ABSTRACT

**Backgrounds:** Somatic and germline mutations in the TP53 gene are one of the most frequent alterations in human. The aim of this study was to evaluate the association between TP53 gene polymorphisms (c.[215G>C]) and predisposition to family cancers.

**Methods and Material:** We reviewed the medical records of 89 (21% TP53 gene homozygotes and 79% heterozygotes) breast cancer patients who were diagnosed and treated in COI in Gliwice. The history of family cancers was collected from medical history. Genetic diagnostics was conducted in years 2012 – 2016.

**Results:** Cancers in family history were detected in 72% of pts with TP53 polymorphisms and they were observed insignificantly more often in heterozygotes than in homozygotes (59% vs. 13%, p=0.161). Renal cancers in family were detected more frequently in TP53 breast cancer homozygotes than in heterozygotes (16% vs. 0, p=0.03). Similarly, there was also observed tendency to the presence of liver cancer (5% vs. 1.5%, p=0.391) in TP53 homozygotes. In contrary, colorectal (13% vs. 0, p=0.196), ovarian (6% vs. 0, p=0.572), breast (26% vs. 6%, p=0.592) and lung cancer (4% vs. 0%, p=0.472) in family were observed insignificantly more often in heterozygotes.

**Conclusion:** TP53 polymorphism predisposed to development renal and liver cancers (TP53 homozygotes) and breast, ovarian and colorectal (TP53 heterozygotes) in family.

**Keywords:** TP53 gene polymorphisms, breast cancer, family cancers.
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35% [11]. This functional polymorphism leads to incorporation of either a proline (CCC, P72) or arginine (CGC, R72) in the amino acid sequence [12]. Some studies have investigated the role of functional Arg72Pro polymorphism in modulation of cancer risk. As indicated by several meta-analyses, Arg72Pro variant has been observed to be involved in susceptibility to breast, lung, colorectal cancer, prostate and gastric cancer [13, 14, 15, 17, 18, 19, 20].

The aim of this study was to evaluate the association between TP53 gene polymorphisms (c.[215G>C]) and predisposition to family cancers in TP53 homozygotes and heterozygotes.

MATERIAL AND METHODS

A retrospective analysis was conducted on the medical records of 89 (21% TP53 gene homozygotes and 79% heterozygotes) breast cancer patients who were diagnosed and treated with chemotherapy, hormonotherapy and/or immunotherapy at Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch in Poland (COI). Genetic diagnostics was conducted in years 2012–2016. All patients (pts) gave written informed consent for genetic examination. The patients were Caucasian women from the southern part of Poland-Silesian region. The median age at diagnosis of patients was 52 years (range from 32 to 76). All of them were in good performance status (ZUBROD 0-1). The complete characteristics of patients with regard to demographic and clinicopathological features are presented in Table 1.

Clinical evaluation included physical examination, blood test, chest X ray, mammography, ultrasound breast exam, breast MRI and tumor core biopsy. The data on the age at onset, overweight, comorbid conditions, menopausal status, the history of cigarette smoking, surgical procedure, disease stage according to TNM classification, histology, estrogen and progesterone receptor status, HER2 status and contralateral breast cancer were gathered from hospital records and pathology reports. The history of family cancers was collected from medical history. The analysis of patients’ medical records was performed according to the national law regulation. Hormone status, HER2 overexpression and Ki-67, was determined by routine immuno-histochemical techniques. Mutation profile was assessed by RFLP-PCR technique. We evaluated the presence of polymorphism TP53 (c.[215G>C]).

Statistical analysis was carried out using STATISTICA 7 software. The frequency of side effects appearance was counted. The qualitative features were presented as the percentage of their occurrence and evaluated with Fisher test.

Table 1. Clinicopathological characteristics of the patients according to TP53 gene polymorphisms (c.[215G>C]).

<table>
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and Chi 2 test with Yates correction. Differences were considered as significant if the p value was ≤ 0.05.

RESULTS

Cancers in family history were detected in 72% of pts with TP53 polymorphisms and they were observed insignificantly more often in heterozygotes than in homozygotes (59% vs. 13%, p=0.161). The most frequently reported cancers were: breast cancer (33%), lymphoma (17%), colorectal cancer (9%), CNS tumor (8%), pancreatic cancer (7%), gastric cancer (6%), ovarian cancer (6%), renal cancer (5%), bone cancer (5%), lung cancer (4%) and liver cancer (2%).

