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Protective Effect of Dehydroepiandrosterone (DHEA) On Pancreatic Cancer Through C-Reactive Protein (CRP) Production Inhibition

Hamid Reza Fazli[1], Ashraf Mohamadkhani*[2], Hamed Reza Godarzi[1], Akram Pourshams[3], Mojtaba Jafarinia[4]

Abstract

Background: The relationship between inflammation and pancreatic cancer (PC) has been previously explored, but the precise role of inflammatory markers in disease risk and progression remains unclear. This case-control study aimed to investigate the association between C-reactive protein (CRP), systemic inflammation marker, and dehydroepiandrosterone (DHEA), systemic cytokines regulator, in relation to pancreatic cancer risk.

Methods: Serum levels of DHEA and CRP were measured in 50 pancreatic cancer patients and 50 age and sex-matched healthy controls using enzyme-linked immunosorbent assay (ELISA) and latex particle-enhanced immunoturbidimetric assay, respectively. Data analysis was performed using STATA software.

Results: The results showed that while DHEA levels were lower in pancreatic cancer patients compared to healthy subjects, the difference did not reach statistical significance (p=0.74). Conversely, CRP levels were significantly elevated in pancreatic cancer patients (p=0.001). Subgroup analysis based on sex revealed significant differences in DHEA and CRP concentrations between male patients and controls. Furthermore, a marginally significant inverse relationship was observed between log CRP and DHEA levels in pancreatic cancer patients (p=0.054). Risk assessment analysis, adjusted for age and sex, demonstrated an increased risk of pancreatic cancer associated with elevated log CRP levels (p=0.001; OR=1.671), and a decreased risk associated with higher DHEA levels (p=0.024, OR=0.479).

Conclusions: our findings highlight the direct association of pancreatic cancer with CRP and the inverse relationship with DHEA, suggesting the involvement of inflammation in pancreatic cancer development. Moreover, the observed inverse correlation between CRP and DHEA among pancreatic cancer patients suggests a potential inhibitory effect of DHEA on CRP levels.

Keywords: C-reactive protein, Dehydroepiandrosterone, Inflammation, Risk factors. Pancreatic cancers.

Introduction

Pancreatic cancer, a formidable illness with a high global impact, has gained significant attention in the medical community. In 2020 alone, there were 495,773 new cases reported, positioning it as the 12th most prevalent cancer worldwide. Tragically, it ranks seventh in terms of cancer-related mortality, accounting for 7.5% of all cancer deaths across genders (1). The burden of pancreatic cancer extends beyond mortality statistics. In

1: Department of Genetics, Marvdasht Branch, Islamic Azad University, Marvdasht, Iran.
2: Liver and Pancreatobiliary Diseases Research Center, Digestive Disease Research Institute, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.
3: Digestive Oncology Research Center, Digestive Disease Research Institute, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.
4: Department of Biology, Marvdasht Branch, Islamic Azad University, Marvdasht, Iran.
***Corresponding author: Ashraf Mohamadkhani; Tel: +98 2182415780; E-mail: mohammadkhani@tums.ac.ir.**
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2017, the global disability-adjusted life years (DALYs) associated with the disease amounted to approximately 9.1 million (2).

Despite recent advancements in diagnosis, therapy, and surgical techniques, over half of newly diagnosed cases still present with distant metastasis (3). This aggressive nature, together with poor prognosis and increased incidence and mortality, further increase the importance of pancreatic cancer as a global health concern (4-6). To address the challenges caused by pancreatic cancer, there is an urgent need to investigate molecular interactions and mutations in DHEA and CRP genes. By exploring these complex mechanisms, early diagnosis, optimal disease management, improved treatment outcomes, and increased prognostic capabilities can be achieved.

The intricate interplay between local immune responses and systemic inflammation has emerged as a crucial factor in the development and progression of tumors, including pancreatic cancer (7, 8). In fact, pancreatic cancer has increasingly been recognized as an inflammation-driven malignancy over the past two decades (9). Despite this understanding, the specific inflammatory mediators involved in the development of pancreatic cancer have not been extensively studied. One such marker of systemic inflammation is C-reactive protein (CRP), a blood protein with a relatively long half-life. During acute inflammatory phases, hepatocytes release CRP in response to pro-inflammatory cytokines like IL-6, IL-1, and TNF-α (10,11). CRP has proven to be a stable indicator of systemic inflammation and has been associated with various conditions, including cardiovascular diseases, type 2 diabetes mellitus, age-related macular degeneration, hemorrhagic stroke, Alzheimer's disease (12), and advanced stages of different cancers (13).

