Am J Cancer Res 2018;8(9):1865-1872
www.ajcr.us /ISSN:2156-6976/ajcr0084166

Original Article

Hydroxyeicosatetraenoic acids in patients with pancreatic cancer: a preliminary report

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Received August 16, 2018; Accepted August 23, 2018; Epub September 1, 2018; Published September 15, 2018

Abstract: Previous experimental reports have demonstrated that lipoxygenase (LOX) derivatives of arachidonic acid (AA), such as hydroxyeicosatetraenoic acids (HETEs), may be of significance in the pathogenesis of pancreatic cancer. However, these observations have not been confirmed in clinical studies. In the current study, we comprehensively evaluated the systemic levels of selected LOX-derived HETEs such as 5-, 12- and 15-HETE in patients with pancreatic adenocarcinoma (n=36), chronic pancreatitis (n=39), and in healthy individuals (n=35). Compared to healthy individuals, patients with pancreatic adenocarcinoma showed 3-8-fold higher levels of 5-, 12- and 15-HETE (at least $P<0.003$). Similar results were observed in patients with chronic pancreatitis, who had elevated concentrations of all examined HETE acids compared to healthy volunteers (in all cases at least $P<0.03$). Interestingly, the levels of the examined HETEs were not significantly associated with the TNM stage of pancreatic cancer in our patients. Finally, analyses of receiver operating characteristic curves demonstrated that all HETEs examined had relatively low area under the curve values for discriminating pancreatic adenocarcinoma from non-cancerous conditions (0.49-0.61; $P>0.05$ in each case). Our study provides first preliminary clinical evidence for the significance of the examined HETEs in the clinical pathogenesis of pancreatic cancer and other pancreatic diseases in humans. Moreover, our data demonstrate that the HETEs examined here do not show sufficient clinical potential to be used as independent (bio)markers for differentiating pancreatic adenocarcinoma from other non-cancerous conditions in humans.

Keywords: Arachidonic acid, hydroxyeicosatetraenoic acids, lipoxygenase, pancreatic cancer

Introduction

Pancreatic adenocarcinoma remains one of the most fatal cancers in humans. Despite substantial progress that has been made in understanding the molecular pathology of this malignancy, the overall prognosis of patients affected by this disease remains very poor and has not improved within the last 40 years. Fortunately, due to multiple multi-center studies, it became possible to assess the significance of certain risk factors for this malignancy, which include an elderly age, male gender, smoking, obesity, and various pancreatic disorders. Unfortunately, however, this has not translated into any effective therapeutics or preventive approaches, which is due to several factors. For example, the molecular pathology of pancreatic adenocarcinoma is very complex and despite intensive studies performed in the last 40 years, it is still is not fully understood, with multiple unknown pathways being responsible for the development, systemic spread, and survival of pancreatic cancer cells [1-9].

During the last few years, it became apparent that metabolic reprogramming and altered signaling of (bio)active lipids are hallmarks of cancer [10-13]. Arachidonic acid (AA), a polyunsaturated fatty acid that is a major component of phospholipids forming cellular membranes, is a precursor of multiple (bio)active lipids. Its active metabolites, termed eicosanoids, have been implicated in the pathogenesis of multiple human diseases including various cancers [14-18]. From a biochemical standpoint, upon

Table 1. General characteristics of analyzed patients and healthy individuals enrolled in the study (data presented as means ± SD or median [interquartile range])

Parameters	Control	Cancer	Other
Age (years)	61 ± 7	63 ± 11	60 ± 5
Gender (M-men/W-women)	13-M/22-W	15-M/21-W	18-M/21-F
BMI (kg/m^2)	24.38 ± 3.89	22.27 ± 7.16	24.81 ± 3.11
RBC (×10^{12} cells/L)	4.72 ± 0.56	4.26 ± 0.68	4.37 ± 0.64
Hb (g/dL)	13.47 ± 1.68	12.50 ± 1.97	13.11 ± 2.20
Platelets count (×10^9 cells/L)	227 ± 60	269 ± 130	291 ± 137
WBC count (×10^9 cells/L)	6.82 ± 1.65	8.60 ± 3.26	8.77 ± 3.94
CRP (mg/L)	3.12 ± 1.64	28.31 [4.80; 76.40]$^{*,\#}$	3.00 [1.85; 7.00]
CA19.9 (U/mL)	11.33 ± 5.77	487.36 [94.78; 1591.22]$^{*,\#}$	11.48 [3.73; 21.44]*