In the analyzed group, renal cancers in family were detected more frequently in TP53 breast cancer homozygotes than in heterozygotes (16% vs. 0, p=0.03). Similarly, there was also observed a tendency to the presence of liver cancer (5% vs. 1.5%, p=0.391) in TP53 homozygotes in comparison to heterozygotes. On the contrary, colorectal cancer (13% vs. 0, p=0.196) was observed more frequently in heterozygotes in comparison to homozygotes. Similarly, ovarian cancers (6% vs. 0, p=0.572), breast (26% vs. 6%, p=0.592) and lung cancer (4% vs. 0%, p=0.472) in family were observed insignificantly more often in heterozygotes than in homozygotes. There was no association between gastric carcinoma (5% vs. 6%, p=1.00), bone cancer (5% vs. 4.5%, p=1.00), lymphomas (16% vs. 16%, p=1.00), CNS tumors (6% vs. 5%, p=1.00) and TP53 polymorphism (c.[215G>C]) (Table 2). There was no association between the number of cancers in the family and TP53 polymorphisms (47% vs. 43%, p=0.797).

Clinicopathological analysis was conducted (Table 1, Table 2). Lymph node infiltrations were observed more frequently in TP53 homozygotes in comparison to heterozygotes (53% vs. 34%, p=0.182). Similarly, there was reported a tendency to higher Ki67% (>20%) in TP53 homozygotes than heterozygotes (69% vs 46%, p=0.209). TNBC was also detected insignificantly more often in homozygotes (21% vs. 15%, p=0.495). On the contrary, higher tumor size (16% vs. 5%, p=0.450) and HER2 over expression (31% vs. 16%, p=0.568) were reported insignificantly more frequently in TP53 heterozygotes than in homozygotes. There was observed no association between TP53 polymorphisms and tumor histological grade (38% vs. 36%, p=1.00) or hormonal status (74% vs. 75%, p=1.00) in our study.

DISCUSSION

In this retrospective study, TP53 gene homozygotes of breast cancer patients significantly predisposed to the development of kidney cancer in the family members (16% vs. 0, p=0.03). Breast (26% vs. 6%, p=0.592), ovarian (6% vs. 0, p=0.572) and colorectal cancer (13% vs. 0, p=0.196) developed more often in family members of TP53 breast cancer heterozygotes.

P53 codon 72 polymorphisms have also been studied for many cancers. In several meta analyses, Arg72Pro variant has been observed to be involved in susceptibility to breast, prostate, lung, bladder, colorectal and gastric cancers but not cervical cancer [13, 14, 15, 16, 20]. Gonçalves et al found a significant association between the R72P polymorphism (P allele dominant model) in the TP53 gene and the breast cancer risk [29]. In Bangladeshi women mutant homozygous (Pro/Pro) genotype was significantly increased in breast cancer patients as compared with controls and showed 2.52-fold significantly increased risk for breast cancer (OR 2.5199, 95% CI 1.19–5.33, p = 0.0157) [30]. Similarly the association of the TP53 gene polymorphisms Arg72Pro and breast cancer was described for Croatian women and North Indians [31, 32]. In our analysis, there was observed a tendency to the presence of breast cancer in family history of TP53 polymorphisms carriers (heterozygotes) (26% vs. 6%, p=0.592).

A number of studies have reported the role of p53 codon 72 polymorphisms in gastric cancer. Zhou et al have reported in their meta analysis that the p53 codon 72 polymorphism may be associated with gastric cancer among Asians, and that difference in genotype distribution may be associated with the location, stage, and histological differentiation of gastric cancer [14]. Ezzikouri et al. evaluated the association between the TP53 codon 72 polymorphism and hepatocellular carcinoma (HCC) in a Moroccan population. In their study the patients with HCC had a higher frequency of Pro72 homozygosity (13.5% vs. 6.3%, P<0.02) in comparison to the control group and resulted in a 2.3-fold increased risk of liver cancer development [28]. In our group, there was also observed a tendency to the presence of liver cancer (5% vs. 1.5%, p=0.391) in TP53 homozygotes in comparison to heterozygotes. Gastric and...
colorectal cancer was observed in 6% and 9%, respectively. Colorectal cancer (13% vs. 0, p=0.196) was observed more frequently in heterozygotes in comparison to homozygotes. On the contrary, we observed a tendency to the presence of liver cancer (5% vs. 1.5%, p=0.391) in TP53 homozygotes in comparison to heterozygotes. There was no association between gastric carcinoma (5% vs. 6%, p=1.00) and the p53 codon 72 polymorphism.