Dehydroepiandrosterone (DHEA) is a naturally occurring steroid hormone that serves as a precursor to other hormones in the human body. It is synthesized in various organs and tissues, including the brain, adrenal cortex, gonads, and gastrointestinal tract (14). DHEA is present in high concentrations in human serum and plays a crucial role as precursors for the synthesis of sex hormones such as estrogen and androgen (15). The growing body of research suggests that DHEA may have diverse physiological benefits beyond its role as a hormone precursor. Its potential anti-cancer properties, in particular, hold promise for the development of novel therapeutic approaches in the treatment of various malignancies (15). A notable finding from the study was the strong negative correlation between CRP and DHEA, suggesting that DHEA may have a distinct impact on inflammation (16). The aim of this study is to examine the relationship between CRP and DHEA in the context of pancreatic cancer risk. The findings of this study have the potential to enhance our understanding of pancreatic cancer risk factors, identify potential biomarkers, improve risk assessment and prevention strategies, and suggest potential therapeutic implications.

Materials and Methods

Patients and Sampling

In this case-control study, a total of 100 participants were recruited from the Endoscopic Ultrasound Center at Shariati Hospital in Tehran, Iran, between 2012 and 2015. The study population consisted of 50 pancreatic cancer patients and 50 healthy volunteers. All participants underwent endoscopic ultrasound (EUS) using the Pentax linear EUS device (model EG 3830 UT). The inclusion of healthy controls was based on EUS confirmation of a regular pattern of the pancreas. Additionally, the healthy subjects underwent screening to ensure the absence of a history or current diagnosis of liver or kidney failure, as well as any cancer diagnosis.

The diagnosis of pancreatic adenocarcinoma was established through histopathology of pancreatic tissue obtained via fine needle aspiration (FNA) biopsies and surgical tissues after the identification of solid

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or cystic lesions using EUS. Prior to participation, all individuals provided their informed consent and completed a demographic questionnaire. Blood samples were collected and processed following standardized protocols and stored at a temperature of -80 °C for further analysis. The present investigation was conducted in accordance with the tenets of the Declaration of Helsinki and received approval from the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (ethical approval number IR. TUMS. DDRI.REC.1394.8). Informed consent was obtained from all participants, ensuring their voluntary participation in the study.

DHEA and CRP Levels Measurements

In this study, the serum concentration of DHEA was measured using a highly specific enzyme-linked immunosorbent assay (ELISA) method provided by Demeditec Diagnostics GmbH in Germany. This ELISA method allows for accurate and precise quantification of DHEA levels in the serum samples. The results of the DHEA measurements were expressed in micrograms per deciliter (μg/dL). The standard range for DHEA concentrations in this assay was reported to be 0.37–30 ng/mL, providing a reliable reference range for comparison and interpretation of the results. On the other hand, the quantitative assessment of C-reactive protein (CRP) levels in serum was performed using the latex particle-enhanced immunoturbidimetric assay (ITA) on a Hitachi 747-200 analyzer. The ITA method utilizes latex particles coated with specific antibodies that bind to CRP molecules present in the serum samples. The interaction between the latex particles and CRP leads to the formation of aggregates, which causes turbidity in the solution. The degree of turbidity is measured by the analyzer, allowing for the quantification of CRP concentrations in the serum samples. This method provides a reliable and widely used approach for assessing CRP levels, which serves as an important marker of systemic inflammation.

Statistical Analysis

The statistical analysis in this study was conducted using STATA software version 12.0 (Stata Corp, College Station, TX, USA). Descriptive statistics were used to summarize the data, including reporting percentages, means, and standard deviations for the variables of interest. For the analysis of continuous data, the Mann-Whitney test, a non-parametric test, was employed. The Chi-square test, a commonly used test for categorical data, was utilized to analyze the association between categorical variables. To identify variables that were independently associated with disease risk, multivariate logistic regression analysis was performed. Furthermore, linear regression analysis was employed to explore the relationship between serum CRP and DHEA levels. All statistical tests conducted in this study were two-tailed, meaning that both sides of the distribution were considered. A significance level of less than 0.05 was used to determine statistical significance, indicating that results with a p-value below this threshold were considered statistically significant.

