HHS Public Access

Author manuscript

Mol Carcinog. Author manuscript; available in PMC 2018 September 01.

Published in final edited form as:

Mol Carcinog. 2017 September ; 56(9): 2158–2164. doi:10.1002/mc.22667.

Soluble MICA is elevated in pancreatic cancer: results from a population based case-control study

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Abstract

Objectives—Pancreatic cancer is diagnosed at a late stage and has one of the highest cancer mortality rates in the U.S., creating an urgent need for novel early detection tools. A candidate biomarker for use in early detection is the soluble MHC class I-related chain A (s-MICA) ligand, which pancreatic tumors shed to escape immune detection. The objective of this study was to define the association between s-MICA levels and pancreatic cancer, in a population-based case-control study.

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Methods—S-MICA was measured in 143 pancreatic cancer cases and 459 controls.. Unconditional logistic regression was used to calculate odds ratio (OR) for pancreatic cancer, and 95% confidence intervals (CI).

Results—There was a positive association between increasing s-MICA levels and pancreatic cancer: compared to the lowest tertile, the ORs for pancreatic cancer were 1.25 (95% CI: 0.75 – 2.07) and 2.10 (95% CI: 1.29 – 3.42) in the second and highest tertiles, respectively (p-trend=0.02).

Conclusions—Our study supports previous work demonstrating a positive association between plasma s-MICA levels and pancreatic cancer.

Keywords

Pancreatic cancer; Population based case-control study; s-MICA

Introduction

Pancreatic cancer is one of the most lethal malignancies in the United States, with an overall 5-year survival rate of <8% and a median survival of 4–6 months, resulting in 40 000 deaths annually.[1]. The majority of pancreatic cancer cases are diagnosed at an advanced disease stage[2], due to lack of robust biomarkers. As a consequence, treatments such as surgery, radiation, and chemotherapy have little impact on patients' survival and are mainly administered for palliative care[3, 4]. Hence, there is an urgent need for the development of novel early detection tools as population screening tests.

Pancreatic tumors secrete proteins that could be used for cancer screening. Specifically, these tumors shed proteins to evade detection by natural killer (NK) cells, which play a critical role in anti-tumor immunity[7, 8]. NK cells detect stress molecules on abnormal or infected cells through the interaction between an activating receptor (NKG2D) with its NKG2D ligands such as the MHC class-I related ligands MICA and MICB, as well as the UL16 binding protein (ULBP-16) [9, 12]. Tumor cells release both MICA and MICB in soluble form (called s-MICA and s-MICB) by proteolytic shedding from the tumor cell surface by disentegrin and metalloproteinases (ADAM) 10 and 17 [6,8,9].

In this study we will focus on elucidating the role of s-MICA in pancreatic cancer, as genetic alterations in the MICA gene have been linked to pancreatic cancer development, making s-MICA a potential biomarker for early cancer detection [8]. The shedding of MICA inhibits NK cells in the tumor microenvironment, enabling tumor cells to avoid lysis by NK cells[7, 8]. Consistent with this mechanism, increased blood levels of s-MICA have been correlated with advanced cancer stage at diagnosis, metastasis, and worse prognosis in liver, [10,11,21] colorectal,[12] oral cancers,[13–16] leukemia,[17–20] and pancreatic cancer.[5,8,9,22–25] In addition, s-MICA has been studied as a potential biomarker to monitor the status and treatment of malignant disease in liver[10,11,21] and pancreatic carcinomas.[22]

Accumulating evidence suggests that s-MICA is associated with pancreatic cancer [6, 7, 11, 12, 13, 14, 31]. However, most evidence comes from hospital-based case-control studies, and there is limited information on whether s-MICA's association with pancreatic

cancer is affected by risk factors for pancreatic cancer such as age, sex, diabetes, smoking history and alcohol consumption. Thus, we evaluated the association between s-MICA levels and pancreatic cancer in a population-based case-control study. We hypothesized that there would be a positive association between increased s-MICA levels and pancreatic cancer, and that the strength of this association would vary based on demographic and lifestyle characteristics of the participants.

