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Testing for Verification Bias in Reported Malignancy Risks for Side-Branch Intraductal Papillary Mucinous Neoplasms: A Simulation Modeling Approach

Davis T. Weaver^{1,2}, Anna P. Lietz^{1,2}, Sarah F. Mercaldo^{1,2,3}, Mary Linton B. Peters^{1,3,4}, Chin Hur^{1,3,5}, Chung Yin Kong^{1,2,3}, Brian M. Wolpin^{3,6}, Alec J. Megibow⁷, Lincoln L. Berland⁸, Amy B. Knudsen^{1,2,3}, Pari V. Pandharipande^{1,2,3}

¹Institute for Technology Assessment, Massachusetts General Hospital, 101 Merrimac St, Ste 1010, Boston, MA 02114.

²Department of Radiology, Massachusetts General Hospital, Boston, MA.

³Harvard Medical School, Boston, MA.

⁴Division of Hematology and Oncology, Beth Israel Deaconess Medical Center, Boston, MA.

⁵Gastrointestinal Unit, Massachusetts General Hospital, Boston, MA.

⁶Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA

⁷Department of Radiology, New York University Medical Center, New York, NY.

⁸Department of Radiology, University of Alabama Birmingham School of Medicine, Birmingham, AL.

Abstract

OBJECTIVE.—The objective of our study was to test for the possibility that published malignancy risks for side-branch intraductal papillary mucinous neoplasms (IPMNs) are overestimates, likely due to verification bias.

MATERIALS AND METHODS.—We tested for possible verification bias using simulation modeling techniques. First, in age-defined hypothetical cohorts of 10 million persons, we projected the frequency of pancreatic ductal adenocarcinoma (PDAC) arising from side-branch IPMNs over 5 years using published estimates of their prevalence (4.4%) and rate of malignant transformation (1.9%). Second, we projected the total number of PDAC cases in corresponding cohorts over the same time horizon using national cancer registry data. For each cohort, we determined whether the percentage of all PDAC cases that arose from side-branch IPMNs (i.e., side-branch IPMN-associated PDAC cases) was clinically plausible using an upper limit of 10% to define plausibility, as estimated from the literature. Model assumptions and parameter uncertainty were evaluated in sensitivity analysis.

Address correspondence to P. V. Pandharipande (pari@mgh-ita.org).

Based on presentations at the Radiological Society of North America 2018 annual meeting, Chicago, IL, and at the Society for Medical Decision Making 2018 annual meeting, Montreal, QC, Canada.

RESULTS.—Across all cohorts, percentages of side-branch IPMN–associated PDACs greatly exceeded 10%. In the base case (mean age = 55.7 years), 80% of PDAC cases arose from side-branch IPMNs (7877/9786). In the oldest cohort evaluated (mean age = 75 years), this estimate was 76% (14,227/18,714). In a secondary analysis, we found that if an upper limit threshold of 10% for side-branch IPMN–associated PDAC was imposed, the model-predicted rate of malignancy for side-branch IPMNs would be less than 0.24% over a 5-year time horizon, substantially lower than most literature-based estimates.

CONCLUSION.—Our results suggest that reported malignancy risks associated with side-branch IPMNs are likely to be overestimates and imply the presence of verification bias.

Keywords

imaging follow-up; intraductal papillary mucinous neoplasm; pancreatic cancer; pancreatic cyst; verification bias

Pancreatic cancer is projected to account for 55,440 new cancer diagnoses and 43,330 cancer deaths in the United States in 2018 [1]. The dominant subtype is pancreatic ductal adenocarcinoma (PDAC), which accounts for more than 90% of all pancreatic cancer cases [2, 3]. There are two known pathways through which PDAC may develop: solid and cystic. The most common precursors associated with each are pancreatic intraepithelial neoplasia lesions and intraductal papillary mucinous neoplasms (IPMNs), respectively. Pancreatic intraepithelial neoplasia lesions are not observable on imaging, but IPMNs can be identified and treated before they progress to PDAC in some patients [2].

IPMNs are subclassified into two primary categories: first, those involving the main pancreatic duct (i.e., main-duct and combined-type IPMNs), both of which harbor a substantial risk of pancreatic malignancy [4]; and, second, side-branch IPMNs, which progress to malignancy infrequently, particularly in the absence of suspicious features [5–10]. Although main-duct and combined-type IPMNs are relatively rare, side-branch IPMNs are commonly encountered at imaging [11–13]. Prevalence estimates are as high as 14.4% in asymptomatic patients [12]. Because of their high prevalence and low malignancy risk, side-branch IPMNs represent a major management challenge for patients, providers, and radiologists [14].

