# The Relationship Between NAT2 Polymorphisms And Dietary Pattern In Colorectal Carcinoma Patients Among Rural And Urban Egyptian Population

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**Keywords:** Colorectal cancer, N-acetyltransferase 2, smoking, gene polymorphism.

**Abstract**

**Background:** Colorectal cancer (CRC) is the second most deadly cancer worldwide. N-acetyltransferase 2 (NAT2) gene polymorphisms can influence CRC risk, particularly when associated with dietary factors like red meat consumption as the dietary westernization occurs among Egyptians especially in urban region, so the aim of this study was to evaluate the association of dietary pattern and NAT2 gene polymorphism in CRC patients.

**Methods:** This is a case control study, included 200 newly diagnosed CRC patients (117 males and 83 females,112 rural and 88 urban) and 200 age and sex matched healthy individuals served as a control group (115 rural and 85 urban). All subjects were genotyped for NAT2 rs1801280 (T341C) polymorphism using real time PCR analysis. Modified food frequency questionnaire (FFQ) was used.

**Results:** TT genotype and T allele of NAT2 gene rs1801280 polymorphism were highly represented in CRC patients with two and one-half times higher risk for TT genotype and T allele respectively to exhibit CRC compared to other genotypes and C allele. NAT2 (T/C) genotype was associated with high score unhealthy diet in CRC patients versus controls. NAT2 (C/C &T/C) genotypes were associated with a high score healthy diet in the control group versus CRC group (protective factor). Healthy dietary pattern was significant protective factor for urban residents while unhealthy dietary pattern was risk factors for rural residents.

**Conclusion:** T/T genotype and T allele (rapid acetylators) could be linked to increased risk for CRC among Egyptians in Dakahlia governorate. Unhealthy dietary pattern was significant risk factor for rural residents, while healthy dietary pattern was significant protective factor for CRC in urban residents.

## Introduction

Colorectal cancer (CRC) is the third most common cancer and the second most common cause of cancer mortality worldwide. There are disparities in the epidemiology of CRC across different populations, most probably due to differences in exposure to lifestyle and environmental factors related to CRC (Roshandel et al., 2024). In particular, the prevalence of CRC is increasing among young individuals in the Middle East and other regions in the world. These changes in the incidence and epidemiology of the disease presentation have also been observed in the Arab world that could be due to westernization of lifestyle (Makhlouf et al., 2021). The ongoing nutrition transition in many developing countries, rural areas are increasingly adopting Western dietary patterns, diminishing the protective effects of the traditional diets rich in fiber, whole grains, and vegetables in rural areas (Bray et al. (2024). Developed countries are at the highest risk of colon cancer. Obesity, sedentary lifestyle, red meat consumption, alcohol and tobacco are considered the driving factors behind the growth of CRC (Ferlay et al., 2021).

Heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) are chemicals found in grilled foods that have become charred. Several studies have analyzed the risk of CRC associated with the consumption of red meat, the total meat intake and the exposure to individual

heterocyclic amines (Tudosie et al,.2022). Intake of heterocyclic amine (HCA) compounds, which are produced from protein precursors in meat cooked at high temperature, is one of the mechanisms that are hypothesized to underline the positive association between red and processed meat intake and CRC risk. HCAs are mutagenic compounds, and experimental studies have shown their ability to induce tumors in various organs in rodents and non-human primates (Budhathoki et al., 2020).

Recent studies highlight the significant role of dietary lifestyle in the development and prevention of CRC. Diets high in red and processed meats, refined grains, and added sugars have been consistently associated with increased CRC risk. In contrast, plant-based diets rich in fiber, fruits, vegetables, and whole grains may offer protective effects by promoting gut health and reducing inflammation. Emerging evidence also supports the role of the gut microbiome as a mediator between diet and colorectal carcinogenesis (Zheng et al., 2024).

Genetic variation in N-acetyl transferases 2 gene (NAT2) has been suggested to modify the association of meat intake with some cancers through its influence on the metabolism of HCAs. Thus, epidemiological studies have reported inconsistent associations between dietary HCA intake via meat consumption and increased cancer risk, as NAT2 allelic variations occur naturally in human population (Walls, 2021)

NAT2 acetylation polymorphism is important because of its primary role in the activation and/or deactivation of many chemicals in the body's environment. In turn, this can affect an individual's cancer risk (Alés-Palmer et al., 2024).

Egypt has high global incidence of early CRC as 35% of Egyptian CRC patients were below age of 40 (Zaki et al., 2022). The estimated rate of CRC is 6.5 % of all malignant tumors in Egypt, CRC became the sixth most recorded tumor in the years 2002-2003, regarding the National Cancer Institute registry at Cairo University, it was 4.2 % in men and 3.8 % in females. CRC is also widespread in Egypt, with 14.0 % of all colonoscopies revealing the presence of the disease (Hassan et al., 2021).

So, the goal of this study was to evaluate the association of NAT2 gene (rs1801280) (T 341 C) polymorphisms and dietary pattern in newly diagnosed CRC rural and urban Egyptian patients in Dakahlia governorate.

