Current status and progress of pancreatic cancer in China

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Abstract

Cancer is currently one of the most important public health problems in the world. Pancreatic cancer is a fatal disease with poor prognosis. As in most other countries, the health burden of pancreatic cancer in China is increasing, with annual mortality rates almost equal to incidence rates. The increasing trend of pancreatic cancer incidence is more significant in the rural areas than in the urban areas. Annual diagnoses and deaths of pancreatic cancer in China are now beyond the number of cases in the United States. GLOBOCAN 2012 estimates that cases in China account for 19.45% (65727/337872) of all newly diagnosed pancreatic cancer and 19.27% (63662/330391) of all deaths from pancreatic cancer worldwide. The population's growing socioeconomic status contributes to the rapid increase of China's proportional contribution to global rates. Here, we present an overview of control programs for pancreatic cancer in China focusing on prevention, early diagnosis and treatment. In addition, we describe key epidemiological, demographic, and socioeconomic differences between China and developed countries. Facts including no nationwide screening program for pancreatic cancer, delay in early detection resulting in a late stage at presentation, lack of awareness of pancreatic cancer in the Chinese population, and low investment compared with other cancer types by government have led to backwardness in China's pancreatic cancer diagnosis and treatment. Finally, we suggest measures to improve health outcomes of pancreatic cancer patients in China.

Key words: Pancreatic cancer; Incidence; Diagnosis; Treatment

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Core tip: The health burden of pancreatic cancer in China is increasing, with annual mortality rates almost equal to incidence rates. Cases in China account for 19.45% of all newly diagnosed pancreatic cancer and 19.27% of all deaths from pancreatic cancer worldwide.
Facts including no nationwide screening program for pancreatic cancer, delay in early detection resulting in a late stage at presentation, lack of awareness of pancreatic cancer in the Chinese population, and low investment compared with other cancer types by government have led to backwardness of China's pancreatic cancer diagnosis and treatment.


WORLDWIDE EPIDEMIOLOGY OF PANCREATIC CANCER

Pancreatic cancer, one of the most frequent cancers in the world, is a devastating malignant disease with a median survival of 3-6 mo and a 5-year survival rate of less than 5%[1-4]. Despite improvements in surgical techniques and adjuvant medical therapy, these figures have not changed in over four decades, with the mortality approaching the incidence. According to the latest global estimation, GLOBOCAN 2012, the age-standardized rate (ASR) of pancreatic cancer incidence data is 4.9 per 100000 in men, and 3.6 per 100000 in women. Worldwide, the age-standardized rate (ASR-W) for the incidence and mortality of pancreatic cancer is 4.2% (Figure 1) and 4.0% (Figure 2), respectively[5]. In the United States, the ASR incidence and mortality of pancreatic cancer is 7.5% and 7.0%, respectively. The recent data showed that 48960 people were estimated to be diagnosed with pancreatic cancer in 2015, and 40560 people would die from pancreatic cancer in the United States[6].

Epidemiology in China

China is the largest developing country with nearly a fifth of the global population. As a result of rapid urbanization, more and more Chinese people live in urban areas. Combined with other factors such as aging and environmental pollution, the disease spectrum in China has shifted from infectious to non-infectious diseases. Among the non-communicable diseases, the health burden of cancer is increasing. Although China has a lower incidence of pancreatic cancer than western countries, the incidence of this disease in China has increased as fast as that worldwide recently. In 2010, 34509 men and 23226 women died from pancreatic cancer in China, with the number of deaths exceeding that in the United States[5,7,8].

Significant improvements of pancreatic cancer diagnosis and treatment have been achieved by China over the past 30 years. Here, we review the status of pancreatic cancer in China, and describe important epidemiological, risk factors, screening methods, diagnosis and therapy of pancreatic cancer. In addition, we discuss the challenges and trends of pancreatic cancer in China, and explore development of a multicenter cooperative research system to improve its clinical outcome.

