Short-term Results of a Magnetic Resonance Imaging–Based Swedish Screening Program for Individuals at Risk for Pancreatic Cancer

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IMPORTANCE
Pancreatic cancer is the fourth leading cause of cancer-related death in Western countries. In approximately 10% of all patients with pancreatic cancer, it is possible to define a positive family history for pancreatic cancer or for one of the other related genetic syndromes. A screening program for individuals at risk is recommended; however, surveillance modalities have not been defined yet.

OBJECTIVE
To analyze the short-term results of a prospective clinical surveillance program for individuals at risk for pancreatic cancer using a noninvasive magnetic resonance imaging (MRI)-based screening protocol.

DESIGN, SETTING AND PARTICIPANTS
A prospective observational study of all patients with a genetic risk for developing pancreatic cancer who were referred to Karolinska University Hospital between January 1, 2010, and January 31, 2013, using an MRI-based surveillance program. All patients were investigated for the most common genetic mutations associated with pancreatic cancer.

EXPOSURE
A noninvasive MRI-based screening protocol.

MAIN OUTCOMES AND MEASURES
The ability of MRI to identify potential precancerous or early cancers in individuals at risk for pancreatic cancer.

RESULTS
Forty patients (24 women and 16 men) were enrolled. The mean age was 49.9 years. The mean length of follow-up was 12.9 months. The numbers of relatives affected by pancreatic cancer were 5 in 2 patients (5%), 4 in 5 patients (12.5%), 3 in 17 patients (42.5%), 2 in 14 patients (35%), and 1 in 2 patients (5%). In 4 patients (10%), a p16 mutation was found; in 3, a BRCA2 mutation (7.5%); and in 1, a BRCA1 mutation (2.5%). In 16 patients (40%), MRI revealed a pancreatic lesion: intraductal papillary mucinous neoplasia (14 patients, 35%) and pancreatic ductal adenocarcinoma (2 patients, 5%). One patient had a synchronous intraductal papillary mucinous neoplasia and pancreatic ductal adenocarcinoma. Five patients (12.5%) required surgery (3 for pancreatic ductal adenocarcinoma and 2 for intraductal papillary mucinous neoplasia), while the remaining 35 are under continued surveillance.

CONCLUSIONS AND RELEVANCE
During a median follow-up of approximately 1 year, pancreatic lesions were detected in 40% of the patients, of whom 5 underwent surgery. Although the study time was relatively short, the surveillance program in individuals at risk seems to be effective.

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Pancreatic cancer is the fourth leading cause of cancer-related death in the United States and many Western countries. Because the incidence and mortality rates are almost identical, pancreatic cancer can be considered a global lethal disease. Although treatment has improved, the resection rate in patients with ductal adenocarcinoma remains around 30%, and the 5-year survival rate is less than 20%. Because of the low incidence of pancreatic cancer in the general population, population-based screening is not considered cost-effective. In the past 2 decades, data from the literature have demonstrated that pancreatic cancer can be the phenotypic expression of some of the known genetic syndromes, and they have led to the identification of a familial risk factor for the development of pancreatic cancer. In the latter condition, called familial pancreatic cancer (FPC), the increased risk is associated with the number of affected family members. According to prospective epidemiological studies, a positive family history of pancreatic cancer is present in approximately 10% of all consecutive probands. The identification of a population at risk; the suggestion that early surgical treatment of pancreatic cancer can improve the prognosis; and, in particular, the identification of precursor lesions, such as pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasia (IPMN), which are associated with the natural history of FPC, contributed to the development of national and international guidelines for the surveillance of individuals at increased risk. However, to the present day, consensus has not been reached regarding inclusion criteria for a clinical surveillance program, screening modalities, and target lesions. Traditionally, individuals with a 10-fold relative risk for developing pancreatic cancer were considered eligible for entering a screening program. However, the International Cancer of the Pancreas Screening Consortium suggested inclusion of individuals with only a 5-fold relative risk in a surveillance program. Early pancreatic cancer, IPMN lesions, and PanIN lesions are considered the target lesions of clinical screening, although the actual detection of PanIN lesions during a surveillance program remains debatable and uncertain. The imaging modality techniques used in the existing programs are, alone or in combination, magnetic resonance imaging (MRI), computed tomography, endoscopic ultrasonography (EUS), and endoscopic retrograde cholangiopancreatography. Previous recommendations demonstrated a tendency to use low-aggressive modalities such as MRI and EUS. The results of clinical studies that have been conducted so far are inconclusive and difficult to compare owing to the use of different screening modalities and inclusion criteria. The yield of FPC screening programs reported in the literature ranges from 1.3% to 50%. To our knowledge, the cost-effectiveness of a surveillance program for FPC has not been demonstrated yet.

