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# Diagnostic Significance of Serum Fatty Acid Synthase in Patients with Pancreatic Cancer

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## ABSTRACT

### BACKGROUND

Pancreatic cancer is considered as the most deadly tumor among gastrointestinal cancers because of its poor prognosis. The frequently deregulated pathway in the cancer cell is associated with an increased expression of various genes, including the synthesis of fatty acids. We aimed to evaluate the level of serum fatty acid synthase (FASN) as a diagnostic marker for early diagnosis of pancreatic cancer.

### METHODS

Serum FASN levels were measured by ELISA in 92 patients with pancreatic adenocarcinomas and in 92 healthy controls. Logistic regression analysis was used to identify independent predictors of certain diagnostic categories.

### RESULTS

Serum FASN levels were significantly higher in patients with pancreatic cancer than in healthy controls (1.35 [0.98-2.3] ng/mL vs 1.04 [0.19-1.34] ng/mL, $p < 0.001$) and in smokers compared to non-smokers (1.41 [0.79-2.52] ng/mL vs 1.07 [0.21-1.74] ng/mL, $p < 0.001$). FASN levels and smoking were associated with increased risk of PC (1.54 [1.1-2.14] ng/mL, $p = 0.011$ and 5.69 [2.68-12.09] ng/mL, $p < 0.001$, respectively).

### CONCLUSION

Elevated serum FASN levels in patients with pancreatic cancer indicate the need for the production of large numbers of lipids for the survival and proliferation of human cancer cells and the diagnostic value of FASN as a new diagnostic biomarker.

KEYWORDS:
Fatty acid synthase, Pancreatic cancer, Smoking, Biomarker

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## INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) as one of the malignancies with the highest mortality rates among other cancers, with extremely poor prognosis.[1,2] Diabetes and cigarette smoking with pro-carcinogenic effects are important risk factors for PDAC.[3] The incidence of pancreatic cancer is associated with

smoking which is responsible for about 20% of pancreatic cancer cases.[4]

Pancreatic cancer cells that are performed by metabolic reprogramming require additional lipids as energy sources compared to normal cells by activating numerous lipogenic enzymes.[5-7]

Phospholipid bilayers are fundamental structural components of lipid construction that allow cell division. Many tumors due to inactivation of tumor suppressors contribute to the production of large numbers of lipids for the survival and proliferation of tumor cells and induce de novo synthesis of fatty acid regardless of circulating lipids levels.[7,8,9]

The homodimeric fatty acid synthase (FASN), a housekeeping protein, is primarily considered for the synthesis of palmitate from acetyl-CoA and malonyl-CoA, as well as stearate and myristate in a NADPH-dependent manner. Seven catalytic activities plus an acyl carrier protein construct this multifunctional protein. FASN expression is regulated by hormonal signals mainly from sterol regulatory elements binding proteins (SREBP) at the transcriptional level and also from dietary fat.[8,10] In human tumors the expression of FASN occurs at very high rates that is indispensable in cancer development.[2,11]

Most cancer cells vigorously synthesize other fatty acids by the use of arachidonic acid to produce phospholipids for building membranes that support cell growth and proliferation.[2,12] This makes FASN-dependent tumor cells become enriched with monounsaturated or saturated fatty acids 16-18C to create a resistant cellular plasma membrane.[13] Patients with pancreatic cancer with positive FASN expression have worse prognosis than those with lower or absent FASN expression.[14] Tumor cells with high FASN expression are associated with gemcitabine resistance which can be reversed by inhibiting FASN to reduce the proliferation rate of pancreatic cancer cells by promoting apoptosis in the tumor.[15]

Indeed, the FASN differential expression patterns in tumor cells compared to normal cells propose the potential of FASN as a biomarker of neoplasia.[16,17] An increase in FASN in tumor cells is associated with an increase in serum levels of this enzyme in patients with pancreatic cancer as well as ovarian, prostate, colon, and breast cancers.[2,11,18]

In the present study, in order to propose a new treatment target and find a new biomarker in early diagnosis, we examined serum FASN concentration in patients with pancreatic cancer.

## MATERIALS AND METHODS

### Participant selection

In this case-control study, 92 patients with pancreatic cancer from the Gastroenterology Department of Shariati Hospital, Tehran, Iran, were enrolled. The cases were new cases with a histopathological diagnosis of adenocarcinoma. The demographic and clinical characteristics of these patients were obtained from their medical records. According to the WHO's smoking and tobacco use policy, a smoker is someone who smokes any tobacco product on a daily basis. The 92 control samples were selected from Health Examination Cohort with no diseases that can affect lipid metabolism. Informed consent was obtained from all participants. Venous blood samples were also collected in evacuated coagulation tubes and serum samples were prepared and stored at -70 ºC until they were tested according to standard procedures.[19] This study was permitted by the Review Board of the Digestive Disease Research Institute and Ethics Committee of the Shariati Hospital, Tehran University of Medical Sciences with the approval number 84/4.

