# Early detection of pancreatic cancer in high-risk individuals

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# PART IV

## General discussion and appendices

# General discussion and future perspectives

Since the beginning of this work in 2020, more than 1.48 million people worldwide have been diagnosed with pancreatic cancer and 1.39 million have died from the disease.[1] Over the same three-year period, the annual incidence of pancreatic cancer has increased by more than 3% and will continue to rise in the coming decades[2], while remaining one of the most challenging malignancies to treat. It is therefore projected to become the second leading cause of cancer-related death by 2030.[3] This reality underscores the immense challenge we face in combating this "Emperor of All Maladies" (book by Siddhartha Mukherjee).[4]

For breast, colorectal and cervical cancers, there is solid evidence that screening is effective in detecting cancer at an early stage and reducing cancer-related mortality.[5-7] So what currently prevents us from implementing large-scale population-based screening for pancreatic cancer? The main obstacle is the relatively low incidence of pancreatic cancer coupled with the lack of an accurate screening test. Screening in this setting will result in an unacceptably high rate of false positives, leading to unnecessary surgery, patient burden and increased healthcare costs.[8] Instead, the current focus remains on screening subpopulations at increased risk. The overarching goal of this dissertation is to improve early detection of pancreatic cancer in high-risk individuals (HRIs). This is achieved by critically evaluating the existing effectiveness of pancreatic cancer surveillance, exploring strategies to improve surveillance programs, investigating the identification of individuals at high risk, and exploring potential biomarkers for early detection. By addressing these key aspects, this work hopes to provide valuable insights that could lead to improved early detection and better outcomes for those at high risk of pancreatic cancer. This chapter reflects on the key findings of this thesis, places them in the context of the current literature, and discusses areas for future research.

**Effectiveness of pancreatic cancer surveillance**

The first prospective report of a surveillance program involving 14 individuals with a familial predisposition to pancreatic cancer was published in 1999.[9] Over the next two decades, the field has evolved and the number of pancreatic cancer surveillance programs has increased steadily. It was not until 2013 that the first guideline was published, stating that the detection and treatment of high-grade precursor lesions or early invasive cancer should be the goal of surveillance, as this is the best strategy for improving survival outcomes.[10] More than two decades later, a number of evaluations have been published, providing an opportunity to critically assess the current state, challenges and directions for the future.

The long-term evaluation of surveillance in carriers of a germline *CDKN2A* pathogenic variant (PV; **Chapter 2**) is encouraging and supports the rationale for surveillance. In this high-risk population, in which more than one in five individuals is predicted to develop pancreatic cancer, we found that more than 80% of the cancers detected during surveillance were resectable and one-third of patients were diagnosed with stage I pancreatic cancer, resulting in an overall 5-year survival rate of 32%. These improved outcomes were exemplified when compared to a matched control group from the general population (**Chapter 3**), where only 6% were diagnosed with stage I disease and 4% reached 5-year survival, once again underscoring the extremely poor prognosis. One of the major concerns in evaluating the effectiveness of surveillance has been that the observed survival benefit is strongly influenced by lead time. We have shown that even assuming that the surveillance diagnosis was made more than one year prior to symptomatic diagnosis, the survival outcomes

for patients diagnosed under surveillance remained far superior to those not diagnosed under surveillance. Detection of early cancers with significantly improved survival outcomes in more mixed high-risk populations has also been reported from other centers, where an increasing number of screen-detected cases were stage I cancers or high-grade precursor lesions, with excellent long-term survival outcomes.[11, 12]

Although encouraging progress has been made since the inception of pancreatic cancer surveillance, reliance on imaging alone has proven to be challenging, as evidenced by the fact that a substantial proportion of pancreatic cancers diagnosed during surveillance are still in a late stage[13], or were diagnosed as interval cancers between scheduled surveillance examinations. For example, six out of 36 cases in our cohort presented as interval cancers (**Chapter 2**). A retrospective evaluation of MRI scans in our cohort showed that 75% of pancreatic cancer cases had direct or indirect evidence of a tumor on previous examinations, suggesting an opportunity to detect these cancers earlier.[14] Another concern is surgery based on false-positive results, which is commonly reported and places patients at risk of substantial morbidity and mortality.[10, 15]

**Advancing pancreatic cancer surveillance**

The diagnosis of late-stage cancers, interval cancers and false-positive results underscore the urgent need to improve accuracy of imaging, for example through artificial intelligence or novel biomarkers, to enhance our diagnostic capabilities. The introduction of such biomarkers could lead to improved risk stratification of lesions and earlier recognition of malignant progression, ultimately leading to more targeted and effective management strategies for pancreatic cancer surveillance. Ideally, these biomarkers would complement imaging techniques, either during the intervals between annual surveillance or even potentially replacing the reliance on imaging-based surveillance altogether. Imaging would then be reserved for cases where abnormal biomarker findings are detected, thereby reducing the burden on participants and healthcare costs.