The aim of this study was to analyze the short-term results of a prospective clinical surveillance program for individuals at risk for pancreatic cancer using a noninvasive MRI-based screening protocol.
a 6-month follow-up with MRI was recommended. Every patient underwent genetic testing for the most common gene mutations associated with FPC (BRCA1, BRCA2, and p16).

**Target Lesions of Screening**
Solid nodules and suspected IPMN lesions were considered the target lesions of the screening program. Owing to the low specificity and sensitivity of the available techniques for the detection of PanIN lesions and/or associated lobulocentric atrophy, PanIN lesions were not considered a screening target.

**Surgical Treatment of Suspected (Pre-)Malignant Lesions**
Every patient with a positive finding on screening was discussed at the pancreatic multidisciplinary conference. Patients with suspected cancer were treated with a radical surgical procedure. Patients with a suspected premalignant lesion (IPMN) underwent a radical or parenchyma-sparing surgical resection according to guidelines. By principle, no patient underwent total pancreatectomy as a purely preventive measure.

**Statistical Analysis**
Comparison of continuous variables was performed using a t test. Comparison of categorical variables was done by χ² analysis using GraphPad Prism Software.

**Results**
Sixteen men (40%) and 24 women (60%) were included in the study. The mean age was 49.9 years (range, 23-76 years). In 38 of the study individuals, the increased risk was based on a history of FPC (95%), while in 2 more patients (5%) with a single first-degree relative with pancreatic ductal adenocarcinoma (PDAC), a BRCA2 syndrome had been genetically confirmed.
tail had progressed (increased cyst size up to 2 cm), and the main pancreatic duct had become dilated. Consequently, the patient underwent total pancreatectomy, and histology confirmed the presence of a noninvasive mixed-type IPMN lesion with high-grade dysplasia in the tail region and synchronous PDAC (T3N0M0) in the pancreatic head. Two additional patients were treated for a solid pancreatic lesion, which was histologically confirmed to be PDAC. The first patient was treated for an early cancer (T1N0M0). The second patient had missed 1 of the yearly MRI examinations and developed unspecific abdominal pain a few months before the next control was due. The MRI showed an advanced pancreatic cancer in the pancreatic head (T4N1M0) (Figure 4).