Materials and Methods

Study design

This population-based case-control study of pancreatic cancer was conducted by enrolling incident cases diagnosed between 1994 and 1998 in Minnesota. Pancreatic cancer cases were rapidly ascertained and recruited from all hospitals in the seven-county metropolitan area of the Twin Cities of Minnesota (i.e., Minneapolis and St. Paul) and the Mayo Clinic, where cases were restricted to those who lived in the upper Midwest[36–38]. Patients with pancreatic cancer were eligible for the study if they were 20 years of age or older, English-speaking, and gave informed consent[36–38]. All pancreatic cancer cases in this study were cancers of the exocrine pancreas (International Classification of Disease for Oncology, 3rd ed, code C25) and the diagnoses were confirmed by a pathologist [48]. Of the 460 eligible cases, 85 cases were excluded due to death before contact or the interview, 79 cases were excluded due to participant refusal, 31 cases were not invited due to physician refusal, and 7 participants could not be contacted. After those exclusions, 258 cases from the original sample participated in the study (56%).

Controls were selected from drivers' license lists for individuals between 20 and 64 years of age, and from US Health Care Financing Administration records for those aged 65 years and above using stratified random sampling from the seven-county metropolitan area of the Twin Cities. Potential controls were frequency matched to cases by age (within 5 years), sex and race. Inclusion criteria for controls were the same as those for cases, in addition to no prior diagnosis of pancreatic cancer. Of 1145 eligible controls, a total of 676 participated in the study (59%). Written, informed consent was obtained from all study participants prior to their interview. The protocol for this case control study was approved by the Institutional Review Boards of the University of Minnesota and the Mayo Clinic.

At the time of the in-person interviews, all participants were asked about demographics, cigarette smoking, physical activity, dietary and alcohol intake, and medical history, including the history of diabetes. Subjects were also asked to donate a blood sample at the time of their in-person interview. Our analysis was restricted to Caucasians, who represented 96% of all study participants. After excluding participants without blood samples, a total of 163 cases and 542 controls were available for the current analysis (n=705). Vital status for the study participants was ascertained through hospital records and records from the Minnesota Department of Health.

s-MICA measurement

Thirty millimeters of venous blood were drawn from each consenting participant, frozen at −70 °C and stored until analysis. S-MICA plasma levels were assessed using the Luminex Bead-based assay in the Cytokine Reference Laboratory (University of Minnesota). The detection limit for s-MICA was set at 2 pg/ml: fifteen percent of the participants had s-MICA plasma levels below 2 pg/ml (20 out of 163) cases and 83 out of 542 controls). There was no association between case status and s-MICA levels below versus (vs.) above the detection limit (p=0.59), therefore all subsequent analyses were restricted to those with s-MICA levels above the limit of detection (143 cases and 459 controls).

Statistical Analysis

The demographic, lifestyle and other characteristics of cases and controls were compared using a t-test for continuous variables, and a chi-square test for categorical variables. Because of the non-normal distribution of s-MICA and its non-linear association with pancreatic cancer we used unconditional logistic regression and calculated odds ratios (OR) for pancreatic cancer and 95% confidence intervals (95% CI) in relation to s-MICA level categorized as tertiles (the lowest tertile was the reference category). Final models were *a priori* adjusted for established pancreatic cancer risk factors, including age, sex, cigarette smoking status (never, former, current), alcohol consumption (no, 1–6, ≥7 servings per week) and diabetes (yes vs no). We also assessed the interaction of s-MICA with these risk factors. In addition, we conducted an exploratory analysis to examine the relationship between s-MICA levels and overall survival of pancreatic cancer patients among the subgroup of patients with known dates of death (n = 126 out of 143, 88%) using Kaplan-Meier curves. Due to the short survivorship of pancreatic cancer patients, observations were censored after 5 years from the initial contact date.