### Enzyme-linked immunosorbent assay (ELISA)

We tested 100 ml of serum with the ELISA kit for FASN (CUSABIO, USA) based on the manufacturer's recommendations and with a sensitivity of 0.131 ng/mL. FASN concentrations from all patients and controls were determined with respect to the standard curve.

### Statistical analysis

Data from continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR) as appropriated. Categorical variables were presented as frequency and percentage. Baseline characteristics between the two groups were compared using the independent t test or Mann-Whitney U test for continuous variables while Chi-square test was used for categorical variables. The hypothesis of normality was evaluated using the Shapiro-Wick test. The relationship between serum FASN and smoking with pancreatic cancer was assessed by logistic regression which was considered in various forms. SPSS software,

**Table 1:** Baseline characteristics of all participants

| Variables | Total, N = 184 | Case, N = 92 | Control, N = 92 | *p* value |
|---|---|---|---|---|
| Age (y) , Mean ± SD | 62.8 ± 10.7 | 63.6 ± 9.5 | 61.9 ± 11.7 | 0.296* |
| **Sex, N (%)** | | | | |
| Male | 104 (56.5) | 60 (65.2) | 44 (47.8) | 0.017** |
| Female | 80 (43.5) | 32 (34.8) | 48 (52.2) | |
| **Smoking, N (%)** | | | | |
| Yes | 66 (35.9) | 52 (56.5) | 14 (15.2) | < 0.001** |
| No | 118 (64.1) | 40 (43.5) | 78 (84.8) | |

* Independent t test
** Chi-Square test

**Table 2:** Comparison of Serum FASN levels by variables

| Groups | | Serum FASN levels, Median (IQR) (ng/mL) | *p* value |
|---|---|---|---|
| Sex | Male | 1.19 (0.36-2.07) | 0.101* |
| | Female | 1.06 (0.21-1.88) | |
| Smoking | Smoker | 1.41 (0.79-2.52) | < 0.001* |
| | Nonsmoker | 1.07 (0.21-1.74) | |
| Participants | Case | 1.35 (0.98-2.3) | < 0.001* |
| | Control | 1.04 (0.19-1.34) | |

* Mann-Whitney Test

version 13.0, was used for all analyses. $p < 0.05$ was considered as statistically significant.

## RESULTS

Table 1 shows the baseline characteristics of the cases and controls. There was no significant difference between the mean ages of the case and control group. However, the study groups differed significantly with respect to sex distribution with a male/female percentage of 60(65.2%) / 32(34.7%) in the cases and 44(47.8%) / 48(52.1%) in the controls ($p = 0.017$). A significant difference was also found in smokers in the case group compared with the controls (52 [56.5%] vs 14 [15.2%], $p < 0.001$).

### Serum FASN levels in the study groups

The median (IQR) of serum FASN concentrations was 1.35 (0.98-2.3) ng/mL in the case group compared with 1.04 (0.19-1.34) in the control group ($p <0.001$, figure 1). The FASN serum levels differed significantly between smoker and the non-smokers (1.41 [0.79-2.52] ng/mL compared to 1.07 [0.21-1.74] ng/mL, $p <0.001$). Nonetheless, there was no significant difference in the median (IQR) FASN serum levels between the men and women (table 2), and we adjusted the effect of sex in all models (table 3).

### Effect of serum FASN levels in pancreatic cancer

To study whether the variables influence the probability of pancreatic cancer risk, logistic regression was used and the results are presented in table 3. In the multiple logistic regression analysis, the adjusted ORs (with 95% CI) of serum FASN and smoking were statistically significant and showed an increased risk of pancreatic cancer (table 3).

Due to the significant interaction effect between FASN concentration and smoking habit ($p = 0.012$) we accompanied a logistic regression model stratified by smoking status (smokers and non-smokers) adjusted for age and sex. As a result, no significant increase was found with respect to pancreatic cancer risk per FASN concentration among current smokers ($p = 0.706$), while FASN concentration significantly increased pancreatic cancer risk among non-smokers ($p = 0.001$, table 4).

