Research Article

Modulation of Colorectal Cancer Risk by Polymorphisms in 51Gln/His, 64Ile/Val, and 148Asp/Glu of APEX Gene; 23Gly/Ala of XPA Gene; and 689Ser/Arg of ERCC4 Gene

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Polymorphisms in DNA repair genes may affect the activity of the BER (base excision repair) and NER (nucleotide excision repair) systems. Using DNA isolated from blood taken from patients (n = 312) and a control group (n = 320) with CRC, we have analyzed the polymorphisms of selected DNA repair genes and we have demonstrated that genotypes 51Gln/His and 148Asp/Glu of APEX gene and 23Gly/Ala of XPA gene may increase the risk of colorectal cancer. At the same time analyzing the gene-gene interactions, we suggest the thesis that the main factor to be considered when analyzing the impact of polymorphisms on the risk of malignant transformation should be intergenic interactions. Moreover, we are suggesting that some polymorphisms may have impact not only on the malignant transformation but also on the stage of the tumor.

1. Introduction

Currently, we are observing an increase of the incidence of colorectal cancer (CRC). In 2012, according to GLOBCAN, there were 1360000 new CRC cases, which with 9.7% made it the third most common cancer after lung and breast cancers [1, 2]. While causes of CRC remain unknown, it is estimated that about 20% of cancer cases are familial and approximately 3% are caused by mutations of strongly predisposed genes [3, 4]. Studies have shown that individual predispositions for developing this cancer may depend on genetic changes, including changes in genes involved in the process of DNA repair, which is responsible for dealing with DNA damages [5–7]. Several single-nucleotide polymorphisms (SNPs) have been associated with colorectal cancer susceptibility; most of them are part of mismatch DNA repair system (MMR) [8–10]. However, besides MMR system in mammalian cells, there are three more basic mechanisms of DNA repair: BER (base excision repair), NER (nucleotide excision repair), and DSB (double-strand brakes), which are currently under strong investigation in terms of connection with an increased risk of colorectal cancer [11–13].

In this paper, we study the selected polymorphisms of nucleotide excision repair (NER) and base excision repair (BER) pathways and their impact on modulating risk of colorectal cancer occurrence. Among the known polymorphisms of the DNA repair genes, the polymorphisms of ERCC4 and XPA genes from NER pathway have been repeatedly studied as potentially connected with susceptibility to the occurrence of various cancers [14–17]. NER is a particularly important excision mechanism that removes DNA damage induced by ultraviolet light (UV). UV DNA damage results in bulky DNA adducts—these adducts are mostly thymine dimers and 6,4-photoproducts. The importance of NER is evidenced by the severe human diseases that result from in-born genetic mutations of NER proteins such as xeroderma pigmentosum and Cockayne’s syndrome [18, 19]. The second studied pathway—BER—is a DNA repair system that operates on small lesions such as oxidized or reduced bases. A single damaged base is removed by base-specific DNA glycosylases and apurinic/apyrimidinic sites are created (that can occur also by spontaneous hydrolysis or by DNA damaging agents). AP sites are premutagenic lesions that can prevent normal DNA replication and therefore need to be identified.
and repaired. Whole process is initiated by the major AP endonuclease in human cells coded by APEX gene, whose polymorphisms have been so far connected to several types of cancer [20–22]. Moreover, our goal was to evaluate the mutual action of those two DNA repair systems on modulation of CRC risk.

2. Materials and Methods

DNA for genotyping was isolated from lymphocytes of the peripheral blood. The blood samples were taken from 312 unrelated patients hospitalized in the Military Medical Academy Teaching Hospital–Central Veterans Hospital in Lodz. Each patient had histopathologically confirmed colorectal cancer. The studied group included 178 men and 134 women (average age 63 years ± 8 years). The stage of the tumors was established according to the TNM scale. The control group included 320 individuals not diagnosed with cancer and with ages corresponding to the age of the studied group (p < 0.05). Permission to conduct research was granted by the Bioethics Committee of the Medical University of Lodz.

