DARIO SORRENTINO, MD, FRACP
IBD Center
Division of Gastroenterology
Virginia Tech Carilion School of Medicine
Roanoke, Virginia

Department of Clinical and Experimental Medical Sciences
University of Udine School of Medicine
Udine, Italy

VU Q. NGUYEN, MD
IBD Center
Division of Gastroenterology
Virginia Tech Carilion School of Medicine
Roanoke, Virginia

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Conflicts of interest
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Most current article

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Screening of Individuals at High Risk for Pancreatic Cancer

Dear Editor:

Performing a meta-analysis of 19 cohort studies that included 1660 patients, Corral et al[1] recently evaluated the effectiveness of screening in families at risk for developing pancreatic cancer. A total of 59 (3.5%) high-risk lesions were found, including 43 pancreatic cancers and 16 high-risk precursor lesions (ie, high-grade pancreatic intraepithelial neoplasia [PanIN] or cystic lesions), and the authors calculated an incidence rate for high-risk lesions of 0.47 per 100 patient-years. A total of 257 (15%) patients underwent pancreatic surgery for a suspected lesion.

We would like to revisit the outcomes of 2 large studies that were not included in this meta-analysis. In a multicenter European study, published in 2016, we evaluated the results of screening in a large cohort of individuals at high risk for familial pancreatic cancer (FPC), including carriers of a *CDKN2A* mutation.[2]. Screening of 214 individuals with FPC, with a mean follow-up of 34 months, identified only 1 (0.47%) patient with pancreatic cancer. Thirteen patients underwent surgery due to a cystic lesion, 4 (1.9%) of whom harbored high-risk lesions. Screening of 178 Dutch *CDKN2A* mutation carriers, with a mean follow-up time of 53 months, detected pancreatic cancer in 13 (7.3%) patients but no high-risk precursor lesions (PanIN3 or high-grade intraductal papillary mucinous neoplasm) were found. The resection rate was 75% and the 5-year survival rate was 24%. In a subsequent study from the same centers, we evaluated the age at detection of high-risk lesions in 253 individuals from mainly FPC families (median follow-up 28 months).[3] A total of 21 individuals underwent surgery and a relevant lesion was found in 6 (2.4%) individuals (2 pancreatic ductal adenocarcinomas, 3 PanIN3s, and 1 high-grade intraductal papillary mucinous neoplasm). Because no high-risk lesions were detected below 50 years of age, we recommend that screening in FPC commences at this age.

Corral et al[1] calculated that 135 individuals needed to be screened to identify 1 individual with a high-risk lesion, the number varying from 250 patients in the case of a *BRCA1* or *BRCA2* mutation to 51 patients in the case of a *CDKN2A* mutation. These numbers clearly indicate that large groups of individuals would have to participate in an intensive and burdensome screening program. Moreover, as only 59 of 257 operated patients had a high-risk lesion, 198 patients underwent major pancreatic surgery unnecessarily, a procedure associated with morbidity and mortality rates of up to 40% and 2%–4%, respectively.[1] Extrapolating these figures, between 4 and 8 individuals may have died due to surgical complications.

In view of these considerations, surveillance of the pancreas remains a potentially dangerous form of screening that should be limited to expert centers and only performed in a research setting.[4] In addition, the program should only be offered to individuals with a substantially increased risk of pancreatic cancer. This was shown in a simulation study by Pandharipande et al,[5] who found that screening of low-risk individuals was associated with a reduced life expectancy, an outcome attributed to the increased discovery of insignificant lesions and subsequent unnecessary surgical intervention.

In this regard, it is problematic that the risk of pancreatic cancer is unknown for most of the gene defects associated with pancreatic cancer (eg, *BRCA1*, *PALB2*, MMR genes, *ATM*). Current recommendations on which individuals to screen are therefore only based on the expert opinion of the Pancreas Cancer Screening Consortium, see the editorial by Hart and Chari,[6] and not on objectively established risk.

