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Original Article

# Evaluation of the relationship between glycemic parameters and preoperative tumor markers in colorectal, prostate, and breast cancers

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## Abstract

**Objective:** The basic metabolic processes of cancer cells involve growth and proliferation. These cells use glucose as the main source. We aimed to investigate the significance of glycemic parameters and preoperative tumor markers in terms of risk and stage of cancer development.

**Methods:** We employed a total of 400 participants, including 100 patients diagnosed with colorectal cancer, 100 patients diagnosed with prostate cancer, 100 patients diagnosed with breast cancer, and 100 healthy controls. We evaluated glucose, HbA1c, insulin, carbohydrate antigen 15-3 (CA15-3), carbohydrate antigen 19-9 (CA19-9), carbohydrate antigen 72-4 (CA72-4), carcinoembryonic antigen (CEA) and prostate specific antigen (PSA) results of these individuals.

**Results:** We found significantly higher levels of fasting plasma glucose (FPG) and fasting plasma insulin (FPI) in breast cancer patients; FPG, FPI, and HbA1c in prostate cancer patients; and FPG and HbA1c values in colorectal cancer patients compared to control groups ($p<0.05$). Furthermore, we found significantly higher CEA and CA15-3 in breast cancer patients; PSA, CEA, and CA19-9 in prostate cancer patients; and CEA, CA19-9, and CA72-4 in colorectal cancer patients compared to those in the control groups ($p<0.05$).

**Conclusion:** We confirmed the ability of glucose, insulin, and HbA1c to predict breast, prostate and colorectal cancer. In this context, the successful implementation of glycemic control and diabetes mellitus treatment in patients may enhance the efficacy of the treatment incertain cancers and reduce the incidence of the disease. However, more cohort studies are needed to demonstrate this relationship more clearly and to consider it a rule.

**Keywords:** Breast cancer, colorectal cancer, glucose, prostate cancer, tumor markers.

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## INTRODUCTION

Cancer is a complex disease characterized by uncontrolled division and proliferation of cells. Various genetic and environmental factors play a role in cancer development. Cancer is the second leading causes of death worldwide. Due to their rapid division, cancerous cells need more nutrients than normal cells (1). Cells consume glucose as both an energy source and an intermediate product in metabolic processes. Otto Warburg's study showed the difference between the metabolism of malignant tumor cells and normal metabolism. According to this discovery, normal cells produce lactate using glycolysis only under anaerobic conditions, while tumor cells use glucose independently of oxygen and produce lactate through glycolysis under aerobic conditions (2,3). The basic metabolic processes of cancer cells are growth and proliferation, with glucose serving as their primary source. The increased glucose uptake is also used in cancer cell imaging. The metabolic activity of neoplasia is revealed and visualized by determining the glucose intake of a cell using the PET method (2-deoxyglucose and its conjugation with fluorine-18) (4,5).

Numerous studies have investigated the association of malignancies and glucose metabolism disorders at different levels (6,7). These include breast cancer (8), prostate cancer (9), and colorectal cancer (10). There are also articles investigating tumor markers and glucose metabolism in diabetic patients without malignancies (11,12). In addition, numerous recent studies have been published, exploring various features of glucose metabolism and cancer, discovering relationship between them (13).

Because study results may vary based on sex, we included breast cancer specific to women, prostate cancer specific to men, and colorectal cancer depending on the incidence in both sexes.

In this study, we aimed to investigate the significance of glycemic parameters [fasting plasma glucose level (FPG), fasting plasma insulin level (FPI), hemoglobin A1c (HbA1c)], body mass index (BMI), complete blood count (CBC) parameters and preoperative tumor markers [carbohydrate antigen 15-3 (CA15-5), carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), carbohydrate antigen 72-4 (CA72-4), prostate specific antigen (PSA)] in terms of the risk and stage of cancer development.

## MATERIALS AND METHODS

### *Patients and study design*

This is a retrospective study, which included 100 colorectal cancer patients (47 women, 53 men), 100 prostate cancer patients, 100 breast cancer patients and 100 healthy controls who were admitted to Ankara Etlik City Hospital were included in the study between January 2023 and June 2023. It included nondiabetic malignancy patients. Patients with a history of cancer, systemic chronic diseases (such as chronic heart disease, chronic lung disease, chronic renal failure and liver disease), malabsorption diseases (such as celiac disease or radiation enteritis), thyroid and parathyroid diseases, hormone replacement therapy, psychiatric disorders, alcohol consumption, and pregnant women were not included in the control group.

The study assessed clinical chemistry tests, glucose, HbA1c, insulin, complete blood count, CA15-3, CA19-9, CA72-4, CEA and PSA results. The stages of the diseases were divided into two groups, as stage 1-2 and stage 3-4, and then compared. Venous blood and complete blood samples were collected from these individuals after 10-12 hours of fasting. To analyze biochemistry parameters and tumor markers, 8-10 mL of blood was taken into a yellow-capped gel tube containing clot activator. Blood samples were centrifuged at 1500-2000×g for 10 minutes after allowing for 20-30 clotting reactions to complete, and then serum samples were obtained. Using these serum samples, biochemistry parameters were measured and evaluated in a Roche Cobas c 702 (USA) autoanalyzer, and tumor markers (CA15-3, CA19-9, CA72-4, CEA, PSA) and insulin were measured and evaluated in a Roche Cobas e 801 (USA) autoanalyzer. Tumor markers and insulin were measured using electrochemiluminescence immunoassay. HbA1c was measured by placing a complete blood sample into a purple capped tube containing K-EDTA and analyzing it in a Lifotronic H9 (China) HPLC device without centrifugation. For complete blood count, a complete blood sample was taken in a tube with a purple cap containing K-EDTA and analyzed on a Sysmex XN1000 (Germany) device. Besides these parameters, information about age, sex, body mass index and tumor stage at the time of admission was obtained from the hospital information system.

