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Effects of Diabetes on Ovarian Cancer: Data Analysis and Modeling Study

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EFFECTS OF DIABETES ON OVARIAN CANCER: DATA ANALYSIS AND MODELING STUDY

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Abstract

Ovarian cancer has one of the highest mortality rates of all gynecological cancers [13]. Further knowledge of risk factors for the growth of ovarian tumors would be beneficial in both the treatment and prevention of this type of cancer. Previous research has shown a positive correlation between diabetes and prostate tumor growth [22]. The first aim of this study was to determine the effect of diabetes of ovarian tumor growth. The second aim was to develop a model to predict ovarian tumor growth based on the microenvironment within a patient's body. The hypothesis was that there would be a positive correlation between diabetes and ovarian tumor volume. Data from fifty patients was collected from charts at Grady Memorial Hospital in Atlanta, Georgia. Oxygen saturation, tumor volume, blood glucose level, and cancer stage were gathered for each patient. The results contradicted the hypothesis; there was a negative correlation found between blood glucose level and tumor volume. More data is needed to determine if increased blood glucose could be an effective treatment of ovarian cancer, particularly since there other health risks associated with elevated blood glucose levels. The proposed mathematical model also needs modification in order to effectively bridge the gap between the clinical and research aspects of the cancer field.

IRB approval: The study protocols were approved by the institutional review boards (IRBs) at the corresponding institutions. Consent was waived by the IRB since, in this particular study, a retrospective medical record review was utilized as a method of data collection. CSU Protocol number 18-024.

INDEX WORDS: Ovarian, Ovaries, Cancer, Diabetes, Mathematical Model, Tumor.

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1 Introduction

In 2014, 21,161 women in the United States were diagnosed with ovarian cancer, and 14,195 died as a result of this type of cancer [13]. Once ovarian cancer is diagnosed, the stage of the cancer is determined according to its progression. Table 1.1 shows the description of each stage according to the FIGO system for staging ovarian cancer.

Several factors, generally speaking, play a role in the progression and development of cancer. T cells, oxygen levels, and glucose consumption can all affect the growth rate of tumors. T cells, which are a type of immune cell, have been found to suppress tumor immunity, thus rendering the body more susceptible to malignant cell proliferation [18]. Oxygen levels also affect cancer proliferation. Cancer cells proliferate at a higher rate than do blood vessel cells. Because of this, the blood vessels, which carry oxygenated blood, cannot reach the inside of the tumors that are formed due to the high rates of proliferation. This leads to a hypoxic environment. Many cancer cells, including breast cancer cells, form solid tumors, resulting in a hypoxic environment inside the tumor [14]. Although tumors arising from ovarian cancers are epithelial in nature rather than solid, these tumor cells still experience hypoxia [16]. In the presence of oxygen, cells receive 36 ATP after undergoing glycolysis, which fuels the cell cycle,allowing cells to proliferate. Without oxygen, a hypoxic environment, cells undergo fermentation, producing lactic acid and much lower amounts of ATP. Because the cells must rely solely upon the ATP produced during lactic acid formation and fermentation, they only receive 2 ATP instead of 36. In order to counteract this hypoxic environment, the tumor must resort to using glucose outside of the cell to obtain the energy needed to proliferate [19]. In this case, the glucose source will be the blood stream. This is done by increasing the expression of glucose transporters GLUT1 and GLUT3, which alter the structure of the tumor so that glucose outside

of the cells can supply the cells with the necessary glucose to produce the ATP needed for proliferation [15]. Since a higher blood glucose level would supply the cancer cells the glucose needed for proliferation, it is thought that Type 2 diabetic patients, who have excess glucose in their blood stream, could exhibit increased ovarian cancer cell proliferation. Table 1.2 shows the stage of diabetes according to HbA1c, and Table 1.3 shows the stage of diabetes based on blood glucose level while fasting.

The two aims of this study are:

1. To propose a mathematical model involving blood glucose levels, oxygen, and T cell competition that can accurately predict ovarian tumor growth and proliferation.
2. To determine the effect of blood glucose levels on ovarian cancer tumors growth and stage.

