Prevention and Early Detection of Pancreatic Cancer

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KEYWORDS

• Cancer of the pancreas (CaP) • Whole-food plant-based diet (WFPBD)
• Western illness • Latent/indolent disease

KEY POINTS

- Screening for early detection of high-risk patients is based on axial imaging, which detects premalignant lesions much more often than malignant ones.
- Interval cancers that become apparent between screens are aggressive, poor prognostic lesions.
- Prevention of cancer of the pancreas (CaP) involves mimicking food and lifestyle choices of populations where these diseases are uncommon.
- Whole-food plant-based diets (WFPBDs) with abundant fruits, supplemented with exercise and natural active movements significantly lower the risk of cancer and CaP.

An ounce of prevention is worth a pound of cure.

Benjamin Franklin[1]

Let food be thy medicine and medicine thy food. Walking is man's best medicine.

Hippocrates[2,3]

INTRODUCTION

Franklin's[1] wise adage emphasized preventing rather than extinguishing fires, whereas medicine emphasizes extinguishing rather than preventing illness. When Hippocrates of Kos (460–370 BC) 2084 years ago stated food and lifestyle were the mainstay of health, the diseases of today were inconceivable. Imagine his thoughts about big pharma and the food industry. Because the lifestyle that prevents chronic disease, heart disease, and cancer is similar, what is applicable to prevent cancer of the

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pancreas (CaP) is equally effective for chronic and other malignant diseases.[4] Besides, the side effects of a healthy lifestyle are more pleasant than those of drugs/chemotherapy and much less expensive.

DEFINITION

A healthy lifestyle is one which optimizes and maintains health.[5] This lifestyle includes a whole-food plant-based diet (WFPBD) consisting of fruits, grains, legumes, and vegetables augmented by exercise and active lives and avoiding processed foods, salt, sugar, and animal protein.[6]

PREVENTION: WHY NOT?

Prevention of cancer, particularly CaP, draws scant attention for several reasons: (1) CaP takes 10 to 20 years to develop during which time it has undergone several mutations, developed its own blood supply (angiogenesis), avoided sufficient cell death (apoptosis), and possibly metastasized.[7–10] CaPs do not form de novo but progress from benign precursor lesions to invasive and metastatic lesions.[10] (2) The chances of an individual developing a CaP are small; but once established, it is likely fatal. (3) Unhealthy lifestyles are pervasive; many act as if they are immune from chronic disease and cancer. (4) CaP and many cancers present when symptomatic, a time prevention has long past and when the emphasis is on the too-little-too-late treatments. (5) Perhaps the most compelling reason to emphasize prevention is that treatment is directed at symptoms and not cause. By neglecting the cause, latent cancer can progress and new lesions develop. (6) Prevention is "pretreatment directed at causation whose goals are to maximize health, keep indolent disease dormant, and prevention of new cancers."[11,12] Prevention requires active participation, whereas early detection is physician directed and allows for passive patients. Too often, early detection is neither early nor curative.

PROOF OF CONCEPT

The association between diet and cancer is suggested by the wide international incidence of cancer and the study of migrants. Asians living in Asia have a 25 times lower incidence of prostate cancer and a 10 times lower incidence of breast cancer than migrant Asians[13–16] Monozygotic twins who share all genes do not share 85% to 90% of cancers that develop in one twin.[16] Less than 10% of cancers are genetic or familial.[17–19] Genes upregulate and mutate many times before cancer is initiated.[19] A sedentary lifestyle, smoking, animal protein, processed food, sugar, and obesity contribute to many chronic diseases and cancers, including CaP.[20–22] In 1907 a front page article in *The New York Times* noted an increased incidence of cancer in Chicago immigrants who were omnivores but not in immigrant vegetarians.[23] The relationship between diet and cancer is better understood today.[12,24–28]

Western illness including cancer has been rare in native Africans.[29–32] There was only 1 small healed myocardial infarct and 3 healed peptic ulcers. Cholecystitis, appendicitis, diverticulitis, cancer, and other Western illnesses were not evident. This finding affirmed the importance of diet, fiber, and lifestyle.

Burkitt,[30] an English surgeon in sub-Saharan South Africa, noted the native population was free of Western illnesses, that is, obesity, hypertension, appendicitis, cholecystitis, cancer, cardiac or vascular disease, and hiatal hernia, including CaP. High dietary fiber and low animal protein were thought to be important factors. This finding

was not so for those who provided supportive services. They developed the common surgical and medical diseases.[30–32]

Nathan Pritikin[33], an inventor and engineer who had a myocardial infarct as a young man, researched the subject and noted two-thirds of the world's population had no coronary disease. He lived and advocated a healthy lifestyle, including a WFPBD.[33] Postmortem studies of his heart revealed soft pliable coronary arteries suggesting disease reversal.[34] This finding antedated the clinical studies of Ornish[35] and Esselstyn,[36] who independently demonstrated coronary artery disease reversal and relief of cardiovascular symptoms (angina, claudication, impotence, hypertension) in patients who adopt a WFPBD.