Current reported estimates of the malignancy risks of side-branch IPMNs range from 1.9% to 7.8%; these estimates are drawn from studies in which the absence of malignancy at imaging follow-up is used as a surrogate for benignity [5–10]. For many practicing radiologists, these reported malignancy rates seem too high and are difficult to reconcile with the high frequency of cysts encountered in everyday practice. In diagnostic testing, when there is an apparent inconsistency between published reports of disease frequency and clinical experience, one possible explanation is verification bias [15]. Verification bias occurs when there is oversampling of higher-risk patients in observational studies because ascertainment (verification) of disease status is more likely in such patients.

Observational studies that have sought to determine the rate of malignant transformation of side-branch IPMNs have used longitudinal study designs in which inclusion was usually

contingent on a certain length of follow-up [5–10]. However, because only patients with follow-up were included and other patients with side-branch IPMNs that were not reported or not followed were not included, reported malignant transformation rates of 1.9–7.8% may not be generalizable to all side-branch IPMNs detected on imaging [5–10]. Verification bias may have occurred because the studies addressed a subpopulation of patients in whom follow-up was deemed more essential than would be needed for the so-called “average” patient [5–10].

We used simulation modeling to test our hypothesis that reported malignancy rates of side-branch IPMNs are not generalizable to the broader population of all side-branch IPMNs. For a range of age-specified patient cohorts, we projected the expected contribution of side-branch IPMN-associated PDAC to total PDAC cases over a given time period using a current, representative literature-based experience to inform the risk of malignant transformation of side-branch IPMNs [8]. In a surgical series of 1260 consecutive patients diagnosed with PDAC, 10% of cases were associated with an IPMN [16]. We therefore assumed that 10% represented a reasonable upper bound of the percentage of PDAC cases arising from a side-branch IPMN. Model projections that substantially exceeded 10% were presumed to support our hypothesis that available estimates of the malignant risk of side-branch IPMNs are not generalizable to all such findings. Our purpose was to test for the possibility that published malignancy risks for side-branch IPMN are overestimates, likely due to verification bias.

Materials and Methods

Overview of the Modeling Framework and Base-Case Analysis

We developed a microsimulation model to test the hypothesis that current published risks of malignancy from side-branch IPMNs are not generalizable to all such findings detected on imaging. For hypothetical cohorts with a mean age ranging from 55.7 to 75 years (base case: mean age = 55.7 years, SD = 11.1 years) and 5 years of follow-up, we compared the model-predicted number of detected PDACs between two arms: one in which development of PDAC was based only on published data on the prevalence and malignant potential of side-branch IPMNs [8, 11] and the other in which development of PDAC was based on observed PDAC incidence in the United States, elicited from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program [17]. We assumed that if the percentage of literature-predicted side-branch IPMN-associated PDAC cases relative to SEER-predicted total PDAC cases substantially exceeded 10% [16], a bias in the published data was likely to be present.

We developed our model using TreeAge Pro (version 2017, TreeAge Software) using a 1-year cycle length and a 5-year time horizon. Although it is known that some side-branch IPMNs can progress to PDAC after 5 years [9, 10], we used a data source (Moris et al. [8]) in which no patients were reported to experience malignant transformation after 5 years. Use of this study [8] enabled us to model the timing of observed events of malignant transformation at a granular level (see Model Parameters section). We evaluated the implications of our approach by extending the time horizon of our analysis to 10 years in the sensitivity analysis.

To estimate the number of side-branch IPMN-associated PDAC cases over the 5-year period, we assumed that a defined cohort of patients of a given mean age entered the model having just under-gone abdominal MRI. The MRI either discovered or did not discover a side-branch IPMN according to age-adjusted cyst prevalence estimates [11]. Discovered side-branch IPMNs either progressed to PDAC or did not according to time-varying estimates of the probability of malignancy [8]. To estimate the total number of PDAC cases among the cohort over the 5-year period, we applied age-specific SEER-derived probabilities of developing PDAC for 5 years to simulated patients. All simulated patients experienced age-specific all-cause mortality. Further details concerning our extraction of estimates from the literature and the SEER registry are described in the next section.