### *Statistical analysis*

IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) was used for analyses. The Kolmogorov–Smirnov test was performed to assess the normality of the distribution of continuous variables. It was utilized for each subgroup based on cancer type. Continuous variables that showed normal distribution were defined as mean±standard deviation (SD) and compared using student's t test. Continuous variables that showed nonnormal distribution were expressed as medians (interquartile ranges [IQRs]) and were analyzed

using the Mann–Whitney U test. Categorical variables were given as frequencies (percentages) and compared using the chi-square test. Two-tailed Spearman's correlation analyses were performed to analyze correlations between HbA1c, fasting plasma glucose level, fasting plasma insulin level and tumor markers (CA15-3, CA19-9, CA72-4, CEA, PSA). The results were presented as correlation coefficients (R) and p values. Receiver operating characteristic (ROC) curves were performed to assess the ability of HbA1c, fasting plasma glucose level, and fasting plasma insulin level to determine breast, prostate, and colorectal cancer. The results were reported as the area under the curve (AUC), 95% confidence interval (CI), specificity, sensitivity. p value <0.05 was considered significant.

## RESULTS

Table 1 shows the demographic characteristics, laboratory data, and comparative results of tumor markers in breast cancer patients and the healthy control group. BMI, FPG, FPI, white blood cell (WBC), platelet (PLT) and CA15-3 levels were significantly higher in the breast cancer group compared to the healthy group ($p<0.05$). Hemoglobin (Hb), red blood cell count (RBC) and CEA levels were significantly lower ($p<0.05$). There was no significant difference in other data ($p>0.05$). Furthermore, 41% (n=41) of the patients in the breast cancer group were in the stage 3 disease group.

Table 2 shows the results of the correlation analysis of HbA1c, FPG, FPI and tumor markers for patients with breast cancer. There was no correlation between the parameters ($p>0.05$).

Table 3 and Figure 1 show the results of the ROC curve analysis regarding the ability of HbA1c, FPG and FPI to predict breast cancer. FPG predicted breast cancer with 40% sensitivity and 100% specificity (AUC:0.656, 95% CI:0.577-0.734, $p<0.001$) with a cut-off value of 96, while FPI predicted breast cancer with 55% sensitivity and 100% specificity (AUC:0.724, 95% CI:0.650-0.798, $p<0.001$) with a cut-off value of 12.1. HbA1c did not show any ability to predict breast cancer ($p=0.914$).

Table 4 shows the comparative results of demographic characteristics, laboratory data and tumor markers of subgroups of breast cancer patients based on their disease stage. There were 46 (46%) patients in the stage 1-2 group and 54 (54%) patients in the stage 3-4 group. The CA15-3 levels of the patients in the stage 3-4 group were significantly higher than those in the stage 1-2 group ($p<0.001$). There was no statistically significant difference in other parameters ($p>0.05$).

Table 5 shows the comparative results of demographic characteristics, laboratory data and tumor markers of prostate cancer patients and the healthy control group. BMI, FPG, FPI, WBC, PLT, HbA1c level and PSA level were significantly higher in the prostate cancer group compared to the healthy control group ($p<0.05$). Hb, RBC, CEA and CA19-9 levels were significantly lower in the prostate cancer group than in the healthy control group ($p<0.05$). Patients in the prostate cancer group most commonly had stage 2 disease (n=36, 36%), followed by stage 3 disease (n=32, 32%).

Table 6 shows the results of the correlation analysis of HbA1c, FPG and FPI with tumor markers in patients with prostate cancer. There was no correlation between the parameters ($p>0.05$).

Table 7 and Figure 3 show the results of the ROC curve analysis regarding the ability of HbA1c, FPG and FPI to predict prostate cancer. FPG predicted prostate cancer with 48% sensitivity and 92% specificity (AUC:0.704, 95% CI:0.631-0.778, $p<0.001$) with a cut-off value of 92.5, FPI with 56% sensitivity and 100% specificity (AUC:0.765, 95% CI:0.697-0.832, $p<0.001$) with a cut-off value of 12.1, and HbA1c with a cut-off value of 6.1 (AUC:0.665, 95% CI:0.589-0.740, $p<0.001$) with 32% sensitivity and 100% specificity.

Table 8 shows the comparative results of demographic and laboratory data and tumor markers of the subgroups of prostate cancer patients based on their disease stage. There were 55 (55%) patients in the stage 1-2 patient group and 45 (45%) patients in the stage 3-4 patient group. The PSA and CA19-9 levels of the patients in the stage 3-4 group were significantly higher than those in the stage 1-2 group ($p<0.001$ and $p=0.026$, respectively), while the RBC values were significantly lower ($p=0.037$). There was no significant difference in other parameters ($p>0.05$).

Table 9 shows the demographic characteristics, laboratory data and comparative results of tumor markers in colorectal cancer patients and the control group. BMI, FPG, WBC, HbA1c level, CEA level, CA72-4 level and CA19-9 level were significantly higher in the colorectal cancer group than in the healthy group ($p<0.05$). Hb, RBC and PLT levels were significantly lower in this group than in the healthy group ($p<0.05$). Sex ratios and FPI were not significantly different between the groups ($p=0.777$ and $p=0.219$, respectively). Approximately half of the patients in the colorectal cancer group had stage 2 disease (n=49, 49%).

Table 10 shows the results of the correlation analysis of HbA1c, FPG, FPI and tumor markers for patients with

colorectal cancer. The analysis revealed only a significant correlation between FPG and CA72-4 (p<0.05).