DNA isolation was carried out with a commercial kit QIAamp DNA Blood Mini Kit for isolation of high molecular weight DNA (Qiagen).

The occurrence of polymorphic variants in 51Gln/His, 64Ile/Val, and 148Asp/Glu of APEX gene; 23Gly/Ala of XPA gene; and 689Ser/Arg of ERCC4 gene was studied with the TaqMan technique. Briefly, 25 μl of reaction mixture was used for analysis, containing 1 μl of genomic DNA solution, 1 μl of probes designed specifically for each polymorphism, 13 μl of premix with polymerase, and 10 μl of water. The PCR reaction was performed in a Stratagene Mx3005P real-time PCR thermocycler. The RS numbers for polymorphisms and thermal conditions of reaction are shown in Table 1.

### Table 1: The refSNP and thermal conditions used in the PCR reaction.

| Gene | APEX | APEX | APEX | XPA | ERCC4 |
|------|------|------|------|-----|-------|
| Polymorphism | 51Gln/His | 64Ile/Val | 148Asp/Glu | 23Gly/Ala | 689Ser/Arg |
| refSNP | rs1048945 | rs2307486 | rs1130409 | rs1800975 | rs1493642 |
| Thermal conditions | (1) 95°C, 10 min | (2) 92°C, 15 sec | (3) 60°C, 1 min | (4) Steps 2&3, 45× |
| Dyes | ROX, HEX, FAM | Dyes ROX, HEX, FAM | Dyes ROX, HEX, FAM | Dyes ROX, HEX, FAM | Dyes ROX, HEX, FAM |
| Ref dye | ROX | ROX | ROX | ROX | ROX |

2.480);

### Table 2: The distribution of genotypes and allele frequencies and the analysis of the odds ratio (OR) for 51Gln/His polymorphism of APEX gene in patients with colorectal cancer (CRC) and the control group.

| Genotype/allele | Patients | Controls | OR (95% CI) | p |
|-----------------|----------|----------|-------------|---|
| Gln/Gln | 69 | 92 | 1 (ref) | — |
| Gln/His | 206 | 161 | 1.706 (1.174–2.480) | 0.005 |
| His/His | 36 | 49 | 0.979 (0.576–1.667) | 0.920 |
| Gln | 344 | 345 | 1 (ref) | — |
| His | 278 | 259 | 1.077 (0.859–1.349) | 0.522 |

*Genotype distribution in the Hardy-Weinberg equilibrium, χ² = 0.125. Values set in italics denote statistical significance.

### Table 3: The distribution of genotypes and allele frequencies and the analysis of the odds ratio (OR) for 148Asp/Glu polymorphism of APEX gene in patients with colorectal cancer (CRC) and the control group.

| Genotype/allele | Patients | Controls | OR (95% CI) | p |
|-----------------|----------|----------|-------------|---|
| Asp/Asp | 51 | 88 | 1 (ref) | — |
| Asp/Glu | 237 | 158 | 2.588 (1.736–3.859) | <0.0001 |
| Glu/Glu | 21 | 55 | 0.659 (0.358–1.212) | 0.179 |
| Asp | 339 | 334 | 1 (ref) | — |
| Glu | 279 | 268 | 1.026 (0.819–1.285) | 0.823 |

*Genotype distribution in the Hardy-Weinberg equilibrium, χ² = 0.277. Values set in italics denote statistical significance.

Asp/Glu genotype (Table 3) of 148Asp/Glu polymorphism of APEX gene (OR 2.588 (1.736–3.859); p < 0.0001) and Gly/Ala genotype (Table 4) of 23Gly/Ala polymorphism of XPA gene (OR 5.373 (3.418–8.446); p < 0.0001). We did not find any significant influence of 64Ile/Val polymorphism of APEX gene (Table 5) and 689Ser/Arg polymorphism of ERCC4 gene (Table 6) on modulation of CRC risk.