**Subjects and Methods:**

**Subjects:** This is a case-control study which included 200 patients with confirmed diagnosis of CRC (117 males and 83 females,112 rural and 88 urban) with ages ranging from 25 to 89 years, they were selected from Gastroenterology Surgical Center and Oncology Center (OCMU), Mansoura University in the period from May 2021 to November 2024; and 200 age and sex matched healthy individuals with no family history of CRC, served as a control group (115 rural and 85 urban)..

Diagnosis of CRC was confirmed by pelvi-abdominal computed tomography (CT), pelvi-abdominal magnetic resonance imaging (MRI) and histopathological examination. Tumor size, nodal status, and distant metastasis were determined and clinical stages were assessed with the criteria of Union for International Cancer Control.

Exclusion Criteria included diabetes, autoimmune diseases and previous history of cancers.

The study protocol was accepted by Institutional Research Board of Faculty of Medicine- Mansoura University (Code No. MD.21.04.465.). Informed consent was obtained from each participant included in this study.

**Methods: modified Food Frequency Questionnaire (FFQ)**: it was done for all subjects studied. Participants completed a self-administered questionnaire, which inquired about demographic and lifestyle characteristics, personal and family medical history. They also completed a twenty-eight-item food frequency questionnaire (FFQ) with prespecified seven intake frequency categories for most food items. The options for frequency of intake of food items were ≤1 time/mo, 2–3 times/mo, 1 time/wk, 2–4 times/wk, 1 time/d, 2–4 times/d, and ≥4 times/d. The FFQ inquired about the consumption of bread, baked goods, pizza, three dairy products (milk, yogurt, cheese), rice, pasta, potatoes, foul & falafel, dessert, cooked vegetables, fresh vegetables, fruit, five meat items (boiled red meat, fried red meat, mixed red meat, processed meat, liver), four poultry items (Roasted chicken with skin, Roasted chicken without skin, Processed chicken, Grilled chicken) , three fish items ( grilled fish, fried fish, tuna& salmon), egg and fast food.

**Methods:**

**A)- Sampling:** Seven ml venous blood collected from each subject under complete aseptic condition and delivered as follows: 3 ml blood on a plain tube for biochemical investigations, left to clot then centrifuged and the separated serum was used, 2 ml blood on EDTA tube for CBC and 2 ml blood on EDTA tube for genetic study: DNA was extracted and kept frozen at – 20 till the time of real time PCR for detection of NAT2 SNP rs1801280 (T 341 C).

**B)- Routine investigations:** Liver function tests (ALT, AST, Albumin, Total bilirubin), serum creatinine, random blood glucose: were done on clinical chemistry autoanalyzer; COBAS c311; Roche diagnostics, USA. CEA and CA 19-9 (patients only): were done on electrochemiluminescence autoanalyzer; COBAS e411; Roche diagnostics, USA. CBC: done on Cell counter; SYSMEX XN-330 analyzer.

**C)- Genetic study:**

TaqMan SNP Genotyping Assays (Real time PCR) (Budhathoki et al., 2020) for detection of SNP rs1801280 (T 341 C), of NAT2 was used.

**DNA extraction:** was done by GeneJET™ PCR purification kit from Thermo Scientific, USA (Catalog number K0781), and kept frozen at – 20 till the time of real time PCR.

**SNP genotyping Assay**: the kit contains sequence-specific forward and reverse primers to amplify the polymorphic sequence of interest, two TaqMan® probes: One probe labeled with VIC dye detects the Allele 1 (C) sequence& the other probe labeled with FAM dye detects the Allele 2 (T) sequence. The SNP ID is C___1204093_20 for NAT2 rs1801280 and the chromosomal location is Chr.8:18400344, The context Sequence [VIC/FAM] was GTTCACCTTCTCCTGCAGGTGACCA**[C/T]** TGACGGCAGGAATTACATTGTCGAT.

The PCR mixture in each well includes: 10.0 µL Hera® quantitative PCR Master Mix (2X), 0.5 µL SNP genotyping Assay (20x), 7.5 µL De ionized water and 2.0 µL DNA template, so the total volume was 20.0 µL. For each sample, 20 ul of PCR reaction mix was transferred to the 48-well Reaction plate.

Reaction conditions were carried out with the following cycling stages: stage I at 95°C for 10 minutes (initial denaturation), stage II includes 40 cycles of denaturation at 95°C for 15 seconds and annealing/extension at 60°C for 60 seconds, then stage III at 60°C for 30 seconds (final extension).

**Allelic discrimination**:

Allelic discrimination was carried out by measuring fluorescence intensity at the endpoint. The results of the measurement were analyzed using Applied Biosystems, StepOne real time PCR and genotype was determined.

Each sample is interpreted according to the 2 alleles & Genotypes (Homozygous or heterozygous), an increase in either FAM or VIC dye fluorescence indicates homozygosity for FAM- or VIC-specific alleles (T: T or C:C), and an increase in the fluorescence of both dyes indicates heterozygosity (T:C).

