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The Natural Disease Course of Pancreatic Cyst–Associated Neoplasia, Dysplasia, and Ductal Adenocarcinoma: Results of a Microsimulation Model

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BACKGROUND & AIMS: Estimates on the progression of precursor lesions to pancreatic cancer (PC) are scarce. We used microsimulation modeling to gain insight into the natural disease course of PC and its precursors. This information is pivotal to explore the efficacy of PC screening. **METHODS:** A Microsimulation Screening Analysis model was developed in which pancreatic intraepithelial neoplasms and cysts can evolve from low-grade dysplasia (LGD) to high-grade dysplasia (HGD) to PC. The model was calibrated to Dutch PC incidence data and Japanese precursor prevalence data (autopsy cases without PC) and provides estimates of PC progression (precursor lesion onset and stage duration). **RESULTS:** Mean LGD state durations of cysts and pancreatic intraepithelial neoplasms were 15.8 years and 17.1 years, respectively. Mean HGD state duration was 5.8 years. For lesions that progress to PC, the mean duration was 4.8–4.9 years for LGD lesions and 4.0–4.1 years for HGD lesions. In 13.7% of individuals who developed PC, the HGD state lasted less than 1 year. The probability that an individual at age 50 years developed PC in the next 20 years was estimated to be 1.8% in the presence of any cyst and 6.1% in case of an LGD mucinous cyst. This 20-year PC risk was estimated to be 5.1% for individuals with an LGD pancreatic intraepithelial neoplasm. **CONCLUSIONS:** Mean duration of HGD lesions before development of PC was estimated to be 4.0 years. This implies a window of opportunity for screening, presuming the availability of a reliable diagnostic test. The probability that an LGD cyst will progress to cancer was predicted to be low.

Keywords: Pancreatic Cancer; Pancreatic Ductal Adenocarcinoma; Natural Disease Course; Screening.

This study provided insight into the natural development of pancreatic cancer using a microsimulation model. Knowledge on this process, including stage durations, is of pivotal importance to establish the potential success of pancreatic cancer screening.

Pancreatic cancer (PC) is a deadly disease predicted to become the second leading cause of cancer-related death in 2030.[1] Screening may lead to earlier detection and improved survival, as the diagnosis is often established too late for curative treatment.[2,3] According to the Wilson and Junger criteria, a valid screening program not only requires a reliable screen test, but also profound understanding of the natural disease course of the screened condition.[4] Both criteria have an impact on the outcomes of screening and determine the optimal strategy, for example, starting age and screening intervals.

PC can evolve from different precursor lesions, namely intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs), and pancreatic intraepithelial neoplasms (PanINs).[5] Data regarding their onset and stage duration are scarce, due to a paucity of long-term screening studies and to the location of the pancreas, which impedes easy tissue acquisition. A discrepancy between the imaging-based diagnosis and the true histologic state was observed in several screening studies.[6,7] In 1 long-lasting prospective study, 366 individuals underwent annual surveillance.[6] Of the 17 individuals who underwent surgery for a suspect lesion, 6 had PC, 7 had a low-grade dysplastic (LGD) lesion, 2 had neuroendocrine tumors, and 2 had no pathologic abnormality. No high-grade dysplastic (HGD) lesions were found and, despite annual surveillance, 50% of the cancers detected in that study were symptomatic interval carcinomas. A suboptimal test may explain these outcomes, but also, a short HGD stage duration may have provided a too small window of opportunity for detection. Ideally, one would detect and remove HGD lesions before they progress to cancer. Therefore, the duration of the HGD state is an important determinant of the potential effectiveness of screening.

Few studies have provided information on the progression duration of PC. In a quantitative analysis of the genetic evolution time of PC, Yachida et al[8] reported a period of 15 years between the occurrence of the initiating mutation and the ability to metastasize. Meza et al[9] reported the average sojourn time of premalignant pancreatic lesions to be approximately 50 years. A modeling study by Peters et al[10]

Abbreviations used in this paper: **HGD, high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; IQR, interquartile range; LGD, low-grade dysplasia; MCN, mucinous cystic neoplasm; MISCAN, Microsimulation Screening Analysis; PanIN, pancreatic intraepithelial neoplasm; PC, pancreatic cancer.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Pancreatic cancer (PC) survival would improve with detection and treatment of early-stage cancer and high-grade dysplastic (HGD) precursor lesions. The duration of the HGD state is an important determinant for the potential effectiveness of PC screening.

NEW FINDINGS

Our Microsimulation Screening Analysis pancreas model estimated a mean HGD duration of 4 years before development of PC; that in 13.7% of PC cases, the HGD state lasted less than 1 year; and that the 20-year PC risk of an individual with an unspecified cyst is low (1.8% when detected at age 50 years).

LIMITATIONS

The study is limited by the paucity of information on the natural disease course of PC.

CLINICAL RESEARCH RELEVANCE

Our results showed that there is a window of opportunity for PC screening. However, as current screening modalities are underperforming, other modalities, for example, biomarkers, should be explored. Given the low PC progression risk of cysts, evaluation of the efficiency of current surveillance guidelines is necessary.

BASIC RESEARCH RELEVANCE

Our model provides insight into durations of different disease stages. It is important to establish this and the true proportion of PC that evolves from a cyst or from pancreatic intraepithelial neoplasia, as these factors will influence the outcome of a potential screening program.

estimated progression from PanIN1 to PC to take about 35 years and progression from PanIN3 to PC to take 12 years. However, surveillance rarely, if ever, leads to detection of PanIN.

Despite variation in reported durations, potentially caused by the difference in study design, the lesion type reported on, and the lack of available data, these studies all seem to imply a wide timeframe for detection. Unfortunately, the poor results of PC screening do not align with this assumption, leaving unanswered whether this large window of opportunity truly exists. Microsimulation modeling, combined with available, if limited data, can provide new information on the natural disease course.

The well-established Microsimulation Screening Analysis (MISCAN) model has been used to support global decision making on different cancer screening programs, including breast, cervical, and colorectal cancer.[11–14] It consists of the following 3 pillars: demography, natural disease course, and screening. Observable parameters, such as cancer incidence and precursor lesion prevalence, are used to estimate unobservable outcomes, such as precursor lesion onset and stage durations. For this study, we improved our existing MISCAN-pancreas model[15] to gain insight into the natural disease course of PC. This information is pivotal to explore the potential and efficacy of PC screening.

