Association of Glycated Hemoglobin With a Risk of Pancreatic Cancer in High-Risk Individuals Based on Genetic and Family History

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INTRODUCTION: **Screening for pancreatic cancer (PC) is suggested for high-risk individuals. Additional risk factors may enhance early detection in this population.**

METHODS: **Retrospective cohort study among patients with germline variants and/or familial pancreatic cancer in an integrated healthcare system between 2003 and 2019. We calculated the incidence rate (IR) by risk category and performed a nested case-control study to evaluate the relationship between HbA1C and PC within 3 years before diagnosis (cases) or match date (controls). Cases were matched 1:4 by age, sex, and timing of HbA1c. Logistic regression was performed to assess an independent association with PC.**

RESULTS: **We identified 5,931 high-risk individuals: 1,175(19.8%) familial PC, 45(0.8%) high-risk germline variants (*STK11, CDKN2A*), 4,097(69.1%) had other germline variants (*ATM, BRCA 1, BRCA 2, CASR, CDKN2A, CFTR, EPCAM, MLH1, MSH2, MSH6, PALB2, PRSS1, STK11,* and *TP53*), and 614(10.4%) had both germline variants and family history. Sixty-eight patients (1.1%) developed PC; 50% were metastatic at diagnosis. High-risk variant was associated with greatest risk of PC, IR = 85.1(95% confidence interval: 36.7–197.6)/10,000 person-years; other germline variants and first-degree relative had IR = 33 (18.4, 59.3), whereas IR among ≥2 first-degree relative alone was 10.7 (6.1, 18.8). HbA1c was significantly higher among cases vs controls (median = 7.0% vs 6.4%, $P = 0.02$). In multivariable analysis, every 1% increase in HbA1c was associated with 36% increase in odds of PC (odds ratio 1.36, 95% confidence interval: 1.08–1.72). Pancreatitis was independently associated with a risk of PC (odds ratio 3.93, 95% confidence limit 1.19, 12.91).**

DISCUSSION: **Risk of PC varies among high-risk individuals. HbA1c and history of pancreatitis may be useful additional markers for early detection in this patient population.**

KEYWORDS: pancreatic cancer; screening; high-risk; genetics; A1c

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/B28

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INTRODUCTION

Pancreatic cancer is the third leading cause of cancer-related death among both men and women in the United States (1). Based on the relatively low incidence of this disease, the United States Preventative Services Task Force recommends against widespread population-based screening (2). By contrast, targeted screening in specific high-risk populations based on the genetic profile as well as family history is advised by several societies (3–7). Previous cohort studies in the United States (8) and Europe (9,10) used a combination of cross-sectional imaging as well as endosonography in the surveillance of high-risk individuals. However, limitations have been noted with such an approach, including identification of interval advanced cancers among patients undergoing surveillance (11). Several strategies have been suggested to enhance early detection in high-risk individuals (HRI) undergoing screening (12). In addition, recent guidelines have also suggested potentially including glycemic

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parameters as well as broadening the criteria for screening to include patients *BRCA 1 or BRCA 2* germline variants in the absence of family history (7).

In addition to genetic or familial risk factors, several additional clinical parameters may help inform risk of pancreatic cancer among individuals considered at increased risk. New onset diabetes in persons aged 50 years or older has been identified as a potential marker for pancreatic cancer (13,14), and recent guidelines from the International Cancer of the Pancreas Screening consortium recommend inclusion of glycemic parameters as part of the evaluation of patients undergoing screening (3). Although incorporation of glycemic testing is an attractive adjunct to imaging/endoscopy-based screening with the potential to add a low-cost biomarker that can be readily measured on a more frequent basis compared with invasive testing, data regarding the relationship of glycemic testing and risk of pancreatic cancer in HRI are limited with at least one study failing to identify an association among patients undergoing screening (15). Acute (16) and chronic pancreatitis (17) are also associated with an increased risk of pancreatic cancer in the general population. However, it remains unclear the extent to which this risk carries over to HRI and whether such a history should be factored into their clinical assessment.

There has also been increasing recognition of the heterogeneity of cancer risk among HRI who harbor specific germline variants in high-risk genes [*CDKN2A* (18) and *STK11* (19)] in comparison with patients with familial pancreatic cancer in the absence of established genetic risk factors (20). Factors that contribute to this heterogeneity, if confirmed, could allow for a more targeted approach with greater intensity of screening applied to patients at highest risk for developing pancreatic cancer.

