C.S. Pitchumoni, MD, Series Editor

Dissecting the Epidemiology of Pancreatic Adenocarcinoma


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INTRODUCTION

Pancreatic cancer (PCa) is the eighth leading cause of death from cancer in men and the ninth leading cause of death from cancer in women throughout the world.[1] The American Cancer Society estimated that 45,220 Americans will be diagnosed with Pancreatic Cancer in 2013. Delay in diagnosis, surgically inaccessible location of the pancreas, absence of classic symptoms of the disease and poverty of molecular biomarkers result in a diagnostic challenge. PCa represents 2.4% of all cancers and 3.7% of cancer deaths. Early surgical resection has a survival benefit, however, since the disease is often diagnosed at late stages surgery is not curative and adjuvant therapy becomes palliative.[2]

PCa is usually seen in the elderly with a male predominance, the peak incidence being in those aged 65-75 years. Adenocarcinoma accounts for 95% of all cases, about 85% are sporadic with no family history or predisposing genetic syndromes. Although 5-year survival is low (<5%), high volume surgical centers have reported survival rates of up to 40%.[3] Recent studies have shown that distinct molecular subtypes of PDAC exist and are associated with different prognosis and therapy response.[4] Related to improved life-expectancy and probably adoption of cancer associated lifestyles the incidence is growing globally.[3]

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ETIOLOGICAL ASSOCIATIONS

A. ENVIRONMENTAL

Few modifiable risk factors have been implicated in the etiology of PCa.

1. Cigarette Smoking

Cigarette smoking is a well-established risk factor for PCa and a co-factor in chronic pancreatitis secondary to alcoholism.[5] It is attributable for about 20-30% of cases of PCa.[6-13] Studies report a higher risk among current smokers compared to non-smokers, up to 6 fold depending on duration and intensity of cigarette smoking,[14] (RR=1.74, 1.61–1.87) and also in former smokers with respect to never smokers (OR=1.20, 1.11-1.29).[7,9] Smoking 1 pack/day increased the risk by 1% and the risk doubled for those with >40 pack years of smoking.[7] Pipe/cigar smoking had lower risk when compared to cigarette smoking but passive smoking (workplace/household) did not increase the

risk.[12] Though the risk remained elevated for up to 15 years after quitting, a non-significant drop in risk was observed after 20 years.[7,9]

Cigarette smoke contains nearly 4000 chemicals of which more than 60 has been identified as carcinogens[14] (polycyclic aromatic hydrocarbons, N-nitrosamines, aromatic amines, 1,3-butadiene, benzene, aldehydes and ethylene oxide). The toxins reach the pancreas indirectly via bloodstream or biliary regurgitation to exert carcinogenic effect.[8,11,15] Recent studies have looked into genetic variations at carcinogen-metabolizing enzymes to further understand individual susceptibility to PCa.[15] Of the carcinogens the most potent metabolite, NNK mediated pathways is well studied.[14] There have been no major studies on the effect of e-cigarettes on PCa. E-cigarette users were more nicotine dependent than nonusers, had more prior quit attempts, and were more likely to be diagnosed with thoracic and head or neck cancers.[16]

2. Alcohol

An association between alcohol abuse and pancreatic injury was reported by Friedreich as early as 1878.[17] Freidreich recognized an association of alcohol abuse with chronic pancreatic injury.[17] Several studies have evaluated the association of alcohol and PCa but conclusive evidence is lacking.[11,17-21] This could be due to interplay of significant confounders such as smoking, pancreatitis, nutritional and genetic factors.[17,21] However, alcohol has been projected as an independent risk factor, attributable to 2-5% of all PCa cases (where population prevalence of heavy drinking is 10-15%).[11,17,21] Heavy drinking (>40g or >3drinks/day) is associated with moderate risk (RR=1.22, 1.12-1.34) in women and up-to 3.5-fold risk in male binge drinkers (>70g or >5 drinks/day).[17,19,21] The risk with type of beverage consumed (wine, beer, liquor/spirit) is variable but an increased risk with the duration of alcohol consumption is reported.[18,19]

The causal role of alcoholic pancreatitis which is responsible for <5% of PCa cases is not adequate enough to explain the link between alcohol and this PCa.[21] Acetaldehyde (oxidative pathway) and fatty acid ethyl esters (non-oxidative pathway), the metabolic products of alcohol, activate pancreatic stellate cells leading to inflammation, immune response and cancer.[17,21,22] Folate depletion leading to defective DNA synthesis/repair and carcinogen activation via induction of cytochrome P450 is also postulated means of alcohol injury.[18]