Methods

To evaluate the natural disease course of PC, we adapted our previously developed MISCAN-pancreas model.[15] This stochastic model, coded in Python, version 3.8, simulates a population with a PC lifetime risk of 1.5%. The time of death of each simulated individual varies based on statistical life tables providing an age-related mortality risk (Statistics Netherlands, https://www.cbs.nl/en-gb). During their lifetime, each individual is at risk of developing 1 or more pancreatic precursor lesions that can progress to PC, from which a person can die. This MISCAN model provides unique insight into the life histories of each simulated individual. Generally, MISCAN models are used for the evaluation of different screening programs (Supplementary Figures 1 and 2).[11–14] In this analysis, we focused on the natural disease course of PC, without preventive interventions.

Structure of the Model

An extensive description of the MISCAN-pancreas model is provided in the Supplementary Material. The model simulated individuals to be at risk of 2 types of PC precursor lesions (ie, the onset): PanIN and mucinous cystic lesions (ie, IPMN and MCN). We assumed the initial state of a lesion to be LGD, which evolves from HGD to cancer. Stage durations are calibrated. We defined PanIN1 and 2 as LGD and PanIN3 as HGD. For mucinous cystic lesions, we assumed a similar pathway of LGD and HGD states. In line with the current World Health Organization guidelines,[16] the model does not consider intermediate-grade dysplasia. In addition, it assumes regression does not occur. Finally, we assumed a third, blind ending pathway of simple nondysplastic cysts that never progress and have an infinite stage duration.[17] At onset of a lesion, a location in the pancreatic head or corpus/tail is assigned based on observed distribution data.[18] Multiple lesions can develop and co-exist within a simulated individual.

The model divides preclinical cancer into the following 4 stages: local (T1), locally advanced (T2–3), regional (N1), and advanced (T4 or N2 or M1),[19] as they better determine survival and treatment options. Progression to clinical cancer occurs when related symptoms become apparent, which leads to cancer detection. Progression probability from one cancer stage to the next was based on observed PC incidence data by stage and location (head vs corpus/tail). We assumed that once cancer has developed, progression is independent of the precursor lesion type from which it evolved. PC survival by stage and location was based on data from the Netherlands Cancer Registry. An overview of the natural disease course data of PC is presented in Figure 1.

Population Characteristics and Natural Disease Course

Based on our calibration targets and input data, we simulated a general population with a PC lifetime risk of 1.5%. The model makes no distinction between men and women, as PC incidences are comparable and available data on precursor lesions are scarce. Given the low PC risk, we simulated a large population of 25 million individuals to reduce the impact of random variability. We included data on pancreatic ductal adenocarcinoma only, and for the base-case analysis, we assumed 90% of the PCs to develop from PanINs and 10% from mucinous cystic lesions.[20]

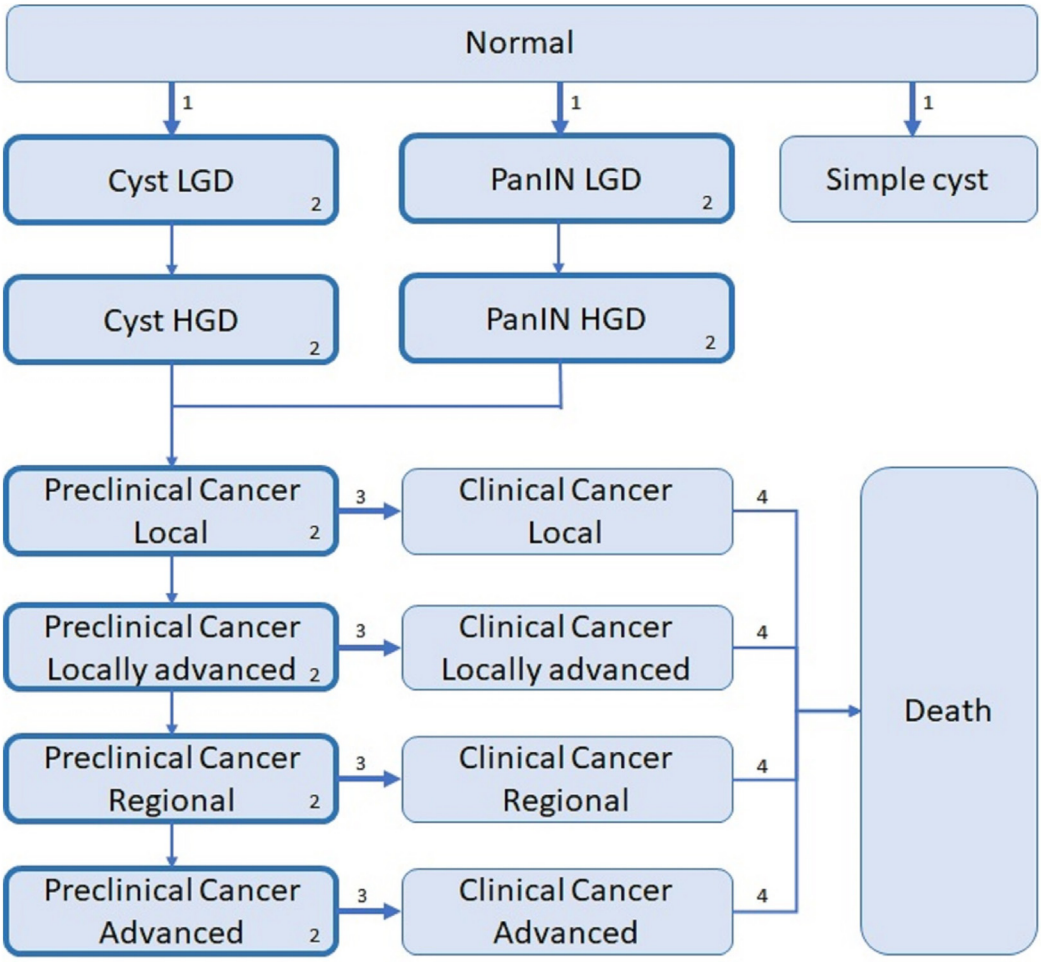

Figure 1. Natural disease course of PC. Schematic representation of MISCAN-pancreas. Individual life histories from birth to death. Each individual is at risk of acquiring 1 or multiple precursor lesions (mucinous cyst or PanIN), which may or may not progress from LGD to HGD to cancer. Most lesions will never progress to the next state within a lifetime. The parts indicated in *bold* were calibrated. (*1*) Onset: Age-specific hazard rates for the onset of the different (precursor) lesions calibrated to age-/location-specific PC incidence, age-/location-specific prevalence of precursor lesions and multiplicity. (*2*) Stage duration: Exponential distribution. Calibrated to precursor lesion prevalence and PC incidence by age and location. (*3*) PC incidence: Age-specific probability of PC being clinically detected because of symptoms. (*4*) Survival: Stage- and location-specific survival of PC. This natural disease course is similar for lesions in the pancreatic head and corpus/tail.

