Impact of MDM2, TP53 and P14ARF Polymorphisms on Endometrial Cancer Risk and Onset

WIOLETTA WUCICKA¹,², AGNIESZKA ZAJĄC³ and GRZEGORZ STACHOWIAK³

¹Scientific Laboratory of the Center of Medical Laboratory Diagnostics and Screening, Polish Mother’s Memorial Hospital - Research Institute, Lodz, Poland;
²Department of Obstetrics, Perinatology and Gynecology, Polish Mother’s Memorial Hospital – Research Institute, Medical University of Lodz, Lodz, Poland;
³Department of Operative Gynecology and Gynecologic Oncology, Polish Mother’s Memorial Hospital - Research Institute, Lodz, Poland

Abstract. Background/Aim: The aim of this study was to determine the joint effect of single nucleotide polymorphisms (SNPs) of MDM2, TP53, and CDKN2A (P14ARF) genes on the onset and course of endometrial cancer (EC) in postmenopausal women. Materials and Methods: The study group consisted of 144 EC women and 50 non-cancer controls. MDM2 rs22279744, TP53 rs1042522, and P14ARF rs3088440, rs3731217, and rs3731245 SNPs were analysed. Results: The double-SNP combinations T-C, T-T, or T-G in MDM2 SNP 309 and P14ARF polymorphisms decreased EC risk. The triple-SNP combinations T-C-T, T-C-G, or T-T-G in MDM2 SNP and two P14ARF polymorphisms decreased EC risk. The multiple-SNP combination T-C-T-G in MDM2 and three P14ARF polymorphisms decreased EC risk. The G-Arg-C-T-G carriers were at increased EC risk, while the T-Arg-C-T-G carriers were at decreased EC risk. Conclusion: MDM2 SNP 309 plays a role in EC onset in postmenopausal women.

Endometrial cancer (EC) being the most common female reproductive tract carcinoma in the developed world, also among Polish women, has the highest prevalence among gynecological invasive neoplasms. EC accounts for about 7% of new female cancer cases (http://gco.iarc.fr/today/home).

There are several risk factors of EC. For example, EC risk was reported to be doubled in women having a first degree relative with EC (1). In recent years, EC research has focused on finding the genetic background of this cancer and on the determination of new genetic risk factors. It is estimated that our current knowledge about the genetic background of EC (e.g. high-risk pathogenic variants in mismatch-repair genes, PTEN, and DNA polymerase genes) explains less than 5% of the familial EC risk (2).

The newest data (meta-analysis of 12,906 EC cases and 108,979 controls) from genome-wide association studies (GWAS) report on the identification of nine novel genome-wide significant loci for EC (3). Using expression quantitative trait locus (eQTL) analyses five candidate causal genes were identified (3). Risk alleles at two of these loci were associated with decreased expression of genes encoding negative regulators of oncogenic signal transduction proteins, such as SH2B3 and NF1. GWAS were able to double the number of known EC risk loci, revealing candidate causal genes for future studies (3). Several meta-analyses have also confirmed the role of single nucleotide polymorphism (SNP) 309 located within the MDM2 gene, encoding E3 ubiquitin ligase, in EC tumorigenesis (4-7). In Japanese women with EC, the GG genotype in MDM2 SNP 309 was non-significantly associated with an increased risk of EC, while the complex GG-TG and Arg-Arg variants for both MDM2 and TP53 codon 72 polymorphisms, respectively, increased the risk significantly (8). Similarly, in Polish postmenopausal women, MDM2 SNP 309 GG and TP53 rs1042522 Arg-Arg genotypes, as well as the combined GG and Arg-Arg variants, have been reported to be associated with increased risk of EC (9-11). So far, alterations in p14ARF-MDM2-p53 tumor suppressor pathway have been reported to be associated with tumorigenesis of different cancers, including EC (12, 13). High expression of p53 accompanied by low
levels of MDM2 and p14ARF, have been shown to be possibly correlated with low differentiated primary EC (14). Furthermore, p14ARF expression correlated with histological grade and Ki-67 in EC (13). The expression of p14ARF was also associated with transtubal dissemination of the primary EC (12). However, there are still no data on the possible joint impact of the genetic changes located within all MDM2, TP53 and P14ARF genes on the onset and course of EC. In our previous work, the relationship between EC risk and specific SNPs of MDM2 and TP53 genes was demonstrated (11). In this present study, we aimed to take a reasonable next step in broadening our knowledge on the contribution of genetic factors to EC risk by adding to the analysis the genetic factor P14ARF, which functions in the cell cycle.