Incidence and mortality

Population-based cancer registries collect data on annual cancer incidence and mortality to provide accurate and up-to-date information that is vital for cancer prevention, control, and research[7]. Since 2006, data contained in the Cancer Registry Annual Report released by the National Central Cancer Registry (NCCR) indicate that the incidence and mortality of pancreatic cancer in China has gradually risen[9]. Although the number of cancer registries in China is increasing, the available data for incidence and mortality of pancreatic cancer covers only about 13% of the nation’s population, while nearly 100% of the population in the United States is covered[6,10]. Currently, the true burden of pancreatic cancer in China cannot be estimated by using data from the Cancer Registry Annual Report alone, due to the above limitation. Thus, expansion of cancer registries covering more population would improve accuracy of estimates of cancer burden.

Incidence

GLOBOCAN 2012 estimated that pancreatic cancer was one of the most frequent malignancies in China, with an ASR-W incidence of 3.6 per 100000 for both sexes[5]. According to the Chinese Cancer Registry Annual Report 2012, the incidence of pancreatic cancer fluctuated according to sex, region and age. The crude incidence rate of pancreatic cancer in registration areas was 7.28 per 100000, with 8.24 per 100000 for men and 6.29 per 100000 for women in 2009. The ASR was 3.35 per 100000 with 4.01 and 2.72 per 100000 for men and women, respectively[10].

The crude incidence rate of pancreatic cancer in Chinese urban populations was 8.19 per 100000 (9.36 per 100000 for men and 7.00 per 100000 for women), which was 51.39% higher than that in rural areas (5.41 per 100000 overall; 5.97 per 100000 for men and 4.83 per 100000 for women). The data remained 27.76% higher after age standardization[10]. Standardized by the age structures worldwide, the ASR incidence in urban areas was 4.96 per 100000, which was also higher than that in rural areas (3.83 per 100000).

Among the urban cancer registration areas, Shanghai had the highest crude incidence rate of 15.19 per 100000 (Figure 3).

The age-specific incidence rates of pancreatic cancer dramatically increased after 40 years old in
China, with the incidence peak at about 80 years old (Figure 4). The trends in urban and rural areas were similar to those in the entire country, with the age-specific incidence rate in urban areas higher than that in rural areas after age 50 years. The cumulative incidence rate for patients aged 0-64 years was 0.21%, while for those aged 0-74 years it was 0.54%\cite{10}. Comparison of age distribution among some major countries and continents showed that more patients younger than 65 years were diagnosed with pancreatic cancer in China, which means that age at diagnosis of pancreatic cancer in China is less than that in western countries (Figure 5). In China, 61.2% of patients with pancreatic cancer were aged 65 years or older, compared with 80.1% of patients in Japan.

Although there were fluctuations according to sex and region, the upward trend in the incidence rate of pancreatic cancer is real in China. According to the Chinese NCCR, the incidence rate increased from 6.26 per 100000 in 2003 to 8.37 per 100000 in 2009\cite{11}. During this 7-year period, the incidence rate increased from 6.83 to 9.48 per 100000 in men and from 5.67 to 7.24 per 100000 in women. The increasing trend of pancreatic cancer incidence was more significant in rural than in urban areas. The incidence rate increased 1.27 times from 2003 to 2009 in urban areas, while the rate was 1.61 times higher in 2009 than in 2003 in rural areas.

**Mortality**

Pancreatic cancer is a rapidly disastrous malignancy with dismal prognosis. Recent mortality rates of pancreatic cancer in developed countries such as Japan have
stabilized after an increase, while in China mortality due to pancreatic cancer is rising. Despite that, the prevalence, incidence and mortality of pancreatic cancer in China are relatively lower than those in developed countries such as Europe, the United States and Japan, and comparison of mortality-to-prevalence ratios showed that survival outcome for pancreatic cancer is worse in China than in most other countries. The mortality-to-prevalence ratio amounts to 0.85 in China, compared with 0.7 in the United States, 0.56 in South Korea, 0.55 in Germany, and 0.4 in Japan (Figure 6). The phenomenon may be due to lack of improvement in the treatment of pancreatic cancer, especially in China.