Results

The study included a total of 100 participants, with 50 individuals diagnosed with pancreatic cancer (28 males and 22 females) and 50 healthy controls (29 males and 21 females). The mean age of the pancreatic cancer patients and controls was 70±12 and 66±10, respectively. Regarding smoking history, 16 patients (32.0%) and 13 controls (26.0%) reported a positive smoking history. Diabetes was observed in 8 pancreatic cancer patients and 14 healthy controls. In terms of body mass index (BMI), 21 patients and 18 controls had a non-normal BMI. Our results also indicated that there were no significant differences in distribution of sex, smoking, diabetes, and BMI between the two groups, with $p > 0.05$. Additionally, the analysis revealed no significant difference in age between the two groups ($p > 0.05$) (Table 1).

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Table 1. The study population characteristics.

Characteristics		Group				P-value	Total	
		Patient		Control				
		N	%	N	%		N	%
Gender	Male	28	56.0	29	58.0	0.840	57	57.0
	Female	22	44.0	21	42.0		43	43.0
Smoking	No	34	68.0	37	74.0	0.509	71	71.0
	Yes	16	32.0	13	26.0		29	29.0
Diabetes	No	42	84.0	36	72.0	0.148	78	78.0
	Yes	8	16.0	14	28.0		22	22.0
BMI	Normal	29	58.0	32	64.0	0.537	61	61.0
	Overweight	16	32.0	16	32.0		32	32.0
	Obese	5	10.0	2	4.0		7	7.0
Age (Year)		70±12		66±10		0.146	68±11	

After conducting a sub-analysis based on sex, it was found that a significant difference was observed between the two groups in terms of DHEA levels (p= 0.004) and CRP levels (p< 0.001) specifically within the male category. However, this significant difference was not observed in the female gender (Fig. 1).

Comparing DHEA and CRP between Pancreatic Cancer Patients and Healthy Controls

In healthy individuals, the median DHEA level was found to be 0.95 (with a range of 0.35-1.70), while in patients with pancreatic cancer, the median DHEA level was 0.50 (with a range of 0.30-1.10). Although the DHEA level was observed to be lower in patients compared to healthy subjects, this difference was not found to be statistically significant (p= 0.74). On the other hand, the median CRP level was 0.75 (with a range of 0.30-2.5) in the control group and 2.30 (with a range of 0.80-6.30) in patients with pancreatic cancer. This indicates a significant elevation in CRP levels among individuals with pancreatic cancer compared to the healthy controls (p= 0.001) (Table 2).

Table 2. Comparison of DHEA and CRP levels between pancreatic cancer patients and healthy controls.

Variable	Group						P-value	Total		
	Control			Patient						
	Median	Q1	Q3	Median	Q1	Q3		Median	Q1	Q3
DHEA	0.95	0.35	1.70	0.50	0.30	1.10	0.074	0.70	0.30	1.30
CRP	0.75	0.30	2.50	2.30	0.80	6.30	**0.001***	1.50	0.50	5.05

The study findings suggest that higher levels of logarithmically transformed CRP (log CRP) are associated with an increased risk of pancreatic cancer (p= 0.001; odds ratio [OR]=1.671). Conversely, higher levels of DHEA are associated with a decreased risk of pancreatic cancer (p= 0.024, OR= 0.479). These associations were determined through a risk assessment analysis that was adjusted for age and sex (Table 3).

Table 3. Logistic regression for evaluation of the association between pancreatic cancer and CRP and DHEA (A significant correlation was found between DHEA and LogCRP).

Variables	P-value	OR	95% C.I for OR	
			Lower	Upper
DHEA	**0.024***	0.479	0.253	0.906
Log CRP	**0.001***	1.671	1.234	2.263

*Adjusted for Age and Sex

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Comparing DHEA and CRP between Pancreatic Cancer Patients and Healthy Controls Based on Gender

After conducting a sub-analysis based on sex, it was found that a significant difference was observed between the two groups in terms of DHEA levels (p= 0.004) and CRP levels (p< 0.001) specifically within the male category. However, this significant difference was not observed in the female gender (Fig. 1).

