The Correlation of Elevated Spermine Levels in Blood and the Incidence of Pancreatic Cancer

Sahir Hai, Sohail Hai, and Shaikh Hai MD

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This study intends to address whether all pancreatic cancer patients have elevated serum spermine levels thereby indicating the potential utility of spermine as a biomarker for the presence of pancreatic cancer. Blood from ten patients with pancreatic cancer and ten healthy volunteers was gathered. This was then tested in the chemical laboratory using a high-performance liquid chromatography (HPLC) chemical analyzer. The results showed that the average spermine blood concentration was higher in the group with pancreatic cancer than in the volunteers. Normal human serum spermine levels range from 10–60 ng/mL, while levels greater than 100 ng/mL are considered markedly abnormal and may indicate pancreatic cancer[1]. The mean for the patients was 106.8 ng/mL, and mean for the volunteers was 33.6 ng/mL. Only one individual in the volunteer group had a spermine level higher than the normal maximum level of 60 ng/mL in blood. A two-sample t-test with an alpha level of 0.01 was conducted, resulting in a p-value of 5.067×10^{-8} and thus showing that there is convincing evidence that spermine levels are elevated in pancreatic cancer patients. These results suggest that spermine may be a valid biochemical test for pancreatic cancer. However, this is not definitive due to the small sample size of this study; therefore, research on a larger scale must be done to confirm this. Thus, this testing method could potentially be a more cost-effective alternative than other diagnostic modalities for pancreatic cancers like computerized tomography (CT) or positron emission tomography (PET) scans, but as of right now this is not yet certain. Doctors could potentially utilize this knowledge in the future to develop different ways of diagnosing pancreatic cancer more effectively and reduce the healthcare cost burden of this disease.

Keywords: Spermine, pancreatic cancer, HPLC

Introduction

The pancreas is a vital component of the human gastrointestinal system located near the stomach and duodenum. This organ releases essential intestinal fluids, such as alkaline succus and digestive enzymes, that assist the body in assimilating nutrients. These catalytic enzymes degrade nutrients like sugars, fats, and proteins into smaller particles so they can be absorbed from the gut mucosal lining and utilized in metabolic processes. Typically, the pancreas stores digestive enzymes in an inactivated form. Once secreted in response to food consumption, the enzymes are discharged from the pancreas and travel through the pancreatic duct into the small intestine, where they become activated to digest food particles. The pancreas also helps to maintain a homeostatic sugar balance in the blood. It produces multiple hormones, like insulin and glucagon, that are released in the bloodstream and help elevate or reduce sugar levels in the body[1].

Cancer is an insidious, infiltrative and progressive process whereby the normal glandular structure of any organ or tissue is replaced by abnormal cells that grow unchecked and subvert the functions of the affected glands. Additionally, more than a hundred distinct forms of cancer can involve almost any bodily organ or tissue. The two primary properties of cancer are an unrestrained expansion of cells within the human body and the ability of these cells to relocate or metastasize from the initial site and distribute to distant locations[2]. Pancreatic cancer arises primarily from the ductal cells of the exocrine pancreas. These aberrant cells in the pancreas undergo alterations in their DNA. Mutations in a cell's DNA can disrupt the expression of genes responsible for the production and regulation of proteins essential to mitochondrial and other organellar functions, potentially leading to impaired energy metabolism, defective cellular signaling, and altered apoptosis pathways. Thus, this genetic transformation leads to modifications in the mitotic activity of cells to grow spontaneously and unrestrained and survive after healthy cells perish. Numerous varieties of pancreatic cancer can occur; the most common is Ductal Adenocarcinoma. These abnormal cells grow from the epithelial cells that line the ducts that transport digestive enzymes[3]. Symptoms of pancreatic cancer are surreptitious and commonly get detected once the cancer has advanced to a hazardous and overtly symptomatic condition; thus, pancreatic cancer is often diagnosed late due to being asymptomatic in early stages[4].