The first aim of this study attempts to develop a mathematical model that accounts for oxygen levels and glucose levels in patients with type 2 diabetes in order to determine tumor cell growth and T cell proliferation. We proposed two models for tumor growth within diabetic patients based on previous modeling studies that have been conducted on the progression of tumors [1-12].

Previous research has shown a positive correlation between diabetes and prostate cancer growth [22]. Due to this, the hypothesis for this study for the second aim of the study was that there would be a positive correlation between diabetes and ovarian cancer stage and a positive correlation between diabetes and tumor size.

Table 1.1. FIGO ovarian cancer staging.

Stage I:	**Tumor confined to ovaries**
IA	Tumor limited to 1 ovary, capsule intact, no tumor on surface, negative washing
IB	Tumor involves both ovaries otherwise like IA
IC1	Surgical spill
IC2	Capsule rupture before surgery or tumor on ovarian surface
IC3	Malignant cells in the ascites or peritoneal washings
Stage 2:	**Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer**
IIA	Extension and/or implant on uterus and/or fallopian tubes
IIB	Extension to other pelvic intraperitoneal tissues
Stage III:	**Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes**
IIIA1	Positive retroperitoneal lymph nodes only
	IIIA1 (i): Metastasis ≤ 10mm
	IIIA1 (ii): Metastasis > 10mm
IIIA2	Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes
IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤ 2cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.
IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.
Stage IV:	**Distant metastasis excluding peritoneal metastasis**
IVA	Pleural effusion with positive cytology
IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Table 1.2. Stage of diabetes based on HbA1c.

	HbA1c (%)	HbA1c (mm/L)
Nondiabetic	<6.0	<42
Prediabetic	6.0-6.4	42-47
Diabetic	>6.4	>47

Table 1.3. Stage of diabetes based on blood glucose levels while fasting.

	Blood Glucose (mg/dL)
Nondiabetic	0-100
Prediabetic	101-125
Diabetic	126+

2 Glucose, Tumor and T cell model

In the following model, we are interested in the impact of glucose (G) on the growth of T cells (I) and tumor cells (T):

$$\begin{cases} \dfrac{\mathrm{d}G}{\mathrm{d}t} = \underbrace{s}_{\text{constant supply}} - \underbrace{h_1(G)T}_{\text{consumed by Tumor cells}} - \underbrace{h_2(G)I}_{\text{consumed by immune-cell}}, \\ \dfrac{\mathrm{d}T}{\mathrm{d}t} = \underbrace{h_1(G)\lambda_1 T}_{\text{proliferation}} - \underbrace{c_1 IT}_{\text{competition}}, \\ \dfrac{\mathrm{d}I}{\mathrm{d}t} = \underbrace{h_2(G)\lambda_2 I}_{\text{proliferation}} - \underbrace{dI}_{\text{natural death}} - \underbrace{c_2 IT}_{\text{competition}}, \end{cases} \tag{2.1}$$

In the model, *G(t)* represents the concentration of glucose level in patients, which varies with time *t*. The unit of *G(t)* is g/ml. Variable *T(t)* represents the total number of ovarian cancer cells in patients. As previously mentioned, ovarian cancer cells are epithelial in nature and spread on the surface of the ovary with a thinner layer of tumors cells oriented side-by-side rather than on top of one another in a spherical nature as in most cancers. If *T(t)* is divided by the concentration of ovarian cancer cells in per unit square area, we can convert *T(t)* into the total surface area of ovarian cancer. The surface area of ovarian cancer is a commonly used clinical criteria by physicians to determine the stage of cancer. In most clinical data sets, the area of ovarian cancer is recorded. Therefore, we can easily fit the clinical data to *T(t)* by converting the surface area to the approximate number of tumor cells by multiplying the concentration of the tumor cells in a unit square area. Variable *I(t)* is the total number of immune cells in the affected cancerous tissue.

For immune cells, we consider the natural death rate d. However, for tumor cells, we ignore the natural death rate because tumor cells have a very low rate of apoptosis [17]. Therefore, the natural death rate of cancer cells is negligible in the model.

The Michaelis-Menten kinetics is adapted for the per capita growth rate of tumor cells (i=1) or immune cells (i=2):

$$h_i(G) = \frac{b_i G}{1 + k_i G} \tag{2.2}$$

By manipulating the constant supply of glucose s, we can mimic the different glucose levels in patients with or without diabetics. Parameter λ_1=1/20, where 20 hours is the doubling time for tumor cells. Parameter λ_2=1/36, where 36 hours is the doubling time for immune cells [20]. The time t is measured in hours. Table 2.1 shows defines the variables for all equations in this study.