We assumed that preclinical cancer progresses to clinical cancer with a location-dependent probability based on clinical PC stage distribution, as cancer in the head leads to symptoms earlier than cancer in the tail. We also assumed that once a lesion progresses to clinical cancer, no new precursor lesions will develop. The survival time is determined for the lesion that led to the cancer diagnosis, using a [piece-wise linear] distribution provided for its location and stage. The effect of treatment on life expectancy is incorporated into the survival after clinical cancer diagnosis, as this is also the case for the reported survival by PC stage. In the rare case when a second cancerous lesion coexists at the time of the first diagnosis, this lesion can continue to grow and can also cause death. If death, caused by any of the lesions, takes place before death by other causes, this individual died from PC.

Calibration Process

Known parameters, such as birth tables, background mortality in the general population (life tables), stage distribution for clinical PC, and PC mortality by disease stage, were collected from Statistics Netherlands and the Netherlands Cancer Registry and were used as input for the model. For unknown parameters, indirect data are often available that may serve as calibration targets. A calibration target is a certain outcome of the model for which a value is known from observed data. In the calibration process, the values of unknown parameters are varied until the simulated model outcomes closely match the observed calibration targets (ie, within observed 95% CIs).

In this model, parameters calibrated were onset of each type of lesion by age group and location (ie, head or corpus/tail) and the duration of each disease stage. These parameters, regarding the natural disease course, were calibrated to age-, stage-, and localization-specific data of PC incidence (eg, calibration targets). Furthermore, we used age- and location-specific prevalence and multiplicity distribution of PanIN lesions from an autopsy study as targets to calibrate age and location of onset and the stage durations of PanIN[18] (Supplementary Tables 6 and 7 and Supplementary Figures 6–9). For this, we obtained the original

Table 1. Calibration Targets and Model Input

Variable	Head	Corpus/tail	Reference
Model input			
Clinical PC stage distribution, %			NCR
Local (T1)	4	1	
Locally advanced (T2–3)	18	3	
Regional (N1)	7	2	
Advanced (T4, N2, M1)	71	94	
Calibration targets			
PC incidence (CR/100,000)			NCR
Age			
51–55 y	6.18	2.43	
56–60 y	7.73	6.62	
61–65 y	12.15	8.04	
66–70 y	18.01	12.20	
71–75 y	32.35	16.25	
76–80 y	23.48	13.31	
Variable	%		Reference
PC-derived pathway			
PanIN-derived PC	90		20
Mucinous cyst–derived PC	10		20
Variable	% (n/N)		Reference
Precursor prevalence[a]			
PanIN LGD			18b
Age			
60–69 y	19 (5/27)		
70–79 y	5 (3/62)		
80–89 y	21 (26/124)		
PanIN HGD			
Age			21
70–79 y	0 (0/62)		
80–89 y	1 (1/124)		
Mucinous cyst			
LGD, age 80–89 y	13 (16/125)		21
HGD, age 80–89 y	1 (1/125)		
Simple cyst			
Age			
70–79 y	18 (11/62)		18b
80–89 y	23 (28/124)		

CR, crude rate; NCR, Netherlands Cancer Registry.
[a]Also provided as prevalence by location (Supplementary Tables 6–8). Values in parentheses are number of individuals with lesion of total age group.
[b]Original data set was provided by Matsuda et al.[18]

data from this study containing information on PanIN and simple cysts. IPMN, MCN, serous cystadenoma, and invasive cancer were not included in this data set.

We reviewed studies regarding pancreatic cyst prevalence by age and location, which varied widely based on population and imaging type (Supplementary Figure 3). Most studies reported imaging-based cyst prevalence, without information on the pathologic diagnosis or dysplastic state. Finally, we used autopsy data from Kimura et al[21] (300 autopsy cases without invasive PC) as a calibration target to estimate mucinous cyst onset and stage duration, as it uniquely involves pathologically confirmed cysts. Also, their reported cyst prevalence represented the median of the other published prevalence rates.[21] Table 1 describes the calibration targets.

For the calibration process, we aimed to find parameter values that best fit the calibration targets (eg, highest goodness-of-fit and the lowest deviance). We calibrated the natural disease course in 2 steps. First, we calibrated parameters for the PanIN and mucinous cyst pathways. Because they eventually share the same disease course (Figure 1), the algorithm evaluates a combination of the 2 values (a parameter set). As a second step, we calibrated the simple cyst pathway.

We used a genetic algorithm to calibrate the model.[22] In this algorithm, inspired by natural selection, a "generation" of parameter sets is defined. A simulation is run for each set and the "fitness" is assessed by comparing the outcomes with the calibration targets. Successive generations are constructed based on the best parameter sets of the previous generation. A detailed description of the calibration process is provided in the Supplementary Material (Supplementary Tables 1–5 and Supplementary Figures 4 and 5).

Assumptions

A calibration with too many unknown factors provides a large variance in possible results, which makes the model hard to calibrate. Therefore, it is important to make assumptions on values that are based on limited information and/or expert opinion. For the calibrated stage duration, we assumed that the duration had an exponential distribution and that there was a 100% correlation with the stage duration of the previous state. For example, if a lesion was fast-growing in a previous stage, it will be so in the next state. Also, the duration of the HGD state was assumed to be shorter than that of the LGD state. Thus, the upper bound of the HGD duration depends on the LGD duration variable. The maximum preclinical cancer duration (local until advanced) was assumed to be equal to the duration of the HGD state. However, as the probability that preclinical cancer becomes clinical is stage- and location-dependent, the actual durations vary by location and stage. We assume that not all lesions will remain asymptomatic (preclinical) until achieving advanced stage, therefore, the preclinical duration is shorter than the HGD duration.

Analysis

First, we present the PC incidence and precursor lesion prevalence by age group and precursor lesion type. Next, the model provides the stage durations of both mucinous cyst and PanIN lesions by grade of dysplasia in individuals who develop PC within a lifetime. The durations are presented as the mean over 100 different calibration runs (each run was based on a different seed). Also, the lower and upper bound of the mean stage duration of the 100 calibration runs are provided.