**Statistical analysis:**

Data was entered and analyzed using IBM-SPSS software (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). Qualitative data were expressed as count (N) and percentage (%). Quantitative data were initially tested for normality using Shapiro-Wilk's test with data being normally distributed if $p>0.050$. The presence of significant outliers (extreme values) was tested for by inspecting boxplots. Quantitative data was expressed as median, minimum, maximum, Q1, and Q3. Chi-square test was used to examine the association between two categorical variables. Phi and Cramer's V were used as correlation coefficients. For significant test results, multiple z-tests were used. Mann-Whitney U-test was used to compare a quantitative variable between two groups. Effect size was presented as rank biserial correlation (r). The median difference was presented as Hodges-Lehmann estimator (HLE). Kruskal-Wallis H-test was used to compare quantitative variables between multiple groups. Significant results were followed by post hoc analysis (pairwise comparisons). Spearman's correlation was used to examine the strength and direction of association between two quantitative variables. For any of the used tests, results were considered as statistically significant if p value $\leq 0.050$

**Principal component analysis (PCA)**

Factor analysis was used to identify patterns of all food items that account for the largest amount of variation in diet between individuals. Then PCA was used for extraction of factors. PCA was supported by KMO (Kaiser-Meyer-Olkin) value for sampling adequacy (KMO= 0.613 and 0.786), KMO values below 0.5 were considered unacceptable, values between 0.5 to 0.7 were considered mediocre, values between 0.7 and 0.8 were considered as good, and values between 0.8 and 0.9 were considered as excellent and Bartlett's test of sphericity <0.001. Varimax rotation was applied to maintain uncorrelated factors and increases interpretability. Extracts were based on Eigen values > 1. Food groups with factor loading <|0.20| for all dietary patterns was omitted. The factor score for each pattern was constructed for the component food items. Factor scores were then categorized into two groups based on the relation to zero.

SNP Statistical analysis: Data were entered and analyzed by using SNPStats software: https://www.snpstats.net/start.htm

Single Nucleotide Polymorphism (SNP) analysis involves Allele frequencies, Genotype frequencies and Hardy-Weinberg equilibrium (HWE). Logistic regression analysis was done for studying association with a response variable. Analysis of interactions involved gene-gene or gene environment interaction

**Results:**

This case-control study included 200 patients with confirmed diagnosis of CRC (117 males and 83 females,112 rural and 88 urban) with ages ranging from 25 to 89 years. The control group individuals were age and sex matched with the patient group.

Demographic characteristics of newly diagnosed CRC patients compared to control group and comparison of laboratory results between the two groups are illustrated in table (1). Regarding healthy dietary pattern, high score is significant more frequent in the control group compared to patient group, on the other hand high score in unhealthy dietary pattern is more frequent in CRC group than the control group (table 1).

T/T genotype and T allele were highly distributed in CRC patients compared to control group (risk genotype& allele). Participants with the T/T genotype have 2 times higher risk to exhibit CRC compared to the C/C genotype (protective genotype) and participants with T allele have 1.5 times higher risk to exhibit CRC compared to C allele (protective allele) table (2).

There were significant associations between NAT2 genotypes (C/C, T/C, T/T) and age more than 63 years (p=0.004, p=0.003, p=0.009 respectively), significant association between NAT2 (C/C) genotype and male gender (p=0.021) and significant association between NAT2 (C/C &T/C) genotypes and current smoking. NAT2 (C/C &T/C) genotypes are associated with a high score healthy diet in the control group versus CRC group (p<0.001) (protective factor). NAT2 (T/C) genotype is associated with high score unhealthy diet in CRC patients versus controls (p=0.002) table (3).

Univariate logistic regression analysis for prediction of CRC in newly diagnosed CRC patients using selected 8 predictor variables (gender, age, residence, smoking, hemoglobin, NAT2 polymorphism and food patterns) on the likelihood of occurrence of CRC revealed that elevated age >63 years, current smoking, Hb ≤ 12g/dl, T/T genotype and high unhealthy dietary pattern score were significant risk factors for CRC, and high healthy dietary pattern score was significant protective factor for CRC table (4).

The results of logistic regression analysis which was run to ascertain the effects of the selected 6 predictor variables (age, smoking, hemoglobin, NAT2 polymorphism and food patterns) on the likelihood of occurrence of CRC were used in multivariate analysis and revealed that elevated age >63 years, current smoking, Hb ≤ 12g/dl, and high unhealthy dietary pattern score were significant risk factors for CRC, and high healthy dietary pattern score was significant protective factor for CRC in all newly diagnosed CRC patients. Current smoking and Hb ≤ 12g/dl are risk factors for both urban and rural residents, while healthy dietary pattern was significant protective factor for urban residents. Age >63 years and unhealthy dietary pattern are additive risk factors for rural residents table (5).