Results

The demographic and lifestyle characteristics of cases and controls are presented in Table 1. As previously reported, participants with pancreatic cancer were more likely to smoke (15% vs 11%; P = 0.06), and be diabetic (32.9% vs 7.9%; P < 0.0001), but less likely to drink alcohol (47% vs 75%; P = 0.05) than control participants.[28] There were no significant differences in the distribution of participants based on sex, or age (p= 0.40 and p = 0.84, respectively). In addition, we examined the plasma levels of s-MICA across participant demographic and lifestyle characteristics, according to case-control status. The median of s-MICA levels was higher in pancreatic cancer cases than in controls: 58.48 vs 43.07 pg/ml (p=<0.05), and s-MICA levels were consistently higher in cases relative to controls across demographic and lifestyle characteristics (Supplementary Table 1). When cases and controls were examined separately, there were no notable differences in plasma s-MICA levels across strata of sex, smoking history and alcohol consumption in any group (p-value >0.05 for all). Among cases, s-MICA levels were significantly higher in participants under 70 years old, than in those above 70 years old. Among controls, s-MICA levels were significantly higher among participants with vs those without diabetes (p-value = 0.02) (Supplementary Table 1).

In the model adjusted for age and sex, ORs for pancreatic cancer were 1.29 (95%CI: 0.80–2.09) and 2.04 (95%CI: 1.29–3.24) in the second and third tertiles, respectively, compared to the first tertile (p-trend=0.002; Table 2). In the model further adjusted for smoking history, alcohol consumption and diabetes, the association between s-MICA and pancreatic cancer was similar: OR=1.25 (0.75 – 2.07) and 2.10 (1.29 – 3.42) for the second and third tertiles, respectively, vs the first tertile (p-trend=0.02).

In addition, we examined whether the s-MICA and pancreatic cancer association is modified by age, sex, smoking history, alcohol consumption, or diabetes. We found a statistically significant interaction between s-MICA and diabetes (p-interaction=0.03). Although positive associations were observed in both participants with diabetes (OR=5.22, 95% CI: 1.08–25.15) and those without (OR=1.88, 95% CI: 1.14–2.06) for the highest vs lowest tertiles of s-MICA levels, the s-MICA and pancreatic cancer association was stronger in diabetic participants (Table 3). Further, the odds ratios of pancreatic cancer for the highest vs lowest s-MICA tertiles were significantly increased in men (OR = 3.39, 95%CI: 1.88 – 6.09) but not in women (OR=1.03, 95% CI: 0.45–2.34; p-interaction=0.10). Additionally, odds ratios of pancreatic cancer for the highest vs lowest s-MICA tertiles were significantly increased in those under the age of 70 (OR=2.23, 95% CI: 1.18–4.41) vs those over the age of 70 (OR=1.55, 95% CI: 0.80–2.98; p-interaction = 0.07) (Table 3). Finally, in a subset of 143 pancreatic cancer cases with known dates of death in our study, we did not observe any differences in survival for those with higher vs. lower s-MICA levels (p-value for the log-rank test = 0.66) (Supplementary Figure 1).

Discussion

To date, several epidemiological studies have demonstrated elevated s-MICA levels in multiple cancers,10-21,31 and its association with pancreatic cancer risk.[5,8,9,22–25] We sought to confirm these findings using a more robust design through a population-based case control study, after adjusting for demographic and lifestyle characteristic of the study participants. In this population-based case-control study, we observed a positive association between s-MICA levels and odds of pancreatic cancer.

Several epidemiologic studies have reported positive associations between s-MICA levels and pancreatic cancer.[5,8,9,22–25] Specifically, previous case control studies found that pancreatic cancer was associated with significant increases in s-MICA. In contrast, one case-control study by Dambrauskas et al. found no association between plasma s-MICA concentration and pancreatic cancer (n=22), but that study had limited power[13]. Consistent with these reports, we observed a positive dose response relationship between s-MICA levels and pancreatic cancer in the present study.