BMI-body mass index, RBC-red blood cells, Hb-hemoglobin, WBC-white blood cells, CRP-C-reactive protein. *P<0.05 (vs "control" group), $^{\#}$P<0.05 (vs "other" group).

liberation from membrane phospholipids AA may be metabolized via three major pathways to various eicosanoids-either via cytochrome P450, cyclooxygenase, or lipoxygenase (LOX). Data from multiple experimental studies indicate that mainly LOX-derived AA metabolites (lipoxins, leukotrienes and/or various hydroxyeicosatetraenoic acids [HETEs]) appear to be of major importance in carcinogenesis [18-20]. Over the years, several investigators have shown that in patients with prostate, ovarian, blood, cervical, renal, and lung cancers, the systemic and/or tissue-expression levels of LOX and LOX-derived HETEs may be increased by up to 10-fold [21-26]. Furthermore, abnormal levels of 5-, 12- and 15-HETE were also found in malignant peritoneal and pleural effusions derived from patients with cancers [22, 27]. Unfortunately, the exact impact of these alterations of systemic HETE levels on carcinogenesis in humans is not fully characterized. However, various investigators have demonstrated that inhibiting 5-LOX activity significantly reduced the number of (prostate) tumors in experimental animals, which strongly indicates that LOX and LOX-derived HETEs may be important in the formation of solid tumors [28].

LOX-derived HETEs may also contribute to the development, progression, and/or survival of pancreatic adenocarcinoma [28], although this possibility is not yet supported by experimental or clinical studies. Thus, we compared the peripheral levels of HETEs in healthy individuals and patients with either pancreatic cancer or other pancreatic diseases (chronic pancreatitis). We hypothesized that LOX-derived 5-, 12- and 15-HETE are involved in the pathogenesis of pancreatic cancer in humans and that their systemic levels are associated with the clinical stage of this disease. Moreover, we wanted to (at least preliminarily) verify whether systemic HETE levels could potentially be used as novel (bio)markers for pancreatic cancer in humans.

Materials and methods

Participants and clinical evaluation

For this study, 110 individuals in generally good and stable health were included. All patients recruited for this study were hospitalized in the Department of Gastroenterology of the Pomeranian Medical University in Szczecin, Poland. These individuals were assigned to the following groups: 1) the "cancer" group, comprised of 36 patients with newly diagnosed pancreatic adenocarcinoma; 2) the "other" group, consisting of 39 patients diagnosed with chronic pancreatitis; 3) the "control" group of 35 generally healthy volunteers.

As in our previous studies [29-32], the definitive diagnosis of pancreatic adenocarcinoma was based on biopsy specimen analysis. To perform disease staging, all patients underwent abdominal ultrasonography, computed tomography, and/or endoscopic ultrasonography, as well as chest x-ray examinations. Among patients with pancreatic adenocarcinoma, 11 patients qualified for surgical removal of the pancreatic tumor (stage I or II according to the tumor-node metastasis [TNM] classification), 8 patients presented with inoperable, locally

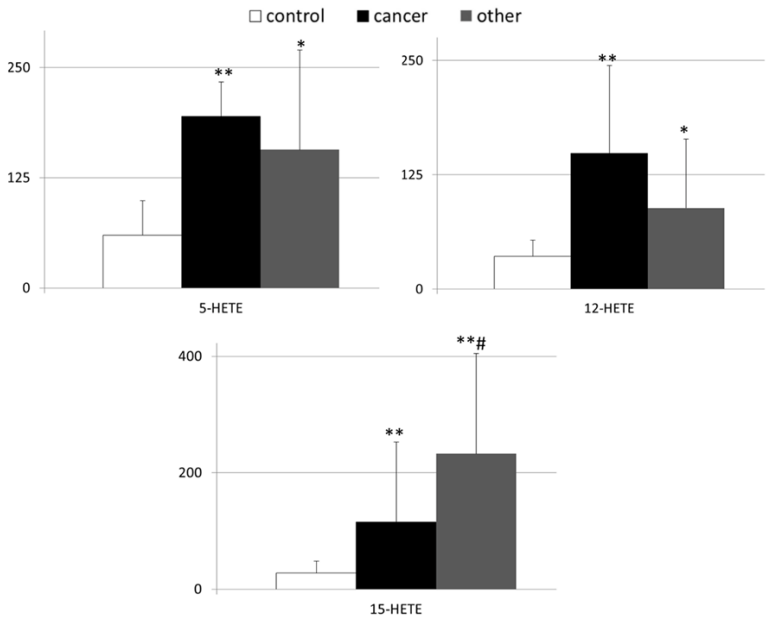

Figure 1. Levels of the examined hydroxyeicosatetraenoic acids in patients with pancreatic cancer, other pancreatic diseases and healthy individuals together with their statistical comparison (values presented as means ± standard deviation in ng/mL). HETE-hydroxyeicosatetraenoic acid, p-level of significance. *P<0.03 and **P<0.001 (vs "control" group), #P<0.00001 (vs "cancer" group).