### Table 3: The distribution of genotypes and allele frequencies and the analysis of the odds ratio (OR) for 148Asp/Glu polymorphism of APEX gene in patients with colorectal cancer (CRC) and the control group.

| Genotype/allele | Patients | Controls | OR (95% CI) | p |
|-----------------|----------|----------|-------------|---|
| Asp/Asp | 51 | 88 | 1 (ref) | — |
| Asp/Glu | 237 | 158 | 2.588 (1.736–3.859) | <0.0001 |
| Glu/Glu | 21 | 55 | 0.659 (0.358–1.212) | 0.179 |
| Asp | 339 | 334 | 1 (ref) | — |
| Glu | 279 | 268 | 1.026 (0.819–1.285) | 0.823 |

*Genotype distribution in the Hardy-Weinberg equilibrium, χ² = 0.277. Values set in italics denote statistical significance.

3. Results

3.1. Genotyping. The genotyping results indicate that Gln/His genotype of 51Gln/His polymorphism of APEX gene (Table 2) increases the risk of CRC (OR 1.706 (1.174–2.480); p = 0.005). The same effect was observed in the case of

3.2. Gene-Gene Interactions. In order to investigate the interaction of the polymorphisms of the studied genes and to
evaluate their mutual influence on the risk of colorectal cancer, gene-gene interactions were analyzed. Results are presented in Table 7; only pairs that modulate the risk at a statistically significant level are shown. For the full set of results showing all pairs of gene-gene interactions, please refer to the tables in Supplementary Material available online at https://doi.org/10.1155/2017/3840243. It has been revealed that genotype pair Gln/His-Val/Val for 51Gln/His APEX-64Ile/Val APEX increases the risk of CRC. For 51Gln/His APEX-148Asp/Glu APEX, we observe increased risk in the case of Gln/His-Asp/Glu pair, but at the same time, coincidence of genotypes Gln/His-Glu/Glu and His/His-Asp/Asp decreases the risk. For pair 51Gln/His APEX-23Gly/Ala XPA, we observed increased risk in the case of genotypes Gln/His-Gly/Ala and His/His-Gly/Ala and decreased risk for Gln/His-Gly/Gly. Moreover, increased risk of colorectal cancer was revealed for pairs Gln/His-Arg/Arg (51Gln/His APEX-689Ser/Arg XPA), Val/Val-Asp/Glu (64Ile/Val APEX-148Asp/Glu APEX), and Asp/Glu-Gly/Ala (148Asp/Glu APEX-23Gly/Ala XPA); while at the same time, risk was decreased for pairs Ile/Val-Asp/Asp (64Ile/Val APEX-148Asp/Glu APEX), Ile/Glu/Gly, and Ile/Val-Ala-Ala (64Ile/Val APEX-23Gly/Ala XPA) as well as Asp/Glu-Gly/Ala and Asp/Glu-Gly/Gly (148Asp/Glu APEX-23Gly/Ala XPA). In addition, worth noticing is the major impact of Asp/Glu genotype of 148Asp/Glu APEX gene when paired with all genotypes of 689Ser/Arg XPA, and similarly, Gly/Ala genotype again paired with all genotypes of 689Ser/Arg XPA.

3.3. Influence on Tumor Progression. In addition, we wanted to investigate potential correlation of our results with clinical data; therefore impact of presence of studied polymorphisms on progression of stage of tumor was tested, by a correlation of the distribution of genotypes with the state of tumor by the American Joint Committee on Cancer classification. Results are presented in Table 8. We found that 148Asp/Glu polymorphism of APEX gene and 23Gly/Ala polymorphism of XPA gene are increasing the risk of cancer in the second degree of advancement in relation to the first degree.