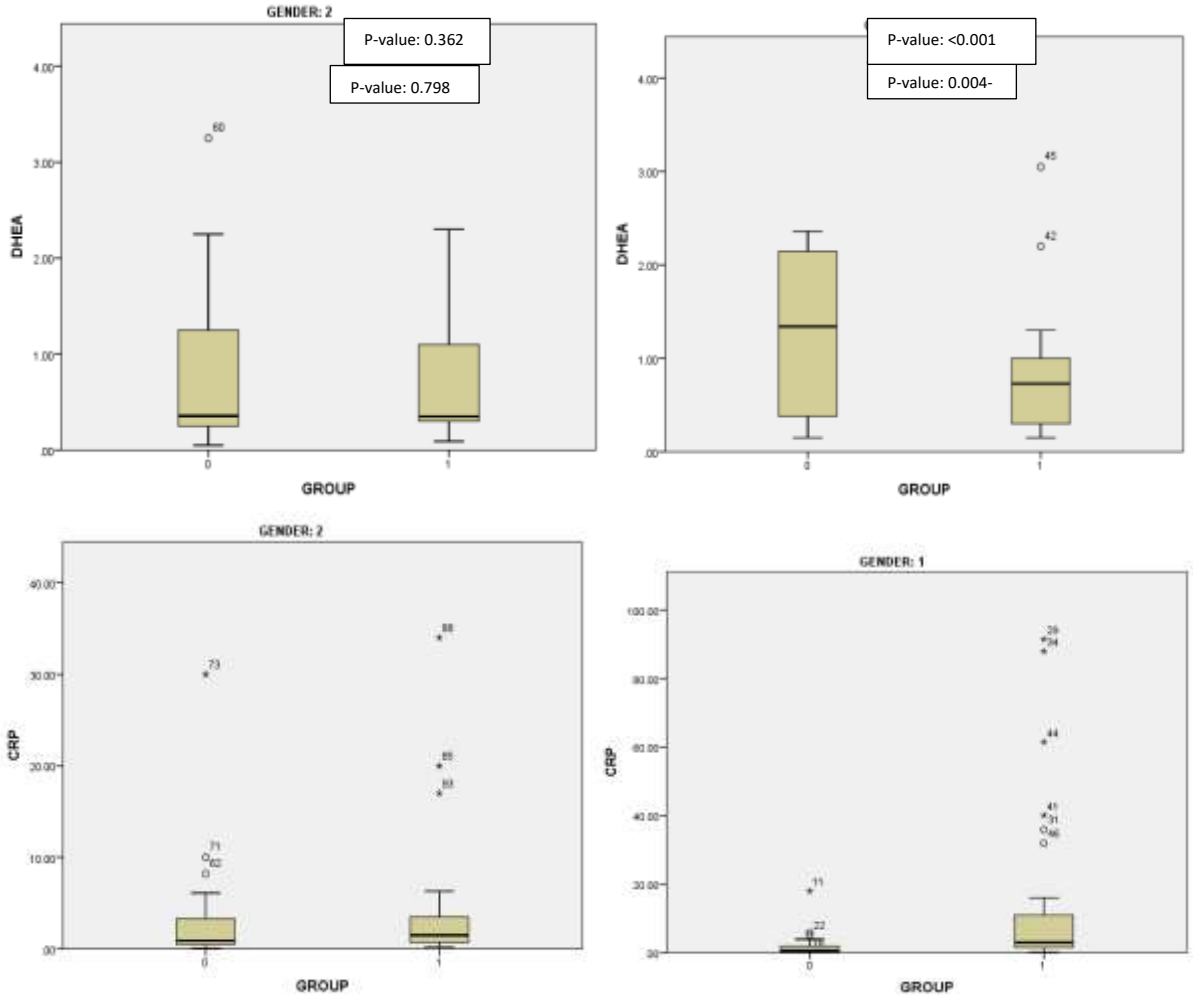

Fig. 1. Comparison of DHEA and CRP levels between pancreatic cancer patients and healthy controls based on gender (Gender 2 indicates a female person and Gender 1 indicates a male person). In all 4 images above, the left column corresponds to the control group and the right column corresponds to the patient group.

After conducting a sub-analysis based on sex, it was found that a significant difference was observed between the two groups in terms of DHEA levels (p= 0.004) and CRP levels (p< 0.001) specifically within the male category. However, this significant difference was not observed in the female gender (Fig. 1).

Evaluating the Association between DHEA and Log CRP in Pancreatic Cancer Patients and Healthy Controls

The study aimed to explore the connection between DHEA and logarithmically transformed CRP (log CRP) levels in patients with pancreatic cancer. The results indicated a potential inverse association, suggesting that as log CRP levels increased, DHEA levels tended to decrease, although this relationship was not statistically significant (p= 0.099). Among the healthy subjects, a potential direct association between the two variables was observed (p= 0.054), but again, it did not reach statistical significance (Fig. 2).