advanced disease (stage III), and 17 patients had distal metastases to other solid organs (stage IV). Patients with chronic pancreatitis also underwent a comprehensive clinical evaluation that included biochemical blood tests, together with endoscopic ultrasonography. At the time of their inclusion in the study, none of the patients was being treated with chemotherapy, had received any cytotoxic agents or drugs within the previous 12 months, or presented any clinical signs of an active infectious disease. The general characteristics of the individuals enrolled in the study, together with a statistical comparison of these features between the examined groups, are presented in **Table 1**.

From all recruited individuals peripheral blood samples (8-10 mL) were collected. These were processed immediately according to standard laboratory protocols, and plasma was separated, frozen, and stored at -80°C until further assessment.

Systemic levels of LOX-derived HETEs

The systemic concentrations of LOX-derived HETEs (5-HETE, 12-HETE and 15-HETE) were measured using commercially available, high-sensitivity ELISA kits (*Wuhan ElAab Science Co, Ltd., China*) according to the manufacturer instructions.

Statistical methods

Analogically as in our previous studies [33-36] received results were subjected to comprehensive statistical analysis. The distribution of the variables was verified using the Shapiro-Wilk test. Continuous variables that were not normally distributed were subjected to log transformation. After verification of the normality of the distribution, mean values of examined parameters between appropriate groups were compared using Student's t-test (parametric variables) or Mann-Whitney U-test (non-parametric variables). In order to calculate the correlations between parametric and non-parametric variables we used Pearson's or Spearman's correlation rank tests (respectively). In addition, we performed a multivariate regression analyses with use of a stepwise selection method. In order to exclude eventual presence of any residual confounding we entered individually the variables that initially were excluded from the constructed model. Finally, we constructed the ROC curves and calculated the AUCs values for all HETEs examined here as eventual diagnostic substances for pancreatic cancer in humans. These statistical analyses were executed with use of SPSS software and P<0.05 values were considered as significant.

The Ethics Committee of the Pomeranian Medical University approved this study. Written informed consent was obtained from all participants.

Results

Analysis of recruited participants

Comparison of the evaluated groups of included individuals revealed significantly higher CA19-9 levels in patients with pancreatic adenocarcinoma than in all other groups of patients

Table 2. Analysis of associations between levels of examined HETEs and clinical presentation of pancreatic cancer in patients (modelling using multivariate regression analysis)

Dependent variable	Independent variable	β	P of the variable	R^2	P of the model
*TNM Staging**	5-HETE	0.01	0.96	0.01	0.96
	12-HETE	0.04	0.82	0.02	0.82
	15-HETE	-0.02	0.89	0.02	0.89

B-standardized coefficient in the regression equation, p-level of significance, HETE-hydroxyeicosatetraenoic acid, *variable was created by assigning 1, 2, 3 or 4 value to appropriate TNM stage detected in patients with pancreatic cancer.