Table 11 and Figure 4 show the results of ROC curve analyses regarding the ability of HbA1c, FPG and FPI to predict colorectal cancer. FPG predicted colorectal cancer with 85% sensitivity and 99% specificity (AUC:0.956, 95% CI:0.930-0.983, p<0.001) with a cut-off value of 94.5. HbA1c predicted colorectal cancer with 59% sensitivity and 100% specificity (AUC:0.845, 95% CI:0.793-0.897, p<0.001) with a cut-off value of 6.1. FPI did not have ability to predict colorectal cancer (p=0.220).

Table 12 shows the demographic and laboratory data of the subgroups of colorectal cancer patients based on their disease stage and the comparative results of tumor markers. There were 56 (56%) patients in the stage 1-2 patient group and 44 (44%) patients in the stage 3-4 patient group. While no statistically significant difference was found in other parameters (p>0.05), only the CEA level was significantly higher in stage 3-4 group than stage 1-2 group (p<0.001).

**Table 1.** Results and comparisons of demographics, laboratory variables, and tumor markers between patients with breast cancer and healthy individuals

| | **Patients with breast cancer (n=100)** | **Control (n=49)** | **P** |
|---|---|---|---|
| **Age (years)** | 52 (47-57) | 55 (51-60) | 0.098 |
| **Sex, female, n (%)** | 100 (100) | 49 (100) | - |
| **BMI (kg/m$^2$)** | 33.85 (29.13-37.7) | 21.2 (19.9-23.35) | **<0.001** |
| **FPG (mg/dl)** | 88.5 (76-108.5) | 80 (71-87.5) | **0.001** |
| **FPI (mU/L)** | 14.25 (7.25-21.75) | 7 (4-9.5) | **<0.001** |
| **Hemoglobin (g/dl)** | 13 (11.25-15) | 15 (13-16.5) | **<0.001** |
| **WBC (10$^3$/µL)** | 9.6 (6.5-12.7) | 6.6 (5.5-8.4) | **<0.001** |
| **RBC (10$^6$/µL)** | 4.29 (3.4-4.86) | 4.9 (4.5-5.3) | **<0.001** |
| **Platelets (10$^3$/µL)** | 293 (209.8-407.25) | 232 (182.5-345) | **0.013** |
| **HbA1c (%)** | 5.3 (4.53-6.06) | 5.1 (4.8-5.8) | 0.779 |
| **CA15-3 (U/ml)** | 234 (159.58-295.88) | 10 (6-14) | **<0.001** |
| **CEA (µg/L)** | 2.35 (1.3-3.48) | 3 (2-5) | **0.012** |
| **CA72-4 (U/ml)** | 5.05 (3.5-6.2) | 5 (4-6) | 0.559 |
| **CA19-9 (U/ml)** | 18.43±10.12 | 20.08±4.81 | 0.178 |
| **Stage of cancer, n (%)** | | | - |
| **Stage 1** | 23 (23) | - | |
| **Stage 2** | 23 (23) | - | |
| **Stage 3** | 41 (41) | - | |
| **Stage 4** | 13 (13) | - | |

***Abbreviations:*** BMI: Body mass index, FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, HbA1c: Hemoglobin A1c, WBC: White blood cell, RBC: Red blood cell, CA15-3: Carbohydrate antigen 15-3, CA19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, CA72-4: Carbohydrate antigen 72-4. *The results are expressed as frequency (%), mean±standard deviation or median (interquartile range). Significant p values are in bold.

**Table 2.** Correlation analyses of HbA1c, fasting blood glucose, fasting blood insulin and tumor markers in patients with breast cancer

| | | CA15-3 (U/ml) | CA19-9 (U/ml) | CEA (µg/L) | CA72-4 (U/ml) |
|---|---|---|---|---|---|
| **FPG (mg/dl)** | R | 0.011 | -0.074 | -0.074 | -0.073 |
| | P | 0.917 | 0.462 | 0.466 | 0.473 |
| **FPI (mg/dl)** | R | 0.037 | -0.020 | 0.073 | 0.123 |
| | P | 0.716 | 0.843 | 0.472 | 0.221 |
| **HbA1c (%)** | R | -0.015 | -0.059 | -0.037 | -0.063 |
| | P | 0.880 | 0.562 | 0.713 | 0.532 |

***Abbreviations:*** FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, HbA1c: Hemoglobin A1c, CA15-3: Carbohydrate antigen 15-3, CA19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, CA72-4: Carbohydrate antigen 72-4

**Table 3.** ROC curve analyses of HbA1c, fasting blood glucose level and fasting blood insulin for predicting breast cancer

| | Cut-off value | AUC | 95% CI Lower | Upper | Specificity | Sensitivity | P |
|---|---|---|---|---|---|---|---|
| **FPG (mg/dl)** | 96 | 0.656 | 0.577 | 0.734 | 1 | 0.400 | **<0.001** |
| **FPI (mg/dl)** | 12.1 | 0.724 | 0.650 | 0.798 | 1 | 0.550 | **<0.001** |
| **HbA1c (%)** | - | 0.496 | 0.412 | 0.579 | - | - | 0.914 |

***Abbreviations:*** ROC: Receiver operating characteristic, FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, HbA1c: Hemoglobin A1c, AUC: Area under curve, CI: Confidence interval. Significant p values are in bold.

