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Polymorphisms of codon 72 of the TP53 gene in endometrial carcinoma of postmenopausal women

Polimorfizm kodonu 72 genu TP53 w raku endometrium u kobiet po menopauzie

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Introduction: The aim of this study was to detect TP53 Arg72Pro polymorphism in postmenopausal patients with endometrial cancer (EC), to evaluate the risk of EC connected with it, as well to check for possible relationships with staging, grading and some risk factors of this neoplasm.

Material and methods: Endometrial samples from 152 women with EC and from 50 cancer-free ones were taken for genetic evaluation to detect TP53 codon 72 variability using PCR–RFLP technique.

Results: The EC group was characterized by higher incidence of Arg/Arg genotype (OR=3.01) as well as lower incidence of Pro/Arg and the Pro allele (OR=0.33 and 0.48). There were no characteristic features linking EC grading and staging with the studied polymorphisms except for stage II with higher incidence of Arg/Arg (OR=4.25) and the Arg allele (OR=1.13), and grade 2 with higher incidence of Arg/Arg (OR=4.49) and lower incidence of the Pro allele (OR=0.22). Overweight and obese EC subgroups revealed higher incidence of Arg/Arg (OR=4.81 and 2.76) and lower incidence of the Pro allele (OR=0.21 and 0.36) compared to controls. The EC subgroup with arterial hypertension had higher incidence of Arg/Arg (OR=3.30) as well as lower incidence of Pro/Arg (OR=0.47) and the Pro allele (OR=0.37) – these differences were more pronounced than in the normotensive EC subgroup.

Conclusion: While Arg/Arg genotype is connected with increased and Pro/Arg and the Pro allele with decreased EC risk, we suppose that evaluation of TP53 codon 72 polymorphism may be of prognostic value, being useful for the prophylaxis of EC as well. Obesity and arterial hypertension seem to affect this polymorphism distribution.

Keywords: TP53 gene • endometrial carcinoma • menopause

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Introduction

Endometrial carcinoma (EC) is a neoplasm which is typical for the menopausal period – its morbidity is related to postmenopausal age (maximum ranging between 55 and 70 years), with the main risk factors (obesity, arterial hypertension, diabetes mellitus) frequently observed after menopause. Unfortunately, none of the available diagnostic tools – transvaginal sonography, Pipelle biopsy, dilation and curettage (D&C) or hysteroscopy – allows for early detection of pre-cancer endometrial pathology, and none fulfils the criteria of a screening method for this kind of neoplasm. Additionally, most of them are invasive procedures increasing the risk of iatrogenic complications, generating excessive costs for our health care system (the number of newly detected cancer cases is too low as compared with the number of the procedures being performed). The observed increase in EC morbidity is another reason to search for new, better diagnostic methods – including genetic tests – of detection of very early-stage endometrial anomalies, which is a trend of great importance nowadays [1,12].

Year after year more and more interest has been paid to the genetics of EC, with some genetic mutations lying at the base of its carcinogenesis.

One of these genes, involved as an important factor in this process, is TP53. It is considered to be one of the most important tumor suppressor genes. TP53 is located on the short arm of chromosome 17 (*locus* 17p13) and consists of 11 exons [9]

TP53 encodes p53, a protein which binds to DNA in a promoter site, with a possibility to activate expression of various genes, e.g. MDM2. Being activated by p53, MDM2 consecutively enhances production of mdm2, a protein which can inhibit p53, reducing its suppressor properties and leading straight to the commencement of carcinogenesis, including EC as well [5].

TP53 mutations occur in many neoplasms, being correlated with severe course and bad disease prognosis. Hereditary mutation of TP53 is known as Li-Fraumeni syndrome. It is a rare, autosomal dominant syndrome of susceptibility to cancer in younger age (before 45 years), including especially osteosarcoma, breast carcinoma, leukemia, adrenal gland and brain tumors [7].

Up to now little is known about the possible linkage between TP53 polymorphisms and EC.

So, in the present study we aimed at: 1/identification of TP53 Arg72Pro polymorphisms in postmenopausal patients with or without EC, 2/evaluation of the risk of EC generated by them, and 3/investigation of their relationships with staging, grading and main risk factors (obesity, diabetes mellitus, arterial hypertension) of this carcinoma.

Material and methods

The 202 postmenopausal women hospitalized in the Polish Mother's Memorial Hospital, Research Institute (PMMH,RI), Department of Menopausal Diseases in Łódź during the years 2004-2009 were qualified for this study.

The study group consisted of 152 women operated on because of histologically diagnosed type I EC (D&C, hysteroscopy). The remaining 50 women, operated on for non-oncological reasons and having normal endometrial tissue, were included in the control group.

Endometrial samples for genetic evaluation were paraffin-embedded tumor tissues from all the operated female patients. Histological evaluation of the obtained endometrial material as well as consecutive genetic tests were performed in the Department of Pathology in PMMH,RI. The detailed characteristics of the study population are shown in Table 1.