Materials and Methods

The study included multiple-SNP analysis performed on previously obtained data for MDM2 SNP309 rs22279744, TP53 rs1042522, as well as CDKN2A (P14ARF) rs3088440, rs3731217, and rs3731245 polymorphisms (9-11). In brief, genetic data were obtained for 194 postmenopausal women, including 144 (74.2%) individuals with EC, and 50 (25.8%) non-cancer control patients. The studied women were treated at the Department of Gynecology and Oncological Gynecology at the Polish Mother’s Memorial Hospital – Research Institute in Lodz, from 1997 to 2009 year. Patients were between 28 and 88 years old (the mean age was 59.1 years). Among them, the females with EC were at the age of 61.24±9.01 years, while the control individuals at the age of 53.06±4.75 years. The study was approved (approval number: 2/2016) by the Research Ethics Committee at the Polish Mother’s Memorial Hospital - Research Institute.

DNA extraction. Genomic DNA was extracted from archival paraffin-embedded endometrial tissues, using QIAmp Kit (Qiagen GmbH, Hilden, Germany) in the case of MDM2 and TP53 SNPs and Syngen FFPE DNA Micro Kit (Syngen Biotech, Wroclaw, Poland) in the case of P14ARF SNPs, according to manufacturer’s guidelines (9-11).

Genotypes within MDM2, TP53 and P14ARF polymorphisms. Genotypes of the studied MDM2 rs22279744, TP53 rs1042522, as well as P14ARF rs3088440, rs3731217, and rs3731245 SNPs, were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assays (9-11). Oligonucleotide sequences and PCR conditions performed in the study are presented in Table I. The obtained PCR products were digested overnight with endonucleases appropriate for the analysed polymorphic site, including MspA1I, BstUI, HaeIII, and MvaI, enzymes (Table II). The digestion products were resolved on 2% agarose gels, stained with ethidium bromide, to determine the genotype profiles of each polymorphism. In the case of P14ARF SNPs, sequencing of selected PCR products representative of distinct genotypes, was also performed, using Sanger’s method, to confirm PCR-RFLP results. The chromatograms obtained at the Genomed Joint-Stock Company (Warsaw, Poland) were analysed by the Sequence Scanner 1.0 (Applied Biosystems) program.

Statistical analysis. Distribution of genotypes within MDM2 rs22279744 and TP53 rs1042522 polymorphisms between postmenopausal women with EC and non-cancer controls, analysis for Hardy-Weinberg equilibrium, and association with the disease, have been determined previously (9-11). Additionally, multiple-SNP analysis for the relationship between distinct complex genotypes in MDM2 rs22279744, TP53 rs1042522, as well as P14ARF rs3088440, rs3731217, and rs3731245 SNPs, and the onset and course of EC in postmenopausal women, was performed by the Expectation Maximization (EM) algorithm, using the SNPStats software (https://www.snpstats.net/start.htm). The results were determined as statistically significant at the significance level of p≤0.05.

Results

Clinical characteristics of postmenopausal women. The rates of diabetes mellitus, arterial hypertension, body mass index (BMI), menopausal hormone therapy (MHT), and endometrial thickness among postmenopausal women with EC and non-cancer controls were determined. Diabetes mellitus was significantly more prevalent among patients with EC, as compared to women without cancer (19.0% vs. 0.0%, p≤0.05). Similarly, arterial hypertension was more prevalent among patients than controls (52.8% vs. 33.3%, p≤0.05). Regarding BMI, the mean values were significantly higher among patients than controls (30.25±6.25 kg/m^2 vs. 27.43±5.17 kg/m^2, p≤0.05). MHT had similar prevalence rates among women with EC and non-cancer individuals. Considering endometrial thickness, the values over 5 mm were significantly more frequent among women with EC as compared to controls (84.3% vs. 51.1%, p≤0.001).