**Table (1) Comparison of Demographic characteristics and laboratory results of newly diagnosed CRC patients versus control group.**

| Characteristic | Control group (N=200) | CRC patients' group (N=200) | Test of significance | |
|---|---|---|---|---|
| **Gender** | | | $\chi^2$ [1] | P-value |
| **Male** | 104 (52%) | 117 (58.5%) | | |
| **Female** | 96 (48%) | 83 (41.5%) | 1.709 | 0.191 |
| **Residence** | | | .092 | 0.762 |
| **Rural** | 115 (57.5%) | 112 (56%) | | |
| **Urban** | 85 (42.5%) | 88 (44%) | | |
| **Positive FH of cancer** | 0 (0%) | 35 (17.5%) | 38.356 | <0.001 |
| **Current smoker** | 29 (14.5%) | 69 (34.5%) | 21.625 | <0.001 |
| **Healthy pattern** | | | | |
| **Low score** | 46 (23.0%) | 99 (49.5%) | 30.388 | <0.001 |
| **High score** | 154 (77.0%) | 101 (50.5%) | | |
| **Un-healthy pattern** | | | | |
| **Low score** | 132 (66.0%) | 103 (51.5%) | 8.676 | 0.003 |
| **High score** | 68 (34.0%) | 97 (48.5%) | | |

| | Median (Q1– Q3) | Median (Q1 – Q3) | Z | P-value |
|---|---|---|---|---|
| **Age (years)** | 56 (52-60) | 57 (50-66) | -1.542 | 0.123 |
| **WBCs count (thousand/ µl)** | 7.28 (5.37-8.77) | 7.9 (6.5-9.7) | -3.909 | <0.001 |
| **RBCs count (million/µl)** | 4.59 (4.04-4.83) | 4.7 (4.3-5.0) | -2.834 | 0.005 |
| **Hemoglobin (g/dl)** | 13.2 (12.5-13.9) | 10.7 (8.9-12.375) | -12.268 | <0.001 |
| **Platelet count(thousand/µl)** | 262.5 (192.25-318.75) | 323 (252.25-411.5) | -6.049 | <0.001 |
| **Total bilirubin (mg/dl)** | 0.6 (0.425-0.8) | 0.5 (0.5-0.6) | -3.336 | 0.001 |
| **Albumin (g/dl** | 4.3 (3.8-4.7) | 4.0 (3.7-4.3) | -4.936 | <0.001 |
| **AST (IU/L)** | 21 (20-23) | 21 (20-22) | -0.723 | 0.469 |
| **ALT (IU/L)** | 21 (20-22) | 20 (20-21) | -3.275 | 0.001 |
| **Serum creatinine (mg/dl)** | 0.8 (0.7-0.9) | 0.8 (0.7-0.9) | -0.766 | 0.444 |
| **Random blood glucose (mg/dl)** | 91.5 (87.25-99) | 102 (90-112.75) | -6.855 | <0.001 |

FH = Family history. significant (p-value <0.05). Data is N (%) for categorical variables ($\chi^{2=}$chi-square test). Data is median (Q1-Q3). Z= Mann-Whitney U-test.

**Table (2) Association of NAT2 (rs1801280) genotypes and alleles in CRC patients versus control group.**

| Genotype | Control group | | CRC patients' group | | Chi-square test of association | | | Binary logistic regression | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | $\chi^2$ [2] | Cramer's V | Sig. | COR | 95% CI Lower | 95% CI Upper | Sig. |
| C/C | 46 a | 23 | 33a | 16.5 | 6.922 | 0.132 | **0.031** | r(1) | | | |
| T/C | 96 a | 48 | 85a | 42.5 | | | | 1.22 | 0.72 | 2.1 | 0.440 |
| T/T | 58 b | 29 | 82a | 41 | | | | 2 | 1.13 | 3.4 | **0.017** |
| C | 188 | 47 | 151 | 37.8 | 7.008 | 0.094 | **0.008** | r (1) | | | |
| T | 212 | 53 | 249 | 62.3 | | | | 1.46 | 1.10 | 1.94 | **0.008** |

significant (p-value <0.05). COR = crude odds ratio. CI = confidence interval. Z-tests are in small letters (significant if different). r (1) = reference category

**Table (3) The association between NAT2 (rs1801280) genotypes and demographic factors in CRC patients versus controls.**