Model Parameters

An overview of model parameters and an overview of sensitivity analysis ranges are in Table 1.

Age-specific prevalence of side-branch intraductal papillary mucinous neoplasms—We identified three studies that estimated the prevalence of pancreatic cystic lesions in a general population health screening setting [11, 18, 19]. Among those studies, two estimated the prevalence of IPMN (defined as pancreatic cysts communicating with the main pancreatic duct) in addition to estimating the prevalence of all cystic lesions [11, 18]. Of these two studies, we selected the study by Mizuno et al. [11] to inform the probability of IPMN detection at abdominal MRI in our model because of its large sample size (5296 individuals), inclusion of MRCP with MRI, and its recent publication year (2017). In that study, 4.4% of all patients had cysts with a communication to the main pancreatic duct (232/5296) [11]; we assumed that these cysts represented side-branch IPMNs. A very small number of combined-type IPMNs could have been included in this estimate; 0.5% (26/5296) of individuals in that study had a main duct that was greater than 2 mm. We tested a range of side-branch IPMN prevalence estimates in the sensitivity analysis.

We estimated the age-specific prevalence of side-branch IPMN at abdominal imaging using additional data available in the analysis conducted by Mizuno et al. [11]. The prevalence estimate described earlier (4.4%) was reported only for the full study population. However, the study also reported the prevalence of all pancreatic cystic lesions at 5-year age intervals. We used these data and the proportion of presumed side-branch IPMNs among all pancreatic cystic lesions in the full study population ($0.044 / 0.137 = 0.32$) to estimate the prevalence of side-branch IPMN at 5-year age intervals. We then developed a linear regression model to predict the prevalence of side-branch IPMN on the basis of single-year age groups, where age groups were modeled flexibly using restricted cubic splines with three knots and model weights based on age-group sample size were applied. The prevalence of pancreatic cystic lesions by age group was extracted from Figure 2 of the article by Mizuno et al. [11] using Engauge Digitizer software (version 10.3, Mark Mitchell) [20]. Regression analysis was conducted in R (version 3.2.2, The R Foundation) using the RMS package.

Time-varying probability of malignancy for side-branch intraductal papillary mucinous neoplasms—We evaluated six studies that examined the malignant

potential of side-branch IPMN [5–10]; two were meta-analyses [5, 10]. Estimates of the malignancy rate ranged from 1.9% to 7.8%, and the follow-up period varied by study [5–10]. We selected the International Intraductal Papillary Mucinous Neoplasms Registry study by Moris et al. [8] to inform the malignancy rate of incidentally detected side-branch IPMNs in our model because of its multicenter design, long length of follow-up, relatively large sample size, and stratification of lesions into low-risk and high-risk categories [8]. Moris et al. [8] found the malignancy rate of low-risk lesions (defined as cysts < 3 cm and lacking a solid component or main pancreatic duct dilatation) to be 1.9%; in that study, all malignancies were detected in the first 5 years of follow-up [8]. In our base-case analysis, consistent with the approach of Moris et al. [8], we counted all cases of high-grade dysplasia and invasive carcinoma as malignant. We used their specific results for low-risk side-branch IPMNs to generate maximally conservative (i.e., lowest possible) estimates of the number of side-branch IPMN–associated PDAC cases. When considering the range of estimated malignancy rates (i.e., 1.9–7.8%) [5–10], Moris et al. [8] reported the lowest overall rate of malignancy for low-risk cysts (1.9%), biasing against our hypothesis.

Moris et al. [8] provided granular detail on each low-risk patient who developed malignancy during their study, including the number of months of follow-up before their diagnosis of malignancy. We used these data and the sample size of the low-risk subgroup (431 individuals) to estimate the yearly probability of malignancy of a side-branch IPMN.

Age-specific all-cause probability of death—Age-specific all-cause probability of death was calculated using the 2014 U.S. Life Tables from the Centers for Disease Control and Prevention [21].

Age-specific pancreatic ductal adenocarcinoma incidence—We elicited the total number of PDAC cases over a 5-year horizon for each age-specified cohort using data from the SEER cancer registry [17]. These years were chosen to match the time period of the study by Moris et al. [8].

Age distribution of cohorts—To inform the age distribution of each simulated cohort, we used the mean age and SD reported in the study by Mizuno et al. [11] (i.e., the study used to inform cyst prevalence [mean age = 55.7 years, SD = 11.1]). We assumed a normal distribution for age. A patient's age affected the all-cause mortality risk, the probability of presenting with a side-branch IPMN, and the SEER-derived likelihood of developing PDAC.