According to the Cancer Registry Annual Report 2012, pancreatic cancer ranks as the seventh highest cause of cancer death in China, with a crude mortality of 6.61 per 100000. The mortality rate in urban areas (7.42 per 100000) was 50.20% higher than that in rural areas (4.94 per 100000). The data remained 27.09% higher after age standardization. The trend might be due to disparities in socioeconomic circumstance, and lifestyle between urban and rural areas. The mortality reached the peak at around 80 years old in both urban and rural areas (Figure 7), which was similar to the incidence. From 2003 to 2009, the mortality rate of pancreatic cancer increased from 5.63 to 7.78 per 100000. The upward trend in mortality concerns both men and women, and both urban and rural areas.
Pancreatic cancer is considered a malignancy correlated with industrialization as suggested by the fact that the majority of deaths occurred in developed countries. Despite the fact that it is unclear what factors cause pancreatic cancer, several risk factors and established genetic syndromes are associated with pancreatic cancer. Although identification of country-specific trends for risk of pancreatic cancer is valuable, risk factors in China are similar to those worldwide. Recent substantial increases in the prevalence of cigarette smoking, obesity, and diabetes mellitus in China may be related to the increasing incidence of pancreatic cancer. Also, studies show that severe deterioration of the environment in China and problems with food contamination may contribute to the increasing occurrence of cancer.

**Tobacco use**

Tobacco use is one of the most important risk factors of pancreatic cancer, and a dose- and duration-related pattern has been demonstrated for earlier age of onset. Around the world, 9% of all cancer deaths are related to smoking among male smokers, and male smokers have a 74% higher risk of pancreatic cancer compared with non-smokers. A recent hospital-based case-control study by Wang et al. showed that current smokers had a significantly increased risk of pancreatic cancer (OR = 1.71, 95% CI: 1.25-2.35) with a decreasing trend in risk correlated with years of smoking cessation. Another case-control study...
by Yin et al\cite{20} revealed that smokers had an OR for pancreatic cancer of 3.53 (95%CI: 3.0-9.6) compared with non-smokers, and smoking in the morning was an increased risk factor for pancreatic cancer (OR = 5.50, 95%CI: 1.22-24.81). In addition, secondhand smoke exposure may increase the risk of pancreatic cancer by 50%, and children exposed passively to tobacco smoke have a double risk of pancreatic cancer as adults\cite{21,22}.

**Obesity and dietary factors**

Obesity, which is associated with increased risk of diabetes mellitus, is also a risk factor for the development of pancreatic cancer\cite{23}. A case-control study including 841 patients with pancreatic adenocarcinoma and 754 healthy individuals showed that being overweight (body mass index (BMI) of 25-29.9) or obese (BMI $\geq$ 30) during early adulthood was associated with an increased risk of pancreatic cancer. A younger age of disease onset and obesity at an older age reduced overall survival in patients with pancreatic cancer, regardless of disease stage or tumor resection status\cite{24}. Studies have shown that the relative risk of pancreatic cancer was 1.16 in men and 1.10 in women per 5-point increase in BMI\cite{25,26}.

Dietary factors are also related to pancreatic cancer. Although there is evidence that folate and folate-containing foods exert a protective effect against pancreatic cancer\cite{27}, this was not confirmed in a recent study\cite{28}. A multicenter case-control study by Chinese researchers\cite{29} showed that reduced vegetable consumption was significantly associated with pan-

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**Figure 5** Comparison of age distribution of patients with pancreatic cancer between China and some major countries and continents.