**Table 4.** Results and comparisons of demographics, laboratory variables and tumor markers between subgroups according to cancer stage in patients with breast cancer

| | Stage 1-2 (n=46) | Stage 3-4 (n=54) | P |
|---|---|---|---|
| **Age (years)** | 50 (47-53) | 54 (51-57) | 0.724 |
| **BMI (kg/m$^2$)** | 33.4 (28.78-36.43) | 34.55 (29.88-38.65) | 0.311 |
| **FPG (mg/dl)** | 89.5 (75.75-110) | 86.5 (75.25-106.25) | 0.491 |
| **FPI (mU/L)** | 10.35 (7.03-17.63) | 15.95 (6.88-23.4) | 0.143 |
| **Hemoglobin (g/dl)** | 12.5 (11-15) | 13 (12-15) | 0.205 |
| **WBC (10$^3$/µL)** | 9.6 (6.2-13.18) | 9.9 (6.65-12.7) | 0.803 |
| **RBC (10$^6$/µL)** | 4.26 (3.3-4.82) | 4.29 (3.43-4.87) | 0.809 |
| **Platelets (10$^3$/µL)** | 270 (191.5-401.25) | 304 (227.5-412.5) | 0.276 |
| **HbA1c (%)** | 5.34 (4.57-6.03) | 5.17 (4.5-6.1) | 0.527 |
| **CA15-3 (U/ml)** | 156.35 (109.7-183.83) | 291.4 (252.95-319.43) | **<0.001** |
| **CEA (µg/L)** | 2.45 (1.3-3.48) | 2.35 (1.28-3.5) | 0.798 |
| **CA72-4 (U/ml)** | 4.7 (3.05-6.3) | 5.15 (3.95-6.28) | 0.347 |
| **CA19-9 (U/ml)** | 18.64±10.2 | 18.24±10.14 | 0.845 |

***Abbreviations:*** BMI: Body mass index, FPG: Fasting blood glucose, FPI: Fasting blood insulin, HbA1c: Hemoglobin A1c, WBC: White blood cell, RBC: Red blood cell, CA15-3: Carbohydrate antigen 15-3, CA19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, CA72-4: Carbohydrate antigen 72-4. *The results are expressed as frequency (%), mean±standard deviation or median (interquartile range). Significant P values are in bold.

**Table 5.** Results and comparisons of demographics, laboratory variables and tumor markers between patients with prostate cancer and healthy individuals

| | Patients with prostate cancer (n=100) | Control (n=51) | P |
|---|---|---|---|
| **Age (years)** | 59 (54-66) | 55 (51-60) | 0.088 |
| **Sex, female, n (%)** | - | - | - |
| **BMI (kg/m$^2$)** | 27.5 (24.55-32.6) | 22.1 (20.7-23.4) | **<0.001** |
| **FPG (mg/dl)** | 91 (79-101) | 82 (72-89) | **<0.001** |
| **FPI (mU/L)** | 14.35 (7.43-24.38) | 9 (4-11) | **<0.001** |
| **Hemoglobin (g/dl)** | 12 (9-14) | 15 (14-17) | **<0.001** |
| **WBC (10$^3$/µL)** | 12.35 (8.1-16.18) | 6.7 (5.6-7.8) | **<0.001** |
| **RBC (10$^6$/µL)** | 4.7 (3.9-5.3) | 5.1 (4.6-5.5) | **0.006** |
| **Platelets (10$^3$/µL)** | 342 (259.25-435) | 261 (222-328) | **<0.001** |
| **HbA1c (%)** | 5.6 (5.2-6.3) | 5.3 (5-5.6) | **0.004** |
| **PSA (ng/mL)** | 41.05 (24-55) | 0.9 (0.6-1.3) | **<0.001** |
| **CEA (µg/L)** | 2.1 (1.23-3.2) | 3 (1-5) | **0.001** |
| **CA72-4 (U/ml)** | 4.25 (2.63-5.75) | 5 (3-6) | 0.175 |
| **CA19-9 (U/ml)** | 16.9±9.21 | 19.41±4.58 | **0.014** |

| | | | |
|---|---|---|---|
| **Stage of cancer, n (%)** | | | - |
| **Stage 1** | 19 (19) | - | |
| **Stage 2** | 36 (36) | - | |
| **Stage 3** | 32 (32) | - | |
| **Stage 4** | 13 (13) | - | |

***Abbreviations:*** BMI: Body mass index, FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, HbA1c: Hemoglobin A1c, WBC: White blood cell, RBC: Red blood cell, PSA: Prostate-specific antigen, CA19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, CA72-4: Carbohydrate antigen 72-4. *The results are expressed as the frequency (%) or median (interquartile range). Significant P values are in bold.

**Table 6.** Correlation analyses of HbA1c, fasting blood glucose level, fasting blood insulin and tumor markers in patients with prostate cancer

| | | **PSA (ng/mL)** | **CA19-9 (U/ml)** | **CEA (µg/L)** | **CA72-4 (U/ml)** |
|---|---|---|---|---|---|
| **FPG (mg/dl)** | *r* | -0.130 | 0.016 | 0.008 | -0.086 |
| | *p* | 0.198 | 0.877 | 0.937 | 0.398 |
| **FPI (mg/dl)** | *r* | -0.072 | -0.028 | 0.091 | -0.084 |
| | *p* | 0.478 | 0.784 | 0.367 | 0.405 |
| **HbA1c (%)** | *r* | -0.154 | -0.099 | -0.090 | -0.118 |
| | *p* | 0.126 | 0.329 | 0.372 | 0.243 |

***Abbreviations:*** FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, HbA1c: Hemoglobin A1c, PSA: Prostate-specific antigen, CA19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, CA72-4: Carbohydrate antigen 72-4. Significant P values are in bold.

**Table 7.** ROC curve analyses of HbA1c, fasting blood glucose level and fasting blood insulin for predicting prostate cancer

| | **Cut-off value** | **AUC** | **95% CI** | | **Specificity** | **Sensitivity** | ***P*** |
|---|---|---|---|---|---|---|---|
| | | | **Lower** | **Upper** | | | |
| **FPG (mg/dl)** | 92.5 | 0.704 | 0.631 | 0.778 | 0.920 | 0.480 | **<0.001** |
| **FPI (mg/dl)** | 12.2 | 0.765 | 0.697 | 0.832 | 1 | 0.560 | **<0.001** |
| **HbA1c (%)** | 6.1 | 0.665 | 0.589 | 0.740 | 1 | 0.320 | **<0.001** |

***Abbreviations:*** ROC: Receiver operating characteristic, FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, HbA1c: Hemoglobin A1c, AUC: Area under curve, CI: Confidence interval. Significant p values are in bold.