Table 2.1. Variables defined.

Variable	Description
$I(t)$	Total amount of immune cells within tumor
$T(t)$	Total number of ovarian cancer cells
$G(t)$	Total glucose available within tumor
s	Constant supply of glucose
d	Death rate of immune cells
m	Half-saturation constants for Michaelis-Menten kinetics
b_i	Maximal growth rate of immune cells or tumor cells
$1/k_i$	Half-saturation rate
c_1	Competition ratio for tumor cells
c_2	Competition ratio for immune cells
O	Oxygen
h_1	Proliferation ratio for tumor cells
h_2	Proliferation ratio for immune cells
λ_1	Doubling time for tumor cells
λ_2	Doubling time for immune cells

3 A comprehensive model with Oxygen and Glucose

Since patients with type 2 diabetes have a higher glucose concentration in blood, the extra glucose may be used to increase tumor growth and proliferation. However, even with a sufficient supply of sugar, the growth of the tumor is still limited by the availability of oxygen. With this in mind, the following comprehensive mathematical model is proposed (3.1). In the following model, the impact of both glucose (G) and oxygen (O) on the growth of immune cells (I) and tumor cells (T) are accounted for:

$$\begin{cases} \frac{dO}{dt} = \underbrace{s_1}_{\text{constant supply}} - \underbrace{f_1(O)T}_{\text{consumed by Tumor cells}} - \underbrace{f_2(O)I}_{\text{consumed by immune-cell}}, \\ \frac{dG}{dt} = \underbrace{s_2}_{\text{constant supply}} - \underbrace{h_1(G)T}_{\text{consumed by Tumor cells}} - \underbrace{h_2(G)I}_{\text{consumed by immune-cell}}, \\ \frac{dT}{dt} = \underbrace{min\{f_1(O), h_1(G)\}\lambda_1 T}_{\text{proliferation}} - \underbrace{c_1 IT}_{\text{competition}}, \\ \frac{dI}{dt} = \underbrace{min\{f_2(O), h_2(G)\}\lambda_2 I}_{\text{proliferation}} - \underbrace{dI}_{\text{natural death}} - \underbrace{c_2 IT}_{\text{competition}}, \end{cases} \tag{3.1}$$

where functions min $\{f_1(O), h_1(G)\}$, and min $\{f_2(O), h_2(G)\}$ are used since sources of oxygen and glucose come from different places, but are essential for the proliferation of cancer cells. Each substance fulfills different physiological needs with respect to growth [21].

4 Methods

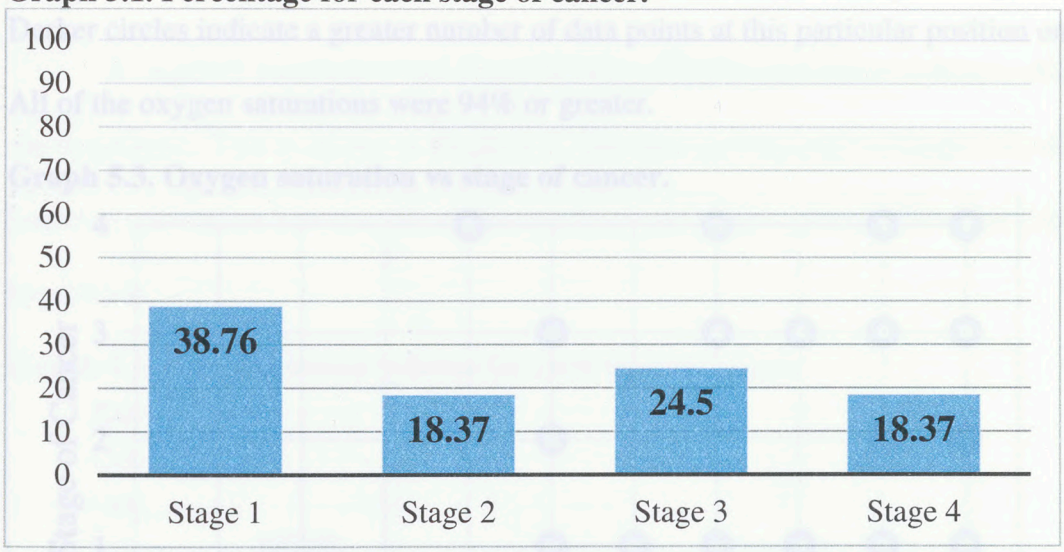
De-identified patient data was collected by Dr. De'smond Henry, MD at Morehouse School of Medicine. The data was obtained from the Georgia Cancer for Excellence at Grady Memorial Hospital in Atlanta, Georgia. Fifty patients who had ovarian cancer were included in the study. Diabetic patients whose diabetes was controlled with medication were excluded from