To this end, several potential markers in blood, pancreatic juice and tissue for the early detection of pancreatic cancer have been investigated over the years, some with promising performance.[16] Similarly, our study examined the longitudinal changes observed in a panel of blood glycosylation markers (*N*-glycans) in two integrated surveillance cohorts (**Chapter 4**). Our findings highlight the potential of a specific set of markers that change over the course of pancreatic cancer development. Interestingly, as compared to controls, changes in some biomarkers were already present at baseline, in some cases several years prior to diagnosis, and continued to change over time to imaging diagnosis. This finding is consistent with previous observations that it can take more than a decade for precursor lesions to progress to a malignant clone.[17] External validation in a larger, preferably independent surveillance cohort, is needed to evaluate if these biomarkers are indeed effective for risk stratification and early detection of PDAC.

Biomarkers may also play a role in more accurate risk stratification, providing opportunities for more personalized surveillance recommendations. In **Chapter 5** we aimed to work towards tailored surveillance strategies for carriers of a germline *CDKN2A* PV by developing a pancreatic cancer risk prediction model. The model highlighted the importance of having a first-degree relative with pancreatic cancer and a history of smoking as risk factors. However, the current model, which relied

solely on readily available clinical features, demonstrated insufficient performance to effectively support clinical decision making, reiterating the need for robust and reliable markers.

In parallel with the discovery of liquid biomarkers, rapid developments in artificial intelligence will have a major impact on radiology. In the potential significant window of opportunity to capture progression to malignancy, we can benefit from deep learning methodologies to detect and even characterize subtle changes, such as parenchymal abnormalities in the presence of pancreatic intraepithelial neoplasia (PanIN) and other features associated with cancer development.[18, 19]

As we look forward to the next decade, we anticipate that the discovery of biomarkers and development in radiology will have a major impact on the ability for early detection. However, an essential and particularly challenging step for both fluid and imaging-based biomarkers is the need for external validation before they can be used in pancreatic cancer surveillance programs. The number of pancreatic cancer cases in individual programs is limited, so dedicated collaboration in global, multi-institutional consortia is essential to make significant progress. Large-scale longitudinal collections of clinical data, imaging and biospecimens will advance biomarker discovery and improve our understanding of disease progression. In addition, these consortia are critical to the development of guidelines for standardized clinical practice worldwide.[20]

As we continue to develop and expand the reach of pancreatic cancer surveillance, it is critical to remain mindful of the psychosocial issues relevant to individuals with high-risk inherited mutations, as their adherence is vital to the success of these programs. Studies have found that, overall, the emotional impact of annual pancreatic cancer surveillance itself may be acceptable, as surveillance does not appear to affect psychological well-being.[21-24] However, there is likely to be variation between different risk groups and certainly between individuals. In our qualitative observations of germline *CDKN2A* PV carriers, we found variation in how individuals perceived their cancer risk and experienced the burden of surveillance (**Chapter 4**). This has prompted us to further investigate who might benefit from additional psychosocial support within our surveillance program. In addition, we should work towards a central source of information on relevant topics, including cancer surveillance, lifestyle choices and family planning. Furthermore, we advocate that psychosocial support by a team with dedicated physicians, specialist nurses and the availability of a psychologist should be an integral part of any pancreatic cancer surveillance program.

We should also strive to gain a deeper understanding of the natural history of pancreatic cancer in the setting of germline mutations. In our cohort of *CDKN2A* germline PV carriers, despite the detection of multiple subcentimeter cancers, we frequently identify positive lymph nodes, suggesting that these cancers may be more invasive than sporadic PDACs. Of particular interest, five carriers (5 of 31; 16.1%) were diagnosed with a secondary primary PDAC (**Chapter 2**), which occurred up to nine years after the primary cancer. Investigation of the genetic clonal relatedness and the microenvironment of these tumors may provide insight into whether these cancers develop independently or whether dissemination within the pancreas occurs from a common precursor lesion. These findings may help determine whether carriers of a germline *CDKN2A* PV should be offered a total pancreatectomy for localized tumor.