To facilitate the identification of gene defects associated with pancreatic cancer development, universal testing using gene panels is currently recommended for all new pancreatic cancers.[7]

However, before initiating the large scale testing of all pancreatic cancers, evaluation of pancreatic cancer risk in carriers of various mutations is urgently needed to permit appropriate selection of individuals for screening.

In an editorial on the Corral et al[1] study, Hart and Chari[6] discussed the challenges of early detection of pancreatic cancer, referring to the Chinese proverb: "the journey of a thousand miles starts with one step." They also stated that "studies evaluating those at increased risk for pancreatic cancer because of a family history, genetic profile, and new onset diabetes represent multiple steps in the right direction." We would like to suggest that these steps are taken in the correct order.

HANS F. A. VASEN
Department of Gastroenterology & Hepatology
Leiden University Medical Center
Leiden, the Netherlands

DETLEF K. BARTSCH
Department of Surgery
University Hospital Marburg
Marburg, Germany

ALFREDO CARRATO
Department of Medical Oncology
Ramon y Cajal University Hospital, Ramón y Cajal Health Research Institute, Centro de Investigación Biomédica en Red Cáncer, Alcala University
Madrid, Spain

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Reply. We thank Professor Vasen and colleagues for their thoughtful commentary on our article. Indeed, we share their concerns that invasive screening tests are largely inappropriate for low-risk populations because of the relatively low yield and positive predictive values.

Pancreatic cancer remains one of the most elusive conditions to prevent. Identifying individuals with subclinical disease who can receive curative surgery is extremely difficult with current technology such as endoscopic ultrasound or magnetic resonance imaging. On the basis of studies from adults with new onset diabetes, the screening window may last only 2 or 3 years.[1] This meta-analysis was motivated by the fact that although diagnostic yield of screening high-risk individuals (HRI) is low, the survival gains can be significant if pancreatectomy can be provided safely.

We recognize that our current understanding of pancreas carcinogenesis is very limited, even in patients with significant family history or high-risk genetic mutations (HRIs). For example, we ignore if pancreas carcinogenesis is a slow linear process in which the low-grade dysplastic lesions develop years before they progress into cancer, or whether such lesions develop in an accelerated fashion. Our limited understanding comes from research cohorts of high-risk mutations (International Cancer of the Pancreas Screening [CAPS] is the most important one).

Surveillance and treatment in research cohorts are far apart from real-life practice. Participants tend to be a very homogeneous population and compliant, with close follow-up encounters. Assuming that any real-life screening program would perform in a similar fashion is illusory. Our study intended to summarize diagnostic accuracy of those programs, not to predict the performance of any particular screening program. We completely agree with Vasen et al that for now, surveillance should be limited to research protocols and registries such as CAPS.

Implementation of preventive services based solely on diagnostic accuracy has significant shortcomings. As we mention in our discussion, "The screening effectiveness should be balanced against treatment complications (ie, number needed to harm). Describing the side effects of surgery is beyond the scope of this review." We acknowledge that the risks of screening go beyond immediate complications of pancreatic surgery. Risks such as developing diabetes complications, decrease in quality of life, ethical concerns of performing surgery based on false-positive results, psychological burden, and societal cost of screening all have to be considered.

Our results can promote expenditure in imaging and surgeries in an already restrained health care system. Compared with other preventive services, HRI surveillance targets a much smaller and specific population. Identifying HRI requires a previous encounter with the health care system and should use precision medicine rather than a one-size-fits-all approach. The challenge for scaling up HRI cancer surveillance will reside in identifying and referring at-risk kindred to high-volume centers rather than completion of any particular test.

As suggested by Hart et al,[2] an attractive strategy to improve screening program impact is to enrich the screening pool with HRI at higher risk for pancreatic cancer, the false-positive rate of subsequent testing is reduced substantially, and the balance of potential benefits and harms becomes more favorable. Future studies are needed to identify additional filters that can be