3. Diet

The role of diet in the pathogenesis of PCa is weak and contradictory. Mediterranean diet rich in plant-based foods, whole grains and fish with modest consumption of meat and dairy products was associated with a decreased risk (OR=0.51, 0.31-0.84).[23-26] A 2.4-fold risk was reported in men on a Westernized diet (red/processed meat, potato, sugary beverage, refined grains, eggs and high-fat dairy).[24] Red meat consumption was associated with an increased risk in men.[27] A statistically significant 19% higher risk in those consuming processed meat (50g/day) was reported in a meta-analysis.[27] Energy-dense diet consumption escalated the risk (up to 72%) while soft drinks did not.[28,29]

Although dietary fat is not associated with increased risk, a recent study attributed a diet rich in cholesterol with low fiber and folate to the increased incidence of PCa in Poland.[30,31] Dietary magnesium especially in overweight men is found to decrease the risk (18% reduction with 100mg increased intake) and cruciferous vegetables (OR=0.90) were protective.[32,33] There is no protective effect for antioxidant consumption while a 2-fold risk is seen in those with high serum levels of 25 (OH) vitamin D (≥100 nmol/L).[34,35] Based on data from the European Prospective Investigation into Nutrition and Cancer Cohort, coffee (total or decaffeinated) and tea consumption are not related to the risk of PCa.[36]

4. Occupation

Certain occupations are associated with an increased risk, especially with exposure to chlorinated hydrocarbons and polycyclic aromatic hydrocarbons (PAH).[37] Dry-cleaning, metal-related work (Gold/silver smith) and electronic work have exposure to chlorinated compounds.[37] Although an increased risk with herbicide and fungicide (not insecticide) was noted in one US study, others failed to demonstrate this risk.[37,38] PAH associated risk was seen among metal workers and those in aluminum industry.[37,39] Occupational exposure to inorganic dust, asbestos and ionizing radiation also amplified the risk.[37,40] Assessment of PCa risk among night shift workers in Japan and food industry workers in Finland did not yield significant result except in Finnish males (SIR=1.5, 1.13-1.96).[41,42]

5. Exposure To Heavy Metals

There are reports in literature to support the risk for PCa from exposure to heavy metals. Higher incidence of PCa in the East Nile delta region of Egypt is now attributed

to cadmium exposure from fertilizers and polluted river water.[43,44] An epidemiological study from Louisiana reported this heavy metal exposure from food (pork, seafood, rice) as the cause of increased incidence of this cancer among the Cajuns.[45] Cigarette smoke is another potent source of cadmium which could be implicated for the increased risk of PCa among smokers.[45] Cadmium exerts its carcinogenic effect via impairment of DNA repair mechanisms to cause genomic instability.[44]

Arsenic with similar carcinogenic mechanism is also incriminated in PCa.[44] A recent study from Florida reported a significant increase in the risk among those living within 1 mile radius of Arsenic-contaminated wells.[46] There are reports about childhood arsenic exposure (from milk powder) and increased mortality associated with this cancer.[44,47] Although asbestos exposure from drinking water was reported to increase PCa, subsequent follow-up and analysis failed to prove this.[48] Similarly there are studies, which link exposure to lead and decreased levels of selenium (toenail concentrations) to PCa.[44]

6. Radiation

In a study of the Hiroshima and Nagasaki, the two sites of atomic bombings, no radiation effect was noted.[49] However one study showed excess deaths from PCa in patients who received therapeutic irradiation for ankylosing spondylitis[50] and another reported two cases of PCa in patients who got abdominal radiation for testicular cancer.[51]

7. Infection

Studies have revealed an infective etiology of PCa, the main agents being H pylori, HBV, HCV and HIV.

H pylori, extensively studied as a gastric carcinogen is being investigated for extra-gastric associations. Several studies including a meta-analysis have found significant association of PCa (AOR=1.38, 1.08-1.75) with this highly prevalent infection (40% in developed countries and 70% in developing countries) and about 2-fold risk with CagA +/ VacA + strains.[52,53] The antral colonization of H pylori and subsequent hyperchlorhydria leading to increased pancreatic secretions and hyperplasia is one of the plausible mechanisms.[52,54] Inflammation (IL 8 and VEGF) and bacterial overgrowth from hypochlorhydria (increased N nitrosamine) are other suggested mechanisms.[52-54]

An increased risk was seen with active (RR=3.83), chronic (RR=1.39) and past (RR=1.41,1.06–1.87) HBV infection.[55] There was a synergic increase in the risk in chronic/inactive HBsAg carriers with DM.[56] HCV with mechanisms similar to HBV was found to double the risk for PCa (SIR=2.1, 1.4, 2.9).[57-59]