The objective of this study was to evaluate the risk of pancreatic cancer among HRI in a real-world setting based on the genetic and family history. We further sought to characterize the relationship between glycated hemoglobin on the risk of pancreatic cancer in this patient population.

METHODS

Study design and setting

This study was approved by the Institutional Review Board of Kaiser Permanente Southern California (KPSC). We performed 2 sets of studies to evaluate the risk of pancreatic cancer in HRI.

1. We first performed a retrospective cohort study among patients in KPSC, an integrated healthcare system from January 1, 2003, through December 31, 2019. The study initiation date was based on the availability of robust electronic health data as well as genetic testing results. The study completion date was determined to limit analysis to the period before the initiation of formal screening for HRI in KPSC.
2. We then performed a nested case-control study to evaluate the relationship between glycated hemoglobin and risk of pancreatic cancer with both cases and controls drawn from the overall study population (January 1, 2003–December 31, 2019, retrospective cohort).

Patient population and exposures

We identified potentially eligible patients based on the family history as well as genetic testing. The family history was determined based on structured data from the electronic health record and categorized based on both extent and degree. Patients with ≥2 first-degree or ≥3 relatives with pancreatic cancer were considered familial pancreatic cancer. Varying definitions of familial pancreatic cancer were incorporated into subsequent analyses (see below). Genetic test results were ascertained from an internal genetics registry with the following included in this study: *ATM, BRCA 1, BRCA 2, CASR, CDKN2A, CFTR, EPCAM, MLH1, MSH2, MSH6, PALB2, PRSS1, STK11,* and *TP53*. Germline hereditary cancer genetic tests were performed by NextGen sequencing in clinical laboratory improvement amendments-certified commercial laboratories (GeneDx, Invitae Genetics, or Myriad Laboratory) for a multigene hereditary cancer gene panel including all the genes of interest using blood, buccal, or saliva sampling. All patients were provided post-test genetic counseling about test results as part of routine clinical care. The KPSC hereditary cancer genetics program has previously been described (PMID: 36261688). Cancer outcomes were identified from the prospectively maintained internal KPSC cancer registry as well as cross-referencing the California State Death Index.

Retrospective HRI patient cohort

Patient index date (start date) was determined as January 1, 2003, for patients enrolled at the time of study initiation and date of enrollment applied for those that entered the healthcare system at any point thereafter up to the study completion date. Patients were censored at the time of pancreatic cancer diagnosis, disenrollment, death, or study end date. Exposure categories were grouped according to the following: familial pancreatic cancer in the absence of known pathogenic or likely pathogenic (P/LP) germline variant as well as individual high-risk germline variant with or without family history of pancreatic cancer in first-degree relative (FDR). We calculated the incidence rate of pancreatic cancer based on age, demographic factors, as well as by genetic/family history exposure category. For comparison, we generated incidence rates for the high-risk, familial risk (family history without meeting criteria for familial pancreatic cancer or P/LP variant) as well as the reference KPSC population. We performed additional sensitivity analyses evaluating the risk of pancreatic cancer based on varying definitions for familial pancreatic cancer (≥2FDR exclusively, ≥2FDR or 3+ family members, or ≥3 FDR) as well as specific gene combinations with or without family history e.g., *BRCA1* or *BRCA2* with or without family history in FDR.

Glycated hemoglobin (A1c), pancreatitis, and risk of pancreatic cancer

We performed a nested case-control study to specifically evaluate the relationship between glycated hemoglobin as well as pancreatitis and risk of pancreatic cancer in a high-risk population. We included cases that developed pancreatic cancer identified from the retrospective cohort. Age-matched and sex-matched noncancer contemporaneous control patients were randomly selected in a 1:4 ratio. Subsequent cancer cases were allowed to serve as potential contemporaneous controls before cancer diagnosis (incidence density sampling). All cases and controls were required to have A1c measurement obtained within 3 years of diagnosis (cases) or before index match date (controls). For both cases and controls, the most recent value for A1c was used in analysis. Controls were further matched to individual cases based on time interval (±3 months) from most recent A1c value. Diabetes status was determined based on a combination of diagnosis codes, medications, and laboratory data applying the following logic: any hospital discharge code for diabetes (*International*