**Figure 6** Comparison of mortality-to-prevalence ratio of pancreatic cancer between China and some major countries and continents.
risk of pancreatic cancer compared with patients with increased duration of diabetes mellitus. Patients with diabetes mellitus, relative to patients without diabetes for developing pancreatic cancer in patients with that the overall risk was 1.82 (95%CI: 1.66-1.89) meta-analyses pancreatic cancer has been summarized in several The association between diabetes mellitus and pancreatic cancer. Studies have shown that 25% of patients diagnosed with pancreatic cancer had diabetes mellitus, among whom 40% were pre-diabetic. The association between diabetes mellitus and pancreatic cancer has been summarized in several meta-analyses. A study by Huxley et al. reported that the overall risk was 1.82 (95%CI: 1.66-1.89) for developing pancreatic cancer in patients with diabetes mellitus, relative to patients without diabetes mellitus. The risk of pancreatic cancer declines with increased duration of diabetes mellitus. Patients with diabetes mellitus within 4 years had a 50% increased risk of pancreatic cancer compared with patients with diabetes mellitus for 5 years or longer. Patients whose diabetes mellitus had lasted 5 years or longer had a 50% greater relative risk than those without diabetes mellitus. This is not surprising because pancreatic-cancer-associated diabetes mellitus is predominantly new onset. In a Chinese retrospective cohort study, male and female patients with type 2 diabetes mellitus were 2.97 and 2.68 times more likely, respectively, to develop pancreatic cancer compared with the general population. Similar results were obtained by Kuang and coworkers, who showed that the incidence of diabetes mellitus was higher in pancreatic cancer patients than in controls.

**Genetic risk factors**

Although the occurrence of pancreatic cancer seems to be sporadic, it has been reported that 5%-10% of pancreatic cancer patients have hereditary factors. Cases of inherited predisposition to pancreatic cancer fall roughly into three categories. The first consists of hereditary cancer syndromes such as Lynch syndrome, familial adenomatous polyposis, Peutz-Jeghers syndrome, and familial atypical multiple mole melanoma syndrome, which are characterized by specific germ-line gene mutations and associated with increased risks of pancreatic cancer. The second category comprises conditions such as hereditary pancreatitis and cystic fibrosis, in which there is an inherited predisposition to the development of pancreatic cancer. The third category is familial pancreatic cancer, defined as two or more first-degree relatives with pancreatic cancer that does not fulfill the criteria of other hereditary cancer syndromes with increased risks of pancreatic cancer.

**Other risk factors**

Additional risk factors including male sex, low income, advanced age, alcohol use, chronic pancreatitis, a history of cholecystectomy or partial gastrectomy, and chronic infections have also been shown associated with pancreatic cancer. Moreover, it has been reported that some pancreatic cystic lesions such as intraductal papillary mucinous neoplasm and mucinous cystic neoplasm have the potential to progress to invasive pancreatic cancer, and patients with these lesions belong to groups at high risk of pancreatic cancer. In addition to the above risk factors, other factors such as environmental pollution and food contamination, which are becoming serious issues affecting public health in China, may be associated with the increased trend of pancreatic cancer. Although so far these associations lack solid epidemiological evidence, a recent cohort study demonstrated that airborne particulate matter of diameter < 10 μm from the incinerator was associated with pancreatic cancer mortality.
SCREEning for early pancreatic cancer

Recent studies suggest that pancreatic cancer develops over a long time with an average of nearly 17 years from cancer-initiating cells to metastatic cancer subclones, followed by death after approximately 2.7 years[51,52]. Patients with small tumors detected at early stages have reportedly better outcomes[53-55]. Thus, a screening program for high-risk individuals has the benefit of better outcomes in patients with pancreatic cancer.

There is no nationwide screening program for pancreatic cancer in China at present. Obstacles to implementation of a population-based screening program include insufficient convincing accuracy and cost-effectiveness data; insufficient equipment; and inadequate insurance coverage for such a screening program. There has been no consensus on the definition of high-risk individuals for pancreatic cancer until now. Patients in China who are at high risk of pancreatic cancer may be characterized by any of the following[56,57]: (1) older than 40 years and presenting with nonspecific abdominal symptoms; (2) a family history of pancreatic cancer; (3) new-onset diabetes mellitus, especially in those older than 60 years with either atypical diabetes mellitus or rapidly developing insulin resistance, without family history or obesity; (4) chronic pancreatitis, especially when accompanied by precancerous lesions; (5) intraduct papillary mucinous neoplasms; (6) familial adenomatous polyposis; (7) distal subtotal gastrectomy for benign disease, especially 20 years after resection; and (8) heavy tobacco or alcohol use or long-term contact with hazardous chemical substances.