Moreover, computerized tomography (CT) scans are used to diagnose this condition by rotating an x-ray beam around the patient to produce cross-sectional images, which are then reconstructed into 3D images by a computer. This imaging modality enables cross-sectional perspectives of the body's organs and tissues[5]. Since pancreatic cancer is commonly detected once the patients are symptomatic, interest has grown in finding a serum biomarker to identify it as early as possible. This led to research on whether specific small molecules called biomarkers may be elevated and easily measured in human malignancies. Polyamines and polypeptides are the primary fundamental central organic molecules in nature. They appear pervasively in all tissues in significant concentrations and are considered to be an integral part of various physiologic processes related to cell expansion and growth. Polyamines are small, positively charged molecules that are essential for normal cell growth and differentiation. In cancer, these molecules become dysregulated and contribute to uncontrolled cell division and tumor progression through several mechanisms. Spermine is synthesized through a multi-step process that begins with the amino acid ornithine, which is converted into putrescine by the enzyme ornithine decarboxylase (ODC). Putrescine is then converted into spermidine, and finally into spermine via the addition of aminopropyl groups provided by the amino acid methionine via decarboxylated S-adenosylmethionine (dcSAM). Spermine is a ubiquitously present polyamine related to numerous cellular amino acid groups. It contributes to each eukaryotic cell's anabolic metabolism significantly. Spermine is one of many polyamines produced in various rapidly proliferating human cancers, including pancreatic cancer. Therefore, spermine is proposed to be an early marker of pancreatic cancer as it is thought to be elevated at the early stage of this disease[6,7].

Fig. 1 Chemical structure of spermine[8].

The purpose of this study is to determine if spermine is elevated in the blood of all pancreatic cancer patients. This study aims to test whether elevated spermine levels do indeed correlate with pancreatic cancer in order to find a potential cost-effective method of diagnosing pancreatic cancer early on and thus minimizing the mortality of this disease. We hypothesize if spermine level is increased in blood, then there is a higher chance of coexisting pancreatic cancer being present, therefore elevated spermine levels in blood may be a biochemical marker of pancreatic cancer.

This study was geographically limited to individuals residing in South Florida with all patients in the study being from Westside Hospital. The number of trials was also limited due to the lengthy process of finding volunteers and patients willing to participate in the study.

Methods

This was an observational study conducted with the use of ten patients with pancreatic cancer and ten volunteers without pancreatic cancer. Participants between the ages of 50 to 80 years old residing in South Florida were selected. Approximately half of the participants were male and the other half female: 6 male and 4 female pancreatic cancer patients along with 5 male and 5 female volunteers. The data for this study was collected through observations of spermine levels of all twenty participants and was then analyzed using a two-sample t-test and by comparing the mean, minimum, and maximum spermine levels of the two groups. The independent variable in this study was the status of the individual (whether they had pancreatic cancer or not), while the dependent variable was the spermine level measured in ng/mL. Ten trials of the measurement of the spermine level of a patient with pancreatic cancer and ten trials of the measurement of the spermine level of one volunteer without pancreatic cancer were conducted, equaling 20 individual trials in total.

This study adhered to the following procedure:

1. The adult physician supervisor will enlist 10 patients with pancreatic cancer and 10 healthy volunteers that are the relatives or friends of the pancreatic cancer patients at the Oncology clinic at Westside Hospital, Plantation, FL., each willing to donate 5 mL of venous blood. Informed consent will be obtained by the physician supervisor after explaining to all the willing participants the purpose of the project, that they will not be charged any cost of the spermine testing on the blood samples. The results of the study will be available to each of them on request. The informed consents will be kept on file at the Oncology Clinic.

2. Each pancreatic cancer patient and normal healthy volunteer will be asked to give a detailed informed consent form. This informed consent form will explain that we are requesting them to donate 5 mL of their blood for laboratory testing of spermine levels. No identifying information like name, date of birth, medical record number will be marked on the blood tubes to maintain anonymity. The certified laboratory phlebotomist will extract 5 mL of each of the 20 patients and volunteers' blood. All precautions will be taken by the certified clinic laboratory phlebotomist working under the direct supervision of the licensed health

care provider. Appropriate personal protective equipment like gloves, gowns, eye protection like goggles or face shields will be utilized while drawing blood. The blood drawn using 23-gauge needles and syringes will be placed in orange top blood chemistry collection tubes and appropriately labeled as either patient or volunteer sample (PC #1-10 v. NV #1-10). All equipment used in the withdrawal of blood including syringes and needles will be disposed of in a standard biohazard waste container or an appropriately marked red colored sharps disposal container.

3. Blood samples taken from both groups as pancreatic cancer samples (PC #1-10) and as normal volunteers (NV #1-10) in the orange top biochemistry glass collection tubes.

4. All the appropriately labeled blood samples were stored in a cooler under refrigerated conditions (between 2ºC and 8ºC) and then sent to the biochemical laboratory at Westside Hospital. All testing of the blood samples was conducted within a week from collection to ensure the viability of the samples[9]. The laboratory technicians utilized the Creative Proteomics high-performance liquid chromatography (HPLC) chemical analyzer, which accurately measures spermine samples with only a 0.5% error. The HPLC chemical analyzer was calibrated regularly (before initial testing and after 10 samples) using a certified external reference standard, specifically spermine tetrachloride, to generate a standard calibration curve for precise quantification of spermine levels in the 20 blood samples.