There is an increased incidence of PCa in HIV patients (SIR=2.2, 1.2-3.6).[60] PCa was diagnosed at a younger age with advanced stages at presentation and had a higher likelihood of unfavorable performance status in HIV positive subjects.[61] Periodontal disease, and *Porphyromonas gingivalis*, a pathogen for periodontal disease, are reported associations in PCa.[62]

B. CHRONIC PANCREATITIS

All types of chronic pancreatitis predispose to PCa (RR=5.1, 3.5-7.3), although <10% is attributed to it.[63,64] A significant risk was associated with both acute (HR=9.1, 3.81-21.76) and chronic pancreatitis (RR=13.1, 6.1-28.9).[63,65,66] Different forms of chronic pancreatitis such as hereditary, autoimmune and tropical pancreatitis are discussed in literature, all of which are significantly associated with PCa. Patients who underwent surgery for the treatment of chronic pancreatitis had significantly lower incidences of pancreatic cancer. Surgery for chronic pancreatitis may inhibit the development of pancreatic cancer in patients with chronic pancreatitis.[67] Acute pancreatitis may be an initial manifestation of PCa.

1. Hereditary Pancreatitis (HP)

Hereditary Pancreatitis (HP) is an inherited form of chronic pancreatitis characterized by recurrent episodes of pancreatitis since childhood.[68-71] Mutation in the cationic trypsinogen gene (PRSS1) was the first identified genetic defect.[68,71] Subsequently several germline mutations such as protease serine 2 (PRSS2), pancreatic secretory trypsin inhibitor (SPINK1), CFTR, chymotrypsinogen C (CTRC) and calcium-sensing receptor (CASR) were discovered.[68] Individuals with HP have a high risk for PCa (SIR=87, 42-114).[69,70,72] The cumulative risk by age of 75 years is about 40%-53.5%.[69,70,72] Smoking and diabetes further increased the risk in these patients.[71]

2.Tropical Calcific Pancreatitis (TCP)

Also known as fibrocalculous pancreatic diabetes (FCPD), Tropical Calcific Pancreatitis (TCP) is a form of chronic pancreatitis in Afro-Asian countries.[73,74]

The exact etiology for this form of chronic

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pancreatitis has not been established. Studies have clearly shown that this is a high risk factor for PCa (RR=5, 1.03-14.6).[73,75] Patients who develop PCa are younger compared to the denovo form. The entity although found in many states in India is well studied in large series of patients mostly from states of Kerala and Tamil Nadu.

Early studies identified TCP as a disease in young malnourished individuals with poor prognosis leading to diabetes and having a high risk for PCa. But recent research found strong genetic links to this disease (SPINK1/CFTR mutations) and dismissed the notion of regional predominance, links to nutrition and grave prognosis.[76,77]

The pathogenesis of malignancy in pancreatitis is postulated via inflammatory mediators, activation of signaling pathways (cyclooxygenase2 expression, Notch signaling, Hedgehog signaling) and oxidative damage.[66,67] Ueda et al. reported a decreased risk in chronic pancreatitis patients managed surgically (HR=0.11, 0.014-0.80) which provides further evidence for the inflammatory etiology.[67]

3. Autoimmune Pancreatitis

Autoimmune Pancreatitis is a steroid responsive type of chronic pancreatitis, which mimics PCa.[78-80] Although several case reports have been published, conclusive evidence regarding its association with cancer is lacking other than an increased occurrence of K-ras mutations.[78-80] AIP features a significant inflammatory phase, and hence it is biologically plausible that AIP patients are similarly at increased risk for developing PCa. The potential for systemic inflammation in this multiorgan disease could also contribute to risk for extra pancreatic cancers. Finally, the late age at presentation of type 1 AIP and reports of cancer being discovered shortly before and after AIP diagnosis have fueled speculation that AIP is a paraneoplastic manifestation of an underlying cancer.[81]

C. DIABETES AND PANCREATIC CANCER

This is a clinically important but controversial topic. Type 2 Diabetes (DM) with its temporal association with PCa is described both as cause and result of the cancer.[82-84] This is an independent risk factor with approximately two-fold increased risk compared to general population.[82,83] Risk is inversely associated with the duration of DM, the highest risk being with <1year of DM (OR=5.38;3.49–8.30).[83] No increased risk was seen in subjects with >9 years of DM (OR=1.02; 0.68-1.52) which contradicted the findings of a previous meta-analyses.[82,85,86] The association between DM and PCa was not modified by gender, smoking, age, or BMI.[82] History of diabetes in a first degree relative increased the risk (OR=1.37, 1.10-1.71) per the PACIFIC study (pancreatic cancer: investigation into finding causes).[87] A meta-analysis observed equal risk in diabetic men and women but some disparity exists in this regard.[83,84,88] Higher risk was seen among those using insulin compared to those without (OR=3.34 vs. 1.50) in the Iowa Women's Health Study (IWHS).[84]