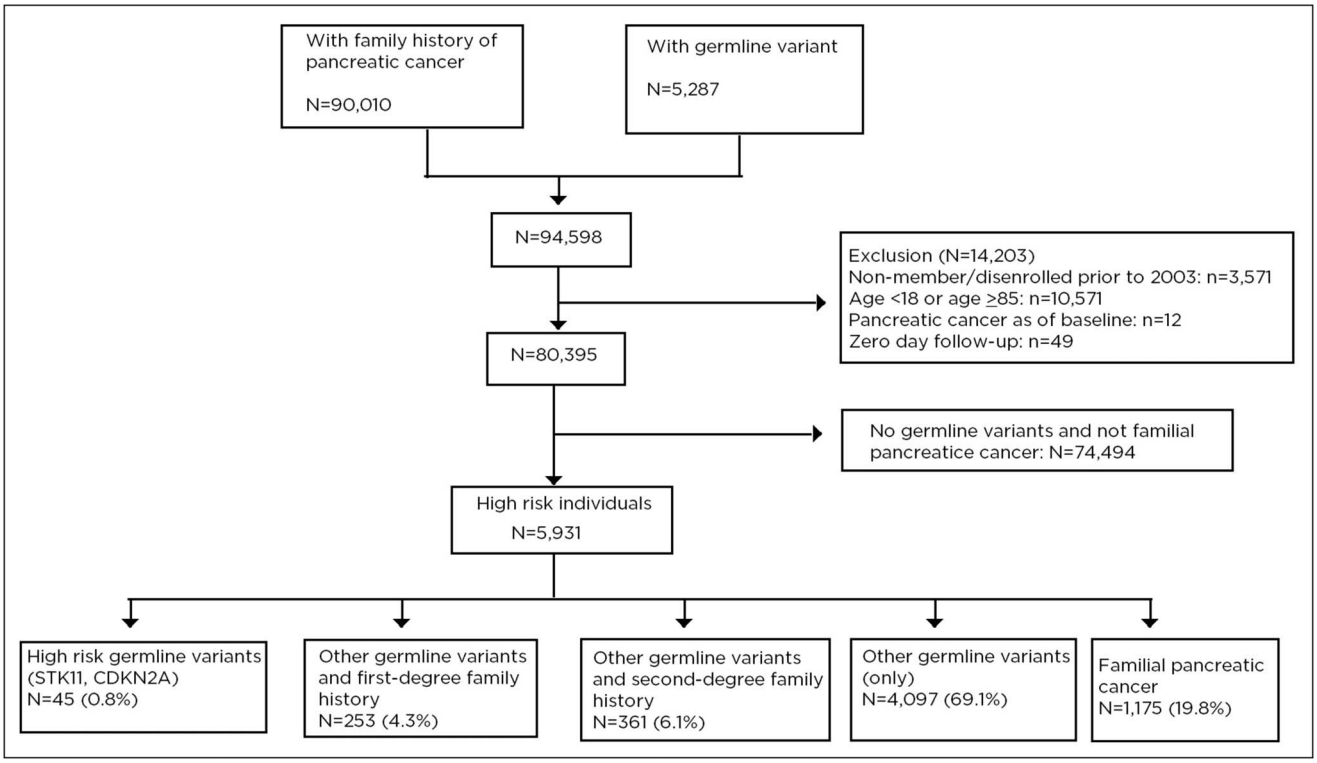

Figure 1. Identification of high-risk individuals.

Classification of Diseases, Ninth Revision [*ICD-9*] code 250.XX), any KPSC internal code for diabetes (ie, 200, 1201, 1202, 1203, 1204, 1839, 3141, 3186, 3639, 4124, or 5782), any prior HbA1c level greater than 7.0%, or any dispensing record for insulin or an oral hypoglycemic medication (not including metformin). Patients identified with diabetes were then subclassified as new onset if diagnosed ≤6 months of cancer/index date or long standing if >6 months. Pancreatitis was identified based on the diagnosis code (*ICD-9* 577.0, 577.1, *ICD-10* K85.*, K86.*).

We performed conditional logistic regression to determine the relationship between most recent A1c and risk of pancreatic cancer adjusting for genetic/family history exposure category, acute or chronic pancreatitis history (*ICD-9/10* 577.0 577.1/K85 K86.0 K86.1), and body mass index (obese, overweight, normal, or underweight).

RESULTS

Retrospective HRI patient cohort

We identified a total of 5,931 patients meeting criteria for high-risk screening based on current clinical recommendations (3–5,7). Cohort assembly is presented in Figure 1. The baseline demographic and clinical characteristics of the study cohort are presented in Table 1. The average duration of follow-up was 12.3 years with a total of 72,678 person years. A total of 1,175 patients met criteria for familial pancreatic cancer based on at least 2 FDR (n = 894) or ≥3 family members in total (n = 281). The distribution of entry criteria (genetic and family history) is also presented in Table 1.