Complex variants for MDM2 and P14ARF polymorphisms. Occurrence of EC among postmenopausal women with distinct complex variants for both MDM2 309 and CDKN2A (P14ARF) SNPs was determined (Tables III-V). Considering MDM2 SNP 309 and one of the analysed P14ARF SNPs, a significantly decreased risk for EC was observed among carriers of the combined double-SNP T-C (SNP309-rs3088440, OR=0.41, 95%CI=0.26-0.67, p≤0.001, Table III), T-T (SNP309-rs3731217, OR=0.53, 95%CI=0.34-0.83, p≤0.05), and T-G variants (SNP309-rs3731245, OR=0.50, 95%CI=0.33-0.76, p≤0.05). Taking into account MDM2 SNP and two of the studied P14ARF polymorphisms, decreased risk for disease was determined among carriers of the combined triple-SNP T-C-T (SNP309-rs3088440-rs3731217, OR=0.45, 95%CI=0.27-0.76, p≤0.05, Table IV), T-C-G (SNP309-rs3088440-rs3731245, OR=0.42, 95%CI=0.26-0.69, p≤0.001), and T-T-G variants (SNP309-rs3731217-rs3731245, OR=0.55, 95%CI=0.35-0.86, p≤0.05). Moreover, among multiple-SNP variants for MDM2 and all the three P14ARF polymorphisms, the carriers of T-C-T-G combined genotype in SNP309-rs3088440-rs3731217-rs3731245 SNPs, were also at significantly decreased risk for EC (OR=0.46
95% CI = 0.27–0.79, \( p \leq 0.05 \), Table V). Considering clinical data, the analysed combined variants were distributed similarly between the studied postmenopausal women.

Multiple-SNP variants for MDM2, TP53 and P14ARF polymorphisms. Multiple-SNP analysis performed for all the studied MDM2 SNP309, TP53 rs1042522, and P14ARF rs3088440, rs3731217, and rs3731245 SNPs, showed that the carriers of G-Arg-C-T-G genotype had a significantly increased risk for EC (OR = 2.61, 95% CI = 1.06–6.43, \( p \leq 0.05 \)), while the carriers of T-Arg-C-T-G genotype had a significantly decreased risk for the disease (OR = 0.42, 95% CI = 0.19–0.93, \( p \leq 0.05 \), Table VI). Similar prevalence rates of the studied combined genotypes were estimated for patients with various clinical characteristics.

Table I. Primer sequences, annealing temperatures and PCR products obtained in the assays for genotyping of the polymorphisms located within MDM2, TP53 and P14ARF genes.