| Genotype | Demographic factors | Frequency (N %) | | AOR | 95% CI | | P-value |
|---|---|---|---|---|---|---|---|
| | | Control | CRC patients | | Lower | Upper | |
| C/C | Female | 26 (56.5%) | 10 (30.3%) | 2.99 | 1.163 | 7.684 | 0.021 |
| | Male | 20 (43.5%) | 23 (69.7%) | | | | |
| | Age> 63 | 4 (8.7%) | 12 (36.4%) | 6.00 | 1.724 | 20.878 | 0.004 |
| | Rural | 26 (56.5%) | 19 (57.6%) | 0.958 | 0.388 | 2.364 | 0.926 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Urban** | 20 (43.5%) | 14 (42.4%) | | | | |
| | **Current smoking** | 6 (13.0%) | 12 (36.4%) | 3.810 | 1.251 | 11.597 | 0.015 |
| | **High healthy dietary pattern score** | 38 (82.6%) | 14 (42.4%) | 0.155 | 0.055 | 0.434 | <0.001 |
| | **High unhealthy dietary pattern score** | 17 (37.0%) | 8 (24.4%) | 0.546 | 0.202 | 1.478 | 0.231 |
| **T/C** | **Female**<br>**Male** | 40 (41.7%)<br>56 (58.3%) | 35 (41.2%)<br>50 (58.8%) | 1.020 | 0.564 | 1.846 | 0.947 |
| | **Age> 63** | 11 (11.5%) | 25 (29.4%) | 3.220 | 1.472 | 7.040 | 0.003 |
| | **Rural**<br>**Urban** | 58 (60.4%)<br>38 (39.6%) | 53 (62.4%)<br>32 (37.6%) | 0.922 | 0.506 | 1.679 | 0.790 |
| | **Current smoking** | 14 (14.6%) | 33 (38.8%) | 3.717 | 1.818 | 7.600 | <0.001 |
| | **High healthy dietary pattern score** | 78 (81.3%) | 41 (48.2%) | 0.215 | 0.110 | 0.419 | <0.001 |
| | **High unhealthy dietary pattern score** | 28 (29.2%) | 44 (51.8%) | 2.606 | 1.413 | 4.807 | 0.002 |
| **T/T** | **Female**<br>**Male** | 30 (51.7%)<br>28 (48.3%) | 38 (46.3%)<br>44 (53.7%) | 1.241 | 0.633 | 2.433 | 0.530 |
| | **Age> 63** | 9 (15.5%) | 29 (35.4%) | 2.979 | 1.283 | 6.919 | 0.009 |
| | **Rural**<br>**Urban** | 31 (53.4%)<br>27 (46.6%) | 40 (48.8%)<br>42 (51.2%) | 1.206 | 0.615 | 2.364 | 0.586 |
| | **Current smoking** | 9 (15.5%) | 24 (29.3%) | 2.253 | 0.958 | 5.299 | 0.059 |
| | **High healthy dietary pattern score** | 38 (65.5%) | 46 (56.1%) | 0.673 | 0.336 | 1.348 | 0.262 |
| | **High unhealthy dietary pattern score** | 23 (39.7%) | 45 (54.9%) | 1.851 | 0.935 | 3.663 | 0.076 |

AOR = adjusted odds ratio. CI = confidence interval. significant (p-value<0.05). FH= family history

**Table (4) Univariate logistic regression analysis for prediction of CRC in newly diagnosed CRC patients.**

| | **Univariate** | | | |
|---|---|---|---|---|
| | **P-value** | **COR** | **95% CI** | |
| | | | **Upper** | **Lower** |
| **Male sex** | 0.191 | 1.301 | 0.877 | 1.932 |
| **Age > 63 years** | <0.001 | 3.612 | 2.151 | 6.066 |
| **Urban residence** | 0.762 | 1.063 | 0.716 | 1.579 |
| **Current smoking** | <0.001 | 3.106 | 1.903 | 5.069 |
| **Hemoglobin ≤ 12 g/dl** | <0.001 | 24.962 | 14.279 | 43.639 |
| **SNP (T/T genotype)** | 0.012 | 1.701 | 1.123 | 2.578 |
| **Healthy dietary pattern (high vs low)** | <0.001 | 0.305 | 0.198 | 0.469 |

| | | | | |
|---|---|---|---|---|
| **Unhealthy dietary pattern (high vs low)** | 0.003 | 1.828 | 1.222 | 2.736 |

significant (p-value <0.05). COR = crude odds ratio. 95% CI = Confidence interval

**Table (5) Multivariate logistic regression analysis for prediction of CRC in newly diagnosed CRC patients.**

significant (p-value <0.05). AOR = Adjusted odds ratio. 95% CI = Confidence interval

**Discussion**

| | **Multivariate for newly diagnosed CRC patients** | | | | **Multivariate for urban patients** | | | | **Multivariate for rural patients** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **P-value** | **AOR** | **95% CI** | | **P-value** | **AOR** | **95% CI** | | **P-value** | **AOR** | **95% CI** | |
| | | | **Lower** | **Upper** | | | **Lower** | **Upper** | | | **Lower** | **Upper** |
| **Age > 63 years** | 0.004 | 2.817 | 1.387 | 5.723 | 0.189 | 2.182 | 0.681 | 6.992 | 0.016 | 3.123 | 1.231 | 7.922 |
| **Current smoking** | <0.001 | 7.274 | 3.668 | 14.425 | <0.001 | 9.234 | 2.916 | 29.244 | <0.001 | 7.145 | 2.932 | 17.410 |
| **Hemoglobin ≤ 12 g/dl** | <0.001 | 32.569 | 16.887 | 62.814 | <0.001 | 76.527 | 21.643 | 270.589 | <0.001 | 21.462 | 9.635 | 47.806 |
| **SNP (T/T genotype)** | 0.242 | 1.433 | .784 | 2.619 | 0.127 | 2.216 | .797 | 6.160 | 0.788 | 1.113 | 0.508 | 2.428 |
| **Healthy dietary pattern (high vs low)** | 0.001 | 0.361 | 0.198 | 0.659 | 0.006 | 0.236 | 0.085 | 0.658 | 0.102 | 0.517 | 0.234 | 1.140 |
| **Unhealthy dietary pattern (high vs low)** | 0.024 | 1.990 | 1.096 | 3.614 | 0.478 | 1.459 | 0.514 | 4.140 | 0.005 | 3.236 | 1.417 | 7.393 |

Globally CRC is one of the cancers whose incidence is increasing comprising 11% of all cancer diagnoses (Wong et al., 2021). CRC is the second most common cause of death from cancer, estimated to be responsible for almost 935,000 cancer deaths (Arnold et al., 2017).

