancreatic adenocarcinomas in United States. Finally, to establish the number of mucin-producing adenocarcinoma stratified by gender, this number was multiplied by the relative rates of mucinous lesions in men and woman based on the Crippa manuscript and SEER data.[15]

Establishing the Denominator

Currently no national database exists which accurately reflects the prevalence of pancreatic cysts in the United States. US census data from 2010 was used to determine the population of adults aged 40–84 years.[17] The rate of cysts in this population was determined using what was felt to be the two most scientifically rigorous studies published to date on the rate of cysts in asymptomatic patients undergoing cross-sectional imaging for reasons not related to pancreatic disease. These two studies also were chosen because they both had low cyst prevalence rates, and were therefore considered the most conservative estimate of prevalence. The first study found a cyst prevalence rate of 2.4% (95% C.I. 1.9–3.0) in 2,803 consecutive patients undergoing abdominal magnetic resonance imaging at an institute of preventative medical care in Germany from December 2006-September 2008.[2] The second study found a cyst prevalence rate of 2.6 (95% C.I. 2.0–3.2) in 2,832 consecutive patients undergoing computed tomography (CT) imaging for conditions other than known or suspected pancreatic disease at a major United States academic center.[1] For the purposes of this report, the two cyst prevalence rates (no significant rate difference between men and women) from the Laffan and De Jong[1, 2] studies were combined and then multiplied by the total population to determine the rate of cysts in adult patient in the United States.

Statistical Analysis

SEER*Stat statistical software (Surveillance Research Program, National Cancer Institute (seer.cancer.gov/seerstat) version 7.1.0) was used to access the SEER 18 data.[16] Prevalence

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rates were calculated as a rate per 100,000. Since the exact time intervals for development of the malignancies was not known, the Poisson distribution could not be used to calculate 95% CIs. However, because the sample size was large, a normal distribution was assumed and the formula $1.96*\sqrt{(r/100{,}000)*(1-(r/100{,}000))/100{,}000}$ where r=prevalence was used to calculate the 95% C.I.

RESULTS

Data interrogation from the SEER 18 database determined that the rate of pancreatic malignancy in the United States was 13.8 per 100,000 for males and 10.8 per 100,000 for females. Multiplying by 2010 United States census data (151,781,326 men and 156,964,212 women), the annual total number of pancreatic malignancies was 37,898 (20,946 men and 16,952 women). Based on SEER 18 Table 1.10, 85.1% of pancreatic malignancies occurred in patients between the ages of 40 and 84 years (35–44-years age group divided by 2 to reflect a 5-year interval), yielding 17,825 men and 14,426 women. Because, according to SEER table 22.2, 86% of pancreatic malignancies represented adenocarcinoma, 15,330 mean and 12,406 women were therefore affected between ages 40 and 84 years. As 4.1% of all adenocarcinomas were mucinous in origin based on SEER 18 Table 22.2, a total of 1,137 adenocarcinomas were mucinous in origin. The number was the multiplied by 51.5%, the relative rate of invasive mucinous lesions in women calculated from the Crippa manuscript and SEER data, to determine the final count of 551 men and 586 women.

Table 1 demonstrates the calculation of cyst number in the US adult population. For each age group, the US population based on the 2010 census was multiplied by the cyst prevalence rate found by taking the mean rate of the De Jong and Laffan studies stratified by age.[1,2]

The annual crude and age-specific prevalence rates of pancreatic mucin-producing adenocarcinoma in 40- to 84-year old US patients with pancreatic cysts is shown in Table 2. As expected, the prevalence rate increased in each age group, with 80- to 84-year old men having the highest prevalence rate at 38.6 per 100,000.

The overall prevalence rate of mucin-producing adenocarcinoma in all US adults between the ages of 40 and 84 years, irrespective of cyst presence, was 0.83 per 100,000.