Finally, the PC progression probability was calculated as the probability that a person with a certain lesion develops PC within a certain period (irrespective of the type of lesion from which it occurs). The PC progression probability is provided by age of detection of the lesion for the next 1–5 decades.

Sensitivity Analysis

First, we performed a sensitivity analysis on the proportion of PC that evolves from PanINs or mucinous cystic lesions. In the base-case analysis, this proportion is assumed to be 90% from PanINs and 10% from mucinous cysts. Subsequently, we analyzed the effect of altered PanIN/cyst proportions (80%/20%, 70%/30%, and 10%/90%) on stage durations.

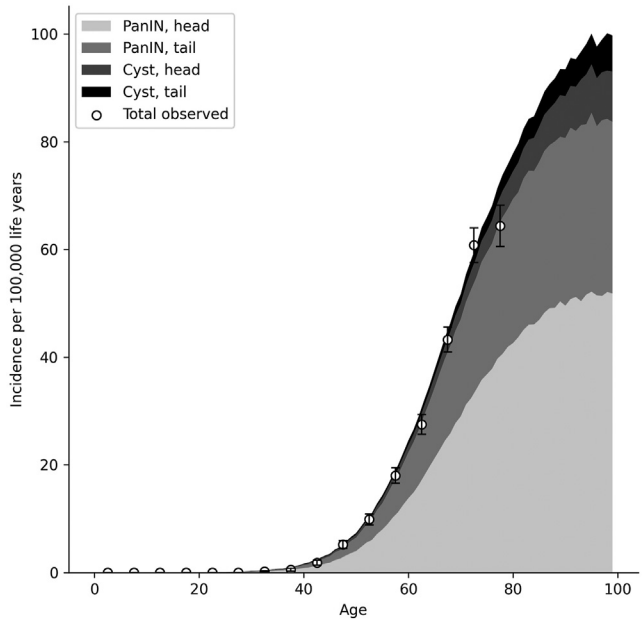

Figure 2. Stacked area *chart* of the simulated PC incidence by age and type of precursor lesion per 100,000 life-years. The dip at age 95 years is most likely caused by the small number of individuals in older age groups. The *dotted line* represents the observed pancreatic cancer incidence used as calibration target.

Second, as studies reported various PanIN prevalence rates (mainly due to differences in LGD PanIN prevalence), we recalibrated the model with data reporting an increased PanIN prevalence of 52% at age 80 years.[23] Due to lack of information on the location and age distribution of PanINs, we assumed similar prevalence rates by age and lesion location (head/corpus tail), as in the base case (Supplementary Table 8 and Supplementary Figures 10–13).

In order to show the impact of an increased PanIN prevalence on stage duration and PC progression probability, we did not alter any other calibration targets.

Finally, we evaluated the effect of increased cyst prevalence on stage durations and PC progression risk. We adjusted the base-case prevalence for each age group and used a final prevalence of 45% (Supplementary Table 9 and Supplementary Figures 14–17).

Results

Pancreatic Cancer Incidence and Precursor Lesion Prevalence

The simulated PC incidence and precursor prevalence closely matched the observed incidence and prevalence, for example, we were able to fit the model to the calibration targets. Figure 2 shows the observed incidence and the simulated PC incidence by age and precursor type per 100,000 life-years. PC incidence at age 50 years was estimated to be 7.6 per 100,000 life-years and 76.2 per 100,000 life-years at age 80 years. An overview of the observed PC incidence in the Netherlands in relation to the simulated cancer incidence by age and lesion of origin is provided in Supplementary Figure 6.

Figure 3 shows the model-estimated prevalence of lesions in various dysplastic states by age. Prevalence of PanINs was estimated to be 5.7% at age 50 years and 19.7% at age 80 years. The prevalence of any cystic lesion was 6.1% at age 50 years and 29.6% at age 80 years. The prevalence of a mucinous cyst (LGD and HGD) was estimated to be 1.6% at age 50 years and 9.5% at age 80 years. However, the prevalence of HGD cysts was estimated to be very low; at most 0.3% at age 90 years. Simulated prevalences are depicted next to the observed prevalences in Supplementary Figures 8 and 9.

Calibration results regarding multiplicity are available in Supplementary Figure 7. PanINs were estimated to be mainly multifocal (3 or more lesions) in individuals older than 80 years. By this age, almost 12% had at least 2 PanINs. For cystic lesions, 5% had at least 2 cysts at age 80 years.

Stage Duration

Mean duration of an LGD PanIN was estimated to be 17.1 years and for LGD it was 5.8 years. For PanINs that progress to PC within a lifetime, the mean duration of the LGD state was estimated to be 4.9 years and for HGD it was 4.1 years (Table 2). It takes an average of 9 years for PanIN to develop into preclinical cancer. The HGD duration was shorter than 1 year in 11.7% of the individuals who developed PC from a PanIN.

The mean duration of LGD mucinous cyst was estimated to be 15.8 years and 5.8 years for LGD. For mucinous cysts that progress to PC, the mean duration of the LGD state was estimated to be 4.8 years and for the HGD state it was 4.0 years. In 14.8% of individuals with a cyst that progressed to PC, the HGD state lasted less than 1 year. For all HGD lesions that progressed to cancer combined, this percentage was 13.7%.

The mean duration of the preclinical local cancer (T1) state was 1.3 years. For an individual that developed clinical PC within a lifetime, the mean time since PanIN onset was 9.0 years. When PC progressed from a cystic lesion, the mean time was estimated to be 8.8 years.

Pancreatic Cancer Progression Risk

Within a lifetime, 92.8% of the LGD lesions do not progress to the next state (ie, HGD). The PC progression probability, presented in Figure 4, was calculated as the probability that a person develops PC within a certain period (irrespective of the lesion type from which it occurs). A similar PC risk is seen for individuals with a PanIN or a cystic lesion at age 50 years. The PC progression risk of an individual with any pancreatic lesion (eg, simple cyst, IPMN, or PanIN) present at age 50 years was estimated to be low in the first 20 years (<5%) and increased from age 70 years onward. Individuals with a PanIN lesion at age 50 years had an estimated PC risk of 1.6% within 10 years and 5.1% within 20 years. For a 70-year-old individual, the 10-year risk was estimated to be 3.2%.