A modified food frequency questionnaire containing 28 food items was conducted for newly diagnosed CRC cases and control group in the present study. Food items were classified as healthy and unhealthy dietary patterns using factor analysis (Bergman et al., 2022). Healthy diet included bread, milk, yogurt, cheese, rice, potato, cooked vegetables, fresh vegetables, fruits, boiled red meat, liver, kidney, brain, roasted chicken without skin, grilled chicken, grilled fish, tuna & salmon and egg. Unhealthy diet included baked goods, pizza, pasta, foul & falafel, dessert, fried red meat, mixed red meat, processed meat, roasted chicken with skin, processed chicken, fried food and fast food. The study revealed that high score unhealthy dietary pattern was more frequent significantly ($p=0.003$) in CRC patients than the control group. Moreover, a high score healthy dietary pattern was significantly ($p<0.001$) more frequent in the control group compared to the CRC patient group (table,1).

These findings were in agreement with El-Moselhy et al. (2025) who reported that high red-and/or processed-meats intake, low white-meat intake, low fruits/vegetables, high salty-/spicy-food and low fiber intake were significant risk factors of CRC, while dietary regimens used high white-meat like fish and high fibers exert protective factor against CRC among Egyptian population.

These results are supported by a meta-analysis which reported that suggestive evidence existed for an inverse association of a healthy dietary pattern with CRC incidence and suggestive evidence also existed for positive associations between unhealthy dietary pattern (higher intakes of processed meat) and the incidence of CRC (Veettil et al., 2021).

Another study by Castelló et al., (2022) found that there was no clear effect of the Prudent dietary pattern (high intakes of low-fat dairy products, vegetables, fruits, whole grains and juices) on CRC risk while moderate to high adherence to the Western dietary pattern (high intakes of high-fat dairy products, processed meat, refined grains, sweets, caloric drinks, convenience food and sauces, and low intakes of low-fat dairy products and whole grains) might increase the CRC risk. In addition, a potential protective effect of a high adherence to the Mediterranean dietary pattern (high intakes of fish, vegetables, legumes, boiled potatoes, fruits, olives, and vegetable oil and a low intake of juices) was observed.

CRC risk factors, including environmental and genetic factors, can be divided into modifiable and non-modifiable risk factors. Modifiable risk factors for CRC may be controlled by effective risk-factor reduction measures and therefore are of special interest to policymakers for designing CRC control programs. They include smoking, alcohol consumption, obesity, sedentary lifestyle, unhealthy diet and psychological stress. Non-modifiable risk factors may be considered for identifying high-risk individuals or populations as candidates for taking preventive interventions. They include age, gender, genetic predisposition, family history of CRC, abdominopelvic radiation and intestinal microbiota (Roshandel et al., 2024).

Positive family history of CRC was the most significant risk factor (Hassan et al., 2021). The current study revealed a statistically significant ($p<0.001$) higher positive family history of cancer in CRC patients than in control group (table,1). This finding was in agreement with previous studies (Le Marchand et al., 2001, Song et al., 2021, El-Moselhy et al., 2025), they reported that CRC patients were more likely to have a first-degree relative family history of CRC than controls. Moreover, Sawicki et al. (2021) reported that people with one affected first-degree relatives (parents, siblings and children) have an average, two times higher risk of CRC than those with no family history.

The current study revealed statistically significant ($p<0.001$) higher smoking in CRC patients versus control group. This finding agreed with the finding of Botteri et al. (2020), who had conducted a systematic review and meta-analysis of epidemiological studies on the association between cigarette smoking and CRC risk. They reported that CRC risk increased linearly with smoking intensity and duration. Additionally, Chen et al. (2021) reported that smoking was significantly associated with an increased risk of CRC in the studied German population. El-Moselhy et al. (2025) found that active tobacco-smoking was significant risk factor for CRC among Egyptian population. However, Sørensen

et al., (2008) found that there was no statistically significant association between tobacco smoking and risk of CRC in Danish population.

The direct association between smoking and the risk of CRC was consistently reported by previous studies on different populations, suggesting significant dose–response effects and a reduction in CRC risk after smoking cessation (Le Marchand et al., 2001; Lee et al., 2019). By inhaling toxic chemicals in smokers, the colorectal mucosal cells are exposed to well-known carcinogens, including nitrosamines, heterocyclic amines, polycyclic aromatic hydrocarbons (PAH), and benzene. Long-term exposure to these carcinogens will result in genic and molecular changes in colorectal cells, and, finally, the accumulation of these pro-oncogenic changes may cause the development of CRC (Roshandel et al., 2024).