When encountering these populations, non-invasive screening methods such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and magnetic resonance cholangiopancreatography (MRCP), combined with pancreatic-cancer-related biomarker examination are recommended. Among these high-risk groups, patients with new-onset diabetes mellitus may be an attractive screening target for early pancreatic cancer. The potential clinical benefit of screening for early pancreatic cancer in high-risk groups appears to exceed that for breast cancer[58].

Imaging

The screening modalities applied for detection of pancreatic cancer mainly include ultrasonography, CT, MRI, MRCP, and endoscopic ultrasound (EUS). Ultrasonography, a noninvasive and cost-effective modality, is frequently the first-line screening tool for patients with suspected pancreatic lesions, although it is not a reliable method, and highly dependent on the operator’s experience and body habitus of patients[59]. Contrast-enhanced CT is now the worldwide imaging modality of choice for evaluation of pancreatic disease, and may be the best modality to assess resectability of pancreatic cancer[60]. Nevertheless, radiation exposure and the suboptimal detection rate limit its use as a routine screening tool for asymptomatic high-risk individuals[61]. Studies revealed that MRI and EUS may be better than CT for early diagnosis of pancreatic neoplasms[62]. Thus, it has been proposed that initial screening should include EUS with or without MRI or MRCP, but not CT or endoscopic retrograde cholangiopancreatography (ERCP)[61]. However, the high cost and limited availability of MRI generally mean that it is utilized only after ultrasonography or CT. While EUS has been used as a principal imaging modality for screening pancreatic cancer in multiple international programs[63], a study by Long et al[63] showed that in Shanghai only 5.7% of patients underwent EUS to detect pancreatic cancer. Evaluation of the results of EUS is dependent on the doctor’s experience[64]. It is not widely used in China, and is only regularly performed in a few large medical centers[65].

Molecular markers

A limitation of screening for early pancreatic cancer is the absence of sensitive and specific markers. Compared with unwarranted imaging or more invasive testing, serological markers are always preferred due to the ease of collection, a relatively noninvasive trait. Carbohydrate antigen (CA)19-9, the only currently predictive biomarker for therapeutic outcome of pancreatic cancer, is commonly used to screen the disease. However, given the low incidence of pancreatic cancer, a blood-based marker with high specificity (99%) and sensitivity (100%) will lead to 83 false-positive for every true-positive case based on the incidence rate of 12.1 per 100000 in the United States[66]. Therefore, poor-to-moderate sensitivity and specificity in detecting pancreatic cancer limit its use in screening. For example, according to a study from China, the sensitivity of CA19-9 was only 57%, with an accuracy of 67.7%. These results indicated the limited value of CA19-9 in detecting early pancreatic cancer[67].

Diagnosis

Cancer stage at diagnosis is an important factor influencing survival of pancreatic cancer patients. A multicenter nationwide study in China showed that 18.4% of pancreatic cancer patients received diagnoses at stages I or II, and 81.6% at stages III or IV[68]. A recent study that included 11672 cases recorded in the Shanghai Cancer Registry 2004-2009[69] reported that nearly 42.9% of patients had regional or distant metastasis at diagnosis, whereas 49.2% had localized disease. The median survival was 3.9 mo (95%C1: 3.8-4.0 mo) and the overall 5-year survival rate was 4.1%. Reasons for poor survival of the cohort in that study included delayed diagnosis of pancreatic cancer. In contrast, the United States is better than
China at early detection of pancreatic cancer. In a recent study, Yu et al.\(^{70}\) analyzed 13131 patients with pancreatic ductal adenocarcinoma between 2004 and 2011 in the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database, which was considered representative of the United States population. They found that 62.9% of pancreatic cancer patients received diagnosis at stages I or II, and 37.1% at stages III or IV. Since pancreatic cancer has no distinctive symptoms, it is usually diagnosed when a patient has symptoms of abdominal pain or jaundice. Most patients diagnosed with pancreatic cancer lack the chance of radical surgery due to late stage. It is important to determine the resectability of pancreatic cancer because the rate of postoperative complications after pancreatic surgery is high even in high-volume medical centers\(^{71-73}\). Radiological imaging is an important method for initial detection, staging, and evaluation of pancreatic cancer resectability, which includes identification of the primary tumor, local lesion resectability, and distant metastasis\(^{39}\).