Individuals with a mucinous cyst at age 50 years had an estimated PC risk of 2.0% within 10 years and 6.1% within 20 years. For a 70-year-old individual, the 10-year risk was estimated to be 5.4%. When the third pathway of non-neoplastic, simple cysts was considered, the 10-year PC

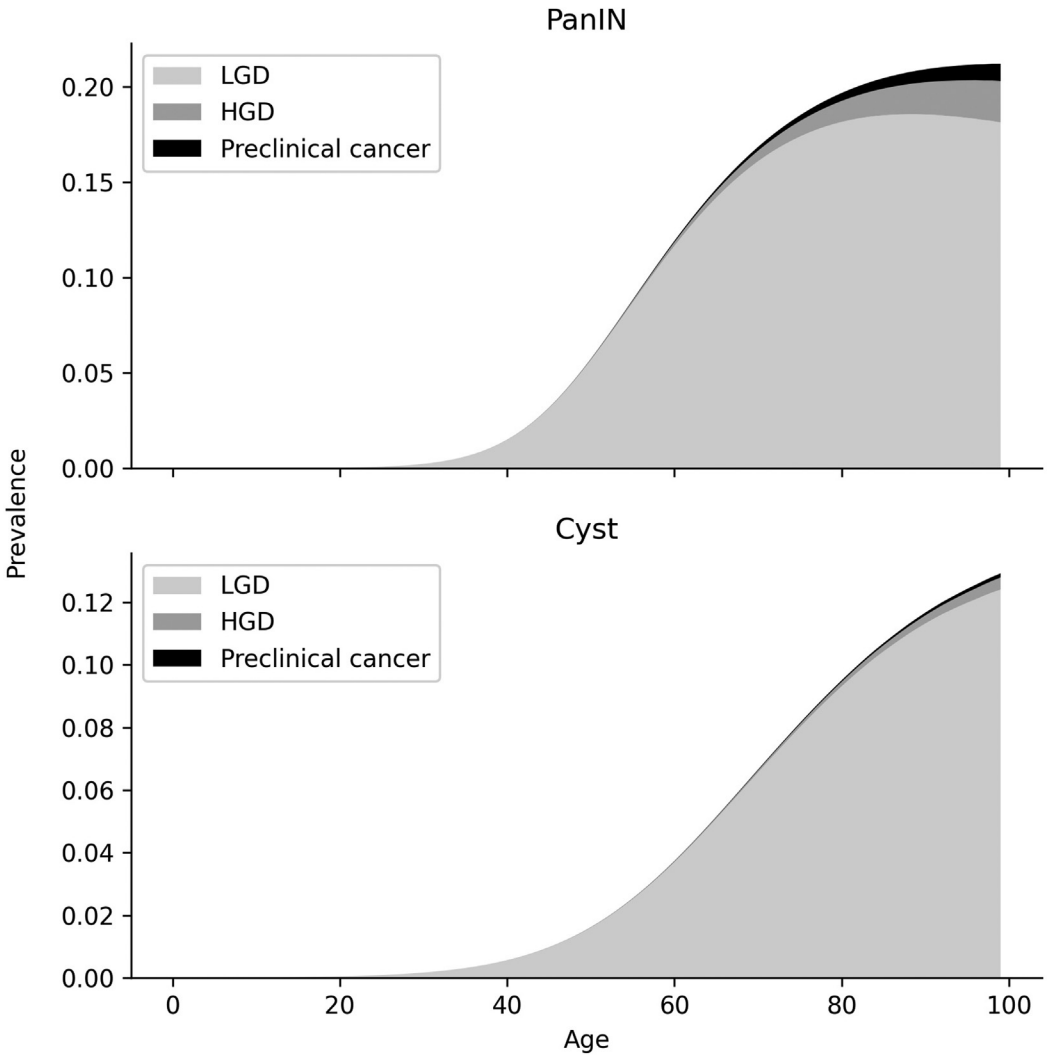

Figure 3. Simulated PanINs and cyst prevalence by age. If multiple cysts are present, only the cyst with the highest grade of dysplasia is represented. The same holds for PanINs. Individuals are no longer represented when clinical cancer or death has occurred.

risk of a 50-year-old individual with any cyst was 0.6%, and 1.8% for 20 years. For a 70-year-old, this 10-year risk was 1.8%.

Sensitivity Analyses

Ratio of pancreatic cancer cyst to pancreatic intraepithelial neoplasm. We evaluated the impact of our assumption that 90% of PCs originate from PanINs and 10% from cystic lesions by varying this ratio to 80%/20%, 70%/30%, and 10%/90%. In the latter scenario, the average LGD PanIN duration shortened slightly from 4.9 years to 4.1 years, and the HGD PanIN state remained practically unchanged (4.1 years vs 3.8 years). For cystic lesions, reversing the ratio led to a longer LGD state (from 4.8 years to 7.0 years) and shorter HGD state (from 4.0 years to 2.9 years) (Figure 5).

Increased pancreatic intraepithelial neoplasm prevalence. The effect of an increased PanIN prevalence as calibration target was assessed in the 10% cyst scenario. As the increase of PanIN prevalence was mainly visible in LGD lesions, the effect on duration of lesions that progress to PC in a lifetime was neglectable (Table 2). However, the mean duration of LGD PanINs, regardless of PC development, was increased (from 17.1 years to 18.4 years). The PC progression probability in this scenario was lower compared with the base case (Supplementary Figures 18–20).

Individuals with a PanIN lesion at age 50 years had an estimated PC risk of 0.6% within 10 years and 2.0% within 20 years (compared with 1.6% and 5.1%, respectively, in the base case). For a 70-year-old individual, the 10-year risk was estimated to be 1.4% (compared with 3.2% in the base case).

