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Model to Determine Risk of Pancreatic Cancer in Patients With New-Onset Diabetes

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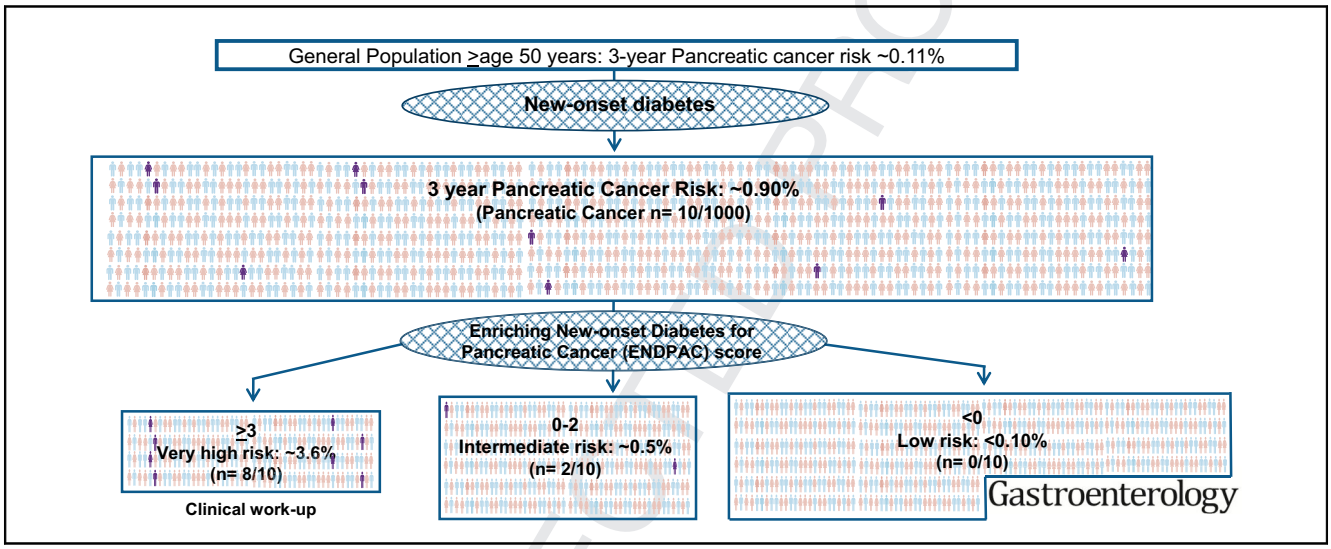

BACKGROUND & AIMS: Of patients with new-onset diabetes (NOD; based on glycemic status) older than 50 years, approximately 1% are diagnosed with pancreatic cancer (PC) within 3 years. We aimed to develop and validate a model to determine risk of PC in patients with NOD. **METHODS:** We retrospectively collected data from 4 independent and nonoverlapping cohorts of patients (N = 1,561) with NOD (based on glycemic status; data collected at date of diagnosis and 12 months previously) in the Rochester Epidemiology Project from January 1, 2000 through December 31, 2015 to create our model. The model weighed scores for 3 factors identified in the discovery cohort to be most strongly associated with PC (64 patients with PC and 192 with type 2 diabetes): change in weight, change in blood glucose, and age at onset of diabetes. We called our model Enriching New-Onset Diabetes for Pancreatic Cancer (END-PAC). We validated the locked-down model and cutoff score in an independent population-based cohort of 1,096 patients with diabetes; of these, 9 patients (82%) had PC within 3 years of meeting the criteria for NOD. **RESULTS:** In the discovery cohort, the END-PAC model identified patients who developed PC within 3 years of diabetes onset (area under receiver operating characteristic curve 0.87); a score of at least 3 identified patients who developed PC with 80% sensitivity and specificity. In the validation cohort, a score of at least 3 identified 7 of 9 patients with PC (78%) with 85% specificity; the prevalence of PC in patients with a score of at least 3 (3.6%) was 4.4-fold greater than in patients with NOD. A high END-PAC score in patients who did not have PC (false positives) was often due to such factors as recent steroid use or different malignancy. An END-PAC score lower than 0 (in 49% of patients) meant that patients had an extremely low risk for PC. An END-PAC score of at least 3 identified 75% of patients in the discovery cohort more than 6 months before a diagnosis of PC. **CONCLUSIONS:** Based on change in weight, change in blood glucose, and age at onset of diabetes, we developed and validated a model to determine risk of PC in patients with NOD based on glycemic status (END-PAC model). An independent prospective study is needed to further validate this model, which could contribute to early detection of PC.

Keywords: Enriching New-Onset Diabetes for Pancreatic Cancer; Biomarker; Pancreas; Screening.