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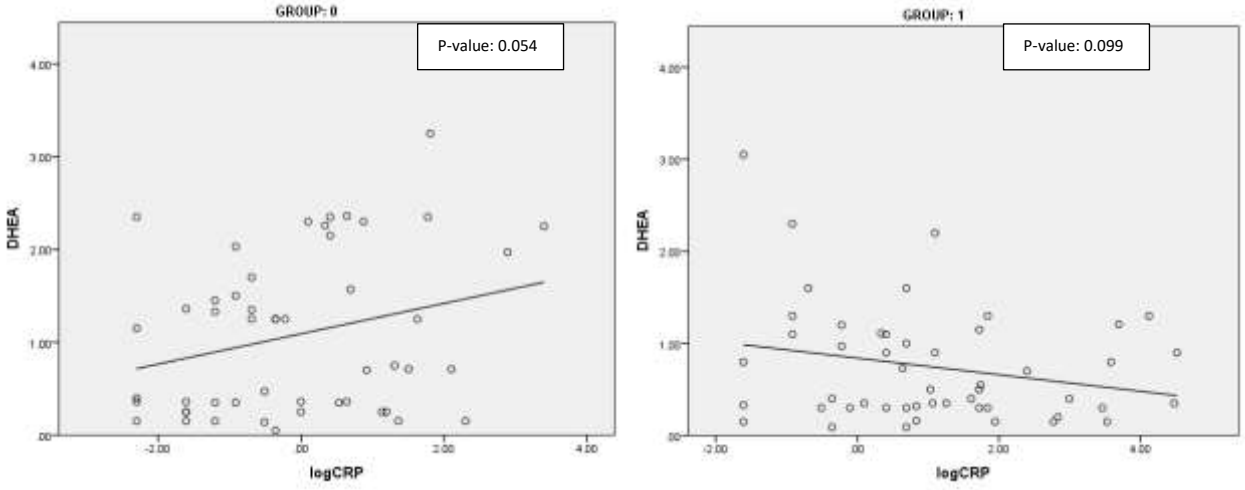

Fig. 2. Scatter Plot for the Association between DHEA and CRP in Cases and Controls (Group 1 represents the patient group and Group 0 represents the healthy group).

Discussion

In this study, we established a negative association between circulating DHEA levels and the risk of developing pancreatic cancer. In addition, according to the findings of the current study, patients diagnosed with pancreatic cancer exhibited notably higher levels of C-reactive protein (CRP). We also discovered a fascinating inverse correlation between CRP and DHEA levels in individuals diagnosed with pancreatic cancer. This finding indicates a deviation in the levels of these biomarkers compared to those of healthy subjects. We believe, the observed inverse association suggests that DHEA may play a distinct role in modulating inflammation in the context of cancer. By negatively influencing CRP levels, DHEA may exert anti-inflammatory effects, potentially contributing to the suppression of tumor-promoting inflammatory pathways. This finding further adds to the growing body of evidence supporting the multifaceted role of DHEA in cancer biology. Regarding the significance of this issue, it is important to note that, in our view, this finding has not been previously investigated in cancer patients. However, existing literature suggests that the correlation between these markers has been observed in various diseases, such as metabolic syndrome in men over 40 years old (17), posttraumatic stress disorder (18), obstructive coronary artery disease (19), and new onset synovitis/rheumatoid arthritis (20). Furthermore, DHEA has the potential to influence CRP levels through its impact on interleukin-6 (IL-6) levels (21). Therefore, if the association between these biomarkers is confirmed in pancreatic cancer patients, their ratio could serve as a valuable diagnostic and prognostic marker.

In certain animal models, the initiation of pancreatic cancer is hindered by DHEA (22). Our laboratory's previous investigation revealed a link between lower serum DHEA levels and reduced 8-OHdG DNA adducts in individuals diagnosed with pancreatic cancer (23). This discovery implies that DHEA could potentially exhibit antioxidant and anti-DNA-damaging properties specifically within the context of pancreatic cancer. However, the specific mechanisms underlying the observed changes in tumor growth have not yet been determined.