A 4- to 5-hour period of vasoconstriction and decrease in brachial artery flow occurs after eating fast, fried fatty foods. The resulting endothelial cell injury caused a 40% to 50% flow decrease in both healthy volunteers and cardiac patients suggesting diet can injure or maintain healthy endothelial cells.[37,38]

PREVENTING CANCER AND PANCREATIC CANCER

The studies on lifestyle and cancer are no less convincing. Several risk factors have been associated with CaP. A landmark study by Doll and Peto[13] in 1981 reviewed environmental and nutritional risks for cancer in the United States. They estimated that lung cancer deaths were tobacco related in 91% of 71,000 deaths in men and in 77% of 24,000 deaths in women. Forty-three percent and 15% of all cancer deaths in men and women were tobacco related.[13] Blot and Tarone[39] in 2015 noted that 23% of men and 19% of women smoked, and it was causal in 80%+ of lung cancers. The current estimates are that 30%+ of CaPs are tobacco related; when smoking is stopped, the cancer incidence decreases.[39] Early estimates were guesstimates, because the epidemiologic methodology was evolving. The original suggestion was 35% of cancers were diet related (range 10%–90%). Site associations were 90% for the stomach and colon; 50% for the endometrium, gallbladder, pancreas, and breast; and 20% for the lung, upper digestive tract, and cervix. Willett[11] confirmed the diet-cancer causal relationship and thought studies had underestimated the cancer risk twofold. The physiologic benefits of physical exercise are through the release of myokines, which kill cancer cells.[40] The microbiome is vital in determining health or disease through the breakdown of ingested food and release of injurious or beneficial substances. This process is directed by the myriad of gut flora.[41] The release of insulin growth factor−1 stimulated by a suboptimal diet promotes cancer growth.[42] All of the preceding favor fruits, vegetables, legumes, and grains as healthier choices and protective against pancreatic and other cancers and chronic illness.

Three large studies confirmed that red meat (animal protein) increased the risk of dying of cancer and heart disease and shortened life span.[27,43,44] The studies controlled for risk factors: alcohol, exercise, smoking, family history, caloric intake, and a WFPBD. Deaths due to meat were accelerated by heterocyclic amines, aromatic hydrocarbons, and perhaps heme iron, found in meat but not vegetables. A meta-analysis of diet and cancer prevention by Belliveau and Gingras[12] from 1980 to 2006 showed 75% of abdominal cancers could be prevented or favorably influenced by a WFPBD.

A World Cancer Research Fund Report from 1997 noted that 144 human studies have shown a statistically significant benefit of fruits and vegetables on cancer, whereas no study has confirmed any protective benefit of animal-based foods.[45] Campbell and Jacobsen[46] think a full complement of WFPB nutrients acting in synergy promotes the protective effects.

Other factors that increase the risk of CaP are obesity, excessive alcohol consumption, and ingestion of animal protein (meat, fish, fowl, or eggs).[11,29,43,44] Great concern exists about the carcinogenic potential of poultry viruses by direct contact or consumption.[47] Thirty thousand poultry workers were studied; those who slaughtered chickens had a 9 times greater risk of developing CaP and liver cancer, a risk far greater than smoking for 50 years. The risk of eating chicken and developing CaP was 72% greater when daily consumption was 50 g (<2 oz or one-quarter of a chicken breast) or more.[48]

CLINICAL STUDIES

Prostate Cancer Studies

Ornish and colleagues[49] studied 93 volunteers with early prostate cancer who were randomized to a control or healthy lifestyle group (plant-based diet, 30 minutes of walking 6 times per week, and meditation). At 1 year, the control group had a mean prostate-specific antigen (PSA) increase of 6% (several required the treatment of progressive disease), whereas in the treated group's PSA decreased 4%. A year after the study ended, 10% of the control patients required radical prostatectomy but none in the healthier group.[49]

Another prostate study showed that decreasing animal protein and increasing vegetables slowed the increase of PSA and the rate of cancer growth. Even though subjects with a healthy lifestyle ate animal protein, the 1:1 animal to vegetable ratio slowed the doubling of PSA from 21 to 58 months.[50]