## DISCUSSION

This study demonstrated that serum FASNs were statistically higher in patients with pancreatic cancer. Furthermore, a direct relationship was observed between smoking and pancreatic cancer. Therefore, it appears that the increase in serum FASN is a consequence of the increased expression of this enzyme by cancer cells.

FASN is a metabolic enzyme that catalyzes the synthesis of long-chain fatty acids. Previous studies have identified overexpression of de novo synthesis of fatty acid in different types of solid tumors in association with cancer pathogenesis.[2,8,10,16,20] High serum FASN levels have been reported in patients with gastric cancer and it may be a useful tumor marker for colorectal carcinoma in assessing cancer prognosis.[15,16] Similarly, overexpression of FASN in pancreatic cancer has been reported in

**Table 3:** Multiple logistic model for adjusted effect of FANS

| Variables | Unadjusted OR (95% CI) | *P value* | Adjusted OR (95% CI) | *P value* |
|---|---|---|---|---|
| Age (y) | 1.01 (0.98-1.04) | 0.295 | 1.01 (0.98-1.05) | 0.389 |
| Sex, M/F | 2.04 (1.13-3.7) | 0.018 | 1.09 (0.54-2.19) | 0.812 |
| Smoking, Yes/No | 7.24 (3.59-14.62) | < 0.001 | 5.69 (2.68-12.09) | < 0.001 |
| Serum FASN (ng/mL) | 1.72 (1.27-2.31) | < 0.001 | 1.54 (1.1-2.14) | 0.011 |

**Table 4:** Age and sex adjusted effect of serum FASN in smokers and non-smokers

| Variables | OR (95% CI) | *P value* | P for interaction |
|---|---|---|---|
| Serum FASN in nonsmokers | 2.27 (1.4-3.6) | 0.001 | 0.012 |
| Serum FASN in smokers | 1.07 (0.7-1.6) | 0.706 | |

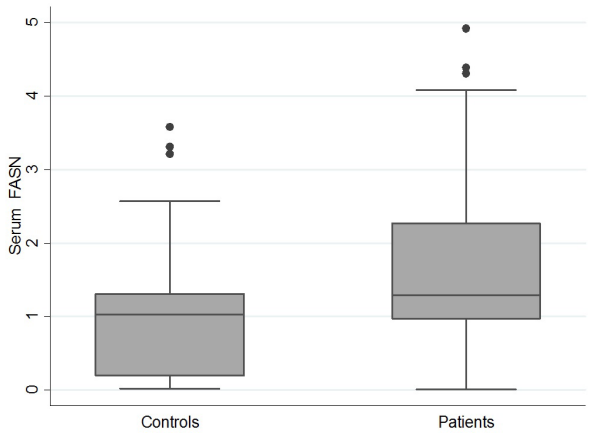


**Fig.1:** The Median (IQR) of FASN serum concentrations in patients with pancreatic cancer and controls ($p < 0.0001$; Mann Whitney U test). FASN, fatty acid synthase

previous studies [11,21] that it was to some extent associated with resistance to gemcitabine.[22] ONCOMINE microarray gene expression datasets demonstrated that FASN and pyruvate kinase M2 (PKM2) were upregulated in pancreatic cancer compared to normal tissue. Further analysis revealed that FASN aided the upregulation of PKM2 expression at the mRNA and protein level, increasing the rate of glucose consumption in pancreatic cancer cells.[22]

Similarly, one study reported an increase of serum FASN concentration in intraductal papillary mucinous neoplasms and chronic pancreatitis.[2] As a result, they suggested the use of FASN as a marker for the early diagnosis of pancreatic cancer.

This study also revealed a positive relationship between smoking and pancreatic cancer because the percentage of smokers was higher in patients with pancreatic cancer than in healthy individuals. The effect of smoking on the risk of pancreatic cancer as the eighth form of cancer death is widely demonstrated in previous reports.[3,5] The carcinogenic material in cigarette smoke arouse pancreatic cancer development.[5, 23] Certainly, cigarette smoke increases the oxidation of polyunsaturated fatty acids (PUFAs) and, consequently, indirectly improves the synthesis of long-chain PUFAs in red blood cells.[5, 24-26] However, serum FASN levels were not affected by smoking in our patients.

## CONCLUSION

Elevated serum levels of FASN were found in patients with pancreatic cancer who were supposed to have higher FASN synthesis in cancer cells. The results of the current study suggest that serum FASN levels could be a new diagnostic biomarker and a probable therapeutic target for pancreatic cancer as well, however it requires further study.

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## ETHICAL APPROVAL

There is nothing to be declared.

## CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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