**Defining individuals at high risk**

One of the remaining challenges is the precise definition of the appropriate target populations to whom pancreatic cancer surveillance should be offered. The consensus among experts is that surveillance should be reserved for those with a lifetime risk > 5%. The rationale behind this is that below this threshold, the potential benefits do not outweigh the risks of overdiagnosis and overtreatment. However, others argue that, given the current limitations, surveillance should perhaps be reserved for subgroups at higher (> 10%) risk.[25] Indeed, current observations suggest that the greatest yield and optimal cost-effectiveness may be achieved in those with the highest risk profiles[26, 27], e.g., carriers of a germline *CDKN2A* PV (20-25% lifetime risk) or Peutz-Jeghers syndrome (11-36% lifetime risk). Therefore, based on recent data from the Dutch Familial Pancreatic Cancer Surveillance Study Group, in which no PDAC was diagnosed in a median follow-up duration of 63 months in 201 PV-negative familial pancreatic cancer kindreds,[28] enrollment of these individuals in surveillance in the Netherlands is currently halted until new convincing data emerge that surveillance is indeed beneficial in this group.

The debate over who should be offered pancreatic surveillance highlights the importance of obtaining an accurate assessment of genetic risk to guide prevention recommendations. This can be accomplished with simple and inexpensive applications (**Chapter 7**) that use family history to identify individuals at increased risk for hereditary predisposition, which can facilitate referral for genetic counseling, subsequent genetic testing, and enrollment in pancreatic cancer surveillance. To further improve the identification of families with a hereditary predisposition to pancreatic cancer, U.S. guidelines recommend expanding germline genetic testing to all pancreatic cancer patients.[29, 30] We have found that using such an approach does indeed detect a pancreatic cancer predisposition gene in one in 10 patients (**Chapter 8**). Unfortunately, our results also show that genetic testing was performed in only one-third of patients, underscoring the severe underutilization of this strategy.

However, if we are to have a significant impact on pancreatic cancer mortality at the population level, at some point we will need to broaden our focus beyond individuals with an inherited predisposition. For example, targeting individuals with new-onset diabetes and concomitant weight loss may help define a subset within the general population who have up to a sixfold increased risk of developing pancreatic cancer.[31] In addition to hyperglycemia, we have found that a number of significant alterations in soft tissue and metabolic markers occur prior to the diagnosis of PDAC (**Chapter 9**). These changes, with profound reductions in subcutaneous and visceral adipose tissue accompanied by changes in serum lipids may serve as additional early indicators of PDAC. Risk stratification together with other known risk factors such as smoking and obesity could be a first step towards selective screening in the general population.[32] However, given the current limitations of imaging-based screening, including the limited accuracy and high cost, reliable biomarkers are needed before such a population-based screening strategy can be implemented. In the coming years, large prospective studies currently underway in individuals with new-onset diabetes from the general population will hopefully lead to the discovery of such markers.[33]

## CONCLUSION

In conclusion, continued efforts to develop and expand pancreatic cancer surveillance are imperative given the escalating global impact of this devastating disease. The alarming statistics showing steadily increasing incidence and mortality rates underscore the urgency of overcoming the challenges posed by pancreatic cancer. While there have been successes in pancreatic cancer surveillance programs, particularly in individuals at highest risk, the limitations of current strategies highlight the need for continued innovation. The search for effective biomarkers, refined imaging techniques, and improved pathophysiologic understanding holds great promise for improving early detection and risk stratification, thereby improving surveillance outcomes. The inclusion of psychosocial support as an integral facet of surveillance programs is crucial to ensure not only adherence but also the holistic well-being of participants. A multifaceted approach, involving collaboration across institutions and global consortia, is essential to advance and validate these advances. As we navigate the path forward, the ultimate goal remains clear: to revolutionize the landscape of pancreatic cancer by equipping ourselves with the tools to detect, manage, and ultimately mitigate the impact of this relentless Emperor of All Maladies.

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