15. Screening for Pancreatic Cancer

RECOMMENDATION

Routine screening for pancreatic cancer in asymptomatic persons, using abdominal palpation, ultrasonography, or serologic markers, is not recommended.

Burden of Suffering

Cancer of the pancreas is the fifth leading cause of cancer deaths in the U.S., accounting for an estimated 27,000 deaths in 1995 (8.4 deaths/100,000 persons).[1,1a] Worldwide, the age-adjusted incidence and mortality of pancreatic cancer have been increasing since the 1930s,[2,3] although in the U.S. these rates have declined since the early 1970s.[1,1a] Incidence rates may be overestimated, because an important proportion of pancreatic cancer diagnoses (as many as half in some studies) are not histologically confirmed.[4] Pancreatic cancer is more common in men, blacks, cigarette smokers, and older persons (the majority of cases being diagnosed between ages 65 and 79).[1,2,3,5] The risk of pancreatic cancer is increased in patients with diabetes, including those with long-standing (≥5 years) diabetes.[5a] Familial aggregations of pancreatic cancer are rare but have been described.[2,6]

Since initial symptoms are usually nonspecific (e.g., abdominal pain and weight loss) and are frequently disregarded, some 80–90% of patients have regional and distant metastases by the time they are diagnosed.[5,7] Only 3% of the 24,000 patients annually diagnosed with pancreatic cancer live more than 5 years after diagnosis.[1,1a] Of pancreatic adenocarcinomas, which account for more than 90% of all pancreatic neoplasms,[5] only about 4–16% are resectable at diagnosis,[4,8–12] and the 5-year survival rate is less than 1%.[7] In addition, 5-year survival does not indicate cure, since further decrements in survival occur after 5 years.[13,14]

Accuracy of Screening Tests

Adenocarcinoma is the principal form of pancreatic neoplasm for which screening has been considered; in this chapter, "pancreatic cancer" refers to adenocarcinoma. There are no reliable screening tests for detecting pancreatic cancer in asymptomatic persons. The deep anatomic location of

the pancreas makes detection of small localized tumors unlikely during the routine abdominal examination. Even in patients with confirmed pancreatic cancer, an abdominal mass is palpable in only 15–25% of cases.[4,5,15,16]

Imaging procedures such as magnetic resonance imaging and computed tomography are too costly to use as routine screening tests, while more accurate tests such as endoscopic retrograde cholangiopancreatography and endoscopic ultrasound are inappropriate for screening asymptomatic patients due to their invasiveness.[17,18] Abdominal ultrasonography is a noninvasive screening test, but there is little information on the efficacy of abdominal ultrasound as a screening test for pancreatic cancer in asymptomatic persons. In symptomatic patients with suspected disease it has a reported sensitivity of 40–98% and a specificity as high as 90–94%.[15,19,20] Conventional ultrasonography is limited by visualization difficulties in the presence of bowel gas or obesity and by its range of resolution (2–3 cm).[7,18,20] Even tumors <2 cm in diameter are frequently associated with metastatic disease,[8,11,21] thus limiting the ability of ultrasound to detect early disease.

Most persons with pancreatic malignancy have elevated levels of certain serologic markers such as CA19-9, peanut agglutinin, pancreatic oncofetal antigen, DU-PAN-2, carcinoembryonic antigen, α-fetoprotein, CA-50, SPan-1, and tissue polypeptide antigen.[22–25] None of these markers is, however, tumor specific or organ specific;[25] elevations of various serologic markers also occur in significant proportions of persons with benign gastrointestinal diseases or malignancies other than pancreatic cancer.[17,22,24,25] Most of these markers have been studied exclusively in high-risk populations, such as symptomatic patients with suspected pancreatic cancer. CA19-9 has probably achieved the widest acceptance as a serodiagnostic test for pancreatic carcinoma in symptomatic patients, with an overall sensitivity of approximately 80% (68–93%) and specificity of 90% (73–100%); sensitivity was highest in patients with more advanced disease.[23,24] Among healthy subjects, CA19-9 has good specificity (94–99%)[26–28] but nevertheless generates a large proportion of false-positive results due to the very low prevalence of pancreatic cancer in the general population.[29] A study of a mass screening of more than 10,000 asymptomatic persons for pancreatic cancer in Japan,[30] using either ultrasonography alone or CA19-9 plus elastase-1, found the likelihood of pancreatic cancer given a positive screening test to be 0.5%; only one of the four cancers discovered could be curably resected.

The predictive value of a positive test could be improved if a population at substantially higher risk could be identified. Diabetes mellitus in older adult patients might be useful as a marker for a population at high risk of having pancreatic cancer.[3,31,32] Cohort studies have reported incidences of pancreatic cancer among diabetic patients ranging from 51 to

166/100,000 person-years.[5a] Studies evaluating screening efficacy might therefore be warranted in this population.