There was a total of 68 pancreatic cancers diagnosed during the study period. Most cancers were pancreatic ductal adenocarcinoma and diagnosed at an advanced stage (III/IV). Distribution of pathology and stage information is presented in Table 2. The incidence rate by the hereditary risk category is presented in Table 3. High-risk germline variants (*STK11* and *CDKN2A*) were associated with the highest incidence of pancreatic cancer 85.1 (95% confidence limit [CL] 36.7, 197.6)/10,000 person-years, whereas other examined germline variants were also linked to a still markedly elevated risk of pancreatic cancer 33 (95% CL 18.4, 59.3)/10,000 person-years. Familial pancreatic cancer as well as the presence of moderate-to-low risk germline variants in the absence of family history of pancreatic cancer in FDR were associated with relatively lower incidence of pancreatic cancer by comparison (Table 3). The cancer incidence rates for HRI, familial cohort, and the KPSC reference population during the study years are presented in Supplementary Table 2 (see Supplemental Digital Content, http://links.lww.com/CTG/B28). Additional incidence rates for pancreatic cancer in the study cohort stratified by demographic factors (age, sex, and race/ethnicity) are presented Supplementary Table 1 (see Supplemental Digital Content, http://links.lww.com/CTG/B28). Figure 2 depicts the age distribution at pancreatic cancer diagnosis stratified by risk category for the study cohort with the median age in the sixth decade for all risk categories. Also of note, only patients with either *CDKN2A* or *STK11* developed cancer before age 50.

Glycated hemoglobin, pancreatitis, and risk of pancreatic cancer

Among the 68 patients that developed pancreatic cancer, 52 (76%) had A1c measurement within 3 years before cancer diagnosis and were matched 1:4 by age and sex to 208 control patients from the high-risk cohort. Descriptive characteristics of the patients included in the case-control analysis are presented in Table 4. Glycated hemoglobin was significantly higher among cancer cases compared with controls in the 3-year period before cancer diagnosis (median 6.5 vs 6.1, $P = 0.02$), Figure 3. In multivariable

Table 1. Demographic and clinical characteristics of the study cohort

	N = 5,931
Age at baseline, median (IQR)	43.5 (32.6, 53.4)
18–39	2,476 (41.7%)
40–49	1,496 (25.2%)
50–59	1,226 (20.7%)
60–84	733 (12.4%)
Sex	
Female	4,546 (76.6%)
Male	1,385 (23.4%)
Race/ethnicity	
Non-Hispanic White	2,852 (48.1%)
Black	404 (6.8%)
Hispanic	1945 (32.8%)
Asian/Pacific Islander	558 (9.4%)
Other/unknown	172 (2.9%)
Risk group	
Highest risk germline variants (STK11, CDKN2A)	45 (0.8%)
Moderate risk germline variant + first-degree family history	253 (4.3%)
Moderate risk germline variant + second-degree family history	361 (6.1%)
Familial pancreatic cancer	1,175 (19.8%)
Moderate-risk germline variant (only)	4,097 (69.1%)
Familial pancreatic cancer	
≥2 first-degree or ≥3 relatives with pancreatic cancer	1,175 (19.8%)
≥2 first-degree	894 (15.1%)
≥3 first-degree	41 (0.7%)
Diabetes mellitus at baseline	956 (16.1%)

IQR, interquartile range.

Table 2. Pathology and stage information of pancreatic cancer

	N = 68
Age at diagnosis	
Mean (SD)	67.9 (8.9)
Median	67.6
Q1, Q3	60.0, 74.5
Range	(45.6–91.6)
Pathology	
Adenocarcinoma	51 (75%)
Carcinoma	2 (2.9%)
Invasive carcinoma	7 (10.3%)
Mucinous adenocarcinoma	1 (1.5%)
Mucinous cystadenocarcinoma	1 (1.5%)
Neuroendocrine carcinoma	1 (1.5%)
Missing	5 (7.4%)
Primary site	
Head of pancreas	27 (39.7%)
Body of pancreas	15 (22.1%)
Tail of pancreas	9 (13.2%)
Overlapping lesion of pancreas	8 (11.8%)
Pancreas not otherwise specified	4 (5.9%)
Missing	5 (7.4%)
SEER summary stage	
Distant	34 (50%)
Regional	16 (23.5%)
Local	15 (22.1%)
In situ	1 (1.5%)
Indeterminate	1 (1.5%)
Missing	1 (1.5%)

SEER, Surveillance Epidemiology and End Results.

analysis, every 1% increase in HbA1c was associated with 36% increase in odds of pancreatic cancer (odds ratio [OR] 1.36, 95% CI 1.08–1.72) (Table 5). This relationship held when adjusted for genetic risk category as well as body mass index and history of acute or chronic pancreatitis in multivariable analysis (Table 5). The history of pancreatitis (acute or chronic) was also an independent risk factor for pancreatic cancer (OR 3.93, 95% CL 1.19, 12.91). There were too few cases of new onset diabetes (n = 1) to include as a separate category for the case-control analysis.