DNA isolation and determination of TP53 genotypes

DNA extraction was carried out using the commercially available QIAamp (Qiagen GmbH, Hilden, Germany) DNA purification kit according to the manufacturer's instructions.

The detection of TP53 codon 72 variability was carried out using PCR–RFLP technique. A 309 bp fragment from exon 4 of TP53 containing the codon 72 BstU1 polymorphism site was amplified using the following exon 4 primers:

Forward primer 5' TTC ACC CAT CTA CAG TCC 3'
Reverse primer 5' CTC AGG GCA ACT GAC CGT 3'

The PCR was carried out in a PTC-100 MJ Research Inc. (Walthman, MA, USA) thermal cycler. The 25 µL PCR mixture contained about 100 ng of DNA, 0.5 µL of each primer, 2 µL of dNTP (10 mM), 2 mmol/L $MgCl_2$ and 1 U of Taq DNA polymerase (TaKaRa, Japan). The PCR cycle conditions were 94°C for 4 min, initial denaturation and 94°C for 30 s, 62°C for 30 s then 72°C for 30 s, repeated for 35 cycles. The 309 bp amplified product was digested overnight with 1 U of BstU1 (BioLabs, New England) at

Table 1. Basic group characteristics

	EC group n=152	Control group n=50	P
Age (yrs) – mean±SD	60.90±8.96	53.06±4.75	
Postmenopausal status	152 (100%)	50 (100%)	
BMI (kg/m2) - mean±SD	30.29±6.29	27.43±5.17	
≤24,99	32 (21%)	18 (36%)	0.086
25-29,99	49 (32%)	20 (40%)	
≥30	71 (47%)	12 (24%)	
MHT			
yes	96 (63%)	11 (22%)	0.305
no	56 (37%)	39 (78%)	
Staging			
I	83 (54%)		
II	34 (22%)		
III	35 (23%)		
Grading			
G1	66 (50%)		
G2	45 (34%)		
G3	21 (16%)		
Uterine bleeding (%)			
no	52 (35%)	15 (30%)	0.223
yes	100 (65%)	35 (70%)	
Endometrial thickness: TVU average			
(mm)	14.2	6.2	0.120
> 5 mm (%)	115 (75%)	29 (58%)	
Arterial hypertension (%)	80 (53%)	16 (32%)	0.077
Diabetes mellitus (%)	28 (18%)	2 (4%)	0.010

60°C. After digestion, the fragments were electrophoresed on 2% agarose gel and visualized by UV light after ethidium bromide staining. The Pro allele was 309 bp, while the Arg allele was restricted into two fragments of 175 and 134 bp.

Statistical analysis

Deviation of genotypes and alleles was analyzed and assessed for consistency with Hardy-Weinberg equilibrium using the χ^2 test. Genotype and allele frequencies in the studied groups were compared by χ^2 test also. The relationship of genotypes and alleles with the risk of EC was estimated using odds ratios (ORs) analysis with associated 95% coincidence intervals (95%CI) by the method of unconditional logistic regression (statistical significance with P-value<0.05).

Results

Analysis of genotype distribution of TP53 codon 72 polymorphism revealed some significant differences between the EC group and the controls in case of: a/Pro/Arg genotype – incidence of 26% and 42% respectively, OR=0.48 (0.24-0.94); b/Arg/Arg genotype – incidence of 33% and 14% respectively, OR=3.01 (1.33-7.75) and c/Pro allele – incidence of 54% and 65% respectively, OR=0.33 (0.13-0.75). In the EC group genotype distributions were inconsistent with the Hardy-Weinberg model – Table 2.

There were no characteristic features linking EC grading and staging with the studied genotype distributions, although some significant differences were observed in case of: a/the stage II subgroup (S II) and the controls Arg/Arg genotype incidence of 41% and 14% respectively, OR=4.25 (1.34-14.18); Arg allele incidence of 50% and 35%

respectively, OR=1.13 (0.41-3.21)] and b/the grade 2 subgroup (G 2) and the controls Arg/Arg genotype incidence of 42% and 14% respectively, OR=4.49 (1.72-12.86); Pro allele incidence of 47% and 65% respectively, OR=0.22 (0.08-0.58)]. Except for G 3, in all the remaining staging/grading subgroups genotype distributions did not conform to the Hardy-Weinberg equilibrium – Tables 3a-3b.