4. Discussion

All cells of the human body are constantly exposed to damaging agents, which can cause changes in the DNA. These changes, if not repaired, may lie at the basis of the process of carcinogenesis. To cope with these damages, the human body has developed a number of DNA repair mechanisms, including BER and NER systems. One of the key elements of BER is APEX gene product—class II AP endonuclease. Endonuclease cleaves the phosphodiester backbone 5’ to the AP site, thereby initiating a repair process [23]. Polymorphisms in APEX gene have been for a long time a subject of interest in the area of modulating risk of malignant transformation and many of them have been connected to several types of cancers such as lung cancer, breast cancer, or bladder cancer [24–28]. In the case of colorectal cancer, it has been estimated that APEX Asp148Glu is involved in increasing CRC risk [21, 29] which is consistent with our results. However, some researchers suggest that there is no association between increased cancer risk and the APEX Asp148Glu polymorphisms [20] or even that its occurrence decreases

Table 4: The distribution of genotypes and allele frequencies and the analysis of the odds ratio (OR) for 23Gly/Ala polymorphism of XPA gene in patients with colorectal cancer (CRC) and the control group.

| Genotype/allele | Patients (n = 310) | Controls (n = 304*) | OR (95% CI) | p |
|-----------------|-------------------|--------------------|--------------|---|
| Gly/Gly         | 31                | 95                 | 1 (ref)      |   |
| Gly/Ala         | 263               | 150                | 5.373        | <0.0001 |
| Ala/Ala         | 16                | 59                 | 0.831        | 0.597   |
| Gly             | 325               | 340                | 1 (ref)      |   |
| Ala             | 295               | 268                | 1.152        | 0.218   |

* Genotype distribution in the Hardy-Weinberg equilibrium, \( \chi^2 = 0.988 \). Values set in italics denote statistical significance.

Table 5: The distribution of genotypes and allele frequencies and the analysis of the odds ratio (OR) for 64Ile/Val polymorphism of APEX gene in patients with colorectal cancer (CRC) and the control group.

| Genotype/allele | Patients (n = 307) | Controls (n = 304*) | OR (95% CI) | p |
|-----------------|-------------------|--------------------|--------------|---|
| Ile/Ile         | 93                | 78                 | 1 (ref)      |   |
| Ile/Val         | 148               | 159                | 0.781        | 0.195   |
| Val/Val         | 66                | 67                 | 0.826        | 0.409   |
| Ile             | 334               | 315                | 1 (ref)      |   |
| Val             | 280               | 293                | 0.901        | 0.365   |

* Genotype distribution in the Hardy-Weinberg equilibrium, \( \chi^2 = 0.408 \).

Table 6: The distribution of genotypes and allele frequencies and the analysis of the odds ratio (OR) for 689Ser/Arg polymorphism of ERCC4 gene in patients with colorectal cancer (CRC) and the control group.

| Genotype/allele | Patients (n = 309) | Controls (n = 304*) | OR (95% CI) | p |
|-----------------|-------------------|--------------------|--------------|---|
| Ser/Ser         | 93                | 101                | 1 (ref)      |   |
| Ser/Arg         | 155               | 160                | 1.052        | 0.777   |
| Arg/Arg         | 61                | 43                 | 1.541        | 0.078   |
| Ser             | 341               | 362                | 1 (ref)      |   |
| Arg             | 277               | 246                | 1.195        | 0.123   |