DISCUSSION

These data demonstrate that the malignant transformation of pancreatic cysts into mucin-producing adenocarcinoma is a rare event in US adults, thereby lending support to our clinical observation that pancreatic cysts rarely develop into malignancy when followed longitudinally. Despite the dramatic increase in the number of pancreas cysts being detected, evaluated and resected, no decline in either the pancreatic adenocarcinoma or IPMN-related carcinoma mortality rate has occurred. These findings suggest that the vast majority of pancreatic cystic lesions do not lead to any clinically meaningful disease.

The rising prevalence of pancreatic cysts is probably due to two factors – the increased use and improved quality of cross-sectional imaging and the aging of the population.[11] The

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finding of the “incidental pancreatic lesion” often leads to clinical and patient concern, usually prompting referral for subspecialty surgical, gastroenterology or oncology consultation with subsequent cross-sectional imaging, endoscopic ultrasound/percutaneous biopsy, and even primary surgical resection.

However, while there are certainly incidentally found mucinous lesions, such as nodular main duct IPMN, that warrant up-front resection, the natural history of these lesions is unknown.[7,10] Because of this, even when the lesion is well characterized, the optimal means of maximizing survival and quality of life while minimizing cost, is extensively debated.[11, 18–22]

This study attempted to provide information on the natural history of pancreatic cysts by using a population-based cross-sectional methodology as a substitute for a prospective, longitudinal study. The most striking finding was the rarity of mucin-producing adenocarcinoma in the US adult population, given the assumed large total number of cysts. When considering the entire US adult population, and not just those with pancreatic cysts, the risk becomes miniscule.

This analysis is meant neither to undermine the importance of identifying and treating cystic lesions that are at high risk to harbor malignancy nor to discourage aggressive evaluation of lesions found in high-risk individuals, e.g., those with hereditary pancreatitis, Peutz-Jeghers syndrome or familial atypical mole melanoma syndrome.[8] Furthermore, patients with symptoms directly attributable to the pancreatic cystic lesion, such as those with obstructive acute pancreatitis, should usually have resection.

However, this study should be used a caution against overly aggressive diagnosis and treatment of pancreatic cystic lesions. Simply stated, in the vast majority of patients, aggressive diagnosis using endoscopic ultrasound and fluid DNA analysis is not warranted based on the epidemiological findings.

One potential criticism of this work centers around the means by which the numerator and denominator were defined and its reliance on several assumptions with regard to prevalence rates. The most robust United States cancer registry is the SEER database, as it allows for the determination of lesions based on histological classification. Although there certainly could be misclassification bias with regard to histology – i.e. more than 4.1 % of adenocarcinomas actually do arise from mucin-producing cystic lesions – it is unlikely that a bigger numerator would appreciably change the findings of the study. In addition, because the relative percent of invasive mucin-producing adenocarcinoma stratified by gender is unknown, the exact rate in men and women has to be estimated based on best available data.

With regard to the denominator, it is important to recognize that not every incidental pancreatic cyst is mucin-producing and, as such, the rate of mucin-producing cysts undergoing malignant transformation is higher than the rate reported in this study. However, the study aimed at determining the prevalence rate of those cysts found incidentally on cross-sectional imaging undergoing transformation -this reflects the situation in clinical practice. Furthermore, if studies with higher cyst prevalence rates were used instead of the Laffan and De Jong rates, the prevalence rate of malignant transformation would have been

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even lower. (see Table 3). Conversely, if one used a lower rate of cyst prevalence, e.g., 0.7% as was found in the large retrospective series evaluating pathologic, surgical, and radiographic data at a single tertiary medical center, the rate of malignant transformation would still be only 139.2 per 100,000.[25]

We also chose to report prevalence rates rather than incidence rates for two reasons. For one, the incidence rates of incidental pancreatic cysts are not known; cross-sectional studies performed universally report prevalence rates. In addition, since pancreatic adenocarcinoma is almost a universally fatal disease, the incidence of disease on an annual basis closely approximately disease prevalence.

Acknowledging the above limitations, the current data further underscore the importance of developing a prospective national database to understand the true malignant transformation rate of mucin-producing pancreatic cysts. In the interim, clinicians need to carefully weigh these reported results in the context of an increasing focus on limiting unnecessary testing, improving patient-centered care, and reducing health care costs.