Multidetector row computed tomography (MDCT) is a worldwide imaging modality for evaluation of pancreatic cancer. More than 75% of patients who received a diagnosis of pancreatic cancer in China had undergone MDCT\(^{63}\). MDCT has good spatial and temporal resolution with anatomical coverage\(^{74}\). MDCT can assess both local tumor resectability and distant metastasis. It is also the best imaging modality for assessment of vascular involvement, which is crucial for prediction of tumor resectability\(^{75,76}\). MRI is also currently used for patients with pancreatic diseases\(^{77}\). Compared with CT, MRI is not only an outstanding tool for characterizing pancreatic mass, but also a successful technique for noninvasively delineating the pancreatic ductal system, as an alternative to ERCP. Positron emission tomography (PET)/CT is useful for detecting pancreatic cancer, especially metastases throughout the body\(^{78,79}\). However, widespread application of PET/CT is limited in China by its high rate of false-positive results, low spatial resolution, and high cost\(^{80,81}\).

Expert for MDCT, other imaging modalities such as MRI and PET/CT are not widely used in Chinese patients\(^{63}\). In western countries, EUS has been widely used for detection of pancreatic cancer in recent years\(^{82}\), especially for high-risk groups and patients with small tumors\(^{58}\). Furthermore, EUS-guided fine-needle aspiration (FNA) has the unique ability to acquire specimens for histopathological diagnosis of this devastating disease, especially in unresectable patients. A most recent study by Ngamruengphong et al.\(^{83}\), using the SEER-Medicare data including 2034 patients with pancreatic cancer, showed that preoperative EUS-FNA did not impair survival of pancreatic cancer. However, EUS-FNA is not widely performed in China, although it is now the standard of care in western countries. Less than 40% of cases diagnosed with pancreatic cancer in China had histological verification, mostly via surgery with pathological diagnosis\(^{63}\). Limited application of EUS in China may explain why so many patients diagnosed with unresectable pancreatic cancer lack histological confirmation.

**THERAPY**

Fewer than 20% of patients are eligible for curative resection as pancreatic cancer is usually detected at a late stage. Surgical resection is the cornerstone of treatment, which offers the only chance to cure patients with pancreatic cancer. Many patients have disease recurrence even after radical surgery. Adjuvant chemotherapy, radiotherapy, targeted therapy, and traditional Chinese medicine have been commonly used to improve quality of life.

**Surgery**

Surgical resection is the only potentially curative therapy for pancreatic cancer. Assessment of the involvement of local vessels is the key to determine tumor resectability. With improvements in safety of pancreatic surgery in recent decades, in the hope of improving long-term survival, surgeons have continued to explore the role of more extensive surgery. Whether patients should receive extended lymphadenectomy or not is controversial. A meta-analysis comparing standard lymphadenectomy with extended lymphadenectomy during pancreaticoduodenectomy for pancreatic cancer revealed that the extended procedure did not benefit overall survival, and might even cause a trend towards increased morbidity\(^{83}\). Due to no benefit in long-term survival being demonstrated, standard pancreaticoduodenectomy continues to be the choice for pancreatic head cancer.

A noteworthy change in pancreatic surgery in China may be towards a minimally invasive approach, particularly distal pancreatectomy, which could gain wide acceptance for benign and low-malignancy tumors\(^{84,85}\). A recent meta-analysis reported that laparoscopic distal pancreatectomy resulted in less loss of blood and time in hospital, and lower rates of overall complications and infections, but did not lower rates of postoperative pancreatic fistula or mortality\(^{86}\).