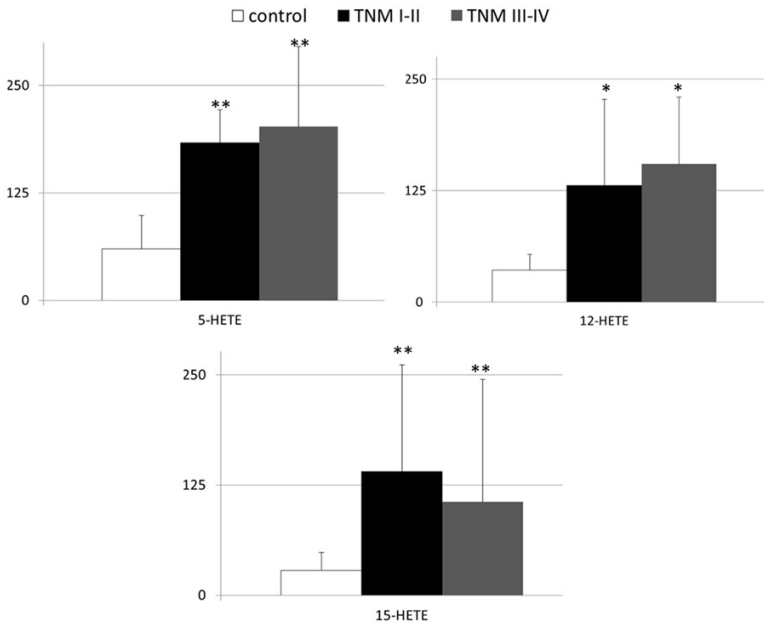

Figure 2. Levels of examined hydroxyeicosatetraenoic acids in patients with pancreatic cancer subdivided according to the TNM staging and healthy individuals together with their statistical comparison (values presented as means ± standard deviation in ng/mL). HETE-hydroxyeicosatetraenoic acid, p-level of significance. *P<0.005 and **P<0.001 (vs "control" group).

(**Table 1**). Furthermore, cancer patients had significantly higher C-reactive protein levels than control individuals and subjects diagnosed with other types of pancreatic diseases (**Table 1**).

Comparison of systemic levels of examined LOX-derived HETEs in patients with pancreatic cancer, chronic pancreatitis, and control volunteers

The mean systemic concentrations of examined 5-, 12- and 15-HETEs in patients with pancreatic adenocarcinoma, chronic pancreatitis and healthy volunteers are depicted in **Figure 1**. We found that levels of all of the examined HETEs are significantly higher in patients with pancreatic cancer than in healthy individuals. Similar results were received when we performed comparison of mean 5-, 12- and 15-HETE levels between healthy controls and patients with other than carcinoma types of pancreatic diseases (**Figure 1**). We observed no significant differences in 5- and 12-HETEs levels between cancer patients and individuals with chronic pancreatitis (P=0.45 and P=0.11, respectively). However, mean concentrations of 15-HETE were significantly higher in the "other" group than in patients with pancreatic cancer (**Figure 1**).

Analysis of associations between examined HETEs values and clinical staging of pancreatic cancer

Furthermore, we verified potential associations between systemic levels of examined LOX-derived HETEs and the clinical staging of pancreatic adenocarcinoma in our patients. Using analyses of correlations we found that levels of the examined eicosanoids were not significantly associated with staging of the pancreatic cancer established according to the international TNM classification (r=-0.8 for 5-HETE; r=0.6 for 12-HETE; and r=-0.5 for 15-HETE, in all cases P>0.65). Similar results were received in multivariate regression analyses (**Table 2**). Moreover, we divided the pancreatic "cancer" group into two subgroups depending on the TNM staging and found that the systemic levels of all examined HETEs were statistically comparable between patients with TNM I-II stage of pancreatic cancer and those diagnosed with more advanced disease evaluated as TNM III-IV (depicted on **Figure 2**).