the study. Tumor volume, blood glucose level, oxygen saturation, HbA1c (for those with diabetes), and stage of ovarian cancer were collect from the medical records of each of the fifty patients. For patients who underwent surgery, the data was collected at the time of surgery. For those who opted out of surgery, the data was collected at the time of diagnosis. Patients were assigned a diabetic stage according to Table 3. The data was then analyzed to determine the effect of diabetes on ovarian cancer. The data will be used for later incorporation into the models that were developed for this study.

5 Results

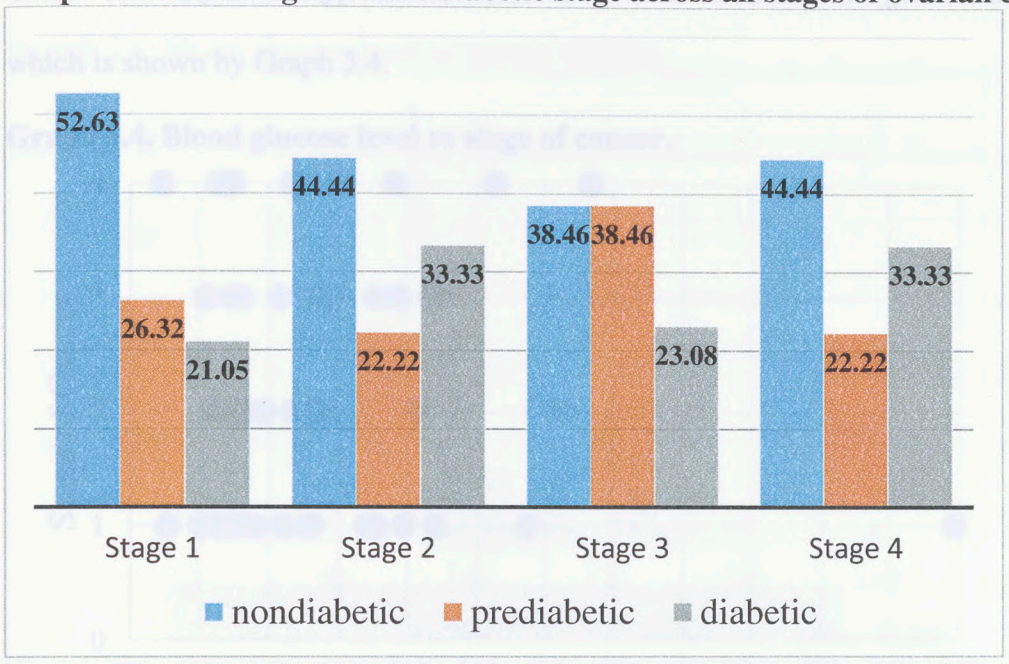
Graph 5.1 shows the percentages for each stage of cancer within the study.

Graph 5.1. Percentage for each stage of cancer.



The data was broken down into both stage and diabetic category in Graph 5.2. There was no correlation between diabetic category and stage of cancer, although overall the greatest percentage in each stage of cancer was comprised of nondiabetic patients.

Graph 5.2. Percentage for each diabetic stage across all stages of ovarian cancer.