The shedding of MICA into the blood leads to the surface depletion of MICA and downregulation of NKG2D receptors on NK cells.[6,7,25,32–38] By binding to the NKG2D receptor, MICA can block the activation of NK cells, thereby decreasing the ability of NK cells to recognize and mount a response to kill tumor cells. Thus, the ability of s-MICA to facilitate the tumor escape from immune surveillance may be a possible explanation of the observed association between s-MICA and pancreatic cancer. In line with this mechanism,

Duan et al reported that successful pancreatic tumor resection significantly decreased plasma levels of s-MICA and increased NKG2D expression on NK cells.[5]

Further, we reported that not only is s-MICA detected in the blood of cases, but also in healthy population controls, although at lower levels. This finding is consistent with a previous report of moderately increased s-MICA in benign conditions, such as non-malignant tumors and chronic inflammation[40]. The reason for detecting s-MICA in the blood of controls in the present study is unclear, but its presence is likely indicative of increased cell turnover, so that the detected MICA reflects the protein in cell fragments[35, 6]. Importantly, the presence of s-MICA in healthy controls has implications regarding the suitability of this biomarker for cancer screening.

Another interesting finding in this study was that the positive association between s-MICA and pancreatic cancer was observed among male, but not female participants. This finding is in agreement with different mechanisms of immune evasion in men and women. For example, it has been reported that NKG2D expression varies by sex[43], and this association further varies by age[43, 44, 45]. It is reasonable to hypothesize that differences in NKG2D expression and activity in men vs women may explain the interaction observed in our data: lower NGK2D activity in women could have led to lower selective pressures for pancreatic tumors in women to develop NK immune invasion mechanism through MICA shedding.

Finally, in the exploratory analysis, we did not find any association between the s-MICA levels and pancreatic patient survival. These findings agree with studies by Xu et al. and Dambrauskas et al., which reported that plasma MICA/B levels were significantly elevated in patients with pancreatic adenocarcinomas, but were not correlated with the stage of pancreatic cancer at diagnosis or patients' survival[12, 13]. However, Duan et al. reported that tumors which did not express MICA were associated with better survival in the 3 years following tumor resection[32]. It is reasonable to assume that more tumors which express and shed MICA in its soluble form are better suited to escape immune surveillance. Given the limited sample size in all these studies, leading to an increased chance in false positive or false negative results, future studies will be needed to examine the association between s-MICA levels and patient survival in pancreatic cancer cases.

The strengths of this population-based study included a large number of cases and controls, and the ability to adjust for potential confounders. However, there are some limitations inherent in the present study. First, the response rate for both cases and control was less than 60%. Due to this low response rate, selection bias could have been introduced in the study, but it is unlikely that respondent differed significantly from non-respondents with regards to MICA levels among our controls. Second, although s-MICA levels were significantly associated with increased odds ratios of pancreatic cancer in both participants with and without diabetes, adjusting for diabetes could be an over adjustment in our statistical models, as diabetes may be on the causal pathway between s-MICA and pancreatic cancer. Pancreatic cancer risk is increased by 82% in those with diabetes vs those without[35], and several studies have reported evidence that MICA gene polymorphisms are linked to diabetes[47–50]. In addition, diabetes is often diagnosed at the time or after pancreatic cancer diagnosis and may be a consequence of pancreatic cancer rather than its cause. However, our

results indicate that the s-MICA and pancreatic cancer association was independent of diabetes status in our study. Finally, we did not have information about pancreatic cancer staging, and we were not able to compare s-MICA plasma levels to CA-19 plasma levels, a biomarker used for pancreatic cancer screening. Furthermore, we were not able to collect blood from pancreatic cancer patients with the most advanced disease, since they had died before they were enrolled into the study. This limited our power to make direct comparison between potential biomarkers for pancreatic cancer screening, and look at the association between s-MICA levels and pancreatic cancer survival in the present study.