Hyperglycemia associated with altered glucose metabolism, chronic inflammation, oxidative stress, and activation of insulin signaling cascades increases the risk of pancreatic cancer.[89] The development of DM within a few years of a pancreatic cancer diagnosis is more likely to suggest an effect of the tumor, whereas diabetes of longer duration is more likely to contribute to the development of cancer.[90]

However in a study from Japan, PCa was diagnosed within 2 years of DM onset (new-onset) in 0% of the patients with early-onset DM, and in 33% of those with late-onset DM. Pre-existing type 2 diabetes, acute alcoholic hepatitis, acute pancreatitis, cholecystitis, and gastric ulcer independently or jointly predict subsequent pancreatic cancer risk.[91]

The notion that new-onset diabetes in pancreatic cancer is a paraneoplastic phenomenon caused by tumor secreted products was strengthened by a recent study that proposed adrenomedullin, a 52 amino-acid polypeptide, as a strong candidate for mediator of diabetes in pancreatic cancer. Adrenomedullin was also shown to be overexpressed in human pancreatic cancer and plasma levels of adrenomedullin were also increased in pancreatic cancer patients, especially those with diabetes.[92] Earlier concept of beta cell destruction has given way to the role of hormonal secretions from the tumor causing insulin resistance, up-regulation of IGF-1 leading to carcinogenesis via enhanced angiogenesis and cell growth without apoptosis.[82,83,89] Supported by the fact is the observation that IGF receptor and insulin receptor substrate-2 (IRS-2) are over-expressed in cancer cells of the pancreas.[93] Other+ studies have shown the presence of diabetogenic factors (2030 MW peptide, Amylin/IAPP) in the serum.[83,94] Thus patients with new-onset DM with a family history of DM should be screened for underlying malignancy.[87] Similarly

Table 1. Hereditary Cancer Syndromes Affecting the Pancreas.[176]

Syndrome	Gene mutation		Relative risk
Peutz Jeghers Syndrome	STK11/LKB1	Autosomal Dominant	132 fold
Familial Breast and Ovarian Cancer syndromes	BRCA1 and BRCA2		10 fold
Familial atypical multiple mole melanoma	TP16	Autosomal Dominant	13 fold
Familial Pancreatic Cancer	BRCA2 in up to 20%	Autosomal Dominant	9 fold
Hereditary pancreatitis	PRSS1 in up to 80%	Autosomal Dominant	35-70 fold
Von Hippel-Lindau syndrome	VHL		
Ataxia Telangectiasia	ATM	Autosomal Recessive	Unknown
Li- Fraumeni syndrome	TP53	Autosomal Dominant	Unknown
Cystic fibrosis	CFTR		
Familial Adenomatous Polyposis	APCA		
HNPCAC	MLH1, MSH2, MSH6, PMS1, PMS2	Autosomal Dominant	4.5 fold

new-onset DM in older patients (>65 years) with a negative family history and low BMI (<25) or recent weight loss (>2kg) also have a likelihood for associated PCa.[95] Reducing diabetes by controlling obesity could benefit pancreatic cancer rates, in addition to the many other known health benefits.[82] One study showed that dyslipidemia, but not diabetes, is a significant risk factor for PCa. Patients with new-onset diabetes and a history of dyslipidemia are at an especially high risk of PCa.[96] DM is also an independent risk factor for liver, colorectal and breast cancers but decreases the risk of prostate cancer.[97]