5. Analyze the data once all the results are back from the laboratory by conducting a two-sample t-test with an alpha level of 0.01 and calculating the 95% confidence intervals (CIs) of both groups. Normal human spermine levels range from 10–60 ng/mL, noting that any spermine level greater than 100 ng/mL is considered markedly abnormal and indicative of pancreatic cancer[1].

6. Construct a table and violin plots showing the levels of spermine in both groups

Ethical concerns about confidentiality and consent were properly addressed with all twenty participants remaining anonymous and confirming to have given their consent to being a part of this study.

Results

The mean serum concentration for the patients was 106.8 ng/mL, and the mean value for the healthy volunteers was 33.6 ng/mL. There were no outliers in either the sample of pancreatic cancer patients or volunteers utilizing Tukey's interquartile range method; however, one regular volunteer [#5] in the study had a mildly elevated spermine level just above the normal maximum reference range of 10-60 ng/mL (64 ng/mL). Conducting a two-sample t-test resulted in a p-value of 5.067×10^{-8}, which is less than the specified alpha level of 0.01. Thus, there is convincing evidence in favor of the initial hypothesis that if the spermine level is markedly increased, a patient is likely to have pancreatic cancer. The 95% confidence intervals (CIs) of the spermine levels in both groups were calculated with the CI of the patients' spermine levels being [91.951, 121.649] while the CI of the volunteers' spermine levels was [21.869, 45.331]. Since the two 95% CIs do not overlap, this suggests that there is indeed a statistically significant difference between the mean spermine levels of the two groups. Spermine is a ubiquitous polyamine, and polyamines are aliphatic compounds that play a prime role in human cellular metabolism. Since cancer invariably leads to rapidly proliferating cells that are unchecked by average growth homeostatic mechanisms, it causes an increase in all cellular metabolic pathways. Polyamine metabolism malfunction and polyamine regulatory systems are therefore frequently induced and lead to an increased level in cancer patients. A perusal of the medical literature revealed that blood level concentrations higher than 100 ng/mL strongly correlate with malignancies like pancreatic cancer.

In this study, some of the patients' blood spermine concentrations were measured at less than 100 ng/mL. A possible

Tabulated Data of Blood Spermine Levels by Group		
	Patients	Volunteers
Trial 1	119	18
Trial 2	88	34
Trial 3	112	52
Trial 4	84	33
Trial 5	78	64
Trial 6	139	29
Trial 7	91	11
Trial 8	123	47
Trial 9	106	21
Trial 10	128	27
Mean	106.8	33.6
Median	109	31
Mode	None	None
Std. Deviation	20.757	16.399
Minimum	78	11
Maximum	139	64

Table 1. Data displayed in a tabulated form

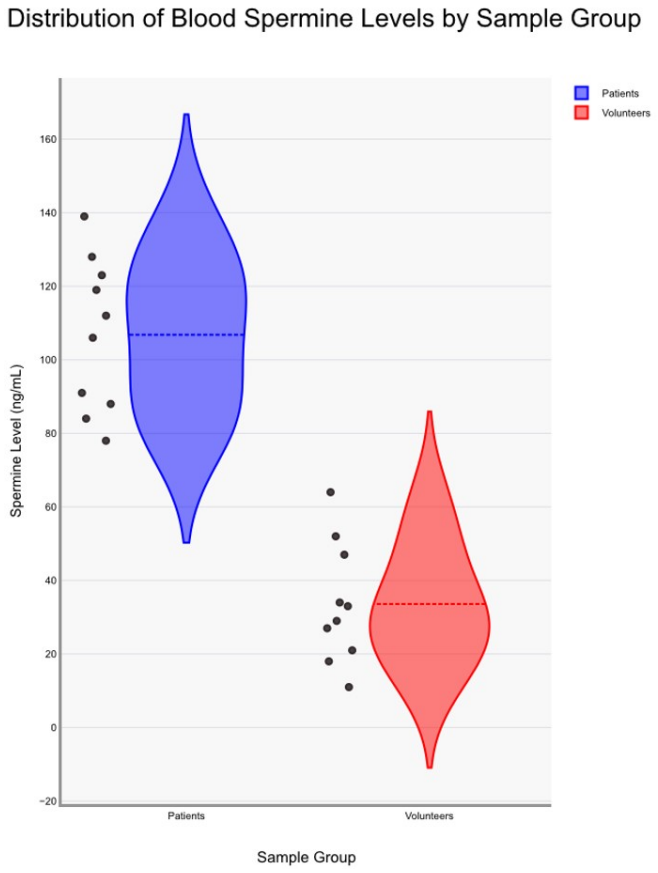

Fig. 2 Violin plots showing the distribution of the data in each group.

explanation for this might be that pancreatic cancer patients are in different stages of their disease. Patients with more advanced-stage disease are more likely to have increased spermine concentration in their blood and vice versa. Some patients might be undergoing treatment, for example, chemotherapy or radiation therapy, for their pancreatic cancer. Therefore, their blood concentration levels are lower but not in the normal range.