Increased cyst prevalence. The effect of increased cyst prevalence was assessed in the 10% cyst scenario. As only a small proportion of PC evolves from a mucinous cyst, the effect of increased cyst prevalence on duration was neglectable (Table 2). However, the mean duration of mucinous LGD cyst, regardless of PC development, was increased (from 15.8 years to 17.6 years). It did impact the PC progression probability: Individuals with a mucinous cystic lesion at age 50 years had an estimated PC risk of

Table 2. Mean Stage Durations of Pancreatic Cancer Precursor Stages

State	Stage duration, *y*, mean (range[a])	
	All lesions	Lesion that progresses to PC
Base case		
Mucinous cyst LGD	15.8 (13.1–20.1)	4.8 (3.9–6.3)
PanIN LGD	17.1 (13.5–19.7)	4.9 (4.3–6.8)
Mucinous cyst HGD	5.8 (4.6–6.7)	4.0 (3.3–4.6)
PanIN HGD	5.8 (4.2–6.8)	4.1 (3.2–4.6)
Sensitivity analysis		
30% PC scenario		
Mucinous cyst LGD	16.2 (13.4–19.2)	5.1 (4.1–7.8)
PanIN LGD	16.5 (13.3–19.6)	4.7 (4.1–7.1)
Mucinous cyst HGD	5.4 (3.0–6.5)	3.8 (2.4–4.5)
PanIN HGD	5.8 (3.8–6.7)	4.1 (3.0–4.6)
Increased PanIN prevalence		
Mucinous cyst LGD	15.9 (12.9–20.0)	4.8 (3.7–5.8)
PanIN LGD	18.4 (16.5–20.3)	5.1 (4.6–5.6)
Mucinous cyst HGD	5.8 (4.4–7.2)	4.1 (3.4–4.8)
PanIN HGD	5.9 (5.1–6.6)	4.2 (3.8–4.6)
Increased cyst prevalence		
Mucinous cyst LGD	17.6 (15.3–19.7)	4.7 (4.3–5.5)
PanIN LGD	15.7 (13.2–18.6)	4.5 (4.0–5.5)
Mucinous cyst HGD	6.2 (5.0–6.9)	4.0 (3.5–4.4)
PanIN HGD	5.8 (4.9–6.7)	4.3 (3.5–4.4)

[a]Ranges in parentheses represent the lower and upper bound of the mean stage duration over 100 calibration runs of lesions that progress to PC (right column) and of all lesions (left column).

0.8% within 10 years and 2.6% within 20 years (compared with 2.0% and 6.1%, respectively, in the base case). For a 70-year-old individual, the 10-year risk was estimated to be 1.7% (compared with 5.4% in the base case) (Supplementary Figures 21–23).

Discussion

Summary of Findings

Our microsimulation model MISCAN-pancreas estimated that it takes an average of 9 years for both PanIN and mucinous cysts to develop from precursor lesion to preclinical T1 PC. For individuals who develop PC, the LGD state is estimated to last approximately 5 years and the HGD state approximately 4 years, irrespective of precursor lesion type. In 13.7% of PC cases, the HGD state was estimated to last less than 1 year. The risk of a cystic lesion progressing to PC seems low and increases with age. An increased PanIN or cyst prevalence did not significantly impact the HGD stage durations of lesions that progressed to PC. It did result in lower PC progression probability.

Stage duration. One previously developed simulation model by Peters et al[10] also reported on stage duration and progression probability as a model outcome. Due to differences in natural disease course, calibration targets, and assumptions, results of these studies are difficult to compare. Their natural history consisted of similar pathways in which PanINs or cysts evolved into PC (90%:10% ratio), but different disease stages were used: PanIN1, 2, and 3 vs LGD and HGD. Based on current World Health Organization guidelines, PanIN1 and 2 are now classified as LGD. Also, source data for PanIN prevalence was higher compared with our more recent data with a higher number of cases. As seen in our results, increased LGD PanIN prevalence leads to a lower progression risk.

Their estimated mean stage durations were 17.4 years (interquartile range [IQR], 6.5–25.6 years) for PanIN1, 13.9 years (IQR, 4.8–20.3 years) for PanIN2, 10 years (IQR, 3.25–14.3 years) for PanIN3, and 35.3 years (IQR, 25.6–44.7 years) from PanIN1 to clinical PC.[10] Our average lifetime stage duration for LGD PanIN (PanIN1+2) is 17.1 years and 5.8 years for HGD PanIN. From LGD PanIN to PC detection, we calculated less than 9 years. More than 90% of our lesions do not progress to PC within a lifetime.

Regarding the PC progression risk, Peters et al[10] reported a lifetime risk of 1.3%–1.5% for PanIN1. This is similar to results from our high PanIN scenario, in which a 50-year-old individual with PanIN has a 2.0% PC progression risk.

In another study that supports our findings, whole-exome sequencing of 17 cases with IPMN-associated pancreatic ductal adenocarcinoma was performed, which estimated that HGD IPMNs took a median of 3.7 years to develop into a pancreatic ductal adenocarcinoma founder cell.[24]

Model validation. Stage durations and PC progression probabilities (ie, our main outcome results) are unobservable parameters. With model calibration, we gained information on PC development in the unscreened general population. As most clinical studies concern imaging-based PC screening in high-risk individuals, their results cannot be used to evaluate the performance of our model.

Therefore, as a validation exercise, we compared the predicted stage durations with reported durations in the literature (from previous modeling and laboratory studies) and found them to be comparable. Also, we compared the predicted PC incidence in simulated individuals with a pancreatic cyst to the observed incidence in our prospective cyst cohort (PACYFIC study) and found a comparable risk (prospective study: 1.5% PC risk (model: 0.6%–1.8% 10- to 20-year PC risk at age 50 years).

Pancreatic intraepithelial neoplasm and cyst prevalence. Most publications on PanIN prevalence are biased surgical series reporting high prevalences.[25,26] Instead, we used data from the autopsy study of Matsuda et al,[18] as they uniquely provide a pathologically proven PanIN prevalence in individuals from the general population without PC.

For the mucinous cystic pathway, we reviewed studies regarding pancreatic cyst prevalence by age and location, which varied widely based on population and imaging type (Supplementary Material). Most studies reported imaging-based cyst prevalence, without information on the pathologic diagnosis or dysplastic state. Finally, we used autopsy data from Kimura et al[21] as a calibration target to estimate