Time horizon—In the study by Moris et al. [8], which was used to inform the malignant potential of a side-branch IPMN, all malignancies in the low-risk group were diagnosed within the first 5 years of follow-up. Therefore, we limited the time horizon of our base-case analysis to 5 years. We further extended our time horizon in the sensitivity analysis, as described in the Sensitivity Analysis section.

Model Outcomes

The primary outcome of our analysis was the percentage of side-branch IPMN–associated PDAC cases (i.e., the number of side-branch IPMN–associated PDAC cases divided by the number of total SEER-predicted cases over 5 years). If the published prevalence and

malignancy rates for side-branch IPMNs are generalizable to an age-matched asymptomatic population, we would expect this percentage to be no more than 10% [16]. This estimate of the percentage of PDAC that arises from IPMN is based on a surgical series of 1260 consecutive patients with confirmed PDAC [16]. This estimate likely represents an overestimate when applied to the current analysis, both because only resected lesions were included in that study and because that study was not specific to side-branch IPMNs [16]. As a result, this estimate may be considered relatively high; however, its use again likely biased against our hypothesis.

We conducted two secondary analyses. For both analyses, we used our base-case age distribution (mean age = 55.7 years, SD = 11.1) [11]. In the first, we assumed fixed values for the percentage of side-branch IPMN-associated PDAC in our analysis (10%) [16] and the prevalence of side-branch IPMN [11], and we estimated the implied rate of malignant transformation of side-branch IPMN. In the second, we assumed fixed values for the 5-year malignancy rate of side-branch IPMN [8], again assumed a 10% rate of side-branch IPMN-associated PDAC, and estimated the implied prevalence of side-branch IPMN in an adult asymptomatic population. These analyses were meant to provide context for the magnitude and direction of error that may be present in one or both estimates.

Sensitivity Analysis

To evaluate the effects of uncertainty in our model parameters on our results, we conducted one-way deterministic sensitivity analyses. We varied estimates of side-branch IPMN prevalence and the rate of malignant transformation of side-branch IPMN, respectively, from 50% to 150% of their corresponding base-case estimates (Table 1). We explicitly considered the circumstance in which high-grade dysplasia does not count as “malignant”; in this analysis, the cumulative probability of malignancy over 5 years was 1.2% [8]. We also varied the mean age of our cohort from 55.7 years (base case) to 75 years to determine whether age affected the corresponding percentage of side-branch IPMN-associated PDAC cases. In addition, we extended the time horizon of our analysis from 5 to 10 years, assuming that no additional incident side-branch IPMN-associated PDAC cases developed in years 6–10. In this way, we estimated the maximum effect—biasing against our hypothesis—that use of a 5-year horizon could have had on our results.

Relevant to our secondary analyses, we varied our assumption of the percentage of PDAC that arises from IPMN from 0% to 200% of the base-case estimate.

Results

Base-Case Analysis

In the base-case analysis and across all sensitivity analyses, percentages of side-branch IPMN-associated PDAC cases greatly exceeded 10%. In the base case (55.7-year-olds), we projected that among a simulated cohort of 10 million individuals, there would be 7877 incident cases of side-branch IPMN-associated PDAC over a 5-year period and 9786 incident cases of PDAC (independent of developmental pathway), yielding a percentage

of 80%. This finding implies an eightfold increase in the number of incident cases of side-branch IPMN–associated PDAC over the expected.

Secondary Analyses

When we assume that 10% of PDAC arises from a side-branch IPMN and apply the base-case value for side-branch IPMN prevalence, the model-predicted malignancy rate of side-branch IPMN over a 5-year period was 0.24%. When we varied this assumed proportion from 0% to 20%, the model-predicted malignancy rate of side-branch IPMN ranged from 0% to 0.46%. When we assume that 10% of PDACs arise from a side-branch IPMN and apply the base-case malignancy rate of side-branch IPMN, the model-predicted prevalence of side-branch IPMN in an adult asymptomatic population was 0.56%. When we varied the assumed proportion of PDAC arising from a side-branch IPMN from 0% to 20%, the model-predicted prevalence of side-branch IPMN ranged from 0% to 1.1%.