Curcumin Studies

Turmeric or curcumin prevents DNA mutations and impedes tumor growth and spread. Urine from patients with lung cancer (smokers) and nonsmokers was plated on bacteria in petri dishes. There were fewer DNA mutations in the bacteria of nonsmokers. After smokers were given turmeric (8 g/d), the DNA mutation rate dropped 38%.[51] Additional in vitro studies have shown curcumin kills cancer cells and prevents the disabling of death cell receptors on cancer cells.[52]

At the MD Anderson Cancer Center, curcumin in large oral doses (8 g/d) was given to 21 patients with advanced CaP. There were 2 responders: in one a 73% tumor reduction later recurred, whereas the second had progressive improvement over 18 months. When curcumin was stopped, tumor markers increased but decreased after resumption. The 10% response rate is similar to chemotherapy outcomes.[53]

EARLY DETECTION? AND SCREENING FOR CANCER/PANCREATIC CANCER

Indolent asymptomatic microtumors and circulating cancer cells are not uncommon in healthy individuals.[54] Autopsies show 40% to 50% of men and 30% to 50% of women aged 40 to 50 years have foci of CaP or early breast cancer and 98% have microthyroid cancers.[12,54] How these cells remain latent and viable for long time periods and do not metastasize is important. Host immunity, and natural killer cells, which are influenced by inhibitory and activating receptors, and altered gene signaling pathways influence latent cell metastases and growth.[12,55] Shed cancer cell metabolites may be detected in the serum of 40% of healthy people.[55] These lesions and cells should not warrant screens or treatment. They are cancer in name but are held in check by a healthy immune system.

Early detection of cancer is a popular concept; patients and families think that treating such lesions, absent symptoms, equals a cure. Early detection places the onus on the physician and screening process. Because the behavior of individual tumors is

unique, outcomes are often unpredictable. Early detection implies curability, and curability implies effective treatment. The optimism holds for many prostate, breast, and colon cancers. For nearly all CaPs and many brain and lung tumors, incurability is the rule no matter when discovered. Favorable tumor biology must be present for any lesion to be curable.[54]

Cancers are sporadic (90%–95%) or familial (5%–10%).[18,19,56] Familial cancers are genetically linked, but the pathway is undefined in most. The number of affected first-degree family members predicts the relative risk for other family members. For example, the relative risk of developing CaP is increased by a factor of 2, 6, and 30 with 1, 2, or 3 affected family members.[56]

Our better understanding of CaP has not yet improved the cure. The two precursor lesions for CaP are intraductal papillary mucinous neoplasia (IPMN) and pancreatic intraepithelial neoplasms (PanIN).[19,57]

Screening for sporadic CaP is impractical and expensive and has a low yield because CaP is uncommon, affecting 12 of 100,000.[58] Risk factors include tobacco, *Helicobacter pylori*, diabetes of recent onset (<4 years), chronic pancreatitis, obesity, and age (>55 years); but each minimally increases the screening yield.[59,60] Two-thirds of the causal factors are modifiable, adaptable, and would reduce the incidence of disease. Fruit and folate were favorable influences.

A meta-analyses of 36 studies of recent-onset diabetes (<5 years) showed a 50% greater risk of CaP than in diabetic patients of greater than 5 years. Approximately 11,000 of 1.9 million patients with newly discovered type 2 diabetes have CaP, but the risk increases by 0.58%.[61] Surgeons find the diabetes-CaP association not uncommon and the subject of several studies.[62–64]

Screening for familial CaP and its syndromes is the subject of ongoing studies and is reviewed in Robert J. Torphy and Richard D. Schulick's article, "Screening of Patients at Risk for Familial Pancreatic Cancer: What is Beneficial?" in this issue. Even when families genetically predisposed to CaP are followed, the detection of a precursor lesion is serendipitous.[56,65]

Several institutions follow high-risk individuals (HRIs) to asses screening. HRIs include a strong family history and several polyposis syndromes.[17–19,56,65] The number screened was from 38 to 216, and the positive yield was from 1.3% to 45.0%. The lesions seen on MRI are further evaluated by endoscopic ultrasound (EUS) and biopsy. IPMN, PanIN, and mucinous cystic neoplasms (MCNs) are premalignant. If the screen is further narrowed to men older than 65 years (the highest risk), the incidence increases to 16%. At present, most lesions excised are atypical and premalignant.[56,65,66] These are the target lesions, as the outcome of treated premalignant lesions is cure while for CaP the outcome are poor. The operative risk for premalignant lesions must be near zero to justify a prophylactic resection.