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Table 1

Calculation of pancreatic cyst prevalence in the United States population in patients between 40 and 84 years old.

	United States Population*	Cyst Prevalence Rate†	Total Number of Cysts
Total Population	**137,154,960**	**2.5%**	**3,428,874**
40–49 year olds	43,599,555	1.35%	588,594
50–59 year olds	41,962,930	2.05%	860,240
60–69 year olds	29,253,187	3.25%	950,729
70–79 year olds	16,595,961	7.3%	1,211,505
80–84 year olds	5,743,327	8.7%	499,669
Total Female Population	**71,444,195**	**2.5%**	**1,786,105**
40–49 year olds	21,996,493	1.35%	296,953
50–59 year olds	21,506,008	2.05%	440,873
60–69 year olds	15,323,140	3.25%	498,002
70–79 year olds	9,169,601	7.3%	669,381
80–84 year olds	3,448,953	8.7%	300,059
Total Male Population	**65,710,765**	**2.5%**	**1,642,769**
40–49 year olds	21,603,062	1.35%	291,641
50–59 year olds	20,456,922	2.05%	419,367
60–69 year olds	13,930,047	3.25%	452,727
70–79 year olds	7,426,360	7.3%	542,124
80–84 year olds	2,294,374	8.7%	199,611

*US population determined from 2010 United States census information[17]

†The cyst prevalence rate was determined by combining the mean cyst rate of the two most scientifically rigorous cross-sectional imaging studies on cyst prevalence (Laffan *et al* and De Jong *et al*)[1,2]

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Table 2

Annual crude and age-specific prevalence rates of mucin-producing adenocarcinoma in 40- to 84-year old US patients with pancreatic cysts.

	Estimated Cases of Mucin-Producing Adenocarcinoma*	Estimated Patients with Pancreatic Cysts†	Prevalence Rate per 100,000	95% Confidence Interval
Crude Population	**1137**	**3,428,874**	**33.2**	**(21.9, 44.5)**
40–49 year olds	111	588,594	18.9	(10.4, 27.4)
50–59 year olds	225	860,240	26.2	(21.1, 31.3)
60–69 year olds	278	950,729	29.2	(18.6, 39.8)
70–79 year olds	351	1,211,505	29.0	(18.4, 39.6)
80–84 year olds	172	499,669	34.4	(23.1, 45.7)
Crude Female Population	**586**	**1,786,105**	**32.8**	**(21.6, 44.0)**
40–49 year olds	59	296,953	19.9	(11.1, 28.6)
50–59 year olds	116	440,873	26.3	(16.2, 37.4)
60–69 year olds	134	498,002	26.9	(16.7, 37.1)
70–79 year olds	186	669,381	27.8	(17.5, 38.1)
80–84 year olds	91	300,059	30.3	(19.5, 41.1)
Crude Male Population	**551**	**1,642,769**	**33.5**	**(22.2, 44.8)**
40–49 year olds	52	291,641	17.8	(9.5, 26.1)
50–59 year olds	109	419,367	26.0	(16.0, 36.0)
60–69 year olds	152	452,727	33.6	(22.2, 45.0)
70–79 year olds	161	542,124	29.7	(19.0, 40.4)
80–84 year olds	77	199,611	38.6	(26.4, 50.8)

* Counts determined using SEER 18 database averaging percent mucincous adenocarcinoma (8480, 8481,8482) from 2005-09[16]

* Determined from data in table 1

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Table 3

Prevalence rate of mucin-producing adenocarcinoma based on cross-sectional imaging studies of pancreatic cyst prevalence.

Study	Number of Patients	Number of Cysts	Prevalence (%)
Zhang *et al*[23] (2004)	1,444	283	All: 19.6 Female: 18.8 Male: 20.4
Laffan *et al*[1] (2008)	2,803	73	All: 2.6 Female: 2.5 Male: 2.6
De Jong *et al*[2] (2010)	2,832	66	All: 2.4 Female: 2.2 Male: 2.4
Lee *et al*[24] (2010)	616	83	All: 13.5 Female: 13.7 Male: 13.2