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Epidemiology of Chronic Pancreatitis

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1. Introduction

Epidemiologic descriptions of chronic pancreatitis (CP) have changed over time. The focus of reports from 1950-1990's was to describe the clinical profile and natural history in a series of patients. Many landmark studies during this period are crucial to our understanding of the disease. In the past 25 years, studies have also focused on describing population distributions of CP, its risk based on the presence of environmental and genetic risk factors, impact of CP on quality of life, and frequency and factors that affect the evolution of acute and recurrent acute pancreatitis (RAP) to CP. In this chapter, we will review the current epidemiology of CP, and changes that have been observed over the past half-century and their potential explanations. For detailed descriptions of the role of environmental risk factors in CP, natural history of disease, and medical and surgical management, the reader is encouraged to refer to chapters of this book dedicated to these topics.

2. Changing role of imaging tests in the diagnosis of CP

A diagnosis of CP can be made by the presence of definitive changes on morphology or histology. Although tissue diagnosis remains the gold standard, pancreatic tissue sampling has been historically difficult (29). Therefore, in clinical practice, the diagnosis relies mainly on the presence of typical clinical presentation, and presence of morphologic changes on imaging studies. In the first half of the 20th century, the presence of epigastric calcifications on plain radiography was the mainstay for the diagnosis of CP (112). In the 1970s, abdominal ultrasound, endoscopic retrograde cholangiopancreatography (ERCP), and computed tomography (CT) emerged as diagnostic tests for CP (31, 41, 117). In 1983, a group of experts met in Cambridge, and developed a grading system using these diagnostic modalities to define CP (89). CT quickly became the modality of choice for diagnosis because it was noninvasive and widely available. With continuing advances in technology over the past 30 years, high resolution CT, magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS) have evolved as important tools in the evaluation of CP (40, 58, 90, 92, 110), and have replaced the use of ERCP for the diagnosis of CP (11, 43, 52, 82, 91).

Due to poor sensitivity of abdominal x-ray, ultrasound and earlier generation CT scanners, it is likely that in earlier studies, many patients received the diagnosis of CP only in the presence of advanced changes (e.g. large calcifications). With advances in technology, it is conceivable that high resolution CT, MRI/MRCP and EUS would diagnose CP at an earlier stage by detecting subtle morphological changes in the

pancreas (e.g. smaller calcifications, duct irregularities, etc.). However, the impact of improvement in imaging techniques on the epidemiology of CP has not been empirically studied.

3. Incidence and prevalence

The number of studies examining the population distributions of CP is scarce, and it is important to note that these data are not available from large parts of the world. This is probably related to difficulties in conducting such studies due to low disease prevalence, establishing an accurate diagnosis, and the focus of earlier studies to describe the clinical profile and natural history of the disease. In the past two decades, there has been an interest to document population distributions for pancreatic disease. The results of the most representative studies on the incidence of CP are presented in **Table 1**, and incidence data from Olmsted County, MN, USA is shown in **Figure 1** (115). The overall incidence ranges from 2-14/100,000 population and shows some variability based on study design and country. In the United States the incidence of CP has increased modestly from 3.3 during 1940-1969 to 4.3 per 100,000 in 1997-2006 (72, 115). In Europe, the incidence of CP appear to be higher than in US (6, 21, 22, 28, 54, 59, 94). In Asia, seven separate surveys from Japan conducted in the past 42 years show a trend towards a much greater increase in the incidence of CP (from 2 to 14/100,000) (44, 45, 47, 61). It is likely that wide availability of better imaging technology may have contributed to this increase. The contribution of changing trends for environmental exposures may also be of importance, especially in developing countries where consumption of alcohol is on the rise with increasing affluence, from where data on population distributions are lacking.

Prevalence estimates for CP are limited to only a few populations and is presented in **Table 2**. The overall prevalence of CP shows high variability. In recent studies the prevalence ranges around 40-50 per 100,000 population. Prevalence data from Olmsted County, MN, USA is shown in **Figure 2** (115). Prevalence is low below age 35 years and reaches 100-120 in middle-aged and older men (115). A Chinese study showed increasing prevalence of CP from 3.1/100,000 in 1996 to 13.5/100,000 population in 2003 (102). The 7 nationwide epidemiological surveys conducted in Japan, have demonstrated increasing prevalence of CP from 28.5/100,000 in 1994 to 52.4/100,000 in 2011 (44, 61). A much higher prevalence of idiopathic CP, termed earlier as 'tropical pancreatitis' was reported from Southern India in up to 126 per 100,000 population in 1994 (8). In this specific case, environmental risk factors (e.g. diet) were suspected to be the main etiologic factors, but recent studies have highlighted an important role of genetic mutations (*SPINK1*, *CFTR*, *CTRC*) in this condition and suggested that the term tropical pancreatitis was a misnomer (67, 75).