One of the regular volunteers (NV #5) had a mildly higher than the upper limit of normal blood spermine concentration of 60 ng/mL. This may be attributed to the subject having an undiagnosed early stage of pancreatic cancer or other gastrointestinal malignancy. Another reason could be that the volunteer may have an abnormal spermine level due to another concurrent illness leading to metabolic pathway defects or could be due to simple laboratory error.

Discussion

The results of this study provide significant value by indicating a potential new way of diagnosing pancreatic cancer. Because the cost of the biochemical test for measurement of polyamines like spermine is very reasonable at about $625 for a spermine Enzyme-Linked Immunosorbent Assay (ELISA) kit containing 96 tests, or around $6 to $7 per individual test, measuring spermine levels could provide a cost-effective method of diagnosing pancreatic cancer in high-risk patients at an early and more treatable stage [10]. This could lead to a reduction in the health care cost burden as currently only costly diagnostic tests like invasive gastrointestinal endoscopy or radiologic tests e.g. computed tomography (CT) and positron emission tomography (PET) scans can detect pancreatic cancer with these costing from a few hundred dollars to thousands of dollars without insurance [11]. This study could potentially contribute to further advancements in the medical world, and could detect pancreatic cancer sooner.

Larger scale studies would be needed to correlate spermine blood levels with the stage of pancreatic cancer, therefore providing diagnostic implications for measuring spermine levels at different stages of the disease. Since spermine is a common polyamine produced by the liver, pancreas, and other gastrointestinal tract malignancies, it may be a biomarker for other cancers apart from pancreatic cancer. A double-blinded study should be undertaken to confirm the results of this initial study. Ethnographic variations in the epidemiology of pancreatic cancer would also lead to variations in spermine blood concentrations. These studies should be done in different countries to validate the results in other ethnic and racial groups. A patient's nutritional status also plays a role in spermine metabolism, as the availability of proteins in the diet, which are the biomolecular precursors of the spermine pathway, need to be present in sufficient quantities. Advanced cancer can lead to malnutrition and wasting of body tissues since cancer acts like a parasite and preferentially diverts nutrients to the rapidly growing cancer cells. The exact relationship between nutritional status and spermine levels needs to be evaluated in future studies.

Some limitations of this project may be that we did not consider the actual cancer treatment stage of the ten pancreatic cancer patients. We enlisted pancreatic cancer patients which had been previously diagnosed with the disease and were following up in the Cancer Clinic at Westside Hospital. Comorbidities and undiagnosed diseases were also not accounted for and could have affected the results as one volunteer did have a spermine level higher than the normal upper limit of 60 ng/mL. This study was also limited geographically to South Florida. Additionally, the HPLC chemical analyzer must be calibrated regularly to maintain an accuracy of less than 0.5% measurement error. The patient's and volunteer's age may also have a confounding effect on spermine levels. Since spermine levels depend on protein and polyamine metabolism, an individual's nutritional status may also theoretically affect blood spermine concentration. Also, this is an extrapolation of results from a small pilot study of only ten patients in each group. A larger-scale study will have to be conducted to confirm the reproducibility and validity of

the results. Future work could include stratifying patients by cancer stage, evaluating longitudinal changes in spermine levels during treatment, or combining spermine with other polyamine metabolites to improve diagnostic accuracy.

In all, this research study suggests that spermine may potentially be a biomarker that could lead to a cost-effective method to diagnose pancreatic cancer early on and potentially reduce deaths from this disease; however, this is not yet certain and we as a society must continue to help researchers in any way we can to hopefully eliminate the morbidity and mortality burden of this cancer.

Conclusion

In this preliminary investigation, pancreatic cancer patients exhibited significantly elevated blood spermine levels compared to the healthy control group of volunteers. These findings support further exploration of spermine as a potential biomarker for pancreatic cancer. However, due to the small sample size and lack of longitudinal data, definitive conclusions cannot yet be drawn. Future studies should include larger, more diverse cohorts and consider confounding variables such as treatment status, diet, and comorbidities.

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