**Table 8.** Results and comparisons of demographics, laboratory variables and tumor markers between subgroups according to cancer stage in patients with prostate cancer

| | Stage 1-2 (n=55) | Stage 3-4 (n=45) | *P* |
|---|---|---|---|
| **Age (years)** | 57 (54-60) | 60 (56-66) | 0.186 |
| **BMI (kg/m$^2$)** | 26.9 (23.1-32.2) | 29.9 (25.7-32.75) | 0.134 |
| **FPG (mg/dl)** | 93 (79-109) | 86 (78-97.5) | 0.133 |
| **FPI (mU/L)** | 13.7 (7.7-24.9) | 16 (6.6-22.7) | 0.482 |
| **Hemoglobin (g/dl)** | 11 (9-14) | 12 (9.5-14) | 0.221 |
| **WBC (10$^3$/µL)** | 12.6 (8.5-16.6) | 12.2 (7.5-15.65) | 0.359 |
| **RBC (10$^6$/µL)** | 4.3 (3.8-5.3) | 4.9 (4.25-5.35) | **0.037** |
| **Platelets (10$^3$/µL)** | 329 (240-435) | 358 (264-444) | 0.647 |
| **HbA1c (%)** | 5.7 (5.2-6.7) | 5.6 (5.15-6.1) | 0.306 |
| **PSA (ng/mL)** | 26.2 (15.3-37.7) | 53 (49.4-69.2) | **<0.001** |
| **CEA (µg/L)** | 2.1 (1.2-3.1) | 2.3 (1.25-3.3) | 0.787 |
| **CA72-4(U/ml)** | 4.2 (2.5-5.6) | 4.6 (3-5.9) | 0.469 |
| **CA19-9 (U/ml)** | 15.08±8.04 | 19.12±10.11 | **0.033** |

***Abbreviations:*** BMI: Body mass index, FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, HbA1c: Hemoglobin A1c, WBC: White blood cell, RBC: Red blood cell, PSA: Prostate-specific antigen, CA19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, CA72-4: Carbohydrate antigen 72-4. *The results are expressed as the frequency (%) or median (interquartile range). Significant P values are in bold.

**Table 9.** Results and comparisons of demographics, laboratory variables and tumor markers between patients with colorectal cancer and healthy individuals

| | Patients with colorectal cancer (n=100) | Control (n=100) | *P* |
|---|---|---|---|
| **Age, years** | 58 (52-66) | 55 (51-60) | 0.095 |
| **Sex, female, n (%)** | 47 (47) | 49 (49) | 0.777 |
| **BMI (kg/m$^2$)** | 31.15 (26.83-36.8) | 21.75 (20.1-23.38) | **<0.001** |
| **FPG (mg/dl)** | 107 (97.25-120.75) | 81 (72-88) | **<0.001** |
| **FPI (mU/L)** | 8.3 (3.23-12.98) | 7.5 (4-10) | 0.219 |
| **Hemoglobin (g/dl)** | 10 (8-12) | 15 (13-17) | **<0.001** |
| **WBC (10$^3$/µL)** | 12.9 (7.95-17.2) | 6.7 (5.5-8.08) | **<0.001** |
| **RBC (10$^6$/µL)** | 3.6 (3.1-4.18) | 5.05 (4.6-5.5) | **<0.001** |
| **Platelets (10$^3$/µL)** | 232.64±91.03 | 264.24±75.8 | **0.008** |
| **HbA1c (%)** | 6.15 (5.5-6.7) | 5.2 (4.9-5.68) | **<0.001** |
| **CEA (µg/L)** | 204.5 (95.8-273.33) | 3 (2-5) | **<0.001** |
| **CA72-4 (U/ml)** | 29.95 (16.95-37.78) | 5 (3-6) | **<0.001** |
| **CA19-9 (U/ml)** | 75.6 (50.75-97.43) | 20 (16-24) | **<0.001** |
| **Stage of cancer, n (%)** | | | - |
| **Stage 1** | 7 (7) | - | |
| **Stage 2** | 49 (49) | - | |
| **Stage 3** | 36 (36) | - | |
| **Stage 4** | 8 (8) | - | |

***Abbreviations:*** BMI: Body mass index, FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, HbA1c: Hemoglobin A1c, WBC: White blood cell, RBC: Red blood cell, CA19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, CA72-4: Carbohydrate antigen 72-4. *The results are expressed as frequency (%), mean±standard deviation, and median (interquartile range). Significant p values are in bold.

**Table 10.** Correlation analyses of HbA1c, fasting blood glucose, fasting blood insulin and tumor markers in patients with colorectal cancer

| | | CA19-9 (U/ml) | CEA (µg/L) | CA72-4 (U/ml) |
|---|---|---|---|---|
| **FPG (mg/dl)** | *r* | -0.135 | 0.055 | 0.011 |
| | *p* | 0.182 | 0.589 | 0.912 |
| **FPI (mg/dl)** | *r* | -0.025 | -0.028 | 0.120 |
| | *p* | 0.809 | 0.785 | 0.235 |
| **HbA1c (%)** | *r* | -0.023 | 0.045 | -0.091 |
| | *p* | 0.821 | 0.658 | 0.369 |

***Abbreviations:*** FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, HbA1c: Hemoglobin A1c, PSA: Prostate-specific antigen, CA15-3: Carbohydrate antigen 15-3, CA19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, CA72-4: Carbohydrate antigen 72-4

