Pancreatic cancer is still a difficult diagnostic and therapeutic challenge. Its prognosis is extremely poor because the disease is generally recognized at a very advanced stage and its clinical course is very rapid. Surgery is the only curative treatment for pancreatic cancer and outcome is related mainly to tumor stage. This aggressive approach is effective only if the tumors are detected at an early stage. Early symptoms of pancreatic carcinoma, including weight loss, anorexia, epigastric discomfort and back pain, are often non-specific and vague (1), so diagnosis may be considerably delayed. In many patients with small pancreatic cancer which has a possibility of cure, the tumor was incidentally detected in laboratory tests and/or imaging. We must try to convert such incidental discovery into more certain diagnosis.

The mortality rate from pancreatic cancer, which is almost equal to the incidence of this cancer, in Japan was 14.9 per 100 000 in 1999. Any mass screening for pancreatic cancer is not feasible in the general population because of the low prevalence of the disease. To devise an effective screening program, the definition of a high-risk group and the development of simple, inexpensive and reliable diagnostic tests are necessary.

RISK FACTORS AND ASSOCIATED MEDICAL CONDITION

Several risk factors for pancreatic cancer have been identified. Among them, smoking is the best corroborated risk factor. The risk of smokers developing pancreatic cancer is 1.6–3.1 times higher than that of non-smokers (2). A dose–response relationship between smoking and pancreatic cancer has been observed.

Alcohol consumption has been reported as a risk factor for pancreatic cancer in studies in Norway and Finland. However, subsequent studies showed no significant relationship between alcohol abuse and pancreatic cancer (3), so the relationship between them remains uncertain. A relationship between coffee consumption and pancreatic cancer has also been reported. However, most subsequent studies showed either a weak or no relationship between coffee consumption and the incidence of pancreatic cancer (4).

Several medical conditions have been also indicated as predisposing conditions for the development of pancreatic cancer. Diabetes mellitus has been seen as both an early manifestation of the disease and as a predisposing factor. A meta-analysis of studies published between 1975 and 1994 showed an increased frequency of pancreatic cancer in patients with long-standing diabetes. However, a more recent study showed no correlation between pancreatic cancer and a long history of diabetes; a relationship would be expected if diabetes functioned as a causative mechanism (5). The relationship between the two conditions remains unclear.

Chronic pancreatitis has also been linked with pancreatic cancer. Pancreatitis may also appear both as a secondary condition induced by cancer and as a predisposing factor. When studies have considered only long-standing pancreatitis, there appears to be a stronger relationship between pancreatic cancer and familial pancreatitis than with acquired pancreatitis resulting from alcoholism (2).

A history of gastrectomy has been reported as a relative risk for pancreatic cancer. It was suggested that the loss of ability to metabolize carcinogens or a loss of pancreatic regulation by the stomach induces the carcinogenic condition. Several hereditary syndromes also linked to pancreatic cancer include Lindau’s disease, familial relapsing pancreatitis, Gardner’s syndrome, neurofibromatosis, ataxia–telangiectasia and Lynch syndrome II.

SERUM MARKERS

Attempts to detect pancreatic cancer at earlier stages by measuring circulating serum markers would be very useful. Among the wide variety of serum markers proposed for use in diagnosing pancreatic cancer are tumor-associated antigens, enzymes and hormones.

CA 19-9 is thought to be the most reliable serum marker for the diagnosis of pancreatic cancer (6). This marker is effective for conducting tests on symptomatic patients, a predictor of recurrence after treatment and a prognostic factor. However, levels of CA19-9 are frequently normal in the early stages of pancreatic cancer and high levels are also present in patients with other cancers, particularly those affecting the bile duct and colon. Therefore, CA19-9 is not suitable for use in screening. Carcinoembryonic antigen is also widely used as a marker, but it has a low sensitivity and is elevated in many other malignant and benign conditions, which reduces its value in the diagnosis and care of patients with pancreatic cancer.