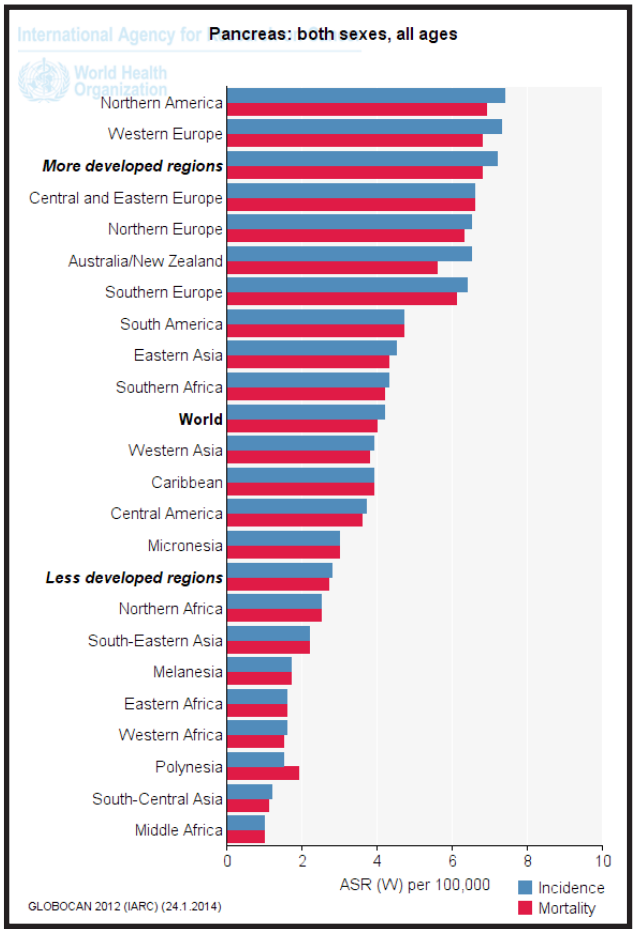
The use of metformin, the most commonly prescribed drug for type 2 diabetes, was repeatedly associated with the decreased risk of the occurrence of various types of cancers, especially of pancreas and colon and hepatocellular carcinoma.[98]

D. OBESITY

Obesity, a rising epidemic, has association with multiple cancers[99-101] and has been discussed in detail in an earlier paper in this series. Most of the studies have found an association of increased BMI (marker of obesity) with PCa (RR=1.2-3).[84,102,103] A meta-analysis observed 19% increased risk in obese people (BMI>30 kg/m^2).[101] Obesity related PCa had a population attributable fraction of 26.9% and 19.3% in US and EU respectively.[102,104] An earlier age of onset was seen in those who were obese/overweight during their adolescence (HR=2.09, 1.25-3.50).[102,105] Similarly in the elderly, obesity was found to reduce survival in PCa patients.[102] Metabolic syndrome (MetS) is associated with many more consequences than generalized obesity. MetS was found to be associated with PCa in both men (SIR=178,144-266) and women (RR=1.58, p<0.0001).[106,107] MetS components were also found to increase the risk [fasting blood glucose (OR=4.24), total cholesterol (OR=1.79), apolipoprotien A (OR=36.06)].[108] One European study reported significant risk with several metabolic factors in women (mid-blood pressure, glucose, triglycerides, BMI).[109]

Physical activity was found to decrease the risk [e.g.: history of sports (HR=0.80, 0.64-0.99), occupational

Figure 1.



physical activity (RR=0.75, 0.58-0.96)].[103,110] Release of cytokines (IL-6, TNF α, CRP) leading to insulin resistance and higher insulin levels result in increased IGF-I: IGFBP-3 (insulin growth factor and binding protein ratio) is probably related to carcinogenesis in obesity.[101,106,111]

INHERITED PANCREATIC CANCER

Genetic predisposition accounts for 5-10% of all pancreatic cancers.[72,87,112,113]

Familial pancreatic cancer (FPCA) -is defined as a family with more than one first degree relative (FDR) with history of PCa without any inherited syndromes.[112] A 2.3 to 4.5-fold increased risk with 1 FDR, 6.4-fold with 2 FDRs and up-to 32-fold with ≥3 FDRs with pancreatic cancer has been noted.[72,114,115] FPCA which is influenced by race (Ashkenazi Jews), smoking and diabetes, and genetic anticipation (younger age or worse prognosis with successive generations).[72] Pancreatic intraepithelial neoplasia with mutations in the K-ras (codon 12) was more frequently (2.75 fold) observed in familial pancreatic cancer when compared to sporadic.[72]

Hereditary pancreatic cancer- is a genetic syndrome with mutations that increase the risk for PCa.[112] Peutz-Jeghers syndrome with STK11/LKB1 gene mutation is associated with up-to 132-fold increased risk for PCa.[72,112,116,117] Hereditary Non Polyposis Colon Cancer (HNPCC) is associated with a lifetime risk of 1.3-4% for PCa.[112] Majority of the Hereditary Breast Ovarian Cancer (HBOC) is due to mutations in BRCA1 and BRCA2 genes.[112] The risk for PCa in BRCA1 carriers is minimally elevated compared to general population (RR=2.8 vs. 1.3%).[112] BRCA2 mutation has a 5-7% lifetime risk in carriers and is the most common inherited gene for development of PCa.[112] Families with Familial Atypical Multiple Mole Melanoma syndrome (FAMMM) are at increased risk (13-22%) for this cancer.[72,112] Individuals with p16/ CDKN2A (FAMMM gene) mutation have a 38-fold higher risk in comparison to general population.[72] Studies have shown a mild elevation of risk in FAP with APCA gene mutation (RR=4.5), Cystic fibrosis (CFTR gene) and Ataxia telangiectasia (ATM gene).[72,112,116] Associations of PCa with PALB2 (partner and localizer of BRCA2) and palladin (cytoskeleton associated protein) mutations are being observed.[72,116,118.] (See table X)