### Table 1. Characteristics of Patients With Positive Findings on Screening

<table>
<thead>
<tr>
<th>Patient/ Age, y/Sex</th>
<th>No. of Relatives Affected</th>
<th>Genetic Mutation</th>
<th>Time to First Detection, mo</th>
<th>Diagnosis at First Detection, mm</th>
<th>Pseudocyst Size at First Detection, mm</th>
<th>Pancreatic Duct Size at First Detection, mm</th>
<th>Progression Under Follow-up (Yes/No)</th>
<th>Type of Progression</th>
<th>Surgery (Yes/No)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Affected</td>
<td>First Degree</td>
<td>Second Degree</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPC 1/54/F</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>p16</td>
<td>0</td>
<td>BD-IPMN</td>
<td>Normal</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>FPC 2/75/M</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>None</td>
<td>0</td>
<td>Mixed-type IPMN</td>
<td>8</td>
<td>5</td>
<td>None</td>
</tr>
<tr>
<td>FPC 3/48/F</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>None</td>
<td>0</td>
<td>MD-IPMN</td>
<td>5</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>FPC 4/47/M</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>None</td>
<td>0</td>
<td>BD-IPMN</td>
<td>8</td>
<td>Normal</td>
<td>Increased cyst size (15 mm) No</td>
</tr>
<tr>
<td>FPC 5/62/F</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>None</td>
<td>0</td>
<td>BD-IPMN</td>
<td>10</td>
<td>Normal</td>
<td>Yes</td>
</tr>
<tr>
<td>FPC 6/49/M</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>None</td>
<td>0</td>
<td>BD-IPMN</td>
<td>10</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>FPC 7/61/M</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>None</td>
<td>0</td>
<td>BD-IPMN</td>
<td>9</td>
<td>Normal</td>
<td>Increased cyst size (12 mm) No</td>
</tr>
<tr>
<td>FPC 8/49/F</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>None</td>
<td>0</td>
<td>MD-IPMN</td>
<td>5</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>FPC 9/59/F</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>None</td>
<td>12</td>
<td>Mixed-type IPMN</td>
<td>9</td>
<td>5</td>
<td>None</td>
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<tr>
<td>FPC 10/72/F</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>BRCA1</td>
<td>0</td>
<td>BD-IPMN</td>
<td>12</td>
<td>Normal</td>
<td>None</td>
</tr>
<tr>
<td>FPC 11/76/M</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td></td>
<td>24</td>
<td>Mixed-type IPMN</td>
<td>10</td>
<td>5</td>
<td>Yes</td>
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<tr>
<td>FPC 12/47/M</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>None</td>
<td>26</td>
<td>BD-IPMN</td>
<td>5</td>
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<td>None</td>
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<tr>
<td>FPC 13/49/F</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>None</td>
<td>0</td>
<td>PDAC</td>
<td>NA</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>FPC 14/71/M</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>None</td>
<td>0</td>
<td>BD-IPMN</td>
<td>18</td>
<td>Normal</td>
<td>None</td>
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<tr>
<td>FPC 15/44/M</td>
<td>2</td>
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<td>0</td>
<td>None</td>
<td>36</td>
<td>PDAC</td>
<td>NA</td>
<td>None</td>
<td>Yes</td>
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<tr>
<td>FPC 16/75/F</td>
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<td>2</td>
<td>0</td>
<td>None</td>
<td>0</td>
<td>BD-IPMN</td>
<td>23</td>
<td>Normal</td>
<td>Increased cyst size (30 mm) Yes</td>
</tr>
</tbody>
</table>

Abbreviations: BD, branch duct; F, female; FPC, familial pancreatic cancer; IPMN, intraductal papillary mucinous neoplasia; M, male; MD, main duct; NA, not applicable; PDAC, pancreatic ductal adenocarcinoma.

### Table 2. General Characteristics of Individuals With Positive or Negative Screening Results

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Screening Positive (n = 16)</th>
<th>Screening Negative (n = 24)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>58.6</td>
<td>44.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>8</td>
<td>.20</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>18.7</td>
<td>4.1</td>
<td>.30</td>
</tr>
<tr>
<td>Mean No. of relatives affected</td>
<td>2.9</td>
<td>2.7</td>
<td>.50</td>
</tr>
</tbody>
</table>

Figure 2. Pattern of Pancreatic Finding Identified by the Screening Protocol
Of these, 7 (63.6%) had a stable finding over a median follow-up time of 9.4 months (range, 0-36 months). Four more individuals (36.4%) showed limited, nonsignificant progression of the lesion during a median follow-up of 19 months (range, 12-26 months).

**Discussion**

While several national and international societies and consortia recommend a surveillance program for individuals at risk for developing pancreatic cancer,\(^{15-17}\) to our knowledge, the actual efficacy of such preventive programs has not been demonstrated so far.

In principle, an efficient surveillance program should allow the detection of early cancer or premalignant lesions. Furthermore, it should be cost-effective and based on noninvasive investigations.\(^{16,17}\) The screening program proposed in this study is based on MRI only as a first investigational modality because it is noninvasive and low cost.