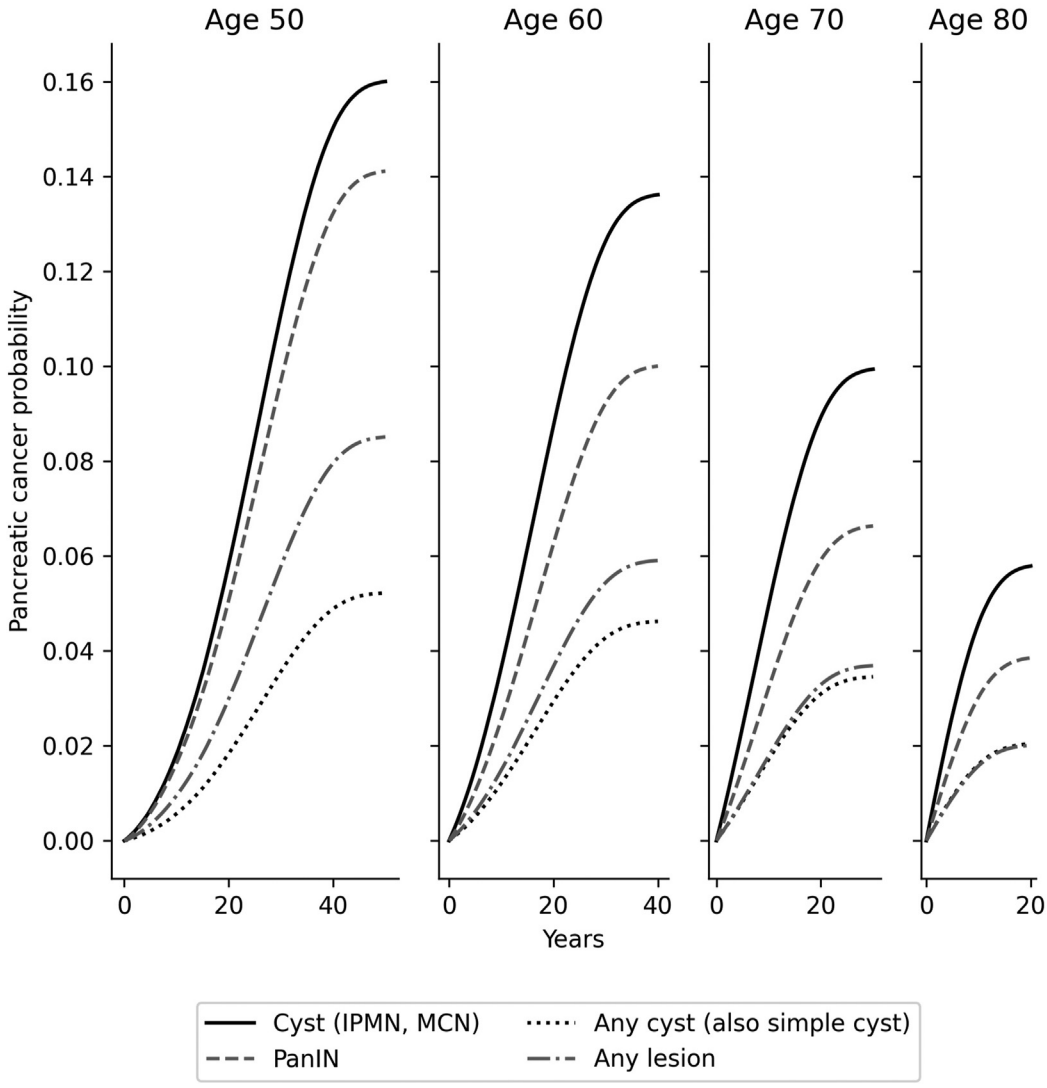

Figure 4. PC progression risk by lesion type and age. This figure shows the PC probability for individuals at a certain age, given the presence of a specific lesion, for the next decades. Cancer probability is not only based on the lesion that is described in the *graph*, in the case of the cyst graph, PC can still also evolve from PanIN.

mucinous cyst onset and stage duration, as it uniquely involves pathologically confirmed cysts. Kimura et al defined *cystic lesions* as restricted dilatations of the pancreatic duct of $\geq$2 mm. Cystic lesions were classified as normal epithelium, atypical hyperplasia, carcinoma in situ, or invasive carcinoma. This grading system is not according to current standards. The adjustment of these data to current standards may have led to an overestimation of the LGD cyst prevalence, which may have resulted in an overestimation of the durations.

We are aware that Kromrey et al[27] reported a cyst prevalence based on imaging that is much higher than the prevalence in the autopsy study of Kimura et al.[21] However, it has been reported that pancreatic cysts tend to be 3 mm smaller at histology compared with their size at imaging.[28] Thus, smaller lesions of 2–3 mm on imaging could be untraceable in histology. Because approximately 60% of all pancreatic cysts detected on imaging are between 2 and 5 mm in the Kromrey et al study, this could explain the discrepancy in prevalence. In this model, we aimed to evaluate the durations of different disease stages based on pathologic confirmed data rather than imaging.

Natural history. In our model, we assumed there are 2 types of precursor lesions of PC: PanINs and mucinous cysts, a concept that is widely accepted.[16,29] However, a third, yet unknown precursor lesion has been suggested based on a combination of observed mutations.[30] As we calibrated to pathologic-proven lesions, we could not take this unknown pathway into account. In addition, it was suggested that, next to a stepwise process, PC may develop nongradually, more explosive.[31] In our model, a proportion of PC developed rapidly, but this is still a step-wise process from LGD to HGD. Finally, we assumed that 90% of the PC evolved from a PanIN and 10% from a mucinous cyst,[20] but this ratio varies in the literature. One analysis suggested that 50% of PCs evolved from PanIN, another suggested