4. Demographics

The mean or median age at time of study enrollment or diagnosis in most published studies show little variation over time and by geography **(Table 3)**. The mean age in European studies was 40 years in 1970-1990s (12, 96) and more recently between 50-55 years (34, 59). In Japan, the mean age reported in 1960s was 48 years (73), and most recently 59 years in 2007 (45). In 2 populations studies from Olmsted County, MN, USA the median age at diagnosis of CP was 51 in the 1940-1960s (72), and 58 in 1970s-2006 (115). In the large multicenter North American Pancreatitis study [NAPS2] (2000-2013) in the US, the mean age at CP diagnosis was 47 (111). From these studies, we can conclude that CP mainly affects middle-aged individuals.

Table 1: Incidence of chronic pancreatitis in selected population-based studies

Country	Year(s) studied	Incidence of CP (all causes) *		
		All	Males	Females
Denmark (Andersen) (6)	1970-1976 1975-1979	6.9 10.0	NA NA	NA NA
USA (O'Sullivan, Yadav) (72, 115)	1940-1969 1977-2006	3.3 4.0	NA 4.2	NA 2.6
Poland (Dzieniszewski) (28)	1982-1987	5.0	NA	NA
Germany (Lankisch) (54)	1988-1995	6.4	8.2	1.9
Czech Republic (Dite) (21)	1999	7.9	NA	NA
Japan (Lin, Hirota, Hirota) (44, 45, 61)	1994 2007 2011	5.4 11.9 14.0	8.4 NA NA	2.7 NA NA
Netherlands (Spanier) (94)	2000-2005	1.8	2.2	1.4
France (Levy) (59)	2003	7.7	12.9	2.6
Spain (Dominguez) (22)	2011	5.5	NA	NA