PATIENT (MIS)PERCEPTIONS ABOUT SCREENING

Patients raise few concerns about the value and pitfalls of screening.[67] Patients overestimate the benefits and underestimate overdiagnosis, false positives, and the implications.[68–70] Most screening information is derived from 3 malignancies (colorectal, prostate, and breast) whose incidence is higher and survival better than for CaP (**Table 1**).

Most patients anticipate a screen will be normal or show an asymptomatic and curable lesion. The concept that indolent tumors can be observed, whereas interval tumors (detected between screens) are aggressive and of poor prognosis is underemphasized.[67] Patients overestimate screening benefits by 70% to 95% and

Table 1
Annual incidence and mortality of 4 common malignancies

Lesion	No. Ann Dx	No. Deaths
Pancreas	43,000	40,000
Colorectal	136,119	56,813
Prostate	176,450	27,681
Breast	230,815	40,800

underestimate the downside by 70%.[68–70] The number of lives saved and incidents prevented per 5000 patients screened annually for 10 years are few; 2 to 15 breast cancers, 5 to 10 colon cancers, 75 to 85 cardiovascular events, and 50 hip fractures.[67,68] The benefits were overestimated by 90% for breast cancer screening, 82% for medicine to prevent hip fractures, 69% for cardiac medicine, and 94% for colon cancer screening. An overestimation of the benefit and an underestimation of the risk obfuscates choices particularly when surgery is involved.[69] Overestimating the benefits of lipid-lowering and antihypertensive medication has been noted as well.[71,72]

SCREENING WITH IMAGES

In the last 20 years, great refinements in imaging allow the detection of more asymptomatic pancreatic lesions.[56,66,67] The increase in imaging has uncovered many lesions, mostly pancreatic cystic lesions (PCLs). Pathologic classifications of cystic lesions are complex.[73] The common lesions include the benign serous cystadenoma, MCNs, IPMN, and its subtypes branch duct (BD), main duct (MD), or combined duct (CD). Malignant IPMNs are better behaved than most CaPs, and the cell type predicts the behavior. Of the subtypes (gastric, intestinal, oncocytic, and pancreatobiliary), pancreatobiliary is the most aggressive. PCLs are best defined by EUS, biopsy, and aspiration.[58] PCLs increase with the frequency of abdominal scans and sonograms. PCLs range from 2% to 27%; but in at-risk patients, it is 45% to 48%.[56,58,67] Canto and colleagues[56] compared the accuracy of PCL detection by EUS (45%), MRI (33%), and computed tomography (CT) (11%). MRI is more sensitive for small cysts (1 cm) and for main duct involvement. CT and MRI are useful after surgery and during chemotherapy to follow the disease. The choice (MRI, CT) depends on local practice and expertise.[74] The detection of incidental lesions does not imply a cure. Prognosis is determined by tumor biology. Newly detected lesions have likely been present for years. The diagnostic inaccuracies of PCL have been emphasized by Correa-Gallego and colleagues[75] who reviewed 136 of 330 excised asymptomatic PCLs. The preoperative diagnostic accuracy for BD lesions was 64%, and 29% had MD involvement. The diagnostic accuracy for MCN was 60%. The final pathology report included 6 invasive cancers (2 BD, 3 MD, and 1 MCN) and 19 cancer in situ (8 MD, 8 cystic endocrine lesions, and 3 unspecified lesions). Because the correct diagnosis is only made after excision, an accurate preoperative diagnosis is problematic and following lesions has a high degree of uncertainty.

SERUM MARKERS AND BIOLOGICAL MARKERS

Save for CaP, the mortality for other cancers has decreased. For CaP, there has been no change in mortality for 50 years.[4] Even if a specific and sensitive biological marker of 90% accuracy was available, 83 false-positive diagnoses would be raised for every

correct diagnosis. As Kaur and colleagues[76] have said "The specific and sensitive markers for early diagnosis of pancreatic cancer remain a distant dream."

Serum markers are ideal, as they are easily obtained. The antigens in the blood stream are diluted by other proteins lessening their accuracy. CA19-9 is the only approved marker to follow CaP. It was found as a colon tumor antigen that reacted better with monoclonal antibody N19.9 in CaP and biliary cancer than colon cancer. Ca19-9 has several drawbacks, including a moderate sensitivity (69%–98%) and specificity (46%–98%), and is not expressed in 5% to 10% who are Lewis a/b negative.[77] Ca19-9 is elevated in benign and malignant conditions, including pancreatitis, cirrhosis, bile duct obstruction, and gastric, uterine, colorectal, and urologic cancers. Only two-thirds of patients with resectable PC have elevated Ca19-9. It is best used to follow patients after surgery or during chemotherapy to evaluate treatment.[78]

