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# *RS17817449 FTO* gene variation associated with familial disease burden rather than individual risk for breast cancer

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## ABSTRACT

**Introduction:** Breast cancer (BC) is the most common malignancy in the female population globally. Obesity is associated with an increased risk of postmenopausal BC, BC recurrence, and mortality. Fat mass and obesity-associated (*FTO*) gene polymorphisms have attracted the most attention due to several single-nucleotide polymorphisms (SNPs) that may have an impact on obesity and different types of cancer. The primary goal of our work was to assess the association of the SNP rs17817449 *FTO*, physical status/metabolic changes, and dietary habits with the occurrence of BC.

**Methods:** We conducted research as a population-genetic study including 93 women with a diagnosis of BC during their lifetime. Genomic DNA was extracted from the swabs of the buccal mucosa. Genotyping was achieved by polymerase chain reaction-restriction fragment length polymorphism. The IBM SPSS Statistics program v. 23.0 was used for statistical analysis. All values of $p < 0.05$ were considered statistically significant.

**Results:** The risk genotype of the *FTO* gene (rs17817449) GG was detected in 16 subjects (17.2%), the heterozygous TG in 46 subjects (49.5%), while the normal genotype TT was recorded in 29 subjects (31.2%). We found no statistically significant difference in the body mass index values of the three genotype groups, $p = 0.72$, $\chi^2 = 2.1$ and no significant relationship between the allelic or genotypic frequencies of the rs17817449 *FTO* gene polymorphism and other variables examined in our study. Analysis of the distribution of hereditary diseases in the family according to the molecular subtype of BC showed statistically significant *p*-values, $p = 0.02$.

**Conclusion:** While previous research has suggested a potential link between FTO gene polymorphism, obesity, and BC, our study did not find a statistically significant association between the aforementioned variables. Future studies with a larger number of subjects in different populations should confirm the role of the *FTO* genotype in the risk of BC.

**Keywords:** FTO; single-nucleotide polymorphism rs17817449; breast cancer; risk; body mass index; obesity.

## INTRODUCTION

Breast cancer (BC) is the most common malignancy and the first cause of death due to malignant disease in the female population in the world. The incidence of BC in female population in 2020 in the world was 24.5%, while the mortality rate was 15.5%. Data for Bosnia and Herzegovina from the same year indicate an incidence of 23.3% with 1554 new cases, while the mortality rate is 15.4% (Figures 1 and 2) (1).

Recommended form of additional therapeutic action in BC that increases the chances of a more successful cure is the avoidance of risk factors (use of hormonal contraception and hormone replacement therapy, overweight and obesity, and daily alcohol consumption) (2).

Body mass index (BMI) is strongly associated with diet and the occurrence and recurrence of BC and overall mortality (3,4). The relationship of BMI to BC risk differs by menopausal status (5). In premenopausal women, most studies have found little or no association between BMI and BC risk. However, in postmenopausal women, the risk of BC increases with increasing BMI. A pooled analysis of seven prospective studies showed that the risk of developing BC was approximately 30% higher among postmenopausal women with a BMI >31 kg/m$^2$ compared to women with a BMI of approximately 20 kg/m$^2$ (5). Due to the high level and increasing prevalence of increased BMI, this is an important potentially modifiable risk factor and there is a need to design effective interventions at the population level.

Nutrigenetics approach can help in finding out if how different nutrients act on proteins and gene expression that changes cellular function in a carcinogenic or protective direction (6). In the future, nutrigenetic analysis is expected to play a key role in the prevention and early detection of BC so that it recognizes the link between nutrition and BC

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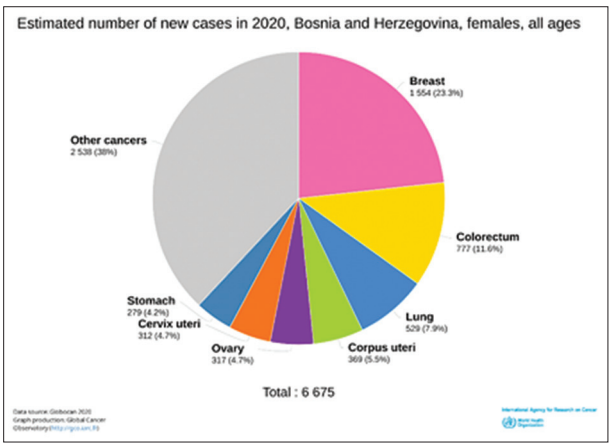