DISCUSSION

In this retrospective cohort study of a racially/ethnically diverse patient population at increased risk for pancreatic cancer based on either genetic or family history, we determined that an elevated glycated hemoglobin was associated with increased risk of cancer development within 3 years before diagnosis. We also confirmed the relationship between previously established high-risk germline variants (*CDKN2A* and *STK11*) and identified pancreatitis as a strong risk factor for pancreatic cancer in this patient population.

Accumulating evidence from prospective cohort studies (8,20,21) support the role for screening of HRI based on either genetic or family history for early detection of pancreatic cancer. As a result, multiple clinical practice guidelines/recommendations have been published in recent years (4,5,7,22) that provide recommendations on various approaches to screening in this population. However, there is substantial variability between several of the guidelines with respect to the appropriate criteria for defining a suitable high-risk population for screening. Recent recommendations from the American Society for Gastrointestinal Endoscopy suggest extending screening to individuals with *BRCA 1* or *BRCA 2* germline variants in the absence of family history of pancreatic cancer (7), which is in contrast to other society recommendations. Although this may be a reasonable recommendation depending on the objectives of a particular screening program, e.g., expanding sensitivity, findings from this study indicate that there is substantial heterogeneity in risk of

Table 3. Incidence rate by hereditary risk category

	Total f/u[a] time (yr)	Average f/u[a] time (yr)	No. of PDAC[b]	Incidence rate of PDAC/10,000 PY[c] (95% CI)
Risk group				
High-risk germline variant (STK11, CDKN2A)	587	13.1	5	85.1 (36.7, 197.6)
Moderate-risk variant + first-degree family history	3,330	13.2	11	33 (18.4, 59.3)
Moderate-risk variant + second-degree family history	4,306	11.9	3	7 (2.2, 21.6)
Familial pancreatic cancer	14,522	12.4	13	9 (5.2, 15.4)
Moderate-risk variant (only)	49,933	12.2	36	7.2 (5.2, 10)
Familial pancreatic cancer				
≥2 first-degree or ≥3 relatives with pancreatic cancer	14,522	12.4	13	9 (5.2, 15.4)
≥2 first-degree	11,227	12.6	12	10.7 (6.1, 18.8)
≥3 first-degree	598	14.6	0	NA

F/u, follow up; PDAC, pancreatic ductal adenocarcinoma; PY, person-years.

pancreatic cancer even among HRI such that a more tailored approach to screening may be indicated. Overall, the current study findings support the framework established by the National Comprehensive Cancer Network (22) that recommend screening in the setting of germline pathogenic and likely pathogenic variants in the *CDKN2A* and *STK 11* genes, irrespective of the family history, whereas screening is advised only in the setting of a FDR with cancer history among carriers of P/LP variants in the other moderate risk genes, included in the present analysis.

This study also addresses the role of glycated hemoglobin as a potential adjunctive marker for cancer risk among HRI. New-onset diabetes in patients after age 50 has been identified as a potential marker for pancreatic cancer in several previous cohort studies with estimated risk 6–8 fold compared with the general population (13,14,23). Although the precise mechanisms underlying this observation have yet to be fully established, a previous experimental study using indirect coculture of rodent cell lines linked activated pancreatic stellate cells with reduced insulin expression and apoptosis of pancreatic β-islet cells (24). Meanwhile, accumulating evidence has also indicated that pancreatic stellate cells play a key role in tumorigenesis in pancreatic ductal adenocarcinoma by modulating signals related to the tumor