Sensitivity Analysis

The results of our one-way sensitivity analyses are depicted in Table 2 and Figure 1. Our results were sensitive to the prevalence of side-branch IPMN and the probability that a detected side-branch IPMN will progress to malignancy. When the probability of side-branch IPMN detection was varied from 50% to 150% of the base case [11], the percentage of IPMN–associated PDAC ranged from 41% to 121%. When applying a reduced risk of progression of side-branch IPMN to malignancy by counting only invasive carcinoma as malignant (i.e., not high-grade dysplasia as malignant) [8], we found that the percentage of IPMN–associated PDAC was 51%, which is still much higher than the upper bound of 10%. When extending the time horizon to 10 years, we found that even when no additional IPMN–associated cancers developed in years 6–10, the percentage of IPMN–associated PDAC was 37%, almost four times the upper bound of 10%.

Discussion

Using simulation modeling, we show that reported malignancy rates in the literature likely overestimate the true malignant potential of side-branch IPMNs and therefore are likely not generalizable to all such findings. In a simulated cohort whose cyst prevalence and malignant potential were informed by reported literature estimates, eight times more cases of IPMN–associated PDAC were detected relative to the upper limit of what would be expected when an upper bound of 10% for the proportion of side-branch IPMN–associated PDAC was assumed. Under the same assumption, we estimated that the probability of malignancy for a side-branch IPMN may be substantially lower than current estimates available in the literature. These findings suggest the presence of verification bias in the published literature.

We are not aware of similar studies that test the hypothesis that reported risk estimates of side-branch IPMN are not generalizable to all side-branch IPMNs using a simulation modeling approach. In 2013, Gardner et al. [22] calculated the prevalence of pancreatic mucin-producing adenocarcinoma (a proxy for cyst-associated PDAC) among individuals with a pancreatic cystic lesion [22]. Using available estimates of pancreatic cyst prevalence from the literature (not specific to IPMN) as well as SEER incidence data, they estimated

that the prevalence of mucin-producing adenocarcinoma arising in patients with pancreatic cysts was 33.2 per 100,000 [22]. As in our study, they found that the rate of malignant transformation among pancreatic cystic lesions was inconsistent with the available literature estimates for the malignant potential of such lesions [22].

Our study is distinct in several ways, including the methods used and data incorporated. Most importantly, our study focuses on side-branch IPMN, the finding associated with the greatest uncertainty in the management of patients with pancreatic cystic lesions, and we incorporated current estimates for both prevalence and risk (published in 2017). Despite these differences, the similar results provide reassurance of the validity of our findings.

Our study has several limitations. First, the estimate of 10% used in our analysis as the upper bound for side-branch IPMN-associated PDAC is associated with uncertainty. As described earlier, it can be argued that this estimate is likely to be artificially high. However, from a biologic standpoint, it is not possible to exclude the possibility that microscopic cysts (i.e., cysts that cannot be seen at imaging) were the initial precursor lesions for a proportion of PDAC cases that are currently classified as arising from the solid pathway. This circumstance would mean that the 10% estimate could be artificially low. In our primary and secondary analyses, with a substantially higher upper bound, our conclusions did not substantially change. However, given this uncertainty, we do not advise that our calculated risk estimate for side-branch IPMN ($< 0.24\%$) be used for clinical purposes. Our objective in generating this estimate was to determine the need for further hypothesis-driven primary data collection. Given the magnitude of difference between this calculated estimate and reported estimates, we believe that related further research is warranted.

Second, when predicting the number of side-branch IPMN-associated PDAC cases among a cohort with a given mean age, we assumed that patients could not develop incident side-branch IPMNs and then side-branch IPMN-associated PDAC during the 5-year follow-up period, because of the absence of robust data to inform this possibility.

Third, the definition of side-branch IPMN used in our study (i.e., cysts with a clear communication to the main pancreatic duct) could result in an underestimate of the total number of IPMNs in the cohort. In reality, many cysts lacking a clear, visible communication to the main pancreatic duct on initial imaging may also be side-branch IPMNs. Both limitations suggest that the proportions presented could be artificially low; in other words, our findings may represent a conservative estimate of the magnitude of bias present in published estimates of the malignancy risk of side-branch IPMN.

Fourth, in the study by Moris et al. [8], which was used to inform our time-varying probability of side-branch IPMN malignancy, only eight malignancies were detected in the 431-patient low-risk cohort; there were very few malignancies in each 1-year time interval (1–3 malignancies) [8]. However, their cumulative probability of malignancy (1.9%) [8] approximated estimates seen in similar studies [5–7], providing reassurance that use of reported data from Moris et al. [8] were reasonable.

