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EDITORIAL

The importance of a well-structured pancreatic screening program for familial and hereditary pancreatic cancer

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In this issue of Familial Cancer, Barnes et al. describe a screening program for individuals at high risk of developing pancreatic ductal adenocarcinoma (PDAC) [1]. Approximately 3–10% of all patients with PDAC have a positive family history for this cancer [2], and 4% have an underlying gene defect, with *ATM, BRCA1 & BRCA2*, and *PALB2* being the most commonly effected genes [3–6] (Table 1). Familial pancreatic cancer (FPC) is defined by the occurrence of PDAC in two or more first-degree relatives, in the absence of an underlying gene defect [2]. The risk of developing PDAC depends on the particular gene defect (Table 1) [7–12], and in FPC, on the number of first-degree family members with PDAC.

Since the first report of pancreatic screening of high-risk individuals by Brentnall et al., several other screening studies have been completed [13]. Most studies involved FPC families, while a few included carriers of a PDAC-associated gene defect [12, 14–16]. The screening protocols used in these studies varied widely, including MRI only, both MRI and endoscopic ultrasound (EUS), or MRI with optional EUS.

Barnes et al. are to be commended on the development of a solid and well-structured clinical program [1]. Adopting a multidisciplinary approach, the program uses gene panels, appropriate genetic counseling, and a protocol that includes annual 3.0 T MRI and additional EUS in case of abnormalities. All results are discussed at a multidisciplinary PDAC conference. Five years into the program, a total of 75 individuals have participated, including 42 (56%) carriers of a PDAC-associated gene defect and 35 (44%) individuals with FPC. One cholangiocarcinoma was detected and cystic lesions were observed in 40% of cases, which is in agreement with previous studies.

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At a consensus meeting of the International CAPS (Cancer of the Pancreas Screening) consortium in 2013 [17], detailed criteria were developed for the selection of individuals eligible for screening of the pancreas. In general, a lifetime risk of 5% or more was considered an indication for screening. Publication of the guidelines has increased interest in these high-risk groups and enhanced the implementation of screening worldwide. However, an important remaining issue is that the value of the proposed screening programs has not yet been proven. These programs are therefore only suitable in a research setting and in specialized centers with high-volume pancreatic surgery and well-defined screening protocols. The protocol developed by Barnes et al. is a good example of a high-quality program [1].

The choice for (3.0 T) MRI as the primary screening tool, followed by EUS in case of abnormalities, seems appropriate, although the optimal screening approach still needs to be defined. A study by Harinck et al. showed that the results of MRI and EUS are complementary, MRI showing greater sensitivity in the identification of cystic lesions and EUS in the detection of solid lesions [18]. The program described by Barnes and colleagues also included the use of tumor markers (CEA, CA19.9). Although both markers have proven value in the follow-up of various cancers after treatment, the value of these markers for screening purposes is unknown. One major drawback is that when elevated levels of a marker are identified without evidence of abnormalities, as reported in a few cases in this study, severe anxiety may result. The possibility of false positive findings should therefore be discussed with patients beforehand.

Another major question is which individuals to screen? Pandharipande et al. developed a simulation model for PDAC that can be used to evaluate the effect of screening of specific high-risk groups [19]. Using this model, they showed an increased life expectancy for individuals with a *BRCA1*/*BRCA2* mutation and a strong family history for PDAC. In contrast, in the overall cohort of

Table 1 Estimated frequency of germline gene defects in sporadic and FPC and reported risk of PDAC [3–12]

Gene defect	Frequency in sporadic PDAC (%)	Frequency in familial PDAC (%)	Estimated lifetime risk of PDAC
BRCA2	1.4	0.8–3.7	< 5%
ATM	1.2	2.6–3.2	Unknown
BRCA1	0.4	0.7–1.2	~ 2%
MMR-genes	0.1	0.7	6% (MSH2)
PALB2	0.2	0.3–0.8	Unknown
CDKN2A	0.1	0.7–2.5	15–25%

BRCA1/*BRCA2* carriers with and without a family history of PDAC, life expectancy was reduced. This was attributed to the increased discovery of insignificant lesions and subsequent surgical intervention. The authors concluded that only those individuals with a sufficiently increased risk may derive benefit from screening.

In view of this conclusion, it is important to recognize that the risk of developing PDAC for most groups of mutation carriers, including those in the Barnes's study, is still unknown (Table 1). A recent study on the frequency and type of gene defects in a large series of sporadic PDAC reported that family history is inconclusive in most patients with an identified gene defect [3] Based on this observation, the authors concluded that routine gene testing of patients with newly diagnosed pancreatic cancer may yield significant clinical benefits for patients and family members. On the other hand, this approach may lead to identification of many individuals with an unknown risk of PDAC and may thus cause considerable anxiety, especially in view of the unproven value of screening. Implementation of routine testing of gene panels in sporadic PDAC may therefore require further consideration.

The prognosis of PDAC is still very poor, and has seen no improvement over the last 50 years. The only path to a better prognosis is early detection of precursor lesions or early stage cancer, particularly by offering screening to individuals at high risk. Despite the many difficulties involved in the screening of these high-risk groups, if we wish to make progress we should continue screening but under strict preconditions. The first step is the development of an appropriate, well-structured surveillance program as presented by Barnes et al. in this issue.

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