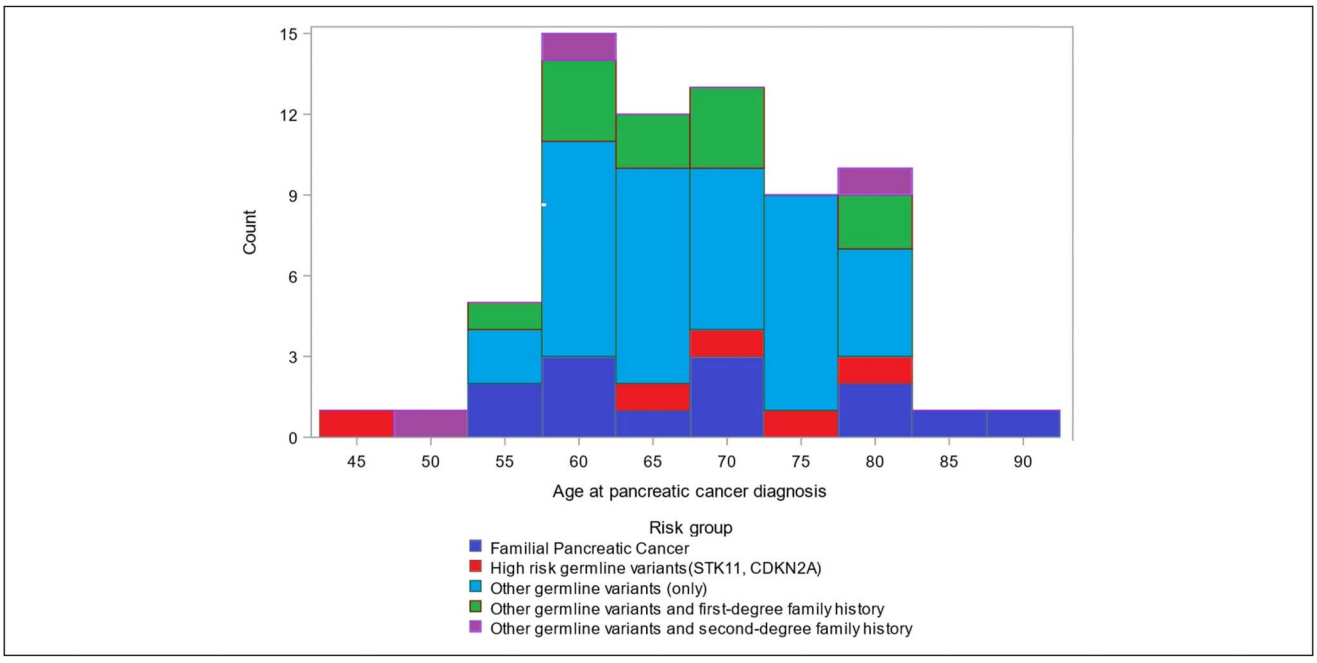

Figure 2. Age distribution at cancer diagnosis.

Table 4. Descriptive characteristics of patients in case-control analysis

	Case (N = 52)	Control (N = 208)	*P*-value
Risk group			0.01
High-risk germline variant (STK11, CDKN2A)	4 (7.7%)	1 (0.5%)	
Moderate variant and family history	11 (21.2%)	22 (10.6%)	
Moderate germline variant only	27 (51.9%)	134 (64.4%)	
Familial pancreatic cancer	10 (19.2%)	51 (24.5%)	
Race/ethnicity			0.31
Non-Hispanic White	28 (53.8%)	111 (53.4%)	
Black	5 (9.6%)	22 (10.6%)	
Hispanic	16 (30.8%)	46 (22.1%)	
Asian/Pacific Islander	3 (5.8%)	29 (13.9%)	
Alcohol use			
Diagnosis of alcohol abuse in the past year	2 (3.8%)	5 (2.4%)	0.57
Diagnosis of alcohol abuse any time in the past	3 (5.8%)	9 (4.3%)	0.67
Tobacco use			0.83
Ever	20 (38.5%)	71 (34.1%)	
Never	31 (59.6%)	134 (64.4%)	
Unknown	1 (1.9%)	3 (1.4%)	
BMI at index date			0.13
Normal weight	20 (38.5%)	57 (27.4%)	
Overweight	16 (30.8%)	58 (27.9%)	
Obese	15 (28.8%)	89 (42.8%)	
Unknown	1 (1.9%)	4 (1.9%)	
Weight change within 1 yr prior			<0.01
N	40	182	
Median (IQR)	−11.9 (−19.7, −3.8)	−0.4 (−5.5, 3.4)	
History of acute pancreatitis	7 (13.5%)	9 (4.3%)	0.02
History of chronic pancreatitis	2 (3.8%)	1 (0.5%)	0.09
Diabetes status as of index date			0.82
New onset (within 6 mo of index date)	1 (1.9%)	0	
Long-standing diabetes	30 (57.7%)	111 (53.4%)	
Not diabetic	21 (40.4%)	97 (46.6%)	
Index A1c			0.02
Mean (SD)	7.0 (1.8)	6.4 (1.2)	
Median (IQR)	6.5 (5.7, 7.9)	6.1 (5.7, 6.8)	
Normal (A1c < 5.7)	12 (23.1%)	43 (20.7%)	0.047
Prediabetes (A1c = 5.7–6.4)	14 (26.9%)	94 (45.2%)	
Diabetes (A1c ≥ 6.5)	26 (50%)	71 (34.1%)	
A1c Change			0.64
N	47	180	
Median (IQR)	0 (−0.4, 0.4)	0 (−0.3, 0.2)	