The present study findings were in accordance with some researchers; Chen et al. (2015), conducted their study on Canadian population, and found that meat-diet pattern and the sugary-diet pattern were associated with a greater risk of CRC while plant-based diet pattern conferred a protective effect against CRC. Another case control study in Brazil, found that CRC was associated with an increase of meat intake, in their different types (beef, pork and chicken) (Angelo et al., 2016).

Controversy to these studies, a study from Southeast Siberia showed no association between the consumption of fruits and vegetables and the risk of developing CRC (Zhivotovskiy et al., 2012). Moreover, Sørensen et al. (2008) and Budhathoki et al. (2020) had reported that there were no statistically significant associations between dietary intake of total meat, red meat, processed meat, fried meat, fried red meat and processed red meat and the risk of CRC.

Several mechanisms have been put forward to explain the association between red meat consumption and CRC. Cooking of meat produces carcinogens such as polycyclic aromatic hydrocarbons, heterocyclic amines, and nitrate and nitroso compounds, which facilitate the development of colorectal cancer (Wang et al., 2016). Red meat contains high levels of heme iron, which promotes colorectal tumorigenesis by stimulating the formation of carcinogenic N-nitroso compounds. Processed meat rich in fat and heme iron also promotes tumorigenesis via the mechanism described above (Vingeliene et al., 2017).

N-acetyltransferase 2 is an important phase II enzyme in detoxification processes, and at the same time, in the activation of dietary HCA procarcinogens (Ishibe et al., 2002). For these reasons, both hypercaloric diet and the polymorphisms in the gene encoding NAT2 may have important implications in the susceptibility to colorectal cancer (Procopciuc et al., 2017).

The association of NAT2 (rs1801280) genotypes and alleles in CRC patients versus control and its relations to food types and dietary patterns were investigated in the present study. To the best of our knowledge, this is the first study to investigate the association of NAT2 (T341C) SNP and dietary pattern among newly diagnosed Egyptian CRC patients.

The present study detected a statistically significant higher T/T genotype ($p=0.031$) and T allele ($p=0.008$) distribution in CRC patients compared to the control group (risk genotype& allele) (table,2). Patients with the T/T genotype have 2 times higher risk to exhibit CRC compared to the C/C genotype (protective genotype) ($p<0.017$, OR, 2.0) and patients with T allele have 1.5 times higher risk to exhibit CRC compared to C allele (protective allele) ($p<0.008$, OR, 1.46) (table,2).

These results were in agreement with Procopciuc et al. (2017) who suggested that the homozygous negative genotypes NAT2*5C-T341C (TT) are significantly risk factors for sporadic colon and rectal cancer.

A possible explanation for the association between colon and rectal cancer and the rapid NAT2 acetylator alleles (TT) refers to the fact that carriers of at least one negative allele are associated with an increased activity of NAT2. In this case, NAT2 transforms at a higher speed procarcinogens such as N-hydroxylated heterocyclic amines present in the colon into carcinogenic compounds, which could predispose individuals to colon or rectal cancer (Ambrosone et al., 2007).

On the other hand, Le Marchand et al. (2001) reported that there was no association between CRC and the rapid NAT2 genotype in all genotyped subjects of Hawaiian Oahu residents. Budhathoki et al. (2020) found that NAT2 acetylation genotype was not associated with colorectal adenoma risk in Japanese Brazilians. Moreover, several studies reported that NAT2 acetylator status did not affect the CRC risk (Sørensen et al., 2008; Ananthakrishnan et al., 2015; Wang et al., 2015).

The association between NAT2 (rs1801280) genotypes with demographic factors in CRC patients versus control (table,3) demonstrated that there were significant association between NAT2 genotypes (C/C, T/C, T/T) and age more than 63 years ($p=0.004$, $p=0.003$, $p=0.009$ respectively). Hubbard et al. (1997) found that the slow acetylator genotype of NAT2 was significantly associated with an earlier age of CRC onset, suggesting that individuals with this genotype may develop CRC at a younger age compared to those with other genotypes. On the other hand, Slattery et al. (2000) reported that there were no statistically significant interactions between CRC with age.

The influence of NAT2 genotypes on the age of CRC onset may be complex and potentially modulated by additional genetic or environmental factors.

Significant association between NAT2 (C/C &T/C) genotypes and current smoking ($p=0.015$, $p<0.001$ respectively) was revealed in the present study (table,3). A study by Lilla et al. (2006) investigated the effect of NAT2 genotypes on CRC risk associated with tobacco exposure. They found that exposure to environmental tobacco smoke was associated with an increased risk for CRC only among NAT2 fast acetylators. This suggests that individuals with the rapid acetylator phenotype may have enhanced ability to activate procarcinogens in tobacco smoke, leading to increased DNA damage and CRC risk. Nöthlings et al. (2009) reported that the enhanced association between smoking and colorectal cancer risk in subjects with the NAT2 rapid (T/T) genotype supports a role for NAT2 and tobacco smoke heterocyclic amines in the etiology of colorectal cancer. On the other hand, Borlak and Reamon-Buettner (2006) did not obtain significant association between smoking and NAT2 allele and genotype frequencies in colon cancer patients and control groups.