**FIGURE 1.** Incidence of cancer according to primary localization in women from Bosnia and Herzegovina (1).

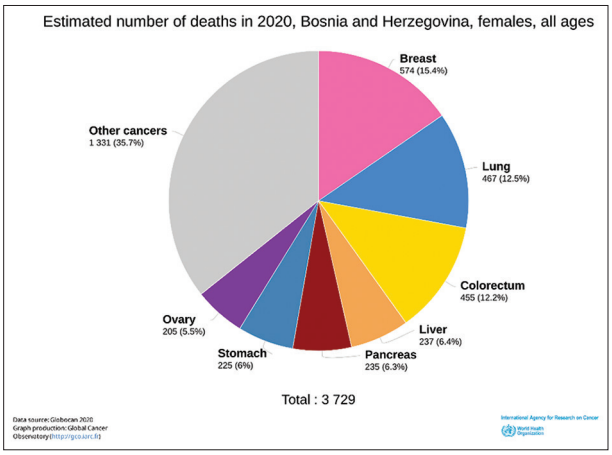


**FIGURE 2.** Mortality rate from cancer according to primary localization in women from Bosnia and Herzegovina (1).

risk increase among sporadic cases and carriers of gene mutations. This knowledge will help identify individuals who will have the greatest benefit from dietary changes, which is important for the development of a personalized diet with maximum benefit and minimum adverse events (7).

A genome-wide association study identified *Fat Mass and Obesity-Associated* (*FTO*) gene as a susceptibility gene for obesity, and many variants of this gene are associated with BMI, body fat percentage, waist circumference, hip circumference, and increased calorie intake. The association between *FTO* polymorphisms and BMI was first observed in 2007 in a European population with diabetes mellitus as it affects food intake – carriers of *FTO* risk alleles consume more high-energy foods (fats and proteins) and have a lack of satiety resulting in overeating (8). *FTO* gene polymorphisms have attracted the most attention due to several single-nucleotide polymorphisms (SNPs) that may have an impact on obesity and different types of cancer (for example, rs9939609, rs17817449, rs8050136, rs1477196, rs6499640, rs16953002, rs11075995, and rs1081212089) (9).

This study was designed to assess the allele and genotype association of the single-nucleotide *FTO* polymorphism (rs17817449) with BC status, metabolic changes, and dietary habits with the occurrence of BC, familial disease burden including other risk factors for BC associated with diet and normal BMI deviation.

## METHODS

A total of 93 women who were diagnosed with BC during their lifetime were included in the study after providing their personal informed consent. Participation in the research was exclusively on a voluntary basis, with a prior explanation by the project holder, the purpose of the research and the procedure for taking samples for molecular genetic analysis, and the signing of an informed consent, the content of which was approved by the independent Institutional Ethics Board.

Successively to biological sampling, personal information (demographic data, data on body weight and height, time of diagnosis and type of BC, current possible oncological therapy and concomitant therapy for comorbidities, family and personal history of malignant and autoimmune diseases, and data on dietary habits and physical activity before and after establishing the diagnosis of BC) have been collected.

Two swabs of the buccal mucosa were taken using sterile collection kits by rubbing the inner surface of both cheeks for 20 s, to ensure that the swabs were well saturated with saliva. Genomic DNA was extracted by adjusted procedure (10). Genotyping was achieved by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

The PCR-RFLP procedure for the *FTO* gene (rs17817449) was performed using a thermal cycler QIAamplifier 96 (Qiagen, Germany) with the following primer sequences: forward primer 5'-AGGACCTCCTATTTGGGACA-3' and reverse primer 5'-AGCTTCCATGGCTAGCATTA-3'. Amplification of this SNP flanking genomic region was done in a total PCR volume of 25 µL containing: 2.5 µL 10× PCR buffer, 0.2 µL Taq polymerase 5 units/µL, 2 µL 25 mM $MgCl_2$, 2 µL 2.5 mM dNTP mixture (Taq DNA Polymerase 1000 units kit, Qiagen, Germany), 2 µL of each primer (10 mM), 13.3 µL of sterile water, and 1 µL of DNA sample. The thermocycling conditions for amplification were as follows: 95°C for 3 min, then 35 cycles of 95°C for 45 s, 61°C for 45 s, 72°C for 1 min, and a final extension at 72°C for 7 min. The expected maximum size of the PCR product is 828 bp which was checked using agarose gel electrophoresis with comigrating DNA marker (50 bp DNA Ladder; New England Biolabs, UK).