Abbreviations used in this paper: **BG, blood glucose; EAG, estimated average glucose; END-PAC, Enriching New-Onset Diabetes for Pancreatic Cancer; EXPAND, Examination of the Pancreas in New-Onset Diabetes; FBG, fasting blood glucose; NOD, new-onset diabetes; PC, pancreatic cancer; PC-NOD, pancreatic cancer in new-onset diabetes; REP, Rochester Epidemiology Project; T2-NOD, type 2 new-onset diabetes.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

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Pancreatic ductal adenocarcinoma has a dismal (9%) 5-year survival,[1] largely because most cases (85%) of pancreatic cancer (PC) are diagnosed at an advanced stage. Developing strategies for early detection of resectable sporadic PC are critical for improving survival.[2] Because PC is uncommon (annual incidence 37 of 100,000 in patients >50 years of age[3]), a 3-step approach to its early detection has been suggested[4]: (1) define a high-risk group for PC, (2) enrich the high-risk group further for PC, and (3) find the lesion in the highly enriched cohort.

The only known high-risk group for sporadic PC is composed of patients at least 50 years of age with glycemia-defined new-onset diabetes (NOD).[2] Compared with the general population, such patients have a 6- to 8-fold higher risk of being diagnosed with PC within 3 years of first meeting the glycemic criteria for NOD, with a 3-year incidence of PC being approximately 1%.[2] Currently, type 2 NOD (T2-NOD) is indistinguishable from NOD in PC (PC-NOD). Facilitating the utility of a clinical workup for PC-NOD requires identifying a very high-risk group for PC.

Three previous prospective studies included some form of enrichment strategy to identify PC in those with incident, physician-diagnosed NOD.[5–7] Although the cohorts were clearly enriched for PC (prevalence 2.5%–12%), all identified PC cases were at an advanced stage,[5,6] likely because of the use of markers of late cancer for risk stratification. Two recent retrospective studies using large databases, the Veterans Administration database[8] and The Health Improvement Network (THIN) database[9] in the United Kingdom, estimated PC incidence in physician-diagnosed NOD and proposed models for enriching the cohort for PC. They found the 3-year incidence of PC to be 0.25% and 0.4%, respectively, consistent with the incidence reported in studies using physician-diagnosed diabetes,[10] but these incidences are significantly lower than when using glycemia-defined NOD as in a previous study[2] and the present study. Munigala et al[8] concluded that despite a 4-fold enrichment, the incidence of PC in physician-diagnosed NOD was too low to warrant further study.

Nearly 60% of PC-NOD cases occur within 12 months of glycemic onset.[2,11] Because physician diagnosis of diabetes occurs months to years after diabetes onset,[11–14] the strategy of using NOD as a clue for early diagnosis of PC would be most effective if NOD could be identified at its glycemic onset rather than at its clinical diagnosis. Our goal was to develop a model that could be used concurrently with glycemic onset of NOD.

We developed our model based on 3 previously noted features that distinguish T2-NOD from PC-NOD. T2-NOD is often accompanied by weight gain,[15] whereas PC-NOD paradoxically occurs with weight loss.[16,17] Progression from a normal fasting blood glucose (FBG) level to T2-NOD is a slow process occurring over approximately 8 years,[18,19] whereas PC-NOD progresses rapidly over 2–3 years.[17,20] Patients with T2-NOD are younger at diabetes diagnosis[21] than patients with PC.[22] In our discovery set of patients with T2-NOD and PC-NOD, we confirmed these features.

We created and tested various models based on these features. The best "predictiveness" for PC was provided by a model that included age, change in weight (Δweight), and change in blood glucose (ΔBG) level during the previous year as categorical variables. The weighted score, termed the Enriching New-onset Diabetes for Pancreatic Cancer (END-PAC) score, classifies patients with NOD into high-, intermediate-, and low-risk groups for PC. We validated the score in a population-based glycemia-defined NOD cohort. An END-PAC score of at least 3 significantly enriched the NOD cohort for PC, even those with a longer than 6-month lead time to PC diagnosis. If the extremely high risk of PC in the END-PAC cohort is validated, then we believe that it would warrant clinical workup for PC.

Methods

This study was approved by the institutional review boards of the Mayo Clinic Foundation and the Olmsted Medical Center (Rochester, MN). The Rochester Epidemiology Project (REP), a unique medical records linkage system funded by the National Institutes of Health since 1966, collects, collates, and indexes patient-level data from all health care providers in Olmsted County, Minnesota and the surrounding 27 county areas[23,24] and allows for accurate population-based epidemiologic research.

Cohorts Assembled

We assembled the following 4 independent and nonoverlapping cohorts from the REP resources: 3 retrospectively identified and annotated cohorts (discovery set of PC-NOD, n = 64; discovery set of T2-NOD, n = 192; and a population-based NOD validation set, n = 1,096) and a prospectively identified cohort of patients with NOD recruited into a pilot screening study for PC-NOD (Examination of the Pancreas in New-Onset