| Gene  | GenBank Accession No. | SNP name | Oligonucleotide sequences (5’-3’) | Annealing temperature (°C) | Amplicon length (bps) |
|-------|-----------------------|----------|----------------------------------|---------------------------|----------------------|
| MDM2  | NC_000012.12          | rs2279744| For: CGCGGGAGTTCAAGGGTAAG        | 62                        | 237                  |
|       |                       |          | Rev: AGCTGGAGCAAGTCAGGACCTAAC     |                           |                      |
|       |                       |          | MspAI                            |                           |                      |
| TP53  | NC_000017.11          | rs1042522| For: TTCCACCCTCTCACAGTCC          | 62                        | 309                  |
|       |                       |          | Rev: CTCAGGGGCACTGACCGT           |                           |                      |
| P14ARF| NC_000009.12          | rs3088440| For: TGCTCACTCCAGAAGAACCTC       | 55                        | 356                  |
|       |                       |          | Rev: ATGGGCCACACATCTTTTGACC       |                           |                      |
|       |                       |          | BstUI                             |                           |                      |
|       |                       |          | Arg: 175, 134                     |                           |                      |
|       |                       |          | Arg-Pro: 309, 175, 134            |                           |                      |
|       |                       |          | Pro: 309                          |                           |                      |
|       |                       |          | HaeIII                            |                           |                      |
|       |                       |          | CC: 142, 39                       |                           |                      |
|       |                       |          | CT: 181, 142, 39                  |                           |                      |
|       |                       |          | TT: 181                           |                           |                      |
|       |                       |          | MspAI                             |                           |                      |
|       |                       |          | TT: 237                           |                           |                      |
|       |                       |          | TG: 237, 189, 48                  |                           |                      |
|       |                       |          | GG: 189                           |                           |                      |
|       |                       |          | BstUI                             |                           |                      |
| P14ARF| NC_000009.12          | rs3731217| For: CAGGTGAAGAATGTGATTTGG        | 55                        | 500                  |
|       |                       |          | Rev: CAAGTGGAAGGTACAGGAG          |                           |                      |
|       |                       |          | BstUI                             |                           |                      |
|       |                       |          | Arg: 175, 134                     |                           |                      |
|       |                       |          | Arg-Pro: 309, 175, 134            |                           |                      |
|       |                       |          | Pro: 309                          |                           |                      |
|       |                       |          | HaeIII                            |                           |                      |
|       |                       |          | CC: 142, 39                       |                           |                      |
|       |                       |          | CT: 181, 142, 39                  |                           |                      |
|       |                       |          | TT: 181                           |                           |                      |
|       |                       |          | MspAI                             |                           |                      |
|       |                       |          | TT: 237                           |                           |                      |
|       |                       |          | TG: 237, 189, 48                  |                           |                      |
|       |                       |          | GG: 189                           |                           |                      |
|       |                       |          | BstUI                             |                           |                      |

Table II. Restriction endonucleases and genotypic profiles used in PCR-RFLP assays.

| Gene  | Polymorphism | Restriction enzyme | Profile (bps) |
|-------|--------------|--------------------|---------------|
| MDM2  | rs2279744    | MspAI              | TT: 237       |
|       |              |                    | TG: 237, 189, 48 |
|       |              |                    | GG: 189       |
| TP53  | rs1042522    | BstUI              | Arg: 175      |
|       |              |                    | Arg-Pro: 309, 175, 134 |
|       |              |                    | Pro: 309      |
| P14ARF| rs3088440    | HaeIII             | CC: 142       |
|       |              |                    | CT: 181, 142, 39 |
|       |              |                    | TT: 181       |
|       | rs3731217    | MvaI               | TT: 280       |
|       |              |                    | TG: 280, 154, 126 |
|       |              |                    | GG: 154, 126  |
|       | rs3731245    | HaeIII             | AA: 195       |
|       |              |                    | AG: 195, 123, 72 |

Discussion

In the current study, MDM2 SNP309, TP53 SNP rs1042522, as well as three polymorphisms of P14ARF were found to be jointly involved in the occurrence of EC. The simultaneous presence of MDM2 SNP and distinct one, two, or three P14ARF polymorphisms, decreased EC risk. In various combined genotypes that included double-, triple- or multiple-SNPs for MDM2 and P14ARF, the occurrence of the T allele within MDM2 SNP309, and the C allele – within P14ARF rs3088440, the T allele – in rs3731217, as well as the G allele – in rs3731245 polymorphic sites, was related to diminished risk of EC. A previous study on Polish postmenopausal women with EC has reported that the GG homozygotes as well as the G allele in MDM2 SNP309 is significantly associated with the occurrence of EC (9). Additionally, the single-SNP analysis, performed previously at the Polish Mother’s Memorial Hospital – Research Institute, on the relationship between the genotypic status of P14ARF polymorphisms and the risk of EC in postmenopausal women, has shown that the CT and TT genotypes, as well as the T allele within rs3088440 are significantly associated with
EC. In turn, the TG heterozygotes and TG-GG variants in rs3731217 were correlated with a decreased risk for EC. Considering other cancers, the presence of the GG genotype or G allele within MDM2 SNP309, have also been reported to be associated with an increased risk of esophageal squamous cell carcinoma or estrogen receptor-positive breast cancer, respectively (15, 16). Similarly to our outcomes, a meta-analysis performed for 27 case-control studies on the role of MDM SNP309 in gynecological cancers, has shown that the TT homozygotes, as well as the T allele within the polymorphism, are associated with decreased risk of disease (6). The additional analysis determined that the relationship stayed significant for EC (6). Other meta-analyses also have shown that the GG genotype, as well as the G allele are associated with increased risk of EC (4, 5, 7). In the case of P14ARF, similarly to our outcomes, the genotypes GA and AA within rs3088440 have been shown to be associated with an increased risk of squamous cell carcinoma of the head and neck, and the T allele with an increased risk of melanoma (17, 18). The polymorphism rs3731217 of P14ARF has been reported to be correlated with ALL in Caucasians, and the G allele to be protective against paediatric B-cell precursor ALL.