**Table 11.** ROC curve analyses of HbA1c, fasting blood glucose and fasting blood insulin for predicting colorectal cancer

| | Cut-off value | AUC | 95% CI | | Specificity | Sensitivity | P |
|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | | | |
| **FPG (mg/dl)** | 94.5 | 0.956 | 0.930 | 0.983 | 0.990 | 0.850 | **<0.001** |
| **FPI (mg/dl)** | - | 0.550 | 0.468 | 0.632 | - | - | 0.220 |
| **HbA1c (%)** | 6.1 | 0.845 | 0.793 | 0.897 | 1 | 0.590 | **<0.001** |

***Abbreviations:*** ROC: Receiver operating characteristic, FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, HbA1c: Hemoglobin A1c, AUC: Area under curve, CI: Confidence interval. Significant p values are in bold.

**Table 12.** Results and comparisons of demographics, laboratory variables and tumor markers between subgroups according to cancer stage in patients with colorectal cancer

| | Stage 1-2 (n=56) | Stage 3-4 (n=44) | P |
|---|---|---|---|
| **Age, years** | 56 (52-60) | 60 (58-66) | 0.205 |
| **Sex, female, n (%)** | 28 (50) | 19 (43.2) | 0.498 |
| **BMI (kg/m$^2$)** | 30.45 (26.53-34.6) | 34 (27.8-38.1) | 0.064 |
| **FPG (mg/dl)** | 102 (95.25-119.25) | 111 (101.25-123.25) | 0.074 |
| **FPI (mU/L)** | 9 (3.03-12.98) | 7.45 (4.6-12.98) | 0.895 |
| **Hemoglobin (g/dl)** | 9.5 (8-12) | 10 (7-12) | 0.646 |
| **WBC (10$^3$/µL)** | 12.3 (7.73-17.58) | 13.8 (8.28-16.7) | 0.687 |
| **RBC (10$^6$/µL)** | 3.55 (3.1-4.28) | 3.6 (2.8-3.98) | 0.430 |
| **Platelets (10$^3$/µL)** | 235.21±90.21 | 229.36±92 | 0.751 |
| **HbA1c (%)** | 6.05 (5.4-6.68) | 6.3 (5.9-6.78) | 0.213 |

| | | | |
|---|---|---|---|
| **CEA (µg/L)** | 112.95 (71.13-160.55) | 274.75 (242.83-297.58) | **<0.001** |
| **CA72-4 (U/ml)** | 24.6 (15.83-36.1) | 33.85 (19.45-40.6) | 0.062 |
| **CA19-9 (U/ml)** | 79.35 (53.95-103.95) | 68.25 (39.95-92.68) | 0.127 |

***Abbreviations:*** BMI: Body mass index, FPG: Fasting plasma glucose, FPI: Fasting plasma insulin, HbA1c: Hemoglobin A1c, WBC: White blood cell, RBC: Red blood cell, CA19-9: Carbohydrate antigen 19-9, CEA: Carcinoembryonic antigen, CA72-4: Carbohydrate antigen 72-4. *The results are expressed as frequency (%), mean±standard deviation, and median (interquartile range). Significant P values are in bold.

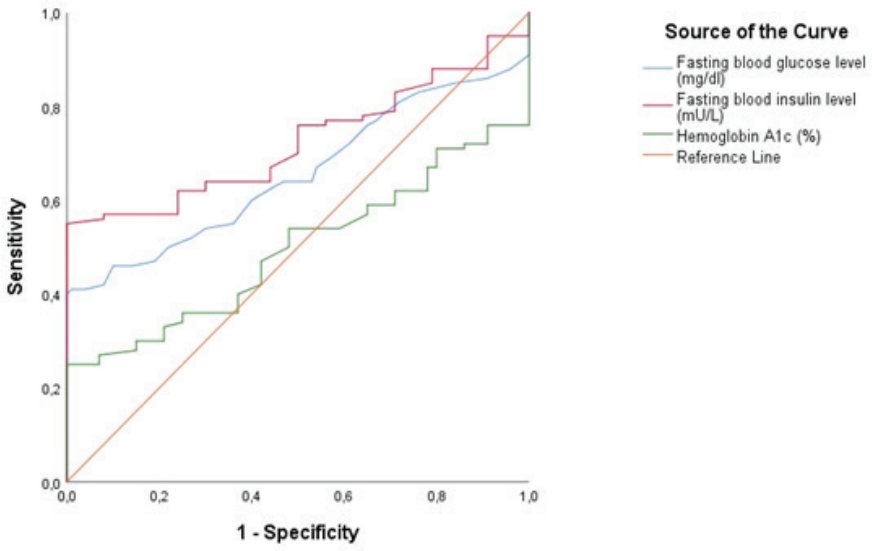


**Figure 1.** Graphic of receiver operating characteristic curve analyses of HbA1c, FPG, and FPI levels for predicting breast cancer.