The *FTO* gene amplification product (10 µL) was digested with restriction enzyme AlwNI (New England Biolabs, UK), using 0.2 µL of this enzyme and 5 µL of rCutSmart Buffer (New Englands Biolabs, UK), as published elsewhere (11). The RFLP products were separated on a 2% agarose gel, where fragments of 498 and 330 bp were observed in the homozygous wild-type TT genotype, fragments of 828, 498, and 330 bp in the heterozygous – GT genotype, and in the homozygous mutated genotype – GG we observed exclusively a fragment of size 828 bp.

Based on the results of the PCR-RFLP analysis of the *FTO* gene (rs17817449), the subjects were divided into three genotypic groups: (1) normal homozygous or wild type genotype TT, (2) heterozygous genotype GT, and (3) risky homozygous or mutated genotype GG, from which two allelic groups were derived: (1) T allele and (2) G allele.

The IBM SPSS Statistics program v. 23.0 was used for statistical analysis. We defined descriptive measures, including

absolute values and percentages. The data are presented in textual and tabular form and are presented as mean value with standard deviation, or as median with interquartile range. The Kruskal–Wallis U-test was used to analyze the difference in BMI values as a ranking variable between three groups of patients formed according to genotype. The Mann–Whitney U-test was used to analyze the difference in BMI values as a quantitative variable in relation to the allelic frequency of alleles 1 and 2. The chi-square test of independence was used to analyze the distribution of the basic characteristics of the examined sample between groups of patients formed according to genotype, and then according to allelic frequencies. The chi-square test of independence was used to analyze the distribution of the presence of hereditary diseases in the family according to patient groups formed according to the molecular type of BC. *Post hoc* chi-square testing was performed to analyze adjusted residual values and identify cells with statistically significant z-scores in the cross-tabulation.

All values of $p < 0.05$ were considered statistically significant.

## RESULTS

The distribution of examined parameters according to genotype frequency is observed, as shown in Table 1. The Kruskal–Wallis's test did not reveal a statistically significant difference in the BMI values of the three groups of subjects categorized by genotype, $p = 0.72$, $\chi^2 = 2.1$.

The allele association with the examined parameters (Table 2) did not reveal a statistically significant difference in BMI values in relation to any of the alleles: $p = 0.14$ and $p = 0.79$, respectively.

Genotype frequency distribution (Chi-square test) did not show a significant relationship between the rs17817449 allele or genotype frequencies regarding variables examined in our study.

The mean age of the studied population is 56.15 (s.d. ±10.75 years). In the examined sample (n = 93), 46 participants (49.5%) were younger than 55 years of age, while 47 of them (50.5%) were over 55 years of age at the time of analysis.

In the tested sample (n = 93), the risk genotype of the *FTO* gene (rs17817449) GG (17.2%) was detected in 16 subjects, the heterozygous genotype TG (49.5%) in 46 subjects, while the normal genotype TT (31.2%) was observed in 29 subjects. In the case of two participants (2.2%), the sample analysis was not technically adequately realized and excluded from further analysis.

The allelic frequencies of the FTO gene (rs17817449) are as follows: (1) for allele T 57.1%, and (2) for allele G 42.8%.

The mean value of the BMI was 26.65 (±5.26) kg/m$^2$, and based on the same, the subjects could be divided into three groups: (I) BMI<18.5 kg/m$^2$, malnourished group, two subjects (2.2%); (II) BMI 18.5–24.9 kg/m$^2$, normal values, 30 subjects (32.3%); and (III) BMI >25 kg/m$^2$, overweight, 58 subjects (62.4%). In three subjects (3.2%), we did not have adequate BMI values recorded. In Group III, 41 subjects (42.3%) had a BMI of 25–30, 17 (17.5%) were obese, of which 14 had a BMI of 30–35 and 3 had a BMI of 35–40 kg/m$^2$.