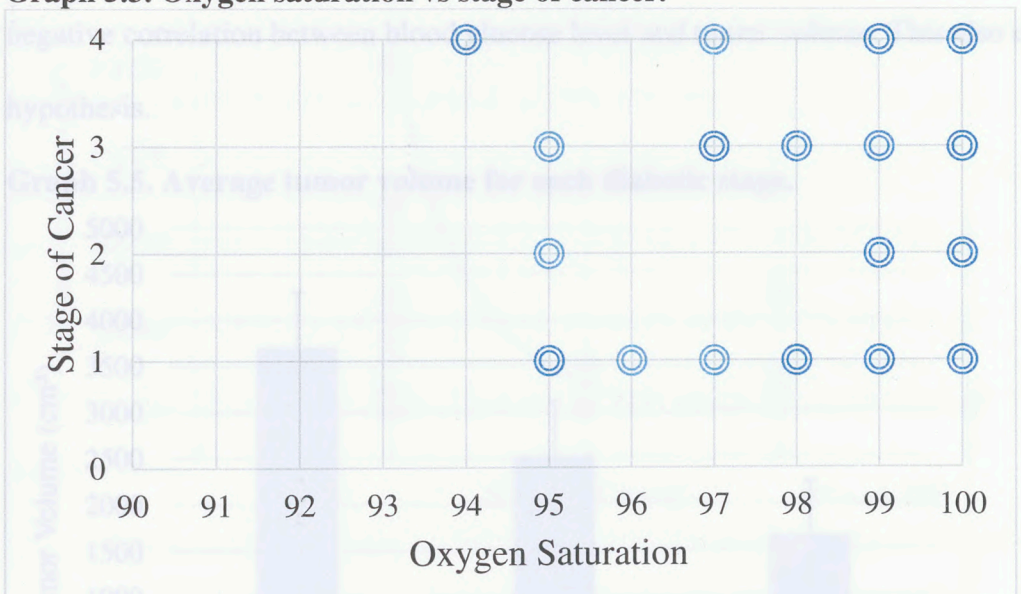


Oxygen was found to have no correlation with cancer stage, as is shown in Graph 5.3.

Darker circles indicate a greater number of data points at this particular position on the graph.

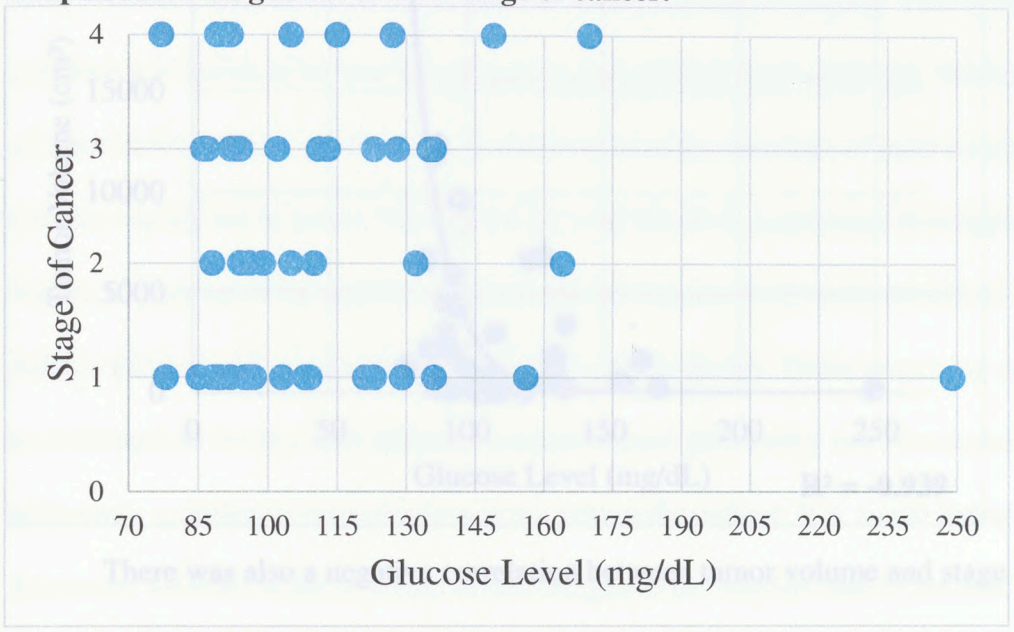
All of the oxygen saturations were 94% or greater.

Graph 5.3. Oxygen saturation vs stage of cancer.