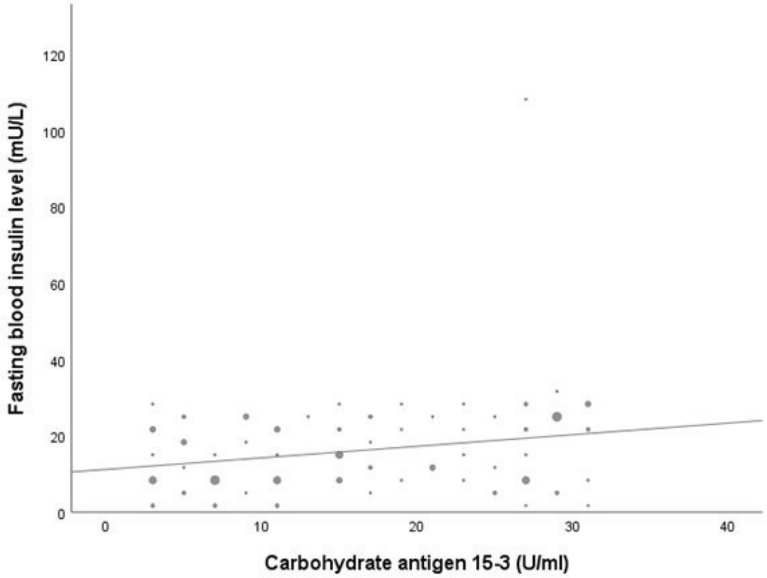


**Figure 2.** Scatter-dot graph of FPI level and CA15-3.

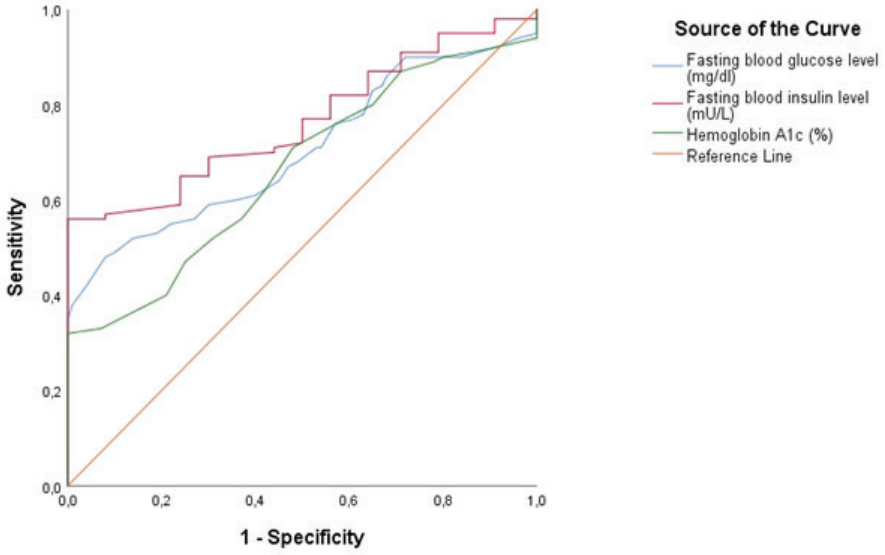


**Figure 3.** Graphic of receiver operating characteristic curve analyses of HbA1c, FPG, and FPI levels for predicting prostate cancer.

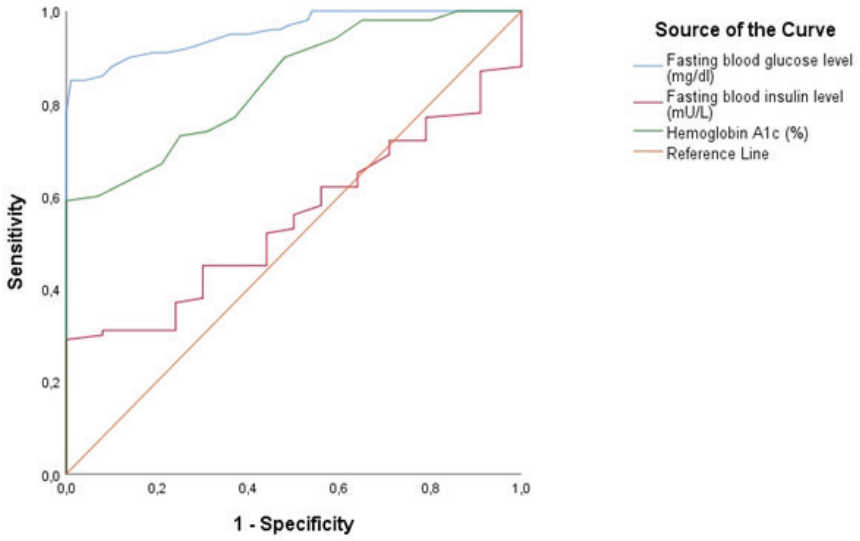


**Figure 4.** Graphic of receiver operating characteristic curve analyses of HbA1c, FPG, and FPI levels for predicting colorectal cancer.

## DISCUSSION

In our study, we examined the significance of glycemic parameters, BMI, complete blood count parameters and tumor markers in terms of the risk and stage of cancer development. We discovered significantly higher FPG and FPI in breast cancer patients; higher FPG, FPI, and HbA1c in prostate cancer patients; and higher FPG, FPI, and HbA1c in colorectal cancer patients compared to the control groups. In addition, ROC analysis was used to assess the predictive ability of these significant values according to cancer groups. The correlation of FPG, FPI and HbA1c with tumor markers in each cancer group was evaluated, finding a correlation between FPG and CA72-4 only in colorectal cancer. Regarding tumor stage, CA15-3 was significantly higher in the stage 3-4 group in breast cancer, PSA in the stage 3-4 group in prostate cancer, and CEA in the stage 3-4 group in colorectal cancer.

CA15-3 is a serum cancer antigen, mostly observed in patients with breast cancer, but it has also been reported in gastrointestinal, lung, and gynecological tumors (14). The sensitivity of CA15-3 varies from 16% to 91% depending on whether breast tumors are benign or malignant, their stage, and metastasis status (15). Very high levels of

CA15-3 can be considered an indicator of advanced stage disease. CA15-3 levels that are 5-10 times higher than the upper limit may suggest liver or bone metastases to clinicians (16). There was a significant correlation between the event-free survival and overall survival times of patients and increased levels of CA15-3 and CEA (17). In our study, we found significantly higher CEA and CA15-3 levels in patients with breast cancer compared to the control group. Furthermore, CEA and CA15-3 levels were significantly higher in the stage 3-4 group than in the stage 1-2 group.