OTHER FACTORS

Several studies among different populations across the world have reported an increased risk associated with non-O blood groups for PCa (OR=1.37, 1.02-1.83).[59,119-121] Mechanisms though not clear; relevance of physiological differences in inflammatory mediators (TNFα, cellular adhesion molecules) is being postulated.[119] Few studies have found a significant co-relation of this disease with a history of cholelithiasis (HR=3.12, 2.05-4.78) and cholecystectomy (higher prevalence 6.2% vs. 2.9%).[108,122] Anti-diabetic medications and NSAID's are found to have an effect on PCa risk. Metformin (HR=0.73, 0.66–0.80) and thiazolidinediones were associated with reduced risk but insulin (HR=4.63, 2.64–8.10) and sulphonylureas (HR=4.95, 2.74–8.96) aggravate the risk.[123-125] DPPV IV inhibitors (sitagliptin) have a theoretical risk for carcinogenesis[126] but a recent meta-analysis on this issue reported conflicting results.[127]

Although not conclusive enough, there is evidence to suggest that high-dose aspirin reduces the risk for PCa (OR=0.78, 0.64-0.95).[128-130] Similarly there is

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lack of satisfactory evidence for other NSAIDs.[130] A combination of aspirin, curcumin and sulphoraphane has been found to be beneficial against PCa in animal studies.[131] One study from Netherlands observed an inverse association of PCa with hypertension.[132] Metformin offers a potential novel approach for pancreatic ductal adenocarcinoma prevention and therapy.[133]

ALLERGIES

A recent meta-analysis reported 30% drop in pancreatic cancer risk among those with history of allergies.[134] Statistically significant risk reduction was observed with hay fever (OR=0.74, 0.56-0.96) and allergy to animals (OR=0.62, 0.41-0.94).[134,135] Other allergies, such as those to foods and medications, have been less well studied and associations with risk are unclear.[136] Heightened immune surveillance is suggested as the plausible explanation.

GLOBAL EPIDEMIOLOGY

The annual incidence and mortality of PCa is the same (ASR incidence =7.2 vs. 2.8 and ASR mortality=6.8 vs. 2.7).[137] Analysis of global data based on human development suggest a higher incidence in areas with high human development (ASR incidence= 4.6) as opposed to areas with less development (ASR incidence= 1.2) (Fig-1).[137] Although reasons are not fully elucidated, it is linked to human lifestyle and diet. Immigrant studies, which found increased risk among Indians who migrated to Australia and UK, support this observation.[138,139] The highest incidence for women is reported in North American and northern Europe. A high incidence of PCa in Ashkenazi Jews[140] and a lower incidence among the Utah Mormons[141] has been noted. A brief summary of the incidence of PCa in different parts of the world is given below.

A. AMERICAS

North America, with isolated exceptions, has the highest incidence and mortality for PCa in the world (Incidence ASR= 7.4 and mortality= 6.9) (Fig-1).[137] Even though rates in South America are lower, French Guyana and Uruguay are ahead of US and Canada.[137] Lowest estimates are seen in Guatemala, Haiti, Panama and the Bahamas (Central America).[137]

Although PCa ranks only 13th among cancers, it is the 4th major cause of cancer-related death[137] with a 5-year survival rate of 6%.[142] Blacks have a higher incidence (33% more) and mortality (32% more) than Whites.[143] Asia Pacific Islanders have the lowest rates and better survival.[142] The rates for the indigenous groups fall between the Blacks and Asia-Pacific Islanders.[142] This racial disparity could not be attributed to any of the known risk factors (smoking, BMI, family history, diabetes and cholecystectomy).[143] Latitudinal variation in the incidence and mortality of this cancer was attributed to solar UV-B exposure.[144]