* Incidence rate per 100,000 of the population

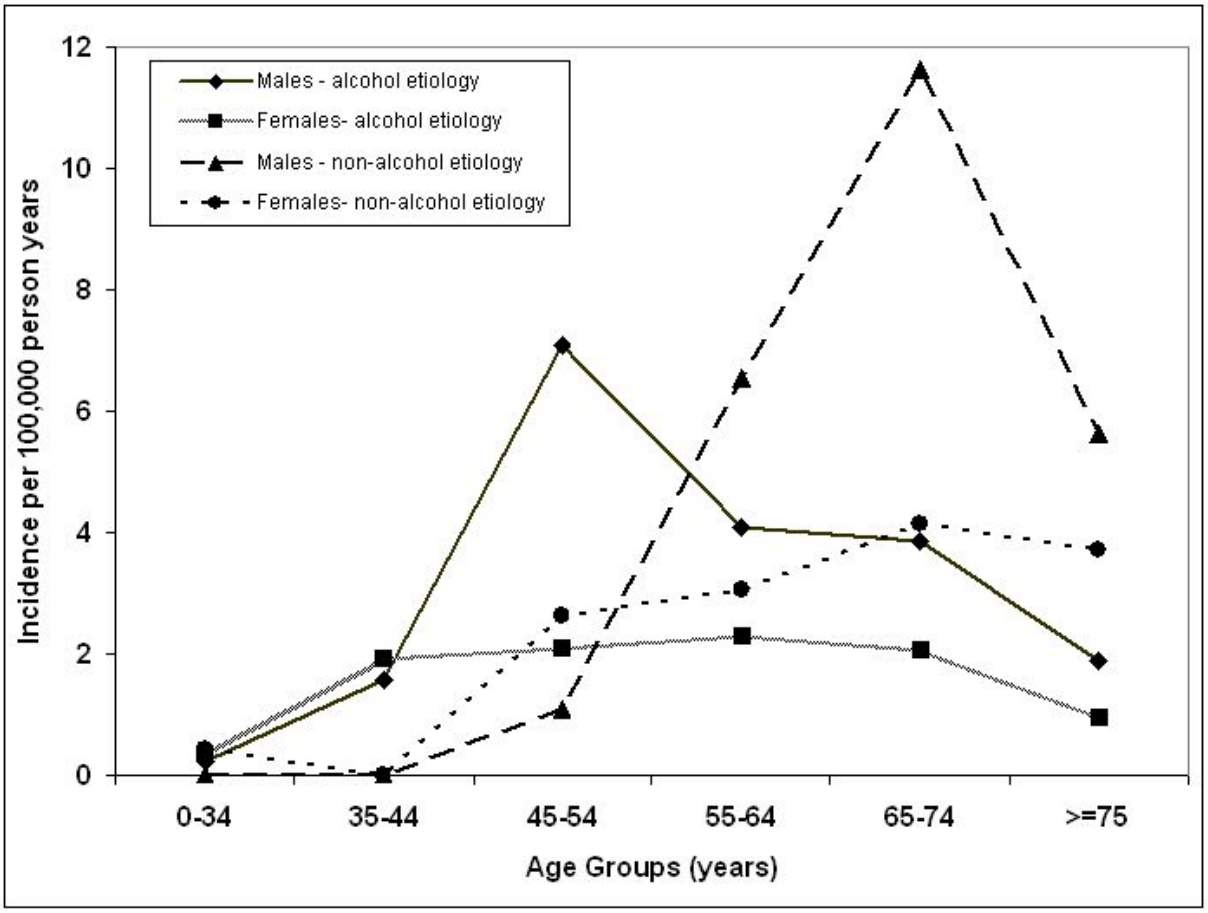

Figure 1. Incidence of CP by age group and sex in 2006 in Olmsted County, Minnesota. Data derived from Yadav et al (115). Permission has been requested.

Table 2: Prevalence of chronic pancreatitis in selected population-based studies

Country	Year(s) studied	Prevalence of CP (all causes) *		
		All	Males	Females
Poland (Dzieniszewski) (28)	1987	17	NA	NA
India (Balaji) (8)	1994	126.1	NA	NA
France (Levy) (59)	2003	26.4	43.8	9.0
China (Wang) (102)	2003	13.5	NA	NA
USA (Yadav) (115)	2006	41.8	51.5	33.9
Japan (Hirota) (44, 45, 61, 74)	1994 1999 2007 2011	28.5 32.9 36.9 52.4	45.4 43.9 53.2 NA	12.4 22.4 21.2 NA
Spain (Dominguez) (22)	2011	49.3	NA	NA