* Genotype distribution in the Hardy-Weinberg equilibrium, \( \chi^2 = 0.107 \).
the risk—Brevik et al. report that carriers of the APEX codon 51 Gln/His genotype had a reduced CRC risk compared with carriers of the Gln/Gln genotype [30]. In contrast to these reports, we in our study found that Gln/His genotype increases the CRC risk. Similar differences can be observed in the case of NER system genes studied by us—23Gly/Ala of XPA gene is suggested to have no influence on risk of colorectal cancer [31, 32], while our results indicate the opposite (odds ratio (OR) 2.464 (1.247–4.870); p = 0.009) and similar increased risk of CRC in the case of co-occurrence of genotype 51Gln/His of APEX gene with 64Val/Val of APEX gene when compared to risk associated only with 51Gln/His (OR 2.266 (1.120–4.585); p = 0.002 versus 1.706 (1.174–2.480); p = 0.005) and similar increased risk of CRC in the case of co-occurrence of genotype 51Gln/His of APEX gene with 689Arg/Arg ERCC4 (OR 2.464 (1.247–4.870); p = 0.009 versus 1.706 (1.174–2.480); p = 0.005). Similar increased risk can also be seen in the case of pairs 51Gln/His APEX-148Asp/Glu APEX and 51Gln/His APEX-23Gly/Ala XPA; however, 148Asp/Glu APEX and 23Gly/Ala XPA also considered individually increased risk of CRC. That is why we want to pay special attention to the first two pairs (51Gln/His APEX-64Val/Val APEX and 51Gln/His APEX-689Arg/Arg ERCC4) in which only 51Gln/His APEX increases the risk, but in the case of coexistence with the aforementioned polymorphisms, this risk becomes even greater. In our opinion, this clearly indicates a much more advanced system of impact of polymorphisms on the risk of cancer than the effect of a SNP. It can also indicate the interaction of BER and NER systems in removing damage which has been suggested by other researchers [40].

### Table 7: The distribution of genotypes and the analysis of the odds ratio (OR) for gene-gene interactions in analyzed polymorphisms in patients with colorectal cancer (CRC) and the control group. Shown are only pairs that modulate the risk at a statistically significant level. All partial results for the gene-gene interaction are shown in the supplementary materials.

| Gene-gene interaction | Genotype                  | Patients | Controls | OR (95% CI)   | p   |
|-----------------------|---------------------------|----------|----------|---------------|-----|
| 51Gln/His APEX-64Ile/Val APEX | Gln/His-Val/Val           | 55       | 32       | 2.266 (1.120–4.585) | 0.022 |
|                       | Gln/His-Asp/Glu           | 174      | 102      | 2.003 (1.091–3.676) | 0.023 |
| 51Gln/His APEX-148Asp/Glu APEX | Gln/His-Glu/Glu           | 8        | 26       | 0.361 (0.137–0.951) | 0.036 |
|                       | His/His-Asp/Asp           | 6        | 28       | 0.252 (0.089–0.714) | 0.007 |
|                       | Gln/His-Gly/Gly           | 6        | 35       | 0.220 (0.078–0.622) | 0.003 |
| 51Gln/His APEX-23Gly/Ala XPA | Gln/His-Gly/Ala           | 193      | 98       | 2.532 (1.362–4.707) | 0.003 |
|                       | His/His-Gly/Ala           | 30       | 8        | 4.821 (1.835–12.670) | 0.001 |
| 51Gln/His APEX-689Ser/Arg ERCC4 | Gln/His-Arg/Arg          | 39       | 24       | 2.464 (1.247–4.870) | 0.009 |
| 64Ile/Val APEX-148Asp/Glu APEX | Ile/Val-Asp/Asp           | 10       | 27       | 0.403 (0.170–0.955) | 0.036 |
|                       | Val/Val-Asp/Glu           | 59       | 18       | 3.567 (1.765–7.211) | 0.0003 |
|                       | Ile/Val-Gly/Gly           | 9        | 37       | 0.269 (0.103–0.700) | 0.006 |
| 64Ile/Val APEX-23Gly/Ala XPA | Ile/Val-Ala/Ala           | 6        | 23       | 0.288 (0.097–0.859) | 0.022 |
|                       | Val/Val-Gly/Ala           | 62       | 14       | 4.895 (2.093–11.445) | 0.0001 |
|                       | Asp/Asp-Gly/Ala           | 26       | 58       | 0.399 (0.176–0.902) | 0.025 |
| 148Asp/Glu APEX-23Gly/Ala XPA | Asp/Glu-Gly/Gly          | 8        | 46       | 0.155 (0.056–0.424) | 0.0001 |
|                       | Asp/Glu-Gly/Ala           | 218      | 81       | 2.392 (1.164–4.915) | 0.015 |
|                       | Asp/Asp-Ser/Arg           | 21       | 48       | 0.844 (0.370–1.924) | 0.689 |
| 148Asp/Glu APEX-689Ser/Arg ERCC4 | Asp/Asp-Arg/Arg          | 13       | 13       | 1.929 (0.707–5.263) | 0.198 |
|                       | Asp/Glu-Ser/Ser           | 69       | 49       | 2.716 (1.293–5.704) | 0.007 |
|                       | Gly/Ala-Ser/Ser           | 76       | 57       | 2.333 (1.061–5.131) | 0.032 |
| 23Gly/Ala XPA-689Ser/Arg ERCC4 | Gly/Ala-Ser/Arg          | 135      | 77       | 3.068 (1.431–6.577) | 0.003 |
|                       | Gly/Ala-Arg/Arg           | 47       | 16       | 5.141 (2.073–12.749) | 0.0003 |