Application of robotic surgery has advantages over laparoscopy, including the rate of R0 resections (i.e., complete resection with no tumor within 1 mm of the resection margins), and greater lymph node yield\(^{87}\). A more recent study from Mayo Clinic showed that total laparoscopic pancreaticoduodenectomy (TPLD, \(n = 108\)) was feasible in the setting of pancreatic ductal adenocarcinoma, and had advantages over open pancreaticoduodenectomy (OPD), including shorter hospitalization and faster recovery, allowing patients to recover in a timelier manner and pursue adjuvant therapy. There was also a significantly longer progression-free survival in the TLPD group than in the OPD group (\(n = 214\)), while the overall survival rates of the two groups were similar\(^{88}\). Despite this, robotic
pancreatectomy is now not a common procedure in China, mainly due to cost pressures. Nevertheless, the effects and benefits need to be confirmed by more data in China.

Chemotherapy and targeted therapy
Chemotherapy for patients presenting with advanced pancreatic cancer is widespread in China. Gemcitabine is the gold standard for pancreatic cancer treatment and achieves a modest improvement in overall survival. Gemcitabine-based combination chemotherapy has been first-line for advanced pancreatic cancer for more than one decade and shows a superior clinical response and survival. In a study by Long et al., more than 30% of 846 pancreatic cancer patients recruited in a population-based study underwent chemotherapy, and 9.6% of patients received combination therapy. Regional intra-arterial infusion chemotherapy for pancreatic cancer has been safely used to suppress tumor growth and was more effective in reducing incidence of liver metastasis. In a study by Jin et al., 50 patients who underwent regional intra-arterial infusion chemotherapy had disease-free and median survival times of 15.5 and 18 mo, respectively. However, the necessity for regional arterial chemotherapy remains controversial due to its invasive nature.

Gemcitabine plus nab-paclitaxel and FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin) have been recently reported to improve survival for metastatic pancreatic cancer significantly. However, these two regimens are currently not popular in China due to increased toxicity and high cost not covered by insurance. The situation is similar for S-1, which is not inferior to gemcitabine for survival rate, with acceptable tolerance for locally advanced and metastatic pancreatic cancer. Only small clinical studies have been conducted to evaluate these regimens for Chinese patients with advanced pancreatic cancer.

Targeted therapy may be promising to improve survival in advanced pancreatic cancer. However, targeted therapy in several phase II trials was not superior to standard chemotherapy. Additionally, drug reimbursement policies strongly affect the availability of systemic therapy in China. Most targeted agents are not covered by insurance, leading to prohibitively high cost for patients and limitation of options for advanced pancreatic cancer.

Radiotherapy
The use of radiotherapy for pancreatic cancer is not popular in China. For instance, in Shanghai, only 3.5% of patients received radiotherapy as part of their primary treatment. In a study by Chen et al. of pancreatic ductal adenocarcinoma, among 565 patients, only 14 underwent postoperative radiotherapy. The proportion of pancreatic cancer patients receiving radiotherapy in China is less than that in the United States. In a study by Mellon et al. using the SEER database including 2966 patients between 2004 and 2008, 62.1% of patients with pancreatic cancer received postoperative radiotherapy and had an associated survival benefit. However, similar to the incidence of new-onset pancreatic cancer in China, use of radiotherapy is also increasing. Given that patients who underwent concurrent chemoradiotherapy had better long-term survival compared with radiotherapy alone or chemotherapy alone, the efficacy of combination of S-1 with gemcitabine followed by concurrent radiotherapy has been investigated and appeared promising in Chinese patients with locally advanced pancreatic cancer. Among the 32 patients who completed the scheduled course of chemoradiotherapy, 30 received chemoradiotherapy. The median overall and progression-free survival was 15.2 and 9.3 mo, respectively. The 1-year and 2-year survival rates were 75% and 34.4%, respectively.