* Prevalence rate per 100,000 of the population

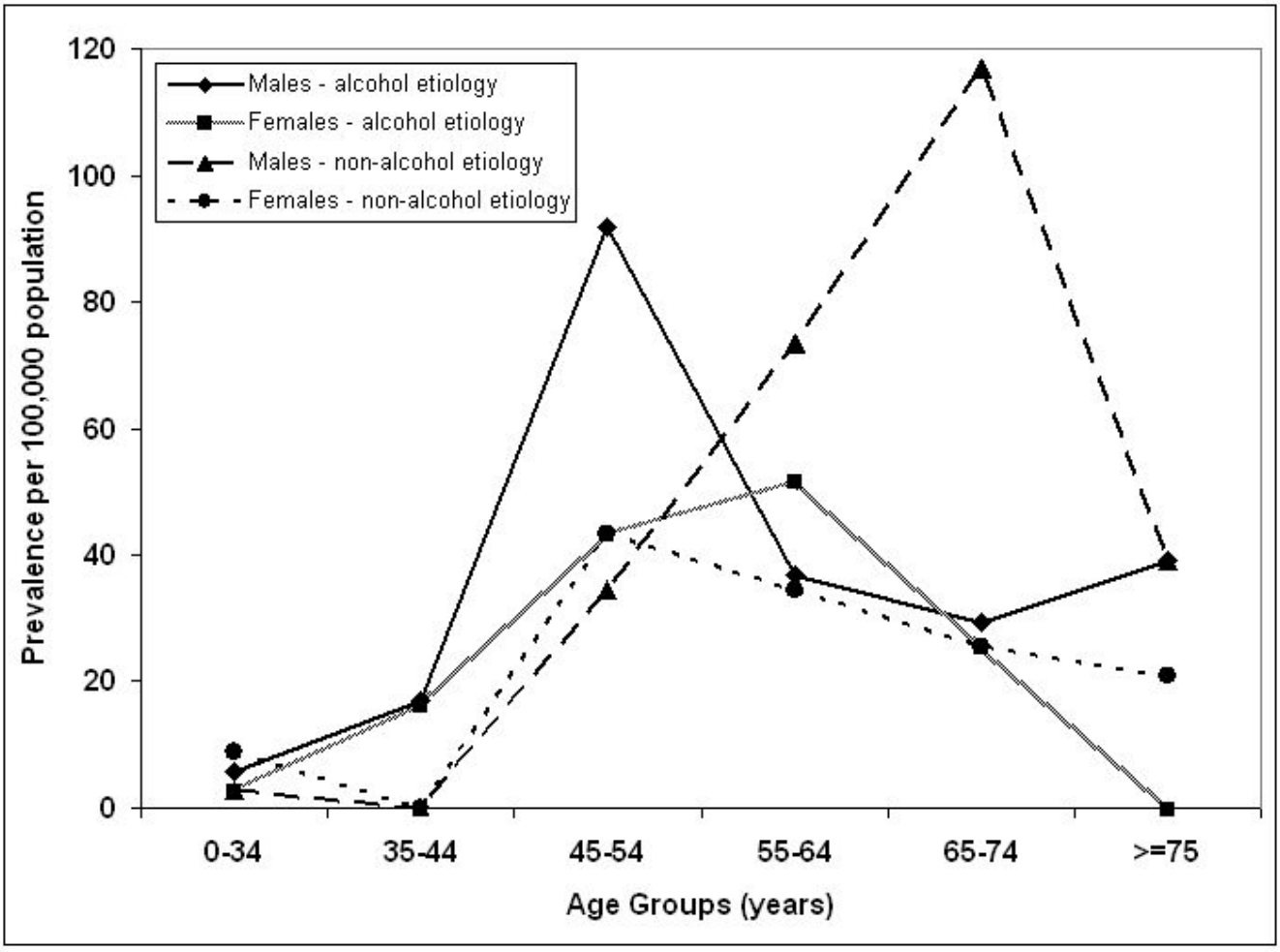

Figure 2. Prevalence of CP by age group, sex, and etiology in 2006 in Olmsted County, Minnesota. Data derived from Yadav et al (115). Permission has been requested.

In most studies, 60-80% of CP patients are male **(Table 3)**, and population studies show higher incidence and prevalence of CP in men when compared with women **(Table 1 and 2)**. In the recently conducted cross-sectional NAPS2 studies, as well as a population-based study in the US, there was only a marginal over-representation of men (52-55%) (109, 111, 115). The reason for a lower than expected prevalence of men in these cohorts is unclear; at least in the NAPS2 studies, accrual of patients from secondary and tertiary referral centers may have accounted for this observation.

Differences in sex and age distribution is primarily related to the etiology of CP **(Figure 1 and 2)**. Alcohol is the most common cause of CP in age group of 35-54 years (54, 115). A greater risk of alcoholic pancreatitis in men when compared with women is believed to be primarily related to higher prevalence of heavy drinking (53, 113). However, results of recent studies suggest that genetic factors also play an important role in this difference (1, 19, 108). Non-alcoholic etiologies are more evenly distributed in men and women. Genetic causes are more common in patients diagnosed earlier in life (<35 years of age) (46, 49, 67, 84, 106), whereas idiopathic CP has a bimodal age distribution (57).

Few studies have evaluated racial differences in CP. A multicenter study reported that half of all CP patients discharged from 3 hospitals in Portugal and USA during a 16-year period were black (65). In comparison to white patients, black patients were 2-3 times more likely to be hospitalized for CP than for cirrhosis (65). A population study using the National Inpatient Sample in the US revealed that the discharges for alcoholic CP between 1988-2004 was higher in blacks (11.3/100,000) when compared with whites (5.1/100,000), Hispanics (3.7/100,000), Asians (1.4/100,000), and American Indians (2.3/100,000) (116). In a recent study from the NAPS2 cohort, patient level data was compared between black and white CP patients. The age at onset of symptoms and diagnosis was similar based on race, but blacks were more likely to be male when compared with white CP patients (61 vs. 53%, $p<0.05$), a difference attributed to differences in the etiology of CP (see below) (111).