B. EUROPE

Western Europe, Central and Eastern Europe have higher incidence (ASR=6.6-7.3) and mortality (ASR=6.6-6.8) for PCa compared to Northern and Southern Europe (Fig-1).[137] Highest incidence is seen in Czech Republic, Slovakia, Hungary, Slovenia and Finland with Czech Republic having the highest incidence rate in the world (ASR=9.7).[137] Sweden, Albania, Cyprus and Bosnia have the lowest rates. Hungary has the highest mortality rate for PCa in Europe (ASR=8.8).[137]

The overall cancer mortality with the exception of PCa has decreased in this region since 1980.[145,146] A higher incidence was reported among people living in most deprived areas, partly linked to high prevalence of smoking.[146] In England, total number of cases was higher in Whites compared to Non-Whites (South-Asian, Blacks, Chinese 17% of population). However, age standardized incidence was higher in Blacks (ASR=5.7 in Blacks vs. 4.9 in Whites).[139] The risk was lower in South-Asians compared to Whites while no significant risk was demonstrated in Blacks and Chinese.[139] Immigrant population in England (non-White) had higher incidence of this cancer compared to their counterparts living in homeland.[139] A 138% increase in incidence of PCa was reported in the Inuit population (SIR=2.38, 1.97-2.86; $p<0.0001$) plausibly due to the high prevalence of diabetes and smoking.[147] Even though a Nordic country, Finland has a high incidence of PCa (ASR=8.7).[137] This is the 5th most fatal cancer in the country (ASR=7.8).[137] The 5-year survival has not improved much over the past 50 years (from 3 to 5%).[148] Although coffee consumption is very high, it is not associated with an increased risk for PCa (HR=0.82, 0.38-1.76).[149]

C. ASIA

Eastern Asia (People's Republic of China, Japan, North Korea, South Korea, Mongolia and Taiwan) followed

by Western Asia (Armenia, Azerbaijan, Middle East, Cyprus, Sinai Peninsula of Egypt, Georgia, Turkey) has the highest incidence of PCa in Asia (ASR=4.5 and 3.9 respectively) (Fig-1).[137] Similar is the trend in mortality (ASR=4.3 and 3.8 respectively). The Central and South-East Asia have lower rates (Fig-1).[137] Highest mortality rate for PCa is in Armenia worldwide (ASR=8.9). Also Armenia has the highest incidence and mortality in this continent followed by Japan, Israel, Kazakhstan and Korea.[137] Lowest rates are seen in India, Nepal, Bangladesh, Pakistan and Sri Lanka.[137]

1. Japan

PCa has a high incidence in Japan (ASR=8.5) and is the 5th common cause of cancer-related mortality in both men and women (ASR=9.5 and 6.1 respectively).[137] Although the 5-year survival is around 5%, resected cases have better prognosis (5-year survival=18.8%).[150] Positive family history and presence of diabetes were reported as major risk factors apart from smoking.[151] Northern Japan has a higher mortality from this cancer as opposed to south which was linked to variations in exposure to solar irradiation and temperature.[152] A high non-linear relationship of PCa death with low-dose external irradiation (<20mSv) was reported in Japanese-A bomb survivors.[153]

2. Korea

With a high incidence (ASR=6.7), PCa in Korea is the 5th most fatal cancer (ASR=6.2).[137] Analysis of trends in incidence from 1999-2010 showed that PCa is increasing in Korea (APCA in both sexes=1.4) with a greater increase in women (APCA=2.2 vs. 0.6 in men).[154] Although hepatitis B is endemic in Korea, it was not found to increase the risk for this malignancy (OR 1.03, 0.69-1.53; p=0.91) as opposed to hepatitis C (OR=2.30, 1.30-4.08; p< 0.01) and non-O blood group (OR=1.29, 1.05-1.58; p=0.01).[59]

3. China

The incidence of PCa is not very high in China (ASR= 3.6) but it is the 8th most common cause of cancer related death.[137] Cigarette smoking (44%), pancreatitis (16%) and family history of PCa (8%) were the major etiologies in young patients with PCa.[155] Incidence of diabetes among PCa patients was much higher (34.6% vs. 8.8%) and 74.56% (in the cancer group) had onset of DM within 2 years of diagnosis of cancer.[156] Energy dense foods increased the risk (OR: 1.72; 95% CI: 1.25, 2.35; P = 0.001) in Chinese.[28] Regular green tea drinking was found to be protective in Chinese women (OR 0.68, 95% CI 0.48–0.96).[157] For reasons not clear, in one study acute pancreatitis patients had a high risk of developing PCa within 5 years of index pain (HR=9.10; 3.81-21.76).[66]