### Table III. Relationship between the most common double-SNP combinations for MDM2 and P14ARF polymorphisms and the occurrence of endometrial cancer.

| Alleles in MDM2 and P14ARF SNPs | Prevalence of double-SNP variants | OR (95%CI) | p-Value |
|----------------------------------|----------------------------------|------------|---------|
|                                  | Endometrial cancer | Non-cancer controls |
| rs3088440                         | | | |
| G                                 | C                      | 0.609 | 0.458 | 1.00 |
| T                                 | C                      | 0.197 | 0.442 | 0.41 (0.26-0.67) | ≤0.001 |
| G                                 | T                      | 0.133 | 0.062 | 1.24 (0.55-2.77) | 0.610 |
| T                                 | T                      | 0.062 | 0.038 | 1.31 (0.43-4.01) | 0.630 |
| rs3731217                         | | | |
| G                                 | T                      | 0.695 | 0.472 | 1.00 |
| T                                 | T                      | 0.259 | 0.428 | 0.53 (0.34-0.83) | 0.006 |
| G                                 | G                      | 0.046 | 0.048 | 0.71 (0.22-2.32) | 0.570 |
| rs3731245                         | | | |
| G                                 | G                      | 0.713 | 0.520 | 1.00 |
| T                                 | G                      | 0.255 | 0.480 | 0.50 (0.33-0.76) | 0.002 |

SNPs: Single nucleotide polymorphisms; OR: odds ratio; 95%CI: confidence interval; logistic regression model; p≤0.05 is considered significant; global double-SNP variants association p-value was estimated to be ≤0.001.

### Table IV. Association of the most common triple-SNP combinations for MDM2 and P14ARF polymorphisms with the occurrence of endometrial cancer.

| Alleles in MDM2 and P14ARF SNPs | Prevalence of triple-SNP variants | OR (95%CI) | p-Value |
|----------------------------------|----------------------------------|------------|---------|
|                                  | Endometrial cancer | Non-cancer controls |
| rs3088440-rs3731217              | | | |
| C-T                              | 0.566 | 0.409 | 1.00 |
| T-C                              | 0.197 | 0.392 | 0.45 (0.27-0.76) | 0.003 |
| G-T                              | 0.133 | 0.062 | 1.16 (0.51-2.61) | 0.730 |
| T-T                              | 0.057 | 0.038 | 1.13 (0.38-3.41) | 0.830 |
| G-G                              | 0.043 | 0.049 | 0.64 (0.20-2.13) | 0.470 |
| rs3088440-rs3731245              | | | |
| C-G                              | 0.584 | 0.458 | 1.00 |
| T-C                              | 0.194 | 0.442 | 0.42 (0.26-0.69) | ≤0.001 |
| G-G                              | 0.129 | 0.062 | 1.26 (0.55-2.86) | 0.580 |
| T-G                              | 0.062 | 0.038 | 1.39 (0.45-4.25) | 0.570 |
| rs3731217-rs3731245              | | | |
| T-G                              | 0.668 | 0.472 | 1.00 |
| T-G                              | 0.255 | 0.428 | 0.55 (0.35-0.86) | 0.009 |
| G-G                              | 0.045 | 0.048 | 0.70 (0.21-2.31) | 0.560 |

SNPs: Single nucleotide polymorphisms; OR: odds ratio; 95%CI: confidence interval; logistic regression model; p≤0.05 is considered significant. 