Table 3: Age, gender, and etiology of CP in selected studies

Country	Year(s) studied	N	Male (%)	Age (mean or median)	ETOH etiology (%)
Switzerland (Ammann) (5)	1963-1986	245	88%	46	71%
Brazil (Dani) (18)	1963-1987	797	91%	38	90%
Italy (Cavallini) (12)	1971-1995	715	88%	41	74%
Mexico (Robles-Diaz) (86)	1975-1987	150	82%	NA	67%
United States (Layer) (57)	1976-1982	448	65%	NA	56%
Denmark (Nojgaard) (71)	1977-1982	249	72%	51	45%
Japan (Lin) (61)	1994	2523	77%		56%
Italy (Frulloni) (34)	2000-2005	893	74%	54	34%
United States (Wilcox) (111)	2000-2014	1159	55%	47	49%
France (Levy) (59)	2003	1748	83%	51	84%
India (Balakrishnan) (9)	2007	1033	71%	40	39%
Netherlands (Ahmed) (2)	2010-2013	1218	67%	48	53%
Japan (Hirota) (44)	2011	1734	82%	62	68%
Spain (Dominguez-Munoz) (22)	2011	937	NA	NA	75%

5. Etiology

Alcohol is the most frequent cause of CP worldwide **(Table 1)**. The proportion of cases attributed to alcohol were as high as 80-90% in earlier studies. In some recent studies, alcohol as the primary cause of CP was identified by physicians less frequently. In the multicenter NAPS2 studies from the US, of 1,158 white and black CP patients, alcohol was assigned as the etiology in 49% cases (111). Blacks were more likely to have alcohol etiology (77 vs. 42%), and in them physicians were 4.3 times more likely to identify alcohol as the etiology when compared with white CP patients (111). Similarly, a large multicenter survey from Italy of 893 CP patients evaluated from 2000-2005 attributed alcohol to be the etiology in only 34% (34), which is much lower than (74-79%) reported in other Italian series from 1971-1995 (12, 97). Other recent studies have also identified a similar pattern (2, 9). A growing recognition importance of genetic factors in causing pancreatitis, wide availability of cross-sectional imaging studies, such as MRCP that can identify anatomic abnormalities (e.g. pancreas divisum), acceptance of the relationship with smoking, and that autoimmune and other factors could explain a patient's disease are likely some of the explanations for physicians to entertain the possibility of factors other than alcohol as the potential cause of CP in an individual patient. This has led to the proposal of the TIGAR-O classification system which recognizes the contribution of different factors in the causation of pancreatitis (29). While smoking is an independent and dose-dependent risk factor, its association with pancreatitis is stronger in the presence of alcohol (7, 39).

In the past 20 years, several genetic susceptibility factors for pancreatitis have been identified, of which mutations in four genes (*PRSS1, SPINK1, CFTR, CTRC*) are now routinely used in clinical practice, especially in patients with unexplained CP (107). In contrast to alcoholic pancreatitis which is more frequent in middle-aged men, genetic factors are more common in early-onset disease, and are equally distributed among men and women. Other well recognized causes of CP include hypercalcemia, hyperlipidemia, autoimmune, post-necrotic, and duct obstruction (e.g. tumor, inflammatory stricture) (29), while the role of pancreas divisum and sphincter of oddi dysfunction remains uncertain (15, 17, 33, 99). Non-alcoholic etiologies are identified more frequently among women, and can account for up to 70% of cases (87).

After alcohol, the largest sub-group among CP patients is those in whom no specific cause has been identified. These patients are labeled to have idiopathic CP. The fraction of patients with idiopathic disease varies from 10-30% in most studies from 1970-2006 (12, 16, 34, 54, 59, 61, 74), but can be up to 60% in India and China (9, 37). Due to differences in clinical symptoms and course, these subjects have been subdivided as early-onset (i.e. <35 years of age) or late-onset (>35 years) disease (57).

6. Clinical features

The most common clinical features of CP are abdominal pain and one or more attacks of acute pancreatitis - either of these are seen in approximately 90% of patients at some time during the clinical course. These are also the presenting symptoms in the majority of patients. Presence, type and severity of pain and the number of episodes of acute pancreatitis during the clinical course can be highly variable (4, 12, 56, 57, 69). Exocrine or endocrine insufficiency are uncommon at the time of initial presentation (57), but their probability increases over time, and during the clinical course up to 80 and 87% develop diabetes and exocrine insufficiency respectively (4, 56, 57, 66). Clinical steatorrhea occurs only in the presence of severe exocrine insufficiency (20). However, consequences of fat malabsorption, such as vitamin deficiencies or

metabolic bone disease are observed more frequently and occur even with moderate insufficiency (24, 25, 27, 70, 93). Other features include local complications such as pseudocysts, abnormal liver function tests or jaundice from common bile duct stricture, vascular complications, or gastric outlet obstruction (4, 56, 57).