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It is also worth noting that the protective effect may have a pair in which none of the polymorphisms, when considered individually, showed no previous effect on the risk of CRC increasing nor decreasing it (64Ile/Val polymorphism of APEX). In addition, it should be also suspected that there can be whole set of variations in the predisposition to the occurrence of cancer.

Table 8: Analysis of correlation of selected polymorphisms with the state of tumor according to classification of American Joint Committee on Cancer.

| Genotype | Patients (n = 311) | II° versus I° | II° + IV° versus I° | II° + IV° versus II° |
|-----------|------------------|--------------|------------------|-------------------|
| I°        | OR (95% CI)      | p             | OR (95% CI)      | p                 |
| Gln/Gln   | 24 21 19 5       | 1 (ref)      | —                | 1 (ref)           |
| Gln/His   | 57 94 48 7       | 1.885 (0.963–3.690) | 0.062 | 0.965 (0.491–1.898) | 0.920 | 0.512 (0.261–1.004) | 0.049 |
| His/His   | 19 15 2 0        | 0.902 (0.369–2.209) | 0.823 | —                | —                | —                | —                |

| Genotype | Patients (n = 307) | II° versus I° | II° + IV° versus I° | II° + IV° versus II° |
|-----------|------------------|--------------|------------------|-------------------|
| I°        | OR (95% CI)      | p             | OR (95% CI)      | p                 |
| Ile/Ile   | 41 32 19 1       | 1 (ref)      | —                | 1 (ref)           |
| Ile/Val   | 64 51 28 5       | 1.021 (0.566–1.843) | 1.000 | 1.057 (0.536–2.086) | 0.862 | 1.035 (0.509–2.105) | 0.920 |
| Val/Val   | 33 17 14 2       | 0.660 (0.313–1.391) | 0.273 | 0.994 (0.446–2.215) | 1.000 | 1.506 (0.623–3.638) | 0.362 |

| Genotype | Patients (n = 309) | II° versus I° | II° + IV° versus I° | II° + IV° versus II° |
|-----------|------------------|--------------|------------------|-------------------|
| I°        | OR (95% CI)      | p             | OR (95% CI)      | p                 |
| Asp/Asp   | 29 17 5 0        | 1 (ref)      | —                | 1 (ref)           |
| Asp/Glu   | 98 133 5 1       | 2.315 (1.205–4.449) | 0.01 | —                | —                | —                | —                |
| Glu/Glu   | 16 5 0 0         | 0.533 (0.166–1.716) | 0.288 | —                | —                | —                | —                |

| Genotype | Patients (n = 310) | II° versus I° | II° + IV° versus I° | II° + IV° versus II° |
|-----------|------------------|--------------|------------------|-------------------|
| I°        | OR (95% CI)      | p             | OR (95% CI)      | p                 |
| Gly/Gly   | 17 9 5 0         | 1 (ref)      | —                | 1 (ref)           |
| Gly/Ala   | 87 165 9 2       | 3.582 (1.533–8.370) | 0.002 | —                | —                | —                | —                |
| Ala/Ala   | 11 5 0 0         | 0.859 (0.227–3.248) | 0.823 | —                | —                | —                | —                |