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Allele in rs3731217, has been found to be distributed similarly among endometrial cancer. GA genotypes of rs3731245 have been shown to be associated with an increased risk of small vessel subtype of cancerous and non-cancerous patients (21). In turn, among Tunisian children with ALL, the T allele in rs3731245 has been found to be distributed similarly among cancerous and non-cancerous patients (21). The GG-GA genotypes of rs3731245 have been shown to be associated with an increased risk of small vessel subtype of cancerous and non-cancerous patients (21).

Table V. Relationship between the most common multiple-SNP combinations for MDM2 and P14ARF polymorphisms and the occurrence of endometrial cancer.

| Alleles in MDM2 and P14ARF SNPs | Prevalence of multiple-SNP variants | OR (95%CI) | p-Value |
|----------------------------------|------------------------------------|------------|--------|
|                                  | Endometrial cancer | Non-cancer controls |
| MDM2 rs2279744 | P14ARF rs3088440 | P14ARF rs3731217 | P14ARF rs3731245 |
| G     | C     | T     | G     | 0.543 | 0.409 | 1.00 |
| T     | C     | T     | G     | 0.194 | 0.392 | 0.46 (0.27-0.79) | 0.005 |
| G     | T     | T     | G     | 0.130 | 0.062 | 1.18 (0.51-2.70) | 0.700 |
| T     | T     | T     | G     | 0.057 | 0.038 | 1.20 (0.40-3.62) | 0.750 |
| G     | C     | G     | G     | 0.041 | 0.049 | 0.64 (0.19-2.12) | 0.470 |

SNPs: Single nucleotide polymorphisms; OR: odds ratio; 95%CI: confidence interval; logistic regression model; p≤0.05 is considered significant; global multiple-SNP variants association p-value was estimated to be ≤0.0001.

Table VI. The most common multiple-SNP combinations for the polymorphisms of MDM2, TP53 and P14ARF genes and the occurrence of endometrial cancer.

| Alleles within MDM2, TP53 and P14ARF SNPs | Prevalence of multiple-SNP variants | OR (95%CI) | p-Value |
|------------------------------------------|------------------------------------|------------|--------|
|                                         | Endometrial cancer | Non-cancer controls |
| MDM2 rs2279744 | TP53 rs1042522 | P14ARF rs3088440 | P14ARF rs3731217 | P14ARF rs3731245 |
| G     | Pro   | C     | T     | G     | 0.283 | 0.316 | 1.00 |
| G     | Arg   | C     | T     | G     | 0.261 | 0.094 | 2.61 (1.06-6.43) | 0.038 |
| T     | Pro   | C     | T     | G     | 0.130 | 0.217 | 0.74 (0.36-1.51) | 0.410 |
| T     | Arg   | C     | T     | G     | 0.062 | 0.173 | 0.42 (0.19-0.93) | 0.035 |
| G     | Arg   | T     | T     | G     | 0.069 | 0.030 | 1.83 (0.40-8.36) | 0.440 |
| G     | Pro   | T     | T     | G     | 0.061 | 0.031 | 1.69 (0.43-6.63) | 0.450 |
| G     | Pro   | C     | G     | G     | 0.033 | 0.035 | 0.87 (0.23-3.26) | 0.840 |
| T     | Pro   | T     | T     | G     | 0.035 | 0.015 | 1.98 (0.30-13.03) | 0.480 |
| T     | Arg   | T     | T     | G     | 0.023 | 0.023 | 1.36 (0.18-10.15) | 0.760 |

SNPs: Single nucleotide polymorphisms; OR: odds ratio; 95%CI: confidence interval; logistic regression model; p≤0.05 is considered significant.