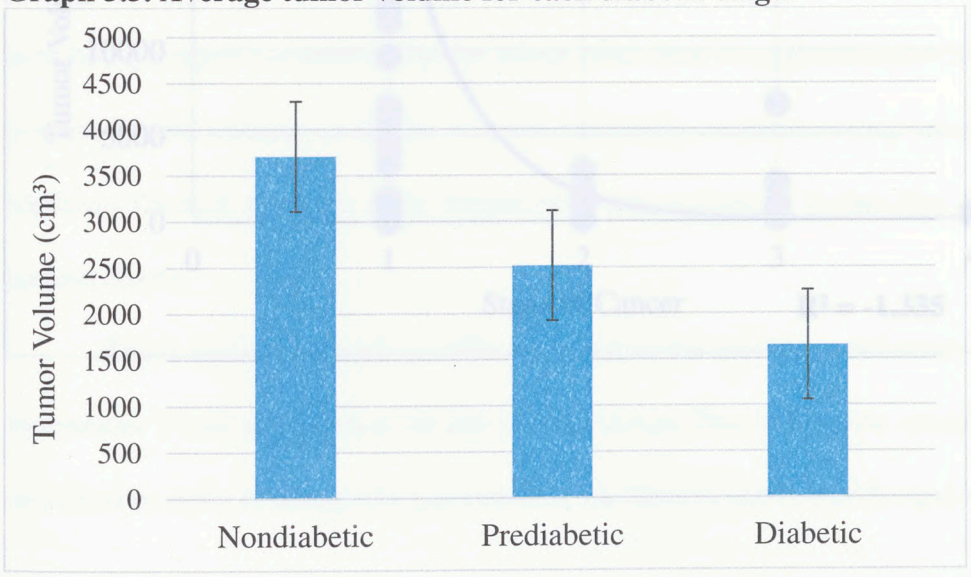
Contrary to the hypothesis, there was no correlation between glucose and stage of cancer, which is shown by Graph 5.4.

Graph 5.4. Blood glucose level vs stage of cancer.

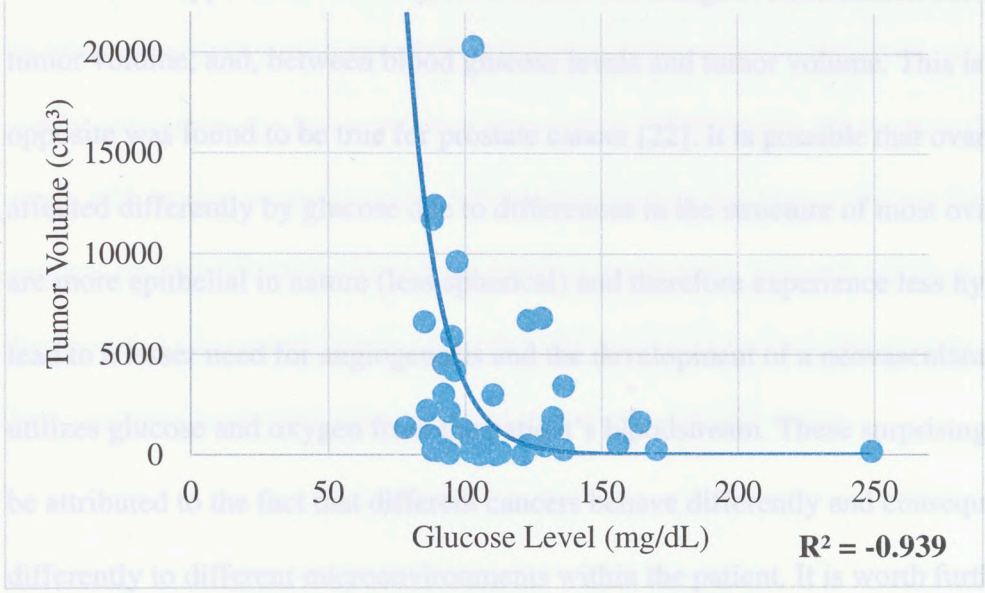


A negative correlation was found between diabetes and tumor volume, which contradicts the hypothesis. This is shown in Graph 5.5. This data corresponds to Graph 5.6, which shows a negative correlation between blood glucose level and tumor volume. This also contradicts the hypothesis.