The diagnostic accuracy is not sufficient in any single serum marker. Therefore, several combined assays or combined use of serum tests and imaging diagnoses have been tried in an
attempt to improve this situation. However, the results are not effective for screening an asymptomatic population from both clinical and economic perspectives.

IMAGING DIAGNOSIS

Computed tomography (CT) is the most frequently used imaging modality for the initial diagnosis, staging, assessment of response to therapy and evaluation of medical complications related to pancreatic cancer, besides screening. The helical CT system with the bolus enhanced technique, which provides thin section, motion-free images through the entire pancreas, improves the accuracy of CT in evaluating pancreatic diseases.

Magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS) are rapidly evolving modalities for the detection, staging and surgical assessment of pancreatic cancer. EUS has been reported to be the most sensitive modality for the detection of pancreatic cancer, although it is usually performed under anesthetic and the results are operator dependent. Regarding MRI, further refinement of the technique is being pursued. Magnetic resonance cholangiopancreatography (MRCP) is a newly developed technique that provides optimum contrast between the hyperdense signal of bile and pancreatic juice and hypodense signal of solid organs and blood. MRCP is non-invasive and does not require the injection of contrast medium, offering advantages over endoscopic retrograde cholangiopancreatography (ERCP). MRCP is replacing diagnostic ERCP and percutaneous transhepatic cholangiography for the evaluation of the biliary and pancreatic ducts (7). Thus, MRCP reduces the patient’s burden. However, this technique has not improved the early diagnosis of pancreatic cancer to date.

Transabdominal ultrasound (US) is used as the first-step examination for subjects suspected of pancreatic carcinoma with respect to convenience, risks, availability and costs. Tumors of more than 2 cm, dilated biliary and pancreatic ducts and extrapancreatic spread are detectable by this means. US was introduced as a diagnostic tool for pancreatic diseases more than 20 years ago. However, the overall survival rate of patients with pancreatic cancer has not been improved since the introduction of US.

In this issue, Tanaka et al. (8) assess retrospectively whether the dilatation of the main pancreatic duct on US could be identified as a sign of pancreatic ductal adenocarcinoma. Between 39 patients with pancreatic cancer and a normal cohort, they compared the proportions having >2 mm dilatation and found significant differences in its incidence and in the odds ratio. They considered that dilatation of the main pancreatic duct may possibly be a sign of the incidence of pancreatic carcinoma and is thus an appropriate target for screening for pancreatic carcinoma. This report is interesting considering the lack of useful measures to detect early pancreatic cancer at the present time.

To confirm this hypothesis, a prospective comparison of the relative risk of developing pancreatic carcinoma between patients with slight dilatation of the main pancreatic duct and others without it is necessary. If the hypothesis is valid, a program should be developed that indicates how patients who have main pancreatic duct dilatation but do not have a tumor are managed. The diagnostic accuracy and impact on survival of the criteria need to be considered.

Recently, Kimura et al. reported that small cystic lesions, which were presumed to be dilatation of the pancreatic branch duct, were observed adjacent to a small pancreatic cancer (9). These cystic lesions could possibly be a target for the screening of pancreatic cancer. Both reports suggested that a hypersecreting mechanism may preclude the occurrence of cancer and induce slight dilatation of the pancreatic duct, which appears as slight dilatation of the main pancreatic duct or small pancreatic cysts. The size of the main pancreatic duct and the presence of cystic lesions are more easily detected than solid lesions by US. Other imaging tools, especially MRCP which is less invasive and sensitive for cystic lesions, may also demonstrate these findings. Thus, if this hypersecreting mechanism is true, these findings could become a diagnostic clue in detecting pancreatic cancer at a much earlier stage.

If a risk factor or a preceding sign heralding pancreatic carcinoma could be identified, additional examinations by recent sophisticated modalities may confirm whether cancer is present, even if the tumor is small. Surgery may contribute to such early-stage patients and the prognosis of this disease could be improved. We must pursue the development of an effective screening system to detect early pancreatic cancer.

References