**TABLE 1.** Distribution of examined parameters according to genotype frequency

| Participants characteristics | All n (%) | Normal genotype TT n (%) | Heterozygous genotype TG n (%) | Risk genotype GG n (%) | *p*-value |
|---|---|---|---|---|---|
| Participants number | 91 | 29 (31.2) | 46 (49.5) | 16 (17.2) | |
| BMI (kg/m$^2$) | | | | | *p*=0.72 |
| >18.5 | 2 (2.2) | 1 (50) | 1 (50) | 0 (0) | |
| 18.5–24.9 | 30 (32.3) | 7 (25) | 17 (60.7) | 4 (14.3) | |
| >25 | 58 (62.4) | 20 (34.5) | 27 (46.6) | 11 (19.0) | |
| BC type | | | | | *p*=0.70 |
| HR+, HER2− | 57 (63.3) | 21 (36.8) | 27 (47.4) | 9 (15.8) | |
| HR+, HER2+ | 20 (22.2) | 3 (15.0) | 12 (60.0) | 5 (25.0) | |
| HR−, HER2− | 5 (5.6) | 2 (40.0) | 2 (40.0) | 1 (20.0) | |
| HR−, HER2+ | 8 (8.9) | 3 (37.5) | 4 (50.0) | 1 (12.5) | |
| Positive family history for hereditary diseases | | | | | *p*=0.86 |
| Yes | 78 (85.7) | 24 (30.8) | 40 (51.3) | 14 (17.9) | |
| No | 13 (14.3) | 5 (38.5) | 6 (46.2) | 2 (15.4) | |
| Excess weight before BC diagnosis | | | | | *p*=0.47 |
| Yes | 30 (33.0) | 10 (33.3) | 12 (40.0) | 8 (26.7) | |
| No | 59 (64.8) | 18 (30.5) | 33 (55.9) | 8 (13.6) | |
| Autoimmune diseases comorbidity | | | | | *p*=0.38 |
| Yes | 17 (19.1) | 3 (17.6) | 10 (58.8) | 4 (23.5) | |
| No | 72 (80.9) | 25 (34.7) | 35 (48.6) | 12 (16.7) | |
| Subjective feeling of more difficult weight control | | | | | *p*=0.93 |
| Yes | 42 (46.2) | 14 (33.3) | 20 (47.6) | 8 (19.0) | |
| No | 47 (51.6) | 14 (29.8) | 25 (53.2) | 8 (17.0) | |
| Concomitant therapy of chronic disease | | | | | *p*=0.83 |
| Yes | 65 (71.4) | 20 (30.8) | 34 (52.3) | 11 (16.9) | |
| No | 25 (27.5) | 9 (36.0) | 11 (44.0) | 5 (20.0) | |

BMI: Body mass index, BC: Breast cancer, HER2−: Human epidermal growth factor receptor 2-negative, HER2+: Human epidermal growth factor receptor 2-positive, HR−: Hormone receptor-negative, HR+: Hormone receptor-positive

In the studied population, 57 subjects (63.3%) reported estrogen (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, 28 (31.1%) HER2-positive, and 5 (5.6%) triple-negative (TNBC) molecular subtypes of BC.

The chi-square test of independence did not show a significant relationship between tumor hormone receptor positivity and genotypic or allelic frequencies of the *FTO* gene polymorphism in subjects in our sample, $p = 0.87$, $\chi^2 = 0.28$.

In Table 3, an analysis of dietary habits of the subjects before and after the diagnosis of BC is presented. A 50% reduction in protein and fat intake was recorded, carbohydrate intake was 3 times lower, and a 50% transition from the traditional Bosnian diet to the Mediterranean diet. About 46.4% of participants practice a balanced diet with controlled intake, 27.8% a Mediterranean diet, while 18.6% maintain a traditional diet. Regular physical activity is practiced by 48 (49.5%) participants, of whom 35 (72.9) practice brisk walking, 13 (27%) aerobics, 5 (10.4%) swimming, 3 (6.2%) cycling, and 2 (4.1%) running. Regular concomitant therapy is used by 66 (68%) participants. Of those who reported concomitant therapy in our study, 39 (59.1%) use food supplements and supplements, 30 (45.5%) antihypertensives, 7 (10.6%) use therapy for diabetes, while 6 (9.1%) use mood stabilizers.

Within the examined group, 64 participants (69.6%) were actively treated with one of the modalities of cancer therapy at the time of the research. In that group, 59 (92.2%) were treated with hormone therapy, 8 (12.5%) with targeted therapy, 5 (7.8%) with radiotherapy, while 3 participants (4.7%) were treated with chemotherapy.