BMI, body mass index; IQR, interquartile range.

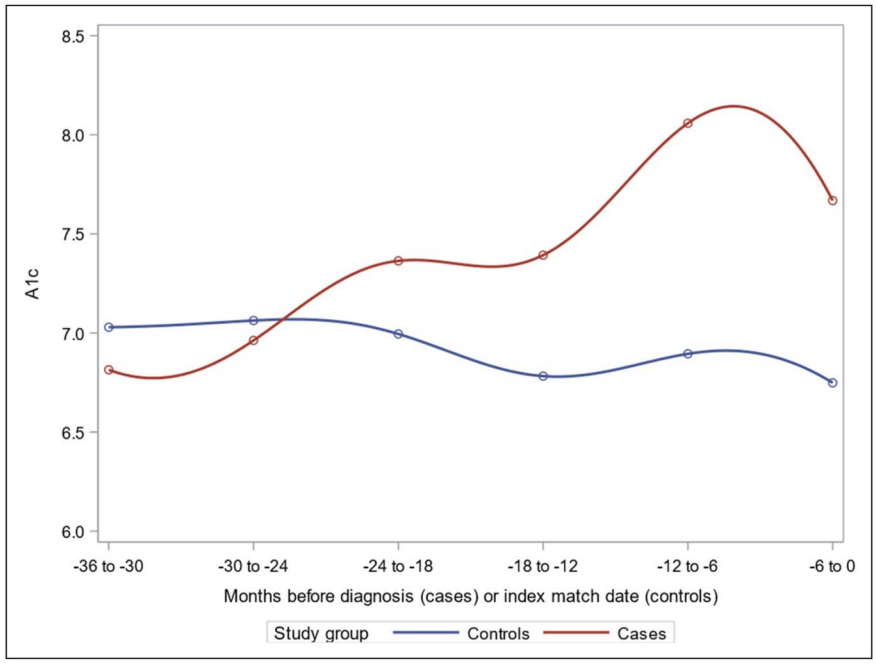

Figure 3. Average A1c before cancer diagnosis (cases vs controls).

microenvironment (25). Subsequent studies using a gene profiling approach through microarray analysis of pancreatic ductal adenocarcinoma cell lines yielded 18 upregulated proteins including adrenomedullin, a 52 amino acid peptide known to inhibit insulin secretion suggesting that cancer-mediated inhibition of insulin secretion may be a paraneoplastic phenomenon resulting from the shedding of exosomes containing adrenomedullin that contribute to endoplasmic reticulum stress and failure of the unfolded protein response in β-cells (26).

As a result of these findings, some clinical practice guidelines have recommended incorporating glycated hemoglobin into the assessment of HRI (3) as part of a screening protocol. However, elevated glycemic parameters and/or new onset diabetes was not associated with cancer in a recent prospective study of n = 100 HRI undergoing screening (15). One plausible explanation for the lack of significance in this study was the sample size (type II error). By incorporating a larger sample size with longitudinal follow-up, we were able to confirm the association between elevated glycated hemoglobin and 3-year risk of developing pancreatic cancer among HRI.

Previous studies have reported cystic neoplasms as one of the most common findings among HRI with prevalence reported as high as 38%–58% among patients undergoing screening (27,28). Although we were unable to determine the prevalence of pancreatic cysts in the current study as the time period was before initiation of widespread screening, the finding that only 2 of 63 (3%) of cancers with established histology were mucinous in nature suggests that malignant transformation of intraductal mucinous neoplasia was not the predominant form of cancer in this patient population. However, this is substantially lower than previous reports that have reported up to 22%–25% of resected lesions in high-risk individuals as intraductal mucinous neoplasia with high-grade dysplasia (8,29). We attribute this discrepancy to differences related to routine care during the study period (no screening) compared with active surveillance protocols with early surgical intervention in the case of these previously published reports.