In a study conducted with1.3 million Koreans, high fasting plasma glucose (>140 mg/dL) caused a 1.29-fold increase in the risk of developing all types of cancer. In particular, there was an increased risk of pancreatic cancer associated with high fasting plasma glucose. Esophageal, liver, and colon/rectum cancers were higher in men, while liver and cervix cancers were higher in women. These findings were similar in all body mass index groups (6). In a comparison between new insulin users and noninsulin users, a 1% increase in HbA1c was associated with a 1.24-fold increase in cancer (7).

Both in vitro and in vivo studies have shown that insulin stimulates proliferation in normal breast tissue cells and breast cancer cells (18). A prospective study conducted in Canada, including 512 women, discovered a relationship between insulin increase and breast cancer development in nondiabetic individuals. In premenopausal and postmenopausal women, there was a correlation between high insulin concentration and high tumor grade, axillary lymph node involvement, high risk of recurrence and lower survival rates.These conditions were independent of BMI (19). In their prospective study conducted in Italy, Muti et al. measured fasting plasma glucose, compared high and low levels after 5.5 years of follow-up, and found that the risk of premenopausal breast cancer increased 3-fold, whereas no relation was found with postmenopausal breast cancer (8). In our study, we assessed the ability of glucose and insulin to predict breast cancer in breast cancer patients, which supports these findings. However, there are studies in the literature that present different results. For example, in a study that compared patients with type 2 DM and HbA1c <7.5% and >7.5%, no significant relationship was found between HbA1c and cancer and specific subgroups (20). Similarly, there was no association between HbA1c and breast cancer development in healthy women in the Women's Health Study (21).

Insulin, functioning as a growth factor molecule, stimulates lipogenesis, steroidogenesis, and protein synthesis. It further stimulates cellular proliferation with anti-apoptotic activities, particularly in hormone-independent prostate cancer cells (22). In a meta-analysis of 10 studies by Gacci et al., high fasting plasma glucose (≥110 mg/dl) or diagnosis of diabetes did not increase the risk of prostate cancer. This was explained by the fact that the duration of diabetes disease and the effectiveness of the treatment in glycemic control were unknown (23). There is an inverse relationship between diabetes and prostate cancer risk. In a recently published meta-analysis including 24 case–control and 32 cohort studies, the relative risk for prostate cancer in patients with diabetes was 0.88 (9). Although the risk of prostate cancer seems to be lower in patients with diabetes, the same cannot be said for prognosis. Recurrence, treatment failure, disease-specific mortality and all-cause mortality were higher in prostate cancer patients with diabetes compared to patients without diabetes (24). In a meta-analysis of nine studies including 4,211 patients, there was no association between hyperglycemia and diabetes and prostate cancer. This relationship differed among races, and differences in prostate cancer screening and cancer detection rates between countries may be contributing factors (25). In a study conducted by Kasper et al.,a diagnosis of diabetes reduced the risk of prostate cancer by 17% (26). In a meta-analysis of 15 studies including 1.2 million patients, elevated fasting plasma glucose decreased the risk of prostate cancer by 12%, and there was an inverse relationship between long-term diabetes mellitus and prostate cancer (27). In our study, we determined the ability of glucose, insulin and HbA1c to predict prostate cancer in breast cancer patients to support these findings.

The diagnostic and prognostic clinical utility of CEA and CA19-9 levels in colorectal cancer is controversial, but some studies have indicated that preoperative tumor marker levels are closely associated with a number of clinicopathological parameters (28). In the study of Ning et al., serum CEA levels were positively correlated with CA19-9 and CA72-4 in the colorectal cancer group. CEA, CA19-9, and CA72-4 were higher in the stage 3-4 group (29). In our study, we found significantly higher levels of CEA, CA19-9, and CA72-4 in our colorectal patients. In addition, we found significantly higher CEA levels in the stage 3-4 group compared to the stage 1-2 group. There are various studies in the literature on high blood glucose and insulin levels and colorectal cancer. Vulcan et al.

discovered a relationship between high blood glucose levels and colorectal cancer risk. However, they found no relationship between plasma insulin and colorectal cancer (30). High glucose levels were associated with colon cancer in men, but this association was not found in women (10). In a comprehensive retrospective study published in 2006, although there was no significant increase in risk in women with type 2 diabetes, the risk of developing proximal localized colorectal cancer increased significantly in men with type 2 diabetes (31). In our study, we determined the predictive ability of glucose and HbA1c for colorectal cancer, but not insulin. In addition, we found a correlation between CA72-4 and glucose value.

***Limitations:***

Our study has limitations such as the complexity of cancer development, multifactorial nature of glucose metabolism, limitations of cross-sectional studies in establishing causal relationships, lack of research according to cancer subtypes and limited size of the patient population.

## CONCLUSION

As a result of our study, we confirmed the ability of glucose and insulin HbA1c to predict breast, prostate and colorectal cancer. In the light of these findings, successful implementation of glycemic control and diabetes mellitus treatment in patients may contribute to the treatment of some cancers and may reduce the frequency of the disease. However, further cohort studies are needed to establish this relationship more clearly and to consider it a rule. Furthermore, it is important to note that the increase in glucose and insulin-related cancer risk is not independent of the effects of factors such as genetics, nutrition, family history of cancer, racial differences, physical activity, and smoking.

**Conflict of interest:** The authors declare no conflicts of interest.
**Ethics committee approval:** We applied to the Ankara Bilkent City Hospital Clinical Research Ethics Committee (Ankara, Turkey) and obtained the necessary ethics committee approval (Acceptance Number: E1/3059/2022). We conducted the study in compliance with the ethical principles of the Declaration of Helsinki.
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