Eighteen participants (19.8%) in our sample were diagnosed with an autoimmune type disease in addition to the diagnosis of BC. In that group, 9 (50%) were diagnosed with Hashimoto's thyroiditis, four with autoimmune diabetes mellitus (22.2%), two with rheumatoid arthritis (11.1%), and one each had a diagnosis of Sjogren's syndrome, multiple sclerosis, and connective tissue disease (5.5%). The analysis of the distribution of hereditary diseases in the

**TABLE 2.** Distribution of the examined parameters according to allelic frequency

| Participants characteristics | Alel G n (%) | *p*-value | Alel T n (%) | *p*-value |
|---|---|---|---|---|
| BMI (kg/m$^2$) | | 0.58 | | 0.70 |
| >18.5 | 1 (1.7) | | 2 (2.7) | |
| 18.5–24.9 | 21 (35.0) | | 24 (32.9) | |
| >25 | 38 (63.3) | | 47 (64.4) | |
| BC type | | | | 0.79 |
| HR+, HER2− | 36 (59.0) | 0.32 | 48 (64.9) | |
| HR+, HER2+ | 17 (27.9) | | 15 (20.3) | |
| HR−, HER2− | 3 (4.9) | | 4 (5.4) | |
| HR−, HER2+ | 5 (8.2) | | 7 (9.5) | |
| Positive family history for hereditary diseases | | | | 0.82 |
| Yes | 54 (87.1) | 0.58 | 64 (85.3) | |
| No | 8 (12.9) | | 11 (14.7) | |
| Excess weight before BC diagnosis | | | | 0.25 |
| Yes | 20 (32.3) | 0.83 | 22 (29.3) | |
| No | 41 (66.1) | | 51 (68.0) | |
| Autoimmune diseases comorbidity | | | | 0.51 |
| Yes | 14 (23.0) | 0.17 | 13 (17.8) | |
| No | 47 (77.0) | | 60 (82.2) | |
| Subjective feeling of more difficult weight control | | | | 0.78 |
| Yes | 28 (45.2) | 0.80 | 34 (45.3) | |
| No | 33 (53.2) | | 39 (52.0) | |
| Concomitant therapy of chronic disease | | | | 0.85 |
| Yes | 45 (72.6) | 0.70 | 54 (72.0) | |
| No | 16 (25.8) | | 20 (26.7) | |

BMI: Body mass index, BC: Breast cancer, HER2−: Human epidermal growth factor receptor 2-negative, HER2+: Human epidermal growth factor receptor 2-positive, HR−: Hormone receptor-negative, HR+: Hormone receptor-positive

**TABLE 3.** Dietary habits of the participants before and after the diagnosis of BC

| Participants dietary habits | Before BC diagnosis n (%) | After BC diagnosis n (%) |
|---|---|---|
| Sweet food, all kinds of food without counting calories | 39 (40.2) | 20 (20.6) |
| Balanced diet with control of the amount of intake | 18 (18.6) | 45 (46.4) |
| Dominantly proteins (meat, dried meat products, and cow's milk) | 10 (10.3) | 5 (5.2) |
| Dominantly carbohydrates (potatoes, rice, pasta, and pastries) | 17 (17.5) | 5 (5.2) |
| Predominantly fat (butter, dairy products, and fried food) | 2 (2.1) | 1 (1.0) |
| Traditional BH nutrition – mandatory stew for lunch with lots of carbohydrates – pastries, pies, potatoes, etc. | 33 (34.0) | 18 (18.6) |
| Mediterranean type – olive oil and fish without frying, salads | 14 (14.4) | 27 (27.8) |

BC: Breast cancer

family (malignant, autoimmune, and others) according to the molecular subtype of BC showed statistically significant *p*-values, $p = 0.02$; 78 participants reported hereditary diseases in the family. Statistical significance refers to the hormone receptor-positive (HR+)/HER2+ subtype of BC, in which the *post hoc* chi-square analysis revealed statistically significant z-values, with 53.8% of subjects without the presence of hereditary diseases compared to 16.7% of subjects with hereditary diseases, for the same molecular subtype of BC.