Table 2. Other Unclear Risk Factors

Gastric surgery	RR of 1.8 at 5-59 years after gastrectomy. 3.6 at 35 years or more.[177]
Gallstones and cholecystectomy	Increased incidence in women with gallstones[178] and cholecystectomy.[179,180]
Primary sclerosing cholangitis	14 fold risk.[181]
Tonsillectomy	Protective. Odds Ratio of 0.67:1[182]

4. India

India has a low incidence (ASR=1.2) and mortality (ASR=1.1) for PCa.[137] Recent studies note an increasing incidence of PCa in both men and women.[158] A greater risk was observed in educated males with about 3-fold risk in those with >12 years of education.[159] Tropical calcific pancreatitis, which has a very high risk for this cancer (RR=100, 37-218), is highly prevalent in some parts of India.[73,75]

5. Israel

PCa in Israel ranks 3rd in men (ASR=8.6) and 4th in women (ASR=6.2) in malignancy related deaths.[137] Jews had a higher incidence than Arabs (ASR males 7.45 vs. 5.61) with the highest incidence (ASR males 8.11 vs. 7.45) in immigrant Jews (European-born).[160] Nevertheless, a decreasing trend is seen in the Jewish population[160] Mutation in BRCA1/2 was the major cause of this cancer in Ashkenazi Jews.[161]

D. AFRICA

The southern part of the continent, which includes South Africa, Mauritius and Zimbabwe, has the highest estimates for PCa in Africa (ASR incidence=4.3, ASR

mortality=4.2) (Fig-1).[137] Libya and Egypt, though in the northern part has incidence and mortality rates similar to Southern Africa.[137] There are few studies, which attribute pollution of the Nile for the increased incidence in Egypt.[43,162] Serum cadmium is suggested as the etiologic agent for the occurrence of early-onset PCa in the East Nile delta region.[43] A Moroccan study reported higher incidence (17%) of pancreatic adenocarcinoma in adults <45 years (3% in the US) which did not correlate with smoking, alcoholic pancreatitis or family history.[163] Lowest incidence (ASR<2) and mortality (ASR<1.9) for this malignancy is seen in Malawi, Guinea and Tanzania.[137]

E. OCEANA

Australia has the highest incidence (ASR=6.6) of PCa in this region followed by New Caledonia (ASR=6.5) and New Zealand (ASR=5.9) while island countries such as Samoa and Vanuatu have the least (Fig-1).[137]

1. Australia

PCa is the 5th common cause of cancer-related death in Australia.[137] A rise in incidence (ASR 7.67 to 8.24) and mortality (ASR 7.02 to 7.58) of PCa was observed in women (from 1977-2006) while these estimates dropped in men[164] attributed to variation in smoking habits.[164] An interesting observation is that mortality from PCa was 9% less in Brisbane (Queensland) when compared to Melbourne (Victoria), which was linked to variations in UV exposure between the two capital cities.[165]

2. New Zealand

PCa is the 5th most fatal cancer in this country.[137] A higher incidence and worse prognosis was reported among the Maori tribe which was attributed to smoking.[166] Blakely et al. analyzed cancer incidence in New Zealand by dividing the population into 4 ethnic groups (Maori, Pacific, Asian and European/others) and found a 1.5-times higher rates for PCa in the Maori and Pacific groups compared to the European group.[167]

CONCLUSION

PCa continues to be a major clinical challenge because of a trend in increase in incidence with no major improvements in survival. Recent studies have reported miRNA-21, c-Myc, L-type amino acid 1 transporter (LAT1), K-ras codon 12 mutation, p38β Mitogen-activated Protein Kinase and SMAD4 as biomarkers in predicting prognosis and survival in these patients.[168-174] Circulating Tumor Cell (CTC) detection in peripheral blood with a diagnostic accuracy of 70% (EUS-FNA=85%) is a promising noninvasive early diagnostic procedure.[175] A study from MD Anderson, Texas reported an association between NAFLD and pancreatic cancer.[175] If this observation is confirmed in further studies, it is concerning since MetS and obesity are rapidly increasing. Furthermore they observed simultaneous pancreatitis and liver cirrhosis in obese pancreatic cancer patients providing additional evidence for the role of obesity.[175]

Endocrine (islet cell tumors) and rare non-endocrine tumors (acinar cell carcinoma, adenosquamous carcinoma, colloid carcinoma, giant cell tumor, hepatoid carcinoma, intraductal papillary-mucinous neoplasm, mucinous cystic neoplasm, pancreatoblastoma) of the pancreas are not discussed in this article.

Regardless of the advances in medical science, PCa remains a challenge. More desirable survival outcomes rely on novel research that focuses on finer diagnostic and therapeutic approach, yet to materialize. ■

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