Lower levels of DHEA have been linked to higher risks of breast cancer and age-related tumorigenesis (24). Additionally, studies have demonstrated that DHEA can decrease the occurrence of carcinogen-induced tumors in animal models, including mammary, skin, and other types of tumors (25-27). These findings are consistent with the results of our study. However, it is important to note that while the relationship between the reduction of DHEA levels and susceptibility to breast cancer has

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been observed, the exact underlying mechanism has not been determined. Nonetheless, there are several theories that have been proposed in this regard. For example, numerous studies have provided evidence of the impact of DHEA on cancer through various signaling pathways. In breast cancer, DHEA has been shown to inhibit metastatic processes such as cell migration, invasion, and anchorage-independent growth. It also partially reverses the epithelial-mesenchymal transition (EMT) process and suppresses tumor growth in mouse xenografts of MDA-MB-231 cells (28-30). In hepatoma, DHEA inhibits the PI3K/AKT signaling pathway, leading to apoptosis induction and decreased cell proliferation in HepG2 cells (31). In colon cancer, DHEA exhibits anticancer effects by inducing cell cycle arrest in the G0/G1 phase in HT-29 cells (31). In myeloma, DHEA reduces cell number and upregulates the expression of PPARb and IkBa genes through the downregulation of interleukin-6 (32). In pancreatic cancer, DHEA administration has been found to significantly suppress tumor growth in vivo by altering plasma sex hormone concentrations (17). Indeed, the findings suggest that DHEA has a significant impact on various aspects of cancer cells. However, it is important to acknowledge that there are still unexplored potential functions and important roles of DHEA in relation to cancer. Further research and investigations are needed to fully understand the extent of DHEA's influence and its mechanisms of action in different types of cancer.

Our findings regarding the increased serum levels of CRP in patients with pancreatic cancer align with previous reports that have also observed elevated CRP levels in pancreatic cancer patients, particularly in those with systemic metastases (33). Additionally, another study has demonstrated that an increased risk of pancreatic cancer is associated with pre-diagnostic serum levels of CRP (34). Furthermore, it has been established that the highest quartile of CRP levels serves as an independent prognostic factor in pancreatic cancer patients, as elevated CRP levels are correlated with unfavorable clinical outcomes (35). Therefore, in addition to the established prognostic role of CRP in pancreatic cancer, further investigations could potentially shed light on the diagnostic value of CRP levels.

According to researchers, there is evidence to suggest that pancreatic cancer may be influenced by sex hormones (36). This is supported by the observation that the incidence of pancreatic cancer is higher in men compared to women. Interestingly, our present study's statistical analysis provides strong support and confirmation for this observation. We discovered a substantial correlation between the disease and CRP and DHEA levels specifically in males, whereas no such correlation was observed in females. This suggests that gender plays a significant role in the secretion of serum markers. Additionally, it is worth noting that males generally exhibit lower CRP levels compared to females, primarily due to their lower subcutaneous fat accumulation. These intriguing findings indicate that sex differences have the potential to influence the identification of markers for pancreatic cancer.

In conclusion, our study aimed to explore the relationship between inflammation and pancreatic cancer by examining the serum levels of CRP and DHEA in a cohort of 50 pancreatic cancer patients and 50 controls. The results of our study demonstrated a positive association between pancreatic cancer and CRP, indicating its role as an inflammatory factor in the disease. Conversely, we observed an inverse association between pancreatic cancer and DHEA, which serves as a regulator of systemic inflammatory cytokines. These findings provide further support for the involvement of inflammation in the development of pancreatic cancer. Furthermore, our study revealed that the association between pancreatic cancer and these markers was particularly prominent in males, highlighting the importance of gender-based differences in molecular markers that influence disease diagnosis, treatment response, and prognosis. Notably, we identified an adverse correlation between CRP and DHEA in pancreatic cancer patients, suggesting their potential as prognostic biomarkers for disease

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progression and development. However, additional investigations are warranted to validate these findings and explore the interplay between these markers. Understanding the impact of DHEA on inflammation and its potential role in mitigating cancer-associated inflammation could pave the way for innovative therapeutic strategies targeting the inflammatory microenvironment of tumors. Further research in this area has the potential to uncover novel therapeutic avenues in cancer treatment and deepen our understanding of the complex interplay between hormones, inflammation, and cancer biology.

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Ethics approval and consent to participate
The present investigation received ethical approval from the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (ethical approval number IR. TUMS. DDRI.REC.1394.8). Informed consent was obtained from all participants, and their participation was voluntary. All stages of the study and data collection were based on the principles of the Helsinki Declaration.

Conflict of interest
All authors have no conflict of interest to report.

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