## DISCUSSION

Quantitative studies on the association of *FTO* gene variants and BC produced different results (depending on disease stage, ER status, and racial differences) (12-17). Research data indicate a connection between ER and BC through the regulation of *FTO* gene expression; estradiol induces *FTO* expression through the PI3K/AKT and MAPK signaling pathways (18). The SNP rs17817449 of the *FTO* gene is located in the non-coding region. There are studies linking this polymorphism and an increased risk of ER+ BC, without association with TNBC, which requires additional research to confirm the activity and define the mechanisms of the *FTO* gene as an ER-mediator in the development of BC (19).

Our research did not find a significant association between the diagnosis of BC and polymorphism of the risk allele of the *FTO* gene rs17817449 in our subjects, which can be partially explained by the limitations of our study (a small sample of subjects, different molecular types of BC, subjectivity of subjects, data on molecular subtype based on anamnestic rather than medical history data, and the fact that the research included only one SNP of the *FTO* gene) (Table 4).

However, the data from previous studies are also not consistent, most likely due to the molecular heterogeneity of BC and the effect of various environmental, genetic, and racial factors (20). Although, in our research, we had a relatively small sample of subjects (n = 93), the allelic frequency correlates with data from the literature where, in the European population, it is about 59% for the T allele and about 40% for the G allele (21). A recently published study on the correlation of mammographic variation of breast tissue and several SNPs of different genes, independent of the mammographic density of breast tissue, showed a genetic correlation of polymorphism rs17817449 (16q12.2) on the *FTO* gene with mammographic variation and density, risk of BC and other risk factors for BC such as BMI, and ER-positivity (22).

It is possible that the *FTO* genotype exerts its risk effect on the development of BC only in overweight individuals. From the data on the BMI value of our subjects, excessive body mass is recorded in 62.4% of the subjects. Of that number, only 17.5% of respondents are in the obese category (BMI 30–35 category I-mild obesity, BMI 35–40 II-severe obesity, and BMI >40 III-extreme obesity) (23). According to the individually calculated BMI, the World Health Organization (WHO) has defined that obesity class I-III has a BMI ≥30 kg/m$^2$ at baseline and BMI <30 kg/m$^2$ is considered non-obese (24). Our research did not find a significant association between the diagnosis of BC, BMI, and polymorphism of the risk allele of the *FTO* gene rs17817449 in our subjects, probably due to the low percentage of obese participants, but also the BMI is defined only in relation to weight and height, which lacks body composition measure. Sometimes BMI might be inaccurate in defining obesity or emaciation. Therefore, the definition of body composition patterns and biomarkers related to the true nature induced by obesity is necessary for more accurate verification (25).

Furthermore, the degree of association between *FTO* gene polymorphism and BC is influenced by estrogen receptor status. Considering the small sample of test subjects, the percentage representation of molecular subtypes correlates with data from the literature. The subjects were not categorized according to menopausal status; the fact that 50% of the respondents are older than 55 years, as well as the data on 70% of the respondents undergoing active oncological treatment (59 on active endocrine therapy), speak in favor of the majority of respondents in natural or iatrogenic menopause.

The influence of lifestyle variables such as smoking, alcohol consumption, caloric and macronutrient intake, and physical activity should not be ignored. A review of studies on the effect of diet on *FTO* gene expression in the hypothalamus showed that macronutrient intake may be associated with the level of *FTO* gene expression (19). Furthermore, Park et al. concluded that the amount of caloric intake from fat and protein in the diet can be influenced by *FTO* gene polymorphisms (26). The biggest changes in the lifestyle of our respondents are reflected in the way and quality of diet and the ratio of macronutrients in the diet before and after the diagnosis of malignant disease. A 50% reduction in protein and fat intake was recorded, carbohydrate intake was 3 times lower, and a 50% transition from the traditional Bosnian diet to the Mediterranean diet. From the aspect of nutrition quality and nutritional recommendations for BC patients during and after oncology therapy (27), especially in postmenopausal women with an HR+ molecular profile, the recorded reduction of carbohydrates and fats is commendable. The reduction of protein in the diet, which is not part of the previously mentioned nutritional

**TABLE 4.** Presence and distribution of hereditary diseases in the family according to the molecular type of BC

| BC molecular type | Presence of hereditary diseases in the family n (%) | No presence of hereditary diseases in the family n (%) | *p*-value |
|---|---|---|---|
| HR+, HER2− | 52 (66.7) | 6 (46.2) | *p*=0.02 |
| HR+, HER2+ | 13 (16.7)* | 7 (53.8)* | |
| HR−, HER2− | 5 (6.4) | 0 (0) | |
| HR−, HER2+ | 8 (10.3) | 0 (0) | |
| Total | 78 (100) | 13 (100) | |

*Table cells with bold numerical values had statistically significant z-values in *post hoc* Chi-square analysis

recommendations, is interesting, which can be interpreted primarily by the reduced consumption of red meat and meat and dairy products. Reducing the intake of red meat is justified, while reducing the intake of dairy products is unfounded unless there are other health reasons for it.