Fifth, in the base-case analysis, we limited the time horizon to 5 years, but some side-branch IPMNs transform beyond 5 years of follow-up [9, 10]. With a longer time horizon, both

the number of detected PDACs and the number of detected side-branch IPMN-associated PDACs would be expected to increase. To verify that modeling a longer time horizon would not result in the percentage of side-branch IPMN-associated PDAC approaching 10%, we extended our time horizon to 10 years. Even when assuming that no side-branch IPMN-associated PDACs developed between years 6 and 10 (an assumption that biases against our hypothesis), we found that the percentage of IPMN-associated PDAC was 37%, almost four times the upper bound of 10%.

Our results expose key deficiencies in the available evidence for the natural history of side-branch IPMNs and provide context for referring physicians tasked with managing these common findings. Our findings suggest that the true malignancy rate of side-branch IPMNs is likely to be smaller than the risks reported in the literature (1.9–7.8%) [5–10]. Our study is not designed to directly inform changes in current management practices and recommendations for side-branch IPMNs [14]. Moreover, side-branch IPMNs that experienced referring providers and radiologists elect to follow may, in fact, be similar to those for which the natural history has been reported [5–10]. In the coming years, our study may be used, together with published observational data on the natural history of side-branch IPMNs and the ongoing experience of physicians who are experts in the diagnosis and management of side-branch IPMNs, to inform future revisions of management recommendations. Present uncertainty surrounding the natural history of side-branch IPMN further highlights the importance of each patient's individual circumstance when making decisions regarding follow-up or treatment of side-branch IPMN. Finally, our findings underscore the need to expand our understanding of the natural history of precursors to PDAC with a particular focus on learning to better discriminate suspicious lesions from those that harbor a negligible risk of malignancy.

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Fig. 1—

Bar graph shows model-predicted number of cases of pancreatic ductal adenocarcinoma (PDAC)—both overall PDAC and side-branch intraductal papillary mucinous neoplasm (IPMN)—associated PDAC—by mean age over 5-year horizon for cohorts of 10 million simulated individuals. Dark gray bars show predicted number of PDAC cases arising from side-branch IPMNs assuming that only 10% of PDACs arise from side-branch IPMNs.

TABLE 1:

Model Parameters

Parameter	Base-Case Value	Sensitivity Analysis Range	Source
Age (y), mean (SD)	55.7 (11.1)	55.7–75	[11]
Length of follow-up (y)	5	10	[8]
Proportion of patients with a side-branch IPMN ^a	4.4×10^{-2}	50–150%	[11]
1-Year incidence of PDAC ^b	1.4×10^{-4}	NA	[17]
1-Year all-cause probability of death ^b	6.7×10^{-3}	NA	[21]
Probability that side-branch IPMN is malignant ^c	1.9×10^{-2}	50–150%	[8]

Note—IPMN = intraductal papillary mucinous neoplasm, PDAC = pancreatic ductal adenocarcinoma, NA = not applicable.

^aParameter varies with age; value shown corresponds to the overall proportion of presumed side-branch IPMN in the source data population (Mizuno et al. [11], $n = 5296$). Using these data, we calculated age-specific side-branch IPMN prevalence estimates to determine the prevalence of each hypothetical population evaluated, as detailed in the Materials and Methods.

^bParameter varies with age; value shown corresponds to the mean age of the population.

^cParameter varies with time since diagnosis of IPMN; value shown corresponds to the cumulative probability over 5 years.

TABLE 2:

Results of Sensitivity Analyses on the Percentage of Side-Branch Intraductal Papillary Mucinous Neoplasm (IPMN)—Associated Pancreatic Ductal Adenocarcinoma (PDAC) to Total PDAC

Parameter	Side-Branch IPMN-Associated PDAC (Model-Predicted)		Parameter Range Tested
	Minimum Percentage	Maximum Percentage	
Proportion of patients with side-branch IPMN on imaging	40.7	121.2	50–150% × age-specific estimate ^a
Probability of malignancy within 5 years after diagnosis	40.7	121.0	0.01–0.03 ^b

^aParameter varies with age. Base-case population reflects a distribution of ages centered around 55.7 years (see Materials and Methods for details).

^bParameter varies with time since diagnosis of side-branch IPMN; value shown corresponds to the cumulative probability over 5 years.