| Genotype | Patients (n = 309) | II° versus I° | II° + IV° versus I° | II° + IV° versus II° |
|-----------|------------------|--------------|------------------|-------------------|
| I°        | OR (95% CI)      | p             | OR (95% CI)      | p                 |
| Ser/Ser   | 49 31 9 4        | 1 (ref)      | —                | 1 (ref)           |
| Ser/Arg   | 83 52 16 4       | 0.990 (0.561–1.747) | 1.000 | 0.908 (0.415–1.986) | 0.806 | 0.795 (0.356–1.776) | 0.578 |
| Arg/Arg   | 32 24 3 2        | 1.186 (0.592–2.374) | 0.632 | 0.589 (0.192–1.811) | 0.351 | 0.431 (0.137–1.352) | 0.143 |

Values set in italics denote statistical significance.

XPA) where one of the polymorphisms previously increased the risk, so we can see a reversal of the trend. It is also worth noting that the protective effect may have a pair in which none of the polymorphisms, when considered individually, showed no previous effect on the risk of CRC increasing nor decreasing it (64Ile/Val APEX-23 Ala/Ala and 148Asp/Glu APEX-23 Gly/Gly XPA). Finally, we want to draw attention to the fact that genotype 148Asp/Glu APEX which itself increases the risk of CRC (OR 2.588 (1.736–3.859); p < 0.0001), when considered along with any polymorphism of 689Ser/Arg ERCC4 (Ser/Ser, Ser/Arg, or Arg/Arg), will always show a greater risk than alone (OR, resp., 2.716 (1.293–5.704), p = 0.007, 2.963 (1.467–5.985), p = 0.002, and 2.643 (1.171–5.965), p = 0.018). In our opinion, this confirms the thesis pronounced earlier that the gene-gene interactions are the main factor that may influence individual differences in the predisposition to the occurrence of cancer.

Given such a complicated set of factors and their mutual interactions that may cause malignant transformation, it should be also suspected that there can be whole set of various factors contributing to the progression of already formed tumor. In order to evaluate the impact of polymorphisms of analyzed genes on the progress of colorectal cancer, we have correlated the distribution of genotypes with the progress of the tumor according to the classification of the American Joint Committee on Cancer. Increased risk of CRC in the II° of advancement in relation to the I° was observed in the case of 148Asp/Glu polymorphism of APEX gene and 23Gly/Ala polymorphism of XPA gene (Table 8). The observed effect is consistent with the effect of the polymorphisms in the increased risk of disease onset, which may
suggest the relationship between specific genotypes and initiation and promotion of carcinogenesis as well as the progression of cancer and metastasis. This is in line with our earlier studies in which we presented similar thesis [38]. In our opinion, this allows not only to identify patients with an increased risk of cancer but also to identify within the group of patients already diagnosed with the disease to predict potential tumor growth and thus allows a more comprehensive approach to treating patients.

5. Conclusions

Genotypes 51Gln/His and 148Asp/Glu of APEX gene and 23Gly/Ala of XPA gene may increase the risk of CRC, while polymorphisms of 64Ile/Val of APEX gene and 689Ser/Arg of ERCC4 gene have no effect on modulating the risk. At the same time, gene-gene interactions may completely change the risk level; therefore, we advocate that they should be considered as very important factors when calculating the risk factor. Moreover, polymorphisms of BER and NER systems may not only initiate malignant transformation but also be able to contribute to tumor growth. We believe that our results are promising, yet further studies are needed on this subject to establish an incontestable link between a given polymorphism and its phenotypic effect in the modulation of BER and NER activity and thus its impact on carcinogenesis.

Conflicts of Interest

The authors declare no competing financial interests.

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