Table 5. Conditional logistic regression for glycated hemoglobin and pancreatic cancer risk

	Odds ratio	95% Wald Confidence limits	
Index A1c	1.36	1.08	1.73
Risk group (ref: familial pancreatic cancer)			
Germline variant only	1.07	0.47	2.47
Germline variant and family history	3.95	1.35	11.53
Baseline BMI (ref: normal weight)			
Overweight	0.65	0.26	1.59
Obese	0.39	0.17	0.91
Acute/chronic pancreatitis (yes vs no)	3.93	1.19	12.91

BMI, body mass index.

Both acute and chronic pancreatitis are also established risk factors for pancreatic cancer. A previous nationwide matched-cohort study from Denmark estimated 2-year and 5-year risk of pancreatic cancer after acute pancreatitis to be 0.7% and 0.87%, respectively (16), whereas studies of chronic pancreatitis have reported cumulative incidence rates of 1%–2% up to 5 years after diagnosis (30,31). The UK biobank cohort also found similar associations between acute and chronic pancreatitis with risk of pancreas cancer with OR 10.6 and 23.9, respectively (32). The independent association between pancreatitis and risk of cancer in the current high-risk study population is consistent with a multihit model of carcinogenesis whereby predisposing pathogenic/likely pathogenic germline variants coupled with environmental exposures, such as inflammation of the pancreas lead to accumulation of additional somatic alterations propagating the cellular processes leading to malignant transformation (33).

This study had several strengths including a relatively large sample size with longitudinal follow-up as well as systematic ascertainment of exposures as well as outcome (pancreatic cancer). There were also notable limitations in this study. First, clinical genetic testing changed significantly during the 16-year study period with a shift toward widespread multigene panel testing. As a result, potentially eligible patients that were evaluated during the early years of the study period may have been missed as we were unable to perform any *post hoc* genetic analysis. In addition, although we were able to evaluate the relationship between A1c and risk of pancreatic cancer in the high-risk population, we were unable to evaluate specifically the role of new onset diabetes due to the limited number of patients with sufficient data to accurately assess timing of diabetes diagnosis based on glycemic parameters. Another limitation is that in the moderate risk genes category, we only ascertained individuals with a family history of pancreatic cancer in a first-degree relative. Finally, it is important to note that the study cohort was female predominant (76% women). We suspect this is a result selection bias rather than a true reflection of the distribution of hereditary cancer risk as previous studies have indicated women may be more likely to self-report family history of cancer (34) and participate in screening programs for hereditary cancer syndromes in real-world settings (35).

In summary, findings from this retrospective cohort study support the framework established by the National Comprehensive Cancer Network with respect to indications for potential pancreatic cancer screening based on a combination of genetic and family history. Specifically, we confirmed that *CDKN2A* and *STK11* constitute high-risk genes independent of family history, whereas the additional genes studied (*ATM, BRCA 1, BRCA 2, CASR, CFTR, EPCAM, MLH1, MSH2, MSH6, PALB2, PRSS1,* and *TP53*) were associated with higher risk of pancreatic cancer in the setting of family history in a FDR. Findings from this study also support monitoring of A1c as a potential adjunct to further aid in risk-stratification for pancreatic cancer as well as attention to the presence of pancreatitis among HRI.

CONFLICTS OF INTEREST

Guarantor of the article: Bechien U. Wu, MD, MPH.

Specific author contributions: B.U.W.: study concept, design, drafting of manuscript + critical revision. Q.C.: data analysis and interpretation, critical revision of manuscript. B.H.M.: collection of data, data interpretation, critical revision of manuscript. E.L.: collection of data, data interpretation, critical revision of manuscript. E.G.N.: collection of data, data interpretation, critical revision of manuscript. M.A.: collection of data, data interpretation, critical revision of manuscript. S.A.A.: study design, data interpretation, critical revision of manuscript.

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ Patients with specific germline variants, family history, or familial pancreatic cancer are considered a high-risk population for whom screening is suggested.
- ✓ Alterations in glucose parameters can be an early indicator for pancreatic cancer.
- ✓ Additional biomarkers are needed to enhance early detection efforts in high-risk individuals.

WHAT IS NEW HERE

- ✓ There is substantial heterogeneity in cancer risk among high-risk individuals.
- ✓ HbA1c was significantly higher among cancer cases in the 3 years leading up to diagnosis compared with controls suggesting a potential role as an adjunctive marker for early detection.
- ✓ History of pancreatitis (acute or chronic) was independently associated with substantially increased risk of pancreatic cancer among high-risk individuals.

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