Differences in the initial presentation and natural course of CP have been observed based on etiology and age at presentation (see chapter on natural course of disease). In general, patients with alcoholic CP have more aggressive disease with evolution from initial presentation to advanced disease occurring over 5 to 10 years. Patients with early-onset idiopathic CP have a prolonged clinical course with long period of symptomatic disease, and development of morphological features, and functional impairment over two to three decades. Patients with late-onset idiopathic CP have less symptomatic disease, and are often diagnosed with obvious morphological changes and functional impairment at initial presentation (5, 57).

In CP patients who present with AP or pain as the initial manifestation, a subset may have morphological features and/or functional abnormalities at initial presentation, while in the remaining patients these develop over a variable period of time. Many recent studies have evaluated the probability of disease progression among patients who present with their first attack of AP without co-existent CP. In a recent meta-analysis of 14 studies, 10% patients with first attack AP and 36% with RAP progress to CP (88). The risk of progression was higher among smokers, alcoholics, and men (55).

7. Quality of life (QOL)

The impact of CP on the patient's overall wellbeing and functioning has become a topic of growing interest in clinical research and practice. This subjective patient's perception has been assessed using different validated health related quality of life (QOL) instruments, such as the SF-36, SF-12, and EORTC QL-C30 (32, 79, 80). More recently, a disease specific instrument has been developed to evaluate QOL in CP (PANQOLI) (103, 104). This includes unique features not found in generic instruments (economic factors, stigma, and spiritual factors).

A uniform finding on these studies has been that QOL in CP patients is significantly affected when compared with historical controls (32, 68, 77-81, 105). Moreover, the QOL in CP is noted to be worse than many other chronic disorders or malignancies (3). In the NAPS2 study (3), the independent effect of CP was also evaluated after controlling for demographics, etiology, risk factors and comorbidities using the SF-12 questionnaire. These data showed that CP has a profound independent effect on physical QOL (~10 points lower) and a clinically significant effect on mental QOL (~4 points lower) when compared with control subjects without pancreatitis. Few studies have assessed the factors that determine the impaired QOL in CP patients. Among the factors assessed, pancreatic pain seems to be the predominant factor, especially if it is constant (32, 68, 69, 80, 105). The effect of interventions, smoking, alcohol consumption, diabetes, exocrine pancreatic insufficiency, and disease duration, is still not well known.

8. Pancreatic cancer, comorbidities and mortality

The risk of pancreatic cancer is increased in subjects with CP. In a landmark multicenter cohort study, the risk of pancreatic cancer in CP patients from 6 different countries was 2.8% during a mean follow-up of 7 years (62). Other studies have reported similar incidence of pancreatic cancer that ranges from 1.2% to 3.8% (71, 76, 98). A meta-analysis showed that when compared

with controls, there is 13-folds greater lifetime risk of pancreatic cancer in CP (83). In subsets of CP patients, this risk is even more pronounced - e.g. the risk of pancreatic cancer in patients with hereditary pancreatitis is 69-fold (46, 64, 85), and in those with tropical pancreatitis it is 100-fold greater (13).

Recently, a nationwide study from Denmark reported the overall risk of having any type of cancer in CP patients to be 20% greater than general population controls (10). The risk of liver cancer (HR, 2), small intestinal cancer (HR, 3), and lung cancer (HR, 1.5), was found to be significantly increased in subjects with CP. This risk was not different between alcoholic and non-alcoholic CP (10). This study also revealed a higher risk of cerebrovascular disease (HR, 1.3), chronic pulmonary disease (HR, 1.9), ulcer disease (HR, 3.6), diabetes (HR, 5.2), and chronic renal disease (HR, 1.7) among CP patients.