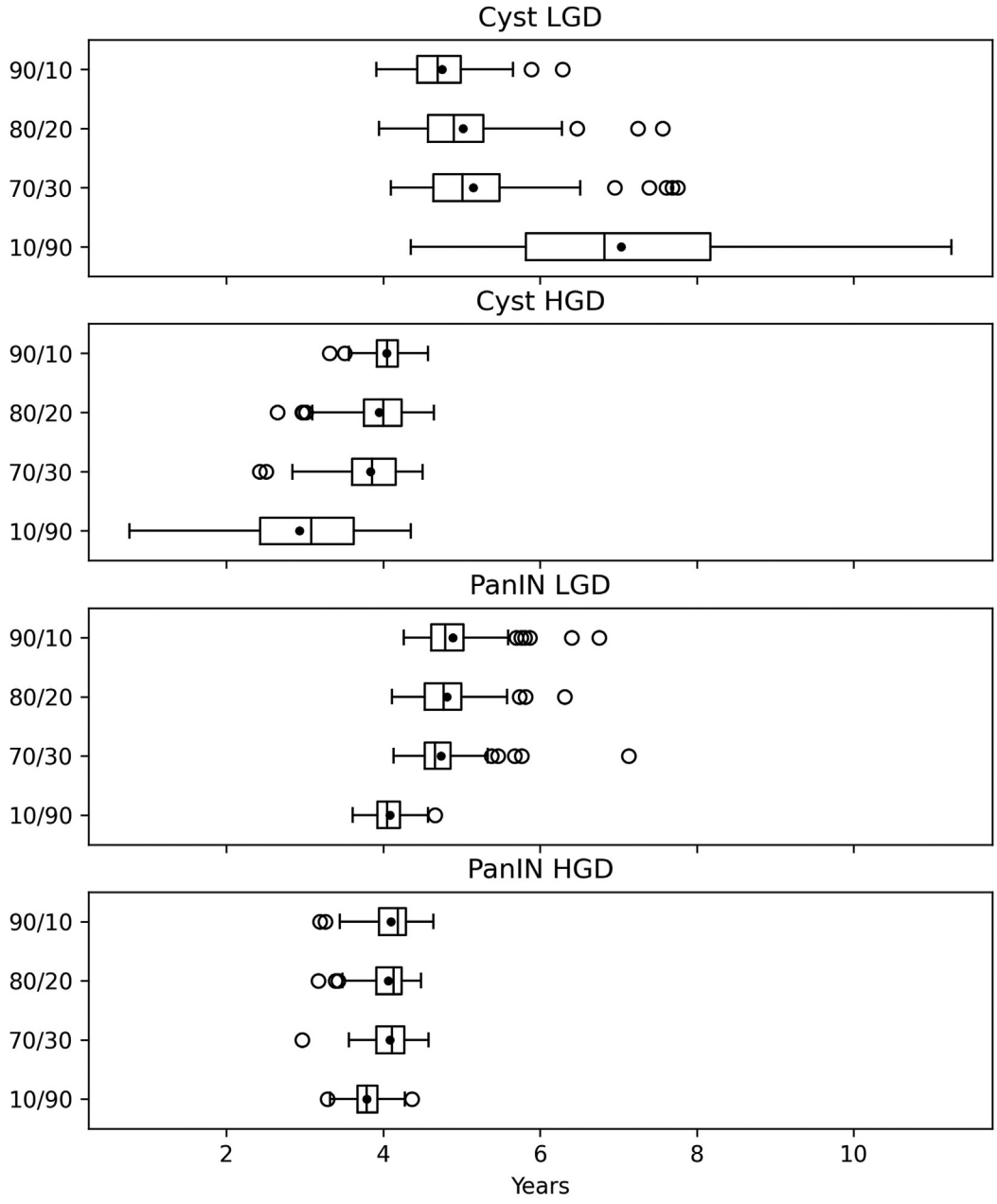

Figure 5. *Box plot* showing the mean duration of LGD and HGD states for both PanIN and cystic precursor lesions that progress to PC within a lifetime over 100 calibration runs for different PanIN to cyst ratios. Base case: 90% of PC evolves from PanIN. Sensitivity analysis: 80%, 70%, and 10% of PC evolves from PanIN. *Black dot*: mean; *solid line:* median. IQR, Q3–Q1. *Circles:* outliers. Minimum: Q1–1.5*IQR. Maximum: Q3+1.5*IQR.

72%.[30,32] Nevertheless, our sensitivity analysis found that this ratio hardly impacts the predicted stage durations.

Limitations

Despite the useful insights our analysis provides, it also has limitations. First, we calibrated our results with precursor prevalence data from Japanese autopsy studies.[18,21] Although the PC incidence is higher in Western countries than in Asia, which could have led to an underestimation of the stage duration, we showed that the cyst prevalence reported by this Japanese autopsy study was comparable with other studies (Supplementary Figure 3).

Second, we used pathologic PanIN-proven data as our calibration target because the authors extensively examined the whole pancreas (5-mm slices) of individuals without PC. With this method, minor microscopic lesions could have been missed. This could have led to an underestimation of the PanIN prevalence, which, in turn, could lead to an underestimation of the durations.

We did not relate PC risk to the number of lesions or the combination of different precursor lesions. The presence of a cystic lesion may lead to a higher PanIN risk and, thus, to a

higher PC risk. We also did not correlate the development of PanINs and cystic lesions. However, we did model multiplicity of precursor lesions. This way, individuals with multiple lesions were at higher risk of PC based on each separate precursor lesion.

Also, we assumed that the different IPMN types (side branch, main duct, or mixed type) share the same progression pathway, but within it, lesions can grow faster or slower. Thus, a fast-growing lesion can represent a main duct IPMN, and a slow-developing one can represent a side-branch IPMN.

Finally, although we are aware of risk factors associated with PC, such as smoking, body mass index, excessive alcohol use, chronic pancreatitis, and multiple genetic mutations, we modeled the general population with an average PC risk. Thus, the model does not address differences between these specific risk groups. However, in this simulated general population, individuals can have a lower or higher PC risk based on their own risk factor, drawn from the gamma distribution.

Implications

The duration of HGD stages implies a window of opportunity for screening, but this seems in contradiction to current clinical experience. Studies evaluating the effect of annual PC screening in high-risk individuals mostly detect and perform surgery on LGD lesions and >T1 cancers rather than on HGD lesions and T1 cancer. These latter 2 are defined, when detected and treated, as screen successes. Symptomatic interval carcinomas occur even in individuals undergoing annual surveillance.[6] This high interval cancer rate, despite annual screening,[6] supports our finding that 13.7% of the simulated PC cases had an HGD duration of less than 1 year.

The lack of test sensitivity is another explanation for the high interval cancer rate. PanINs are small and virtually invisible on imaging.[5] Autopsy data from Matsuda et al[18] support this. Of the PanIN3 lesions that were detected during autopsy, 75% were <4 mm. In the study from Kimura et al,[21] 70% of all lesions with HGD were <5 mm. Thus, better tests for PanINs are needed urgently. More importantly, we also need tests that can accurately predict the grade of dysplasia of both PanINs as cystic lesions. Biomarkers could be the future in this matter.[33]

Future research should also focus on the pathophysiology of PC. It is important to establish the true proportion of PC that evolves from a cyst or from PanIN. Although the effect of this ratio on the state duration is limited, it will influence the outcome of a potential screening program, as current imaging modalities are mainly capable of detecting larger cystic lesions and not PanINs.

The current model will be validated, adjusted, and improved whenever new data from autopsy or prospective surveillance studies become available.

In conclusion, we developed a microsimulation model that describes the development of PC from both PanIN and cystic lesions. Knowledge on the process, including the stage durations, is of pivotal importance to establish the potential success of PC screening. The mean duration of HGD precursor lesions is approximately 4 years and implies a window of opportunity for PC screening. However, its success depends strongly on the ability of screening tools to not only detect small (sub-centimeter) lesions, but also to establish their grade of dysplasia.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2023.08.027.

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The authors disclose no conflicts.

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Data Availability
Data will be made available upon request.