Graph 5.5. Average tumor volume for each diabetic stage.

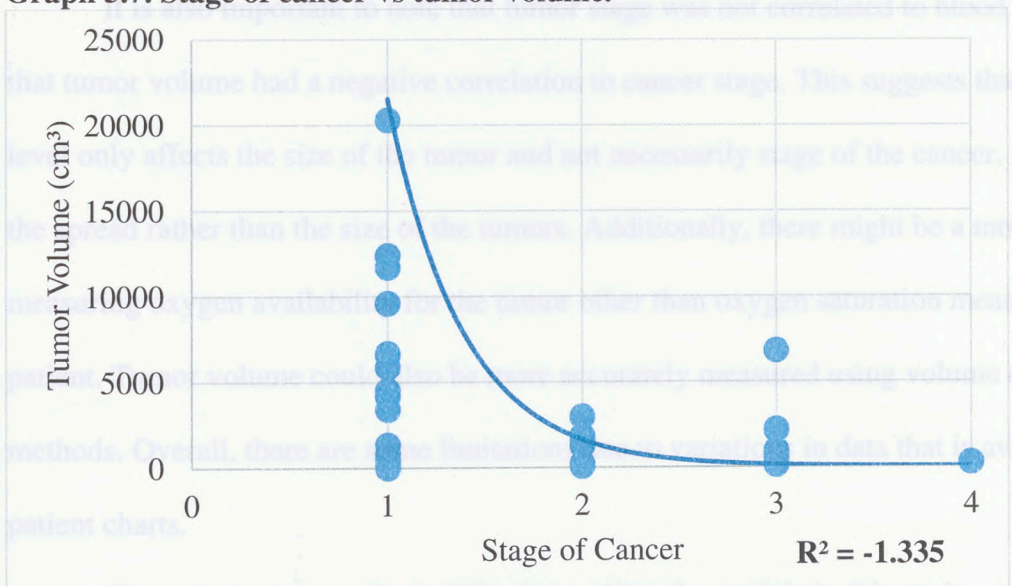


Graph 5.6. Blood glucose level vs tumor volume.



There was also a negative correlation between tumor volume and stage of cancer, as is shown in Graph 5.7.

Graph 5.7. Stage of cancer vs tumor volume.



6 Discussion

Both hypotheses were rejected. There was a negative correlation between diabetes and tumor volume; and, between blood glucose levels and tumor volume. This is surprising, as the opposite was found to be true for prostate cancer [22]. It is possible that ovarian cancer could be affected differently by glucose due to differences in the structure of most ovarian tumors, as they are more epithelial in nature (less spherical) and therefore experience less hypoxia. This could lead to a lesser need for angiogenesis and the development of a neovasculature system that utilizes glucose and oxygen from the patient's bloodstream. These surprising results could also be attributed to the fact that different cancers behave differently and consequently react differently to different microenvironments within the patient. It is worth further research to determine whether or not it would be advantageous for ovarian cancer patients to have higher levels of blood glucose in order to slow the rate of tumor growth.

It is also important to note that tumor stage was not correlated to blood glucose level and that tumor volume had a negative correlation to cancer stage. This suggests that blood glucose level only affects the size of the tumor and not necessarily stage of the cancer, as stage describes the spread rather than the size of the tumors. Additionally, there might be a more accurate way of measuring oxygen availability for the tumor other than oxygen saturation measurements for the patient. Tumor volume could also be more accurately measured using volume displacement methods. Overall, there are some limitations due to variations in data that is available from patient charts.

These limitations make it difficult to utilize the models in this study, as there was no way to measure T cell competition for any of the patients. Due to this, the models may have to be modified in order to bridge the gap between the clinical and research aspects.

In the future, plans are underway to incorporate more patients into the data set. As can be seen by the negative R^2 values for the exponential regressions on Graph 6 and Graph 7, a greater number of patients could potentially give more information to this study, as negative R^2 values can be indicative of a low number of data points. Additionally, plans are underway to repeat this study with breast cancer patients. After sufficient data has been collected for both types of cancers and modifications have been made to the models, research which include plans to utilize the models to accurately predict the effect (if any) of glucose on the growth rate of tumors in both ovarian cancer patients and breast cancer patients will ensue.

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