Interpretation of the results of this study requires careful consideration. The high detection rate of lesions in this study series (40%) is in line with results from previous studies and confirms that high-risk individuals have a higher tendency to develop premalignant precursor lesions.\(^{14,29}\) The observation that patients with a positive finding on screening were older than those with negative screening results confirms that in high-risk individuals, the risk for developing pancreatic lesions is age related. It therewith validates the International Cancer of the Pancreas Screening Consortium guidelines\(^{17}\) regarding the suggested age at which to commence screening. Most lesions were suspected IPMNs, as has been reported previously by others.\(^{14,28}\) However, the real benefit to the individual of early detection of these lesions remains controversial, in particular because the natural history of IPMNs is not well known and may be shorter than in the general population.\(^{14}\)
In the 5 patients who underwent surgery in this study, the preoperative diagnosis was confirmed histologically. In 2 of the patients, surgery had been undertaken for noninvasive IPMNs of mixed type and multifocal BD type, with intermediate-grade dysplasia. In 3 additional patients, PDAC had been the indication for surgical resection. In 1 of these patients, screening had detected a small BD-IPMN lesion in the tail of the pancreas, which after 2 years of 6-month-interval follow-ups showed progression to mixed-type IPMNs and development of a synchronous cancer in the head of the pancreas. In a second patient, screening had allowed resection of an early cancer (T1N0M0). However, in a third patient who had missed the second planned yearly surveillance investigation, cancer was detected at an already advanced stage. Therefore, in only 3 of the 5 patients who underwent resection, or in 7.5% of the entire patient series, surgery was a prophylactic measure or early cancer treatment. Furthermore, because in 2 of these patients the resected lesion was a noninvasive IPMN lesion with only intermediate-grade dysplasia, the real benefit to patients is not really known. One patient who underwent surgery had developed an interval cancer, which screening had failed to detect at an early stage and which must have progressed rapidly during the 6-month intervals between 2 successive MRI investigations. Finally, the last patient had not been compliant with the study protocol and was diagnosed as having operable but locally advanced disease. In how far the inclusion in this screening protocol of EUS as a baseline investigation would allow earlier cancer detection is controversial. Several studies in the literature have shown that MRI can be useful for the detection not only of small cystic lesions, but even of early solid tumors of the pancreas. Furthermore, data in the current study demonstrate that detection of early pancreatic cancer (T1N0M0) was possible in 1 of the patients when using MRI only. Conversely, even in a patient who was under surveillance for IPMNs with MRI and EUS at 6-month intervals, PDAC was detected only at stage T3N0M0. Further, it has to be acknowledged that EUS is significantly less frequently used in Europe than in the United States. Hence, MRI-based screening is likely to find more acceptance in European pancreatic cancer centers. Moreover, MRI has the potential benefit of being less dependent on investigator expertise than EUS.

In this study, PanIN lesions were excluded as a screening target. Although PanINs are well established as precursor lesions, the macroscopic correlate of these lesions (ie, lobulo-centric atrophy) is nonspecific. Moreover, even in the International Cancer of the Pancreas Screening Consortium guidelines, agreement regarding the detection and treatment of PanINs has not been reached.

Conclusions

An MRI-based protocol for the surveillance of individuals at risk for developing pancreatic cancer seems to detect cancer or premalignant lesions with good accuracy. The exclusive use of MRI can reduce costs, increase availability, and guarantee the safety of the individuals under surveillance compared with protocols that are based on more aggressive methods. However, because of the small number of patients and the divergent results, this study did not allow evaluation of the efficacy of MRI as a single screening modality. One principal obstacle to effective surveillance, encountered in the current study as in previous studies, is the lack of knowledge about the natural history of premalignant lesions of the pancreas, as well as the lack of criteria for reliable prediction of progression and outcome of these lesions in individual high-risk patients.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: None reported.

REFERENCES

Screening Strategies for Pancreatic Cancer in High-Risk Patients

Opportunities to Make a Real Impact

But Many Questions and Challenges Still Ahead

Mark S. Talamonti, MD

In this issue of JAMA Surgery, Del Chiaro and colleagues report the early results of a magnetic resonance imaging (MRI)-based Swedish screening program for asymptomatic patients with an increased risk for familial pancreatic cancer. The goals of this study were to determine whether a high-risk population of patients could be screened in a cost-efficient fashion with a noninvasive screening test and whether this strategy yielded enough premalignant lesions and early cancers to justify the strategy.

Inclusion criteria met the current recommendations of the International Cancer of the Pancreas Screening Consortium for high-risk patients, namely, individuals from a familial pancreatic cancer kindred with at least 2 affected first-degree relatives; patients with Peutz-Jeghers syndrome; and p16, BRCA1, or BRCA2 mutation carriers. Magnetic resonance imaging without computed tomographic scans or endoscopic ultrasonography were the screening tools of choice, and the other studies used only selectively for presurgical planning. The diagnostic yield for a pancreatic lesion including solid nodules, cysts, and isolated main duct dilation was 40%. Five patients (12.5%) required surgery, 3 for pancreatic cancers (7.5%) and 2 for intraductal papillary mucinous neoplasms with intermediate dysplasia. The sensitivity of MRI for detecting a significant radiographic finding is higher than earlier, single-modality studies but still not as high as reports combining MRI and endoscopic ultrasonography. However, the diagnostic