Other markers are being developed but are not commercially available or are of limited use. They include autoantibodies, cytokines, messenger RNA, circulating tumor cells, and mononuclear cells in blood and gene mutations.[78]

WHY CAUSATION IS IMPORTANT

Treating symptoms and lesions provides relief and may correct abnormal laboratory tests but does not correct the cause. Reversing coronary artery disease relieves symptoms and corrects the cause when done by a WFPBD as opposed to surgery or a coronary stent. If the cause is not corrected, the disease can recur or progress. For cancer, removing a target lesion does not change the soil that allowed a lesion to develop or recur. Treating breast or colon cancer by local therapy (surgery) does not prevent new or metastatic lesions. Surgically treating chronic pancreatitis by removing a segment of pancreas does not prevent cancer developing in the remaining gland. Observing an IPMN, a precursor lesion of CaP, does not limit the progression of the disease. La Femina and colleagues[79] followed 157 patients with IPMNs, 97 (62%) underwent surgery and 18 (11%) were cancer (4 were away from the IPMN). Of the 153 patients followed, 56 (20%) developed another IPMN and 3 had an invasive cancer.[80]

The two precursor lesions of CaP are ductal: PanIN and IPMN. PanINs progress from low to high grade to invasive cancer.[9,10] The low-grade lesions are present in normal pancreata, whereas high-grade lesions are found near CaP or in nontumor areas in familial syndromes.[56] Ninety percent plus of PanINs have a KRAS mutations. Tumor suppressor genes are also found in PanIN 2 and 3. KRAS is a marker of poor prognosis and is needed to sustain tumor growth.[19,78,80,81] Loss of KRAS results in tumor shrinkage. KRAS promotes the acquisition of cell nutrients, including glucose, lipids, and protein, directly and by autophagy, a way of recycling organelles and protein to sustain tumors. Inhibiting autophagy inhibits tumor growth. Other suppresser genes include SMAD4, p53, and CDKN2A.[19] A case report of KRAS recovered from pancreatic juice during endscopic retrograde cholangiopancreatography suggest an occult malignancy.[82] Absent a visible lesion the patient was followed until a lesion was detected and treated. For CaP, this is less than ideal. Most genetic markers require tissue analyses, which for the pancreas is impractical.

EARLY DETECTION OF CANCER

An ideal test for early detection would include a sensitive, accurate serum marker to detect asymptomatic cancers that are clinically, and radiographically undetectable. Additionally, the marker should allow isolation of the organ involved and since the

lesion is too small to detect be able to be treated with natural products to prevent growth and for the marker to become undetectable.[57]

Such a possibility exists with ecto nicotinamide adenine dinucleotide oxidase disulfide-thiol exchanger 2 (ENOX2), a surface protein shed by cancer cells that is then analyzed by electrophoresis to determine the site of origin. It is then treated with a capsule of decaffeinated green tea and capsicum. Of 110 healthy and apparently cancer-free volunteers, aged 40 to 84 years, 40% had ENOX2 cells detected. The cancers diagnosed were non–small cell lung (20%), breast (16%), colorectal (9%), and blood cell, ovarian, prostate, and cervix (each at 7%). Twelve patients were not retested, and in 5 retesting was done at 1 year. After 3 to 17 months of treatment, ENOX2 was not detected in 94% of patients. In 2 patients, a non–small cell lung cancer and lymphoma were diagnosed; but the patients declined treatment, and the diseases became manifest at 36 and 10 months. As opposed to detection by imaging when billions of tumor cells are present and lesions are larger, ENOX2 is detected when lesions are pinpoint (only 2 million cells).[57]

Whether this will be confirmed in further testing is unknown, but tests like this combine the earliest detection with natural plant nutrients to prevent tumor growth and detection. This practice combines prevention and true early detection.

SUMMARY

Preventing cancer has much to offer. Aside from plummeting health care costs, we might enjoy a healthier life free of cancer and chronic disease. Prevention requires the adoption of healthier choices and a moderate amount of exercise. The supporting evidence is observational, clinical, and partly common sense. Further investigations reveal several substances in WFPBD that have protective affects as well as an inhibitory effect on tumor development.[83–85] For CaP, the basis of cure remains a century old operation that rarely cures. Data notwithstanding, surgeons continue the effort to cure by resection and oncologists pursue a never-ending combination of drugs, while patients languish and suffer before the inevitable sad outcome. With little to lose, prevention deserves center stage and additional studies. Because the ever-increasing health care budget is not sustainable, emphasizing a healthy lifestyle and observing its impact on chronic disease and cancers would take years not decades to determine its efficacy.

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