(19, 20). In turn, among Tunisian children with ALL, the T allele in rs3731217, has been found to be distributed similarly among cancerous and non-cancerous patients (21). The GGA-GA genotypes of rs3731245 have been shown to be associated with an increased risk of small vessel subtype of ischemic stroke, while the GA-AA genotypes - with reduced risk of chronic benzene poisoning (22, 23). Taking into account the functional role of both MDM2 and p14ARF in cell cycle regulation, the N-terminal domain of p14ARF has been reported to inhibit the function of the C-terminal domain of MDM2, therefore inhibiting its ubiquitin ligase activity (13). The MDM2 protein has also been shown to inhibit the function of p53 tumor suppressor protein, by hiding its activation domain, and by inducing its degradation by the ubiquitin-proteasome pathway (24-26). Therefore, the interaction of MDM2 with p14ARF, has been associated with the activation of p53 pathway by preventing its polyubiquitination, nuclear export, and cytoplasmic degradation (25, 27). In the current genetic study, the joint impact of polymorphisms in MDM2, TP53 and P14ARF genes on the onset of EC is presented. Combined genotypes including the G allele within MDM2 SNP309, the Arg allele in TP53 rs1042522 SNP, and the C-T-G alleles within P14ARF rs3088440-rs3731217-rs3731245 polymorphisms, respectively, were correlated with an increased risk of EC. However, the genotypes including the T allele in MDM2 polymorphism were correlated with decreased risk of the cancer. So far, the presence of the G allele in MDM2 SNP 309 located in the first intron of the gene, has been reported to increase the affinity of the transcription activator Sp1 to its promoter, resulting in elevated levels of MDM2 mRNA and protein, followed by attenuation of the p53 pathway (6, 28). In case of the TP53 gene exon 4 codon 72 Arg>Pro polymorphism (rs1042522), the presence of the Arg allele has been suggested to be seven times more susceptible to E6-mediated ubiquitin-dependent proteolysis as compared to Pro variant (29, 30). Regarding
EC, previous studies have also confirmed the increased risk of cancer for both the Arg allele in TP53 rs1042522, as well as the combination GG and Arg-Arg variants in MDM2 and TP53 SNPs (10, 11). The C allele of P14ARF rs3088440 has been found to be associated with the repression of CDKN2A, while the A allele with an impaired binding of miR-663b to the CDKN2A 3’UTR, and therefore with elevated expression of p14/p16 proteins (31-34). The P14ARF rs3731217 polymorphism has been suggested to regulate the alternative splicing of CDKN2A, and the G allele to be related with higher levels of CDKN2A (35). In turn, the rs3731245 polymorphism of P14ARF, located in the first intron of the gene, has been reported to possibly stay in linkage disequilibrium with other functional polymorphisms of the genomic region of CDKN2A or with intron-based transcription regulators, placed in the first intron (22). Considering our results from the multiple-SNP analysis performed for all the studied MDM2, TP53, and P14ARF polymorphisms, the genotype of MDM2 SNP309 out of other SNPs analysed, seems to be the major factor determining the onset of EC in postmenopausal women. Among the studied Polish women, the presence of the G allele in MDM2 polymorphism may be associated with compromised p53 pathway, therefore increasing the risk of EC, while the T allele might decrease expression of the encoded MDM2. The E3 ubiquitin ligase may then be bound by p14ARF, enabling the tumor suppressor function of p53, and resulting in decreased risk of cancer. To the best of our knowledge, this is the first report on the joint effect of MDM2 SNP309, TP53 rs1042522, and three P14ARF polymorphisms on the onset of EC in postmenopausal women. Further studies to confirm and elucidate the role of the genetic changes within MDM2, TP53 and P14ARF in EC tumorigenesis are required.

Conflicts of Interest

The Authors have no conflict of interest to disclose regarding this study.

Authors’ Contributions

Wioletta Wujcicka: Design and performance of genetic research, data collection and management, data analysis and interpretation, manuscript writing and editing, final approval of the submitted version of manuscript; Agnieszka Zając: Conception, data collection, revising the article, final approval of the submitted version of manuscript; Grzegorz Stachowiak: Project development, data collection and management, interpretation of data, manuscript writing and editing, final approval of the submitted version of manuscript.

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Received January 28, 2019
Revised March 1, 2019
Accepted March 4, 2019