Traditional Chinese medicine
Traditional Chinese medicine, which mainly uses combinations of herbs, represents about 40% of the pharmaceutical market in China. Moreover, about 90% of oncologists prescribe herbs and 80% of patients with cancer have taken traditional Chinese medicine. The widespread application of traditional Chinese medicine may be related to the belief that it can improve immune function and quality of life in cancer patients. Huachansu injection, which is a water-soluble preparation made from skin of Bufo gargarizans, has been used in China for pancreatic cancer treatment. However, a recent randomized phase II clinical trial showed that huachansu plus gemcitabine did not improve survival of patients with locally advanced or metastatic pancreatic cancer. Turmeric root has been used medicinally for thousands of years in China. The active component is thought to be curcumin, which is commonly available worldwide and has been shown to exert activity against various malignancies, including pancreatic cancer. In a phase II study including 25 patients, curcumin showed clinical biological activity in some patients with advanced pancreatic cancer, without toxicity. Another phase I/II study of 21 patients showed that patients with gemcitabine-resistant pancreatic cancer who received combination therapy using 8 g/d oral curcumin with gemcitabine-based chemotherapy had a median survival of 161 d (95%CI: 109-223 d) and the 1-year survival rate was 19% (108). However, poor absorption limits the clinical activity of oral curcumin. To enhance curcumin absorption, nanotechnology and liposome-encapsulated curcumin have been studied in vitro and in vivo for pancreatic cancer.

PANCREATIC CANCER RESEARCH IN CHINA
Scientific publications related to pancreatic cancer
from China have rapidly grown since 2007, regardless of the fact that the total number of publications in China is far less than that in the United States (Table 1). The number of publications from China in 2013 exceeded that from Japan, and was second only to the United States (Figure 8). Such great development of pancreatic cancer research in China may benefit from a steady increase in funding from the Chinese government, among which the National Nature Science Foundation of China (NSFC) is one of the most important research funds. Funding for pancreatic-cancer-related research from NSFC has steadily increased. However, investment in different cancer types remains uneven. Funding for research related to pancreatic cancer is less than for other cancer types, such as liver, breast and gastric cancers. The proportion of investment in research funding for pancreatic cancer has not been growing in the field of oncology in the past two decades (Figure 9). Nevertheless, concurrent with the rapid growth in scientific papers published from China, there is a rising concern that many of them are of inferior quality. High-quality clinical trials are imperative for clinical decision making for care of pancreatic cancer patients. As a consequence of research funding shortage, there are only 84 clinical trials published in PubMed and currently 75 clinical trials for pancreatic cancer registered in China (Table 1), with the numbers far less than those in developed countries. This may explain the inadequacy of high-quality pancreatic cancer research in China. Therefore, China needs to develop a multicenter cooperative research system for pancreatic cancer, take part in international multicenter clinical trials, or join an international cooperative group for pancreatic cancer.

### CHALLENGES AND FUTURE DIRECTION

Each year more than 330000 patients are diagnosed with pancreatic cancer worldwide, with survival changing little in the last four decades. The incidence and mortality of pancreatic cancer in China are both increasing. According to the recent prediction from GLOBOCAN 2012, about 77497 men and 52868 women in China will be diagnosed with pancreatic cancer in 2035. Nearly 130000 patients will die from pancreatic cancer annually until then (Figure 10). The prediction means that the incidence and mortality of pancreatic cancer in China may increase faster in the next few years, and China will face a huge pancreatic cancer burden.

Unlike some cancers, pancreatic cancer is difficult...
to detect early, and usually presents at a late stage. With no established screening programs, resources might be allocated for earlier stage detection by offering a comprehensive strategy of imaging and genetics to identify curable cancers in high-risk individuals\(^{[1]}\). Some patients are overtreated with aggressive surgery or adjuvant therapy, while some are undertreated. Multidisciplinary care, which provides comprehensive evaluation and treatment, is the most effective approach to manage cancer patients\(^{[2]}\). However, multidisciplinary teams specialized in pancreatic cancer are currently rarely established in most centers in China, even in high-volume centers. Thus, multidisciplinary management of pancreatic cancer is an urgent need. Although more and more pancreatic cancer centers appear in China, rare multicenter collaborative studies have been conducted. The Chinese government should recognize shortfalls in research funding in areas of pancreatic cancer. More research supported by government funding can help us understand the biological behavior of pancreatic cancer and achieve successful treatment. Increased investment in education and healthcare are needed in order to upgrade the quality of care and to reduce the morbidity and mortality of pancreatic cancer. Last but not least, to improve national pancreatic cancer incidence and mortality statistics, the number of cancer registries still needs to be expanded, covering as much of the population as possible.

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