Effectiveness of Early Detection

Evidence that early detection can lower morbidity or mortality from pancreatic cancer is not conclusive. The reported 5-year survival for localized disease based on 1983–1990 national data is only 9%, not substantially higher than the 5-year survival with regional (4%) and distant (2%) metastases.[1a] A comprehensive review of published reports on surgical resection of pancreatic cancer estimated an overall 5-year survival rate of 8% for small tumors without evidence of local or distant spread.[8] In part, this low rate may reflect the fact that a proportion of patients with localized disease cannot be operated on because of concomitant medical problems, advanced age, or other reasons.[10,11,13] Patients who have small localized tumors that are resected for attempted cure, which account for only 4–16% of the total, may have better 5-year survival rates (as high as 37–48% in the most experienced centers),[8–13,21,33] although the designs of most studies of surgical outcome suffer from lead-time, length, and selection biases. The morbidity associated with surgical resection is high (15–53%), but perioperative mortality is now less than 7% in the hands of experienced surgeons.[8,9,13,33,34]

Reports on the effectiveness of adjuvant external beam and/or intraoperative radiotherapy in improving survival among curatively resected patients, using historical controls, have yielded inconsistent results.[35–37] In one small randomized controlled trial,[38] corroborated by a subsequent case series by the same authors,[39] an adjuvant treatment program using combined radiation and chemotherapy following curative resection was associated with a significant median survival advantage of 9 months and a 5-year survival advantage of 14.5% in treated versus control cases; however, the study was closed early due to poor subject accrual and it did not control for the substantially greater frequency of clinic visits by cases. Adverse effects of combined radiation and chemotherapy include leukopenia and gastrointestinal toxicity.[38,40] Intraoperative radiotherapy frequently causes gastrointestinal bleeding, which may be life-threatening.[37] Additional randomized controlled trials of adjuvant therapy are needed to confirm its effectiveness in improving survival in patients with early pancreatic carcinoma. New modalities being explored include immunotherapy[41] and hormonal therapy.[42]

Primary Prevention

Cigarette smoking has been consistently associated with a modestly increased risk of pancreatic cancer in numerous cohort and case-control

studies of populations in the U.S., Canada, Europe, and Japan.[3,43–46] A clear dose-response relationship has not been demonstrated, however, nor have the biologic mechanisms underlying this association been adequately delineated. Cohort and case-control studies suggest that former smokers have a decreased risk of pancreatic cancer compared with current smokers,[43,44,47–49] but estimates of the duration of abstinence required to show a reduction in risk have varied from as few as 1–3 years to as many as 10–20 years, and some studies have found no risk reduction at all associated with smoking cessation.[43,45] In addition, a number of these studies suffer from selection, misclassification, and other biases. Although the causal relationship between smoking and pancreatic cancer requires further study, counseling patients to discontinue smoking (see Chapter 54) is easily justified by its established efficacy in preventing other malignancies (e.g., lung cancer), coronary artery disease, and other serious disorders.

Several cohort studies and many population-based case-control studies have reported positive associations between pancreatic cancer and dietary factors such as meat, eggs, carbohydrates, refined sugar, cholesterol, fat, and total calorie intake, as well as negative (protective) associations with intake of vegetables and fruits.[3,46,48,50–56] However, study results are inconsistent; many studies suffer from selection, misclassification, and other biases; and large numbers of comparisons make significance testing problematic. Further research to define nutritional risk factors for pancreatic cancer is therefore needed. Studies of the relationship between increased alcohol consumption and pancreatic cancer have yielded inconsistent results;[3,45–48,57,58] few have adequately assessed level and duration of intake, or evaluated the possibility of a link between alcohol, pancreatitis, and pancreatic cancer. Current epidemiologic evidence does not support an association between pancreatic cancer and coffee consumption.[3,58,59]

Recommendations of Other Groups

No groups recommend routine screening for pancreatic cancer in asymptomatic persons. The Canadian Task Force on the Periodic Health Examination recommends against such screening.[60]

Discussion

Given the lack of evidence for improved outcome with early detection of pancreatic cancer, the invasive nature of diagnostic tests likely to follow a positive screening test (e.g., endoscopic ultrasound, laparotomy), and the fact that most positive screening tests would be false positives, screening for pancreatic cancer cannot be recommended at this time. Primary prevention of pancreatic cancer may be possible through clinical efforts directed at the use of tobacco products.

CLINICAL INTERVENTION

Routine screening for pancreatic cancer in asymptomatic persons, using abdominal palpation, ultrasonography, or serologic markers, is not recommended ("D" recommendation). All patients should be counseled regarding use of tobacco products (see Chapter 54). Counseling to reduce fat and cholesterol intake and to increase intake of fruits and vegetables may be recommended on other grounds (see Chapter 56).

The draft update of this chapter was prepared for the U.S. Preventive Services Task Force by Carolyn DiGuiseppi, MD, MPH.

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