In summary, our results support the hypothesis that plasma s-MICA levels are positively associated with pancreatic cancer. These results improve our understanding of this important protein in pancreatic cancer, which may be the key to elucidating the role of immune response by NK cells in pancreatic cancer. Our next step will be to correlate genetic variations in the highly polymorphic MICA gene with s-MICA levels, to clarify MICA's role in pancreatic carcinogenesis and explore immune related associations between the MICA gene and pancreatic cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank the physicians, research and administrative staff involved in the PANC study, as well as all the study participants. We wish to express our thanks to Mr. Mike Ehrhardt and the University of Minnesota Cytokine Reference Laboratory for conducting the laboratory analyses for this study. We are also grateful to our colleagues at the University of Minnesota Molecular Diagnostics Clinical Laboratory for their invaluable insight.

Funding: Research was supported by Institutional Research Grant #124166-IRG-58-001-55-IRG21 from the American Cancer Society. A.E. Prizment was supported by the National Center for Advancing Translational Sciences of the NIH Award Number UL1 TR000114. Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Number R25CA163184 (Jean Forster, PhD, MPH and Kola Okuyemi, MD, MPH, Co-PIs). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Table 1

Distribution of study participants' characteristics by case-control status

Participant's characteristics	Categories	N	Case (%)	Control (%)	P-value
Sex	Female	253	55 (38.46)	198 (43.13)	
	Male	349	88 (61.54)	261 (56.87)	0.40
Age	<70y	340	82 (57.34)	258 (56.20)	
	>70y	262	61 (42.66)	201 (43.80)	0.84
Smoking status	Never	265	56 (39.16)	209 (45.53)	
	Former	266	65 (45.45)	201 (43.79)	
	Current	71	22 (15.39)	49 (10.68)	0.06
Alcohol Consumption (Servings/week)	0	229	72 (50.34)	187 (40.74)	
	0–6	212	51 (35.66)	181 (39.43)	
	≥7	96	20 (14.00)	91 (19.83)	0.05
Diabetic Status	Yes	84	47 (32.86)	37 (7.86)	
	No	518	96 (67.13)	422 (92.14)	<0.001

Table 2

Association between s-MICA levels and pancreatic cancer

Model 1*				
Concentration (pg/ml)	**Cases**	**Controls**	**OR (95%CI)**	**P-value for trend**
2.0–32.0	37	160	Reference	0.002
32.1–64.7	44	151	1.29 (0.80–2.09)	
≥64.7	62	148	2.04 (1.29–3.24)	
Model 2†				
Concentration (pg/ml)	Cases	Controls	OR (95%CI)	P-value for trend
2.0–32.0	37	160	Reference	0.02
32.1–64.7	44	151	1.16 (0.67–2.00)	
≥64.7	62	148	1.83 (1.09–3.06)	
Model 3††				
Concentration (pg/ml)	Cases	Controls	OR(95%CI)†	P-value for trend
2.0–32.0	37	160	Reference	0.02
32.1–64.7	44	151	1.25 (0.75 – 2.07)	
≥64.7	62	148	2.10 (1.29 – 3.42)	

*Model 1: Adjusted for sex and age (modeled as continuous variables).

†Model 2: Adjusted for sex, age (modeled as a continuous variable), smoking status (never, former, and current), and alcohol consumption (no consumption, 1–6 servings per week, and 7 or more servings per week).

††Model 3: Adjusted for sex, age (modeled as continuous variables), smoking status (never, former and current), alcohol consumption (no consumption, 0–6 servings per week and 7 or more servings per week) and diabetes (yes vs no).

Mol Carcinog. Author manuscript; available in PMC 2018 September 01.

Table 3

Association between pancreatic cancer and s-MICA levels stratified by sex, age, smoking status, alcohol consumption, and diabetes status,.