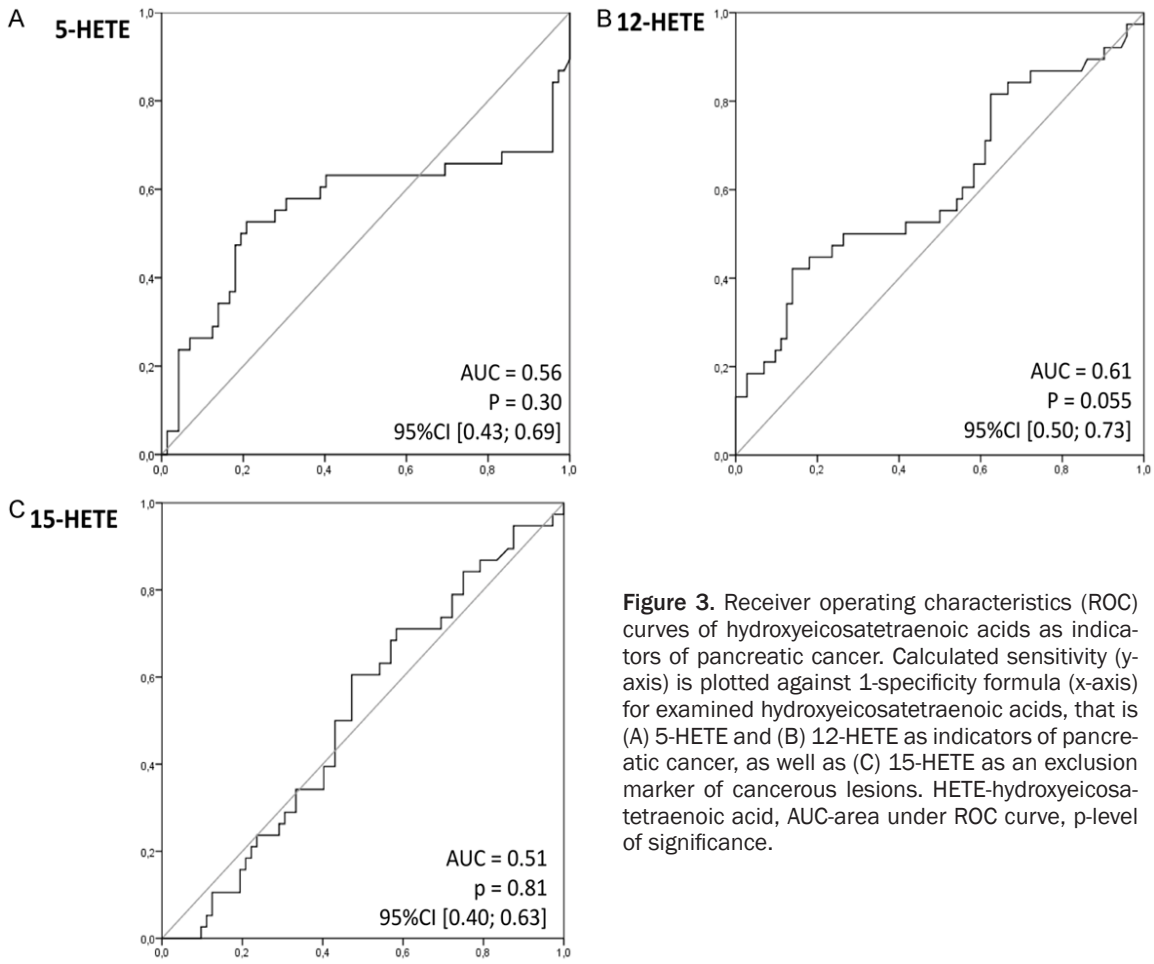

Figure 3. Receiver operating characteristics (ROC) curves of hydroxyeicosatetraenoic acids as indicators of pancreatic cancer. Calculated sensitivity (y-axis) is plotted against 1-specificity formula (x-axis) for examined hydroxyeicosatetraenoic acids, that is (A) 5-HETE and (B) 12-HETE as indicators of pancreatic cancer, as well as (C) 15-HETE as an exclusion marker of cancerous lesions. HETE-hydroxyeicosatetraenoic acid, AUC-area under ROC curve, p-level of significance.

HETEs as eventual (bio)markers of pancreatic adenocarcinoma

Finally, after noting such differences in the levels of LOX-derived HETEs between the examined groups of patients and healthy individuals, we decided to (at least preliminarily) verify the potential diagnostic value of these eicosanoids for the detection/differentiation of pancreatic adenocarcinoma in humans. To determine whether systemic levels of examined HETEs could serve as novel makers of pancreatic cancer, we constructed ROC curves, and calculated the approximate AUC values to assess the suitability of these eicosanoids as diagnostic markers for pancreatic adenocarcinoma. This analysis demonstrated that 12-HETE levels were almost reaching statistical significance to be potentially considered a promising (bio)marker of pancreatic adenocarcinoma in our patients (**Figure 3**). However, 5- and 15-HETE did not possess any potential to be considered as markers of pancreatic malignancy in humans.

Discussion

Active metabolites of AA generated via the LOX pathway are well known as vital players in the pathogenesis of multiple diseases, ranging from cardiovascular diseases through endocrine or metabolic abnormalities. Additionally, growing evidence demonstrates that the activities of various LOX derivatives, such as HETEs, may also be of great significance in the development, progression, and systemic spread of both hematological and solid organ cancers. However, little is known regarding this matter in the context of pancreatic cancer, as studies focusing on AA metabolites in patients with this disease are scarce. Thus, we examined a broad panel of HETEs in patients with pancreatic adenocarcinoma and other pancreatic diseases.