Patients with the p53 Pro/Pro genotype have been reported to be more likely to develop lung cancer (especially smokers), and to have slightly worse outcomes [20, 21]. An association between the Pro/Pro genotype of the TP53 codon 72 polymorphism and lung cancer has been reported by Jin et al [25]. In another study, it was shown that the TP53 Pro72 allele was associated with an increasing frequency of TP53 mutations in NSCLC (non-small cell lung cancer), but no association was found for this polymorphism with lung cancer disease risk or prognosis [26]. In our study, lung cancers in family were observed insignificantly more often in heterozygotes than in homozygotes (4% vs. 0%, p=0.472).

In Klug et al study no association was found between cervical cancer and TP53 codon 72 polymorphism [22]. The Pro72 allele occurred more frequently in patients with chronic myeloid leukemia (CML) than in the control group among CML patients who had no cytogenetic response [27]. We did not observe cervical cancer in the family of TP53 polymorphisms carriers. Ovarian cancers in family were detected insignificantly more often in heterozygotes than in homozygotes (6% vs. 0, p=0.572). There was no association between lymphomas (16% vs. 16%, p=1.00) and TP53 polymorphism (c.[215G>C]).

In Yang analysis, TP53 Arg/Arg genotype was significantly increased in ESCC (esophageal squamous cell carcinoma n=435) cases compared with the control group (n=550) from the same geographical region (85.7 vs. 49.6%, P<0.001), resulting in an elevated ESCC risk (OR = 6.48, 95% CI = 4.65–9.03). The TP53 Arg/Arg homozygosity, HPV infection, smoking, and alcohol using may synergistically increase the risk of ESCC development [23]. The significantly higher frequency of Arg72 homozygotes was also detected in a group of 77 patients with advanced HNSCC (squamous cell carcinoma of the head and neck) [24]. In our study there was no HNSCC reported in family history.

In Wu et al study, allelic distributions of the three genotypes (Arg/Arg, Arg/Pro, Pro/Pro) in patients with renal cell carcinoma (29.4%, 55.3%, 15.3%), urothelial cancers (45.7%, 39.7%, 14.6%), testicular cancer (45.4%, 48.5%, 6.1%) or prostate cancer (42.9%, 50.0%, 7.1%) did not differ significantly from those in the normal controls. The association of genetic predisposition to urologic cancers with p53 gene codon 72 polymorphism in this analysis was not clear but this polymorphism may play some role in urothelial cancers and renal cell carcinoma [33]. In another study, p53 expression on primary RCC was linked to metastatic risk (X² = 6.96, p < 0.01) [34]. In our analyzed group, renal cancers in family were detected more frequently in TP53 breast cancer homozygotes than in heterozygotes (16% vs. 0, p=0.03). Renal cancers in family history were detected in 5% of pts with TP53 polymorphisms.

CONCLUSION

The presence of TP53 polymorphism (c.[215G>C]) (homozygotes and heterozygotes) has been associated with an increased risk of cancer in the family, especially renal, breast and colorectal cancer. TP53 gene homozygotes of breast cancer patients significantly predisposed to the development of kidney cancer in the family members. Breast, ovarian and colorectal cancer developed more often in family members of TP53 breast cancer heterozygotes. TP53 gene homozygotes were characterized by lobular invasive carcinoma subtype, lymph node metastases and higher Ki67 (>20%). On the contrary, a larger tumor size (T>2), HER2 overexpression, cancer in the family history and diabetes were mostly present in TP53 gene heterozygotes. Large, well – controlled studies are needed to establish the full range of risk associated with TP53 polymorphisms gene and predisposition to family cancer.

REFERENCES

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