It is likely that there is a reciprocal relationship between the *FTO* gene and lifestyle habits. *FTO* gene polymorphisms can affect our food intake and physical activity. On the other hand, nutrient intake and physical activity can affect the level of *FTO* gene expression (28-30). The results of our research showed that almost 50% (49.5%) of the respondents practice regular physical activity (according to the Survey form, at least 3 times a week), which is a satisfactory result, but that percentage should be even higher. According to current guidelines for the prevention of BC, at least 30 min of daily physical activity is recommended, and for obese people 60 min a day (27,31). Given the fact that at the time of the research, 16 respondents (17.5%) were being treated with active cancer therapy in addition to hormonal therapy, this could partially explain the lower percentage of recommended physical activity.

Thirty-nine participants in our research (59.1%) use food supplements and supplements. The use of supplements and food supplements in patients after the diagnosis of malignant disease for preventive purposes is not recommended, except for calcium preparations in the prevention of colon cancer. Vitamin B12, iron supplements, and vitamin D intake are warranted in certain patient populations, but it is generally recommended that all mineral and vitamin requirements be met through an adequate diet (31).

In our sample population, 18 participants (19.8%) knew about the diagnosis of an autoimmune disease. Malignant diseases are common in patients with previously diagnosed autoimmune diseases, and autoimmune diseases are often diagnosed during oncological treatment and follow-up (32). Family history of malignant and autoimmune diseases is a risk factor for the development of malignant diseases in general, especially in the presence of other endogenous and exogenous risk factors.

The most significant result of our research is the specific distribution of hereditary diseases according to the molecular subtype of BC. From a total of 78 out of 91 subjects who reported hereditary diseases in the family, the most significant difference in the percentage of the absence of hereditary diseases was recorded in subjects with HR+/HER2+ molecular subtype. HER2+ BC, namely, is not hereditary, and the HR+/HER2+ combination, which is classified as Luminal B HER2+ BC, is a relatively rare combination (10% of all newly diagnosed cases of BC), more common in younger, premenopausal women, and challenging for treatment due to aggressiveness and unpredictable sensitivity to chemo- and hormonal therapy. This result indicates probable other cellular mechanisms involved in the etiopathogenesis of this molecular profile of BC, which is possibly susceptibility factors for other hereditary, that is, familial characteristic diseases.

## CONCLUSION

Our study did not find a statistically significant association between the rs17817449 *FTO* gene polymorphism and BMI deviations, unbalanced nutrition, or hormonal type of BC. Future studies with a larger number of subjects in different populations should confirm the role of the *FTO* genotype in the risk of developing BC, and progress in this particular field of nutritional genomics would allow the presentation of the *FTO* gene as one of the biomarkers for the risk of BC.

Although the specific mechanisms for *FTO* polymorphism and high risk of obesity and cancer are elusive, the correlation is definite. Clearly, the host genotype also plays a role, not only in susceptibility to BC, but also with regard to benefits obtained from typical foods and nutrients in our diet. To maximize the effect of nutrients on genotype, further research is required to discover additional diet-gene interactions, which will enable holistic insight into the recognition, prevention, and monitoring of individual and/or family burden and its connection with the individual risk of certain forms of cancer and lifestyle.

In cancer patients, it is necessary to define the concentrations of nutrients and synergistic effects between nutrients, as well as between nutrients and anticancer drugs in relation to genotype. The identification of more specific biomarkers will provide mechanistic insight into predicting the response to effect, adverse reaction, and resistance of combined targeted therapies of cancer patients with obesity. Nutritional intervention should become a future part of the multidisciplinary therapeutic approach including nutrition counseling and supplementation with some dietary ingredients, which could induce less adverse events and increase therapeutic efficacy.

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## COMPETING INTERESTS

The authors declare that they have no competing interests.

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