In a large multicenter study that enrolled 2015 CP patients between 1946-1992 in 6 countries (Switzerland, Germany, USA, Italy, Sweden, Denmark), the overall mortality rate at 10 years was 30% and 55% at 20 years from diagnosis (63). Other studies have reported similar findings (76, 100). Based on this data, it is believed that the overall median survival of patients with CP is between 15 and 20 years from onset. Patients with idiopathic CP of early-onset may have longer survival. A study from India reported mortality among patients with idiopathic CP to be 17% after 35 years of disease onset (67). Well-designed studies have also compared the mortality rate of CP patients when compared with the general population. In a retrospective study from 30 years ago, Levy et al reported higher mortality rate in CP patients compared with a matched French population (60). This data has been replicated in more recent studies. In a study from Olmsted, Minesota, USA (1977-2006), CP patients had 2-fold mortality compared with age- and sex-matched Minnesota white population (115). Likewise, two Danish studies (1977-1982 and 1995-2010) found mortality among CP patients to be 4-5-fold higher when compared with background population (10, 71). This effect was independent of comorbidities and socioeconomic status. Even though mortality rates increased with age in both CP patients and controls, CP patients died at a younger age than controls (8 years earlier) and had higher adjusted relative risk of death for younger than older patients (10).

Almost three quarters of deaths are unrelated to pancreatitis (115). The most common causes of death in CP patients include malignancy (22-23%), diseases of the alimentary tract (15-23%), and the circulatory system (12-21%) (10, 63, 115). Pancreatic cancer is the most frequent cancer-related cause of death (1/3 of malignancies), followed by lung cancer (10). While age at diagnosis, smoking, and alcohol use were major predictors of mortality in the study of Lowenfels et al (63), a more recent study by Nojgaard et al reported that smoking, alcohol, CP etiology, exocrine pancreatic insufficiency, and diabetes had no impact on survival (71). Interestingly, unemployment was associated with higher mortality in this study.

9. Healthcare utilization and cost of care

Hospitalization in patients with CP could be due to AP flares, pain, maldigestion, and local complications. More than 90% of patients are hospitalized on at least one occasion in their lifetime for pain related to CP (69). In several European studies, there has been a steady increase in the rates of admission for CP. In a UK study that compared annual hospital admissions between 1960-1965 and 1980-1984, the hospitalization admissions increased from 8.3 to 32 per million population (50). In another study, the incident hospitalization rate increased from 4.3/100,000 in 1988 to 8.6/100,000 in 2000 (101).

This trend has also been seen in two studies from the Netherlands (from 5.2/100,000 in 1992 to 8.5/100,000 in 2004) (95) and Finland (10.4/100,000 in 1977 to 13.4/100,000 in 1989) (48). In contrast, 2 US population studies (study periods 1988-2004 and 1996-2005) found hospital admissions for CP to be stable over time (8 per 100,000) (114, 116). Hospital admissions are disproportionately higher in blacks, alcoholics, and in those with constant pain (69, 114). The median length of stay ranges from 4 to 6 days, and is not different between alcoholic and non-alcoholic pancreatitis (51, 114).

CP patients often undergo interventions, mainly for treatment of pain or local complications -- this used to be surgery (resection or drainage procedures) previously (4, 57), but endoscopic therapy, if feasible, is now being performed more frequently (14, 26). There is paucity of population level data on the use of endoscopic therapy for CP. A recent study found the trends for pancreatic surgeries performed for CP to be stable in the US population from 1998-2011 (23). In this study, the number of drainage operations decreased significantly, which likely is a reflection of more frequent use of endoscopic drainage. In the NAPS2 cohort, up to 61% of CP patients underwent at least one pancreatic endoscopic intervention (38). This high rate is likely an overestimation due to referral bias.

There is limited data on the direct and indirect costs related to the management of CP. Direct costs include the value of services used in treatment and care of CP. Indirect costs are related to the personal or family economic loss secondary to the illness. The estimated direct annual cost related to CP in the US is approximately $638 million (35). Based on prescription data, the cost related to AP and CP was $88 million, of which the cost of pancreatic enzymes was $75 million and for narcotics and anti-emetics of approximately $13 million (30). In a recent study from the UK, the estimated direct annual cost was $460 million.(42) The annual cost of hospital admissions and diabetes treatment was $90 million and $145 million respectively (42). The costs related to interventions are unknown.

Regarding indirect costs, more than a third of CP patients are unemployed, more than a quarter are on disability benefit, and the majority report missing significant time from work due to their illness (36, 69). Loss of productivity among CP patients is comparable to other chronic diseases, such as Crohn's disease, chronic obstructive pulmonary disease, and urologic dysfunction (36).

10. Future directions

Studies in the past few decades have informed different aspects of the epidemiology of CP. However, much of these data are limited to Europe, North America, and some parts of Asia. Future studies should focus on population distributions of CP in other parts of the world, the impact of imaging studies, environmental and other factors on disease estimates and trends between and within populations, determinants of healthcare utilization and health care cost from CP.

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