NAT2 (C/C &T/C) genotypes were associated with a high score healthy diet in the control group versus CRC group ($p<0.001$) (protective factor). In agreement with this finding, Martinez-Perez et al. (2024) reported that significant interaction was observed between white meat intake and the CC + CT genotype of rs1801280. While, NAT2 (T/C) genotype was associated with high score unhealthy diet in CRC patients versus controls ($p=0.002$). A meta-analysis encompassing study from Japanese and African American populations conducted by Wang et al. (2015), reported that the association of processed meat (unhealthy diet) with CRC was strongest among individuals with the rapid NAT2 phenotype, intermediate among those with the intermediate NAT2 phenotype, and null among those with the slow phenotype.

A study by Chan et al. (2005) in USA found an association between high intake of red meat and incident colorectal cancer risk, particularly among women with rapid acetylator NAT2 genotypes. Although they did not observe a clear interaction between smoking and NAT2 genotype, it appeared that women with rapid acetylator genotypes who consumed the highest levels of red meat and had the greatest exposure to cigarette smoke had a particularly elevated risk of colorectal cancer.

This positive association is explained because NAT2 is an important enzyme which is involved in the activation of HCA and PAH through O-acetylation. NAT2 rapid acetylation status has been

hypothesized to increase the risk of cancer, particularly in those with higher exposure to HCAs (Budhathoki et al., 2020).

Univariate and multivariate logistic regression analysis of the risk factors for CRC in the present study revealed that elevated age >63 years was significant risk factor as shown in the newly diagnosed CRC patients ($p<0.001$ and $p=0.004$, tables, 4 and 5) and in the rural subgroup by multivariate logistic regression analysis ($p=0.016$).

In agreement with these findings, Lewandowska et al. (2022) showed that a clear peak incidence occurred in the age groups of 56–66 (53%) and 67–77 (33%), which confirmed that the age is a major risk factor for CRC. Advancing age is a major risk factor for CRC incidence. Individuals older than 50 years are specifically at high risk, consisting of more than 90% of all CRC cases (Roshandel et al., 2024).

By univariate and multivariate logistic regression analysis, hemoglobin <12 gm/dl was a predictor for CRC in newly diagnosed rural ($p<0.001$) and urban ($p<0.001$) CRC patients (tables, 4 and 5).

Anemia is considered the most common extraintestinal symptom, appearing in 30-75% of CRC patients caused by chronic blood loss from the gastrointestinal tract and inflammation associated with malignancy and/or increased hepcidin secretion (Chardalias et al., 2023).

By univariate regression analysis, the present study showed that unhealthy dietary pattern was a significant ($p=0.003$) risk factor for CRC and healthy dietary pattern was a significant ($p<0.001$) protective factor for CRC (table,4), while by multivariate regression analysis, unhealthy dietary pattern was a significant ($p=0.024$, $p=0.005$) risk factor for CRC in the whole and rural CRC patients, while healthy dietary pattern was a significant ($p=0.001$, $p=0.006$) protective factor for CRC in both whole and urban CRC patients.

Nöthlings et al. (2009) conducted a multiethnic Cohort Study. They found that a positive association of processed meat intake and colorectal cancer risk in the age-sex-ethnicity–adjusted models, intake was not significantly associated with colorectal cancer risk in the multivariate-adjusted analysis. The meat and fat pattern were positively associated with colorectal cancer in the age-sex-ethnicity–adjusted model but not significantly in the multivariate-adjusted model. Red meat intake, doneness preference, and heterocyclic amine intake were not associated with colorectal cancer risk.

Assessment of NAT2 (rs1801280) genotypes association with CRC by univariate logistic regression analysis showed that T/T genotype is significant ($p=0.012$) predictor for CRC which was insignificant in multivariate analysis.

The NAT2 acetylator status may more effectually modify individual responses to various chemical carcinogens in gastrointestinal tract, and thus, may modify individual susceptibility of cancer. NAT2 capacity varies among humans. Individuals with a slow acetylator status have reduced detoxification capacity compared with those with rapid or intermediate status (Zhang et al., 2009).

**Conclusions**

- T/T genotype and T allele (rapid acetylators) could be risk factors for CRC.
- Age >63 years, positive family history of cancer, current smoking were significant risk factors for CRC.
- Unhealthy dietary pattern was significant risk factor for rural residents, while healthy dietary pattern was significant protective factor for CRC in urban residents.

**Limitations**

Relatively small sample size, one year of dietary recall might cause memory bias, dietary patterns we observed may not be comparable with other studies due to variances in dietary patterns based on ethnicity, culture, religion, geography and other socioeconomic determinants, and NAT2 (rs1801280) was the only assessed gene polymorphism.

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**Conflict of interest**

None

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