In our study, we found that systemic levels of all examined HETEs were significantly higher (approximately 3-8-fold) in patients with pancreatic adenocarcinoma than in healthy individuals. Therefore, our results are in agreement

with and support the results of previous experimental studies demonstrating that higher expression of various LOX forms occurs in the in vitro and in vivo settings of pancreatic adenocarcinoma [37-39]. This phenomenon was observed at both the systemic and tissue levels (i.e., within circulating pancreatic cancer cells and in the pancreatic cancer micro-environment). The results of this study "translate" these previously reported results as here we demonstrated that, in a clinical setting, patients with pancreatic adenocarcinoma showed an imbalance in circulating LOX-derived 5-, 12- and 15-HETE levels. From molecular and biochemical standpoints, such elevated levels of HETEs may be crucial factors enabling developing tumors to survive, progress, and spread systemically. For example, findings by Ding and colleagues [40] demonstrated that 5-HETE alone stimulates the proliferation of pancreatic cancer cells via several independent molecular mechanisms, including the MEK/ERK and PI3 kinase/AKT pathways. Furthermore, 12-HETE is also a very "powerful" mitogen that strongly influences the proliferation of pancreatic cancer cells via intracellular kinases and promotes metastasis by supporting tumor cell interactions with the extracellular matrix, promoting their adhesion, spreading, and motility [41]. Experimental applications of various LOX inhibitors markedly inhibit pancreatic cancer cell proliferation in concentration- and time-dependent manners [42, 43]. Although these results have not been tested and/or confirmed in a clinical setting, when combined with the results of our study, these observations collectively suggest the importance of continuing this line of research and verifying the impact of LOX inhibitors in the (experimental) treatment of patients with pancreatic adenocarcinoma, especially given that various medications that inhibit LOX activity are commonly available and used to treat other medical conditions.

Importantly, elevated systemic HETE levels were not significantly associated with the clinical TNM stage of pancreatic malignancies. In some reports, however, certain investigators were positioning that HETEs levels were tightly linked to various classifications used for description of clinical/pathological presentation (such as tumor grading or proliferation) [44]. Our study is the first to be performed in patients with pancreatic cancer and the results presented here demonstrated that significantly increased HETE levels are present in patients with pancreatic cancer diagnosed at both early (TNM I-II) and more advanced stages (TNM III-IV). These data suggest that the activities of HETEs and/or LOX seem(s) to be of significance during all stages of pancreatic cancer development/progression in humans.

Finally, our results revealed that the systemic levels of HETEs are not specific enough for use in independent and definitive diagnosis of pancreatic adenocarcinoma, since increased 5-, 12- and 15-HETE levels were also observed in patients with chronic pancreatitis. These results agree with the study by Stevens and colleagues [45], who demonstrated that patients with chronic pancreatitis had increased levels of certain HETEs and other oxidized fatty acids in both serum and pancreatic fluid. In their study, the levels of test substances correlated with the severity of pancreatitis, and the authors suggested them as potential (bio)markers for chronic pancreatitis. Our present results revealed that in fact HETE levels cannot be regarded as (bio)markers of either chronic pancreatitis or pancreatic cancer because in both conditions, the systemic concentrations of the examined HETEs increased in humans. Our observations indirectly support the results of previous studies, which demonstrated the limited diagnostic potential of HETEs in detecting or differentiating cancers of other solid organs (i.e., lung or prostate cancer) from non-cancerous tissues. While some data suggest that HETEs may be considered (bio)markers of certain types of neoplasms, we contend that such a conclusion depends on the profile of the reference group recruited for the analysis. In our study, we applied a much stricter clinical protocol to test the diagnostic potential of HETEs as markers of pancreatic adenocarcinoma than did other groups of researchers who examined this matter in the context of other tumors. For example, in our protocol, the reference group (which should be negative for the markers of interest) contained both healthy individuals and patients with other pancreatic diseases. Such a mix of patients represents an important and oftentimes challenging clinical dilemma that needs a precise answer and requires biochemical marker(s) to be very specific and sensitive. According to our results, in the context of pancreatic adenocarcinoma, the HETEs examined here do not possess sufficient differentiating potential to be considered as such (bio)

markers of this malignancy in humans. Nevertheless, our results are based on a single-center study and need to be confirmed in further (preferably multi-center) studies.

In summary, our study provides the first preliminary translational evidence for the significance of LOX-derived HETEs in the pathogenesis of pancreatic adenocarcinoma in humans. We also demonstrated that the HETEs examined here do not possess sufficient diagnostic potential to serve as independent (bio) markers of human pancreatic cancer, as such abnormal levels are also present in patients with other pancreatic diseases.

Acknowledgements

The authors declare that they have any competing financial, personal nor any other private interests that might be perceived to influence the content reported in this paper.

Disclosure of conflict of interest

None.

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