Gender										
Categories	**Males**			**Females**						
Concentration (pg/ml)	**Cases**	**Controls**	**OR (95%CI)** ††	**Cases**	**Controls**	**OR(95%CI)** ††				**P-value for interaction**
2.0–32.0	21	95	Reference	16	68	Reference				
32.1–64.7	24	95	1.41 (0.78 – 2.56)	20	62	1.49 (0.67 – 3.314)				
≥64.7	43	71	3.39 (1.88 – 6.09)	19	68	1.03 (0.454 – 2.345)				0.1
Age										
Categories	Under 70 years old			Over 70 years old						
Concentration (pg/ml)	Cases	Controls	OR (95%CI) ††	Cases	Controls	OR(95%CI) ††				P-value for interaction
2.0–32.0	20	96	Reference	17	67	Reference				
32.1–64.7	26	96	1.058 (0.525 – 2.13)	18	61	1.28 (0.64 – 2.57)				
≥64.7	36	66	2.27 (1.18 – 4.41)	26	73	1.55 (0.80 – 2.98)				0.07
Smoking Status										
Categories	Never			Former			Current			
Concentration (pg/ml)	Cases	Controls	OR (95%CI) †††	Cases	Controls	OR (95%CI) †††	Cases	Controls	OR (95%CI) †††	P-value for interaction
2.0–32.0	17	84	Reference	15	61	Ref.	6	17	Ref.	
32.1–64.7	16	68	1.58 (0.67 – 3.76)	22	68	1.11 (0.48 – 2.56)	8	22	0.44 (0.10 – 1.87)	
≥64.7	23	57	2.12 (0.92 – 4.92)	28	72	1.69 (0.8 – 3.59)	8	10	1.49 (0.35 – 6.43)	0.96
Alcohol										
Categories	0 servings / week			1–6 servings / week			≥ 7 servings / week			
Concentration (pg/ml)	Cases	Controls	OR (95%CI) ††††	Cases	Controls	OR (95%CI) ††††	Cases	Controls	OR (95%CI) ††††	P-value for interaction
2.0–32.0	17	57	Reference	14	65	Ref.	7	45	Reference	

Gender										
Categories	**Males**			**Females**						
Concentration (pg/ml)	**Cases**	**Controls**	**OR (95%CI) ††**	**Cases**	**Controls**	**OR(95%CI) ††**				**P-value for interaction**
32.1–64.7	24	63	1.62 (0.74 – 3.57)	9	64	0.74 (0.29 – 1.89)	6	23	1.15 (0.27 – 4.78)	
≥64.7	29	67	1.83 (0.85 – 3.95)	26	52	1.88 (0.83 – 4.25)	7	23	1.74 (0.45 – 6.69)	0.82
Diabetes										
Categories	Yes			No						
Concentration (pg/ml)	Cases	Controls	OR (95%CI) ††††	Cases	Controls	OR(95%CI) ††††††				P-value for interaction
2.0–32.0	6	9	Reference	31	153	Reference				
32.1–64.7	16	8	8.608 (1.57 – 47.24)	28	150	1.03 (0.06 – 1.71)				
≥64.7	25	20	5.22 (1.08 – 25.15)	37	119	1.88 (1.14 – 3.10)				0.03

† Adjusted for age (modeled as a continuous variable), smoking status (never, former and current), alcohol consumption (no consumption, 1–6 servings per week and 7 or more servings per week) and diabetes (yes vs no).

†† Adjusted for sex, smoking status (never, former and current), alcohol consumption (no consumption, 1–6 servings per week and 7 or more servings per week) and diabetes (yes vs no).

††† Adjusted for sex, age (modeled as a continuous variable), alcohol consumption (no consumption, 1–6 servings per week and 7 or more servings per week) and diabetes (yes vs no).

†††† Adjusted for sex, age (modeled as a continuous variable), smoking status (never, former and current), and diabetes (yes vs no).

†††† Adjusted for sex, age (modeled as a continuous variable), smoking status (never, former and current), and alcohol consumption (no consumption, 1–6 servings per week and 7 or more servings per week).