There were no significant differences in the genotype distributions between the EC subgroup with normal

Table 2. Basic allele and genotype characteristics of the TP53 codon 72 gene polymorphism in the studied groups

	EC group		Control group		OR (95%CI)[c]	P
	number	%	number	%		
Pro/Pro	63	41	22	44	0.90 (0.47-1.73)	0.75
Pro/Arg	39	26	21	42	0.48 (0.24-0.94)	0.02
Arg/Arg	50	33	7	14	3.01 (1.33-7.75)	0.01
χ^2	35.47[a]		0.30[b]			
Pro	165	54	65	65	0.33 (0.13-0.75)	0.01
Arg	139	46	35	35	1.11 (0.58-2.11)	0.75

[a] p<0.05 as compared with Hardy-Weinberg distribution; [b] p>0.05 as compared with Hardy-Weinberg distribution; [c] OR – crude odds ratio

Table 3a. Distribution of genotypes and allele frequencies of TP53 codon 72 gene polymorphism in EC patients vs. controls according to staging

Staging	FIGO/ S I (n=83)		FIGO/ S II (n=34)		FIGO/ S III (n=35)		Controls
	Number (%)	OR(95%CI)	Number (%)	OR(95%CI)	Number (%)	OR(95%CI)	Number (%)
Pro/Pro	36 (43%)	0.96 (0.48-1.93)	14 (41%)	0.88 (0.31-2.42)	16 (46%)	1.11 (0.34-3.57)	22 (44%)
Pro/Arg	23 (28%)	0.54 (0.26-1.10)	6 (18%)	0.31 (0.08-0.97)	7 (20%)	0.35 (0.07-1.25)	21 (42%)
Arg/Arg	24 (29%)	2.51 (1.05-6.72)	14 (41%)	4.25[b] (1.34-14.18)	12 (34%)	3.07 (0.77-11.80)	7 (14%)
Pro	95 (57%)	0.40 (0.15-0.95)	34 (50%)	0.24 (0.07-0.75)	39 (56%)	0.33 (0.08-1.29)	65 (65%)
Arg	71 (43%)	1.04 (0.52-2.08)	34 (50%)	1.13[b] (0.41-3.21)	31 (44%)	0.90 (0.28-2.93)	35 (35%)
χ2	17.17[a]		8.91[a]		5.27[a]		

[a] p<0.05 as compared with Hardy-Weinberg distribution; [b] p<0.05 between SII and controls

Table 3b. Distribution of genotypes and allele frequencies of TP53 codon 72 gene polymorphism in EC patients vs. controls according to grading

Grading	G 1 (n=66)		G 2 (n=45)		G 3 (n=21)		Controls
	Number (%)	OR(95%CI)	Number (%)	OR(95%CI)	Number (%)	OR(95%CI)	Number (%)
Pro/Pro	30 (45%)	1.06 (0.51-2.23)	16 (36%)	0.70 (0.30-1.60)	8 (38%)	0.78 (0.27-2.20)	22 (44%)
Pro/Arg	19 (29%)	0.56 (0.26-1.21)	10 (22%)	0.51 (0.18-1.47)	6 (29%)	0.55 (0.17-1.61)	21 (42%)
Arg/Arg	17 (26%)	2.13 (0.83-5.96)	19 (42%)	4.49[c] (1.72-12.86)	7 (33%)	3.07 (0.91-10.54)	7 (14%)
Pro	79 (60%)	0.47 (0.17-1.20)	42 (47%)	0.22[c] (0.08-0.58)	22 (52%)	0.33 (0.09-1.10)	65 (65%)
Arg	53 (40%)	0.94 (0.45-1.98)	48 (53%)	1.42 (0.62-3.29)	20 (48%)	1.28 (0.45-3.74)	35 (35%)
χ2	10.61[a]		13.79[a]		3.83[b]		

[a] p<0.05 as compared with Hardy-Weinberg distribution; [b] p>0.05 as compared with Hardy-Weinberg distribution; [c] p<0.05 between G II and controls

BMI and the controls. In the overweight EC subgroup (BMI=25-29.99 kg/m^2) we observed differences in genotype distributions in case of Arg/Arg genotype incidence of 43% and 14% respectively, OR=4.81 (1.82-13.96) and Pro allele incidence of 46% and 65% respectively, OR=0.21 (0.07-0.55). Similar results were found in the obese EC subgroup (BMI>30 kg/m^2): Arg/Arg genotype incidence of 31% and 14% respectively, OR=2.76 (1.12-7.55), Pro allele incidence of 56% and 65% respectively, OR=0.36 (0.13-0.90). In all the BMI subgroups genotype distributions were not in conformity with the Hardy-Weinberg equilibrium – Table 4a.

In the EC subgroup with arterial hypertension the following differences in genotype distributions as compared to the controls were observed: Pro/Arg genotype incidence of 25% and 42% respectively, OR=0.47 (0.22-0.99); Arg/Arg genotype incidence of 35% and 14% respectively, OR=3.30 (1.38-8.84) and Pro allele incidence of 52.5% and 65% respectively, OR=0.37 (0.14-0.92). These differences were more pronounced than in the normotensive EC subgroup – see Table 4b.

Diabetes mellitus (DM) seemed to have little association with the studied TP53 polymorphisms and there were no differences in genotype distributions between the controls and the diabetic EC subgroup. In contrast to this, some differences were observed with the EC subgroup with normal glycemia – see Table 4c.

Discussion

Higher frequency of TP53 expression was found in type II than in type I EC tumors (54.5% and 23.7% respectively; p=0.006), with a positive correlation being observed between TP53 immunoexpression and patient survival rate [3].

High expression of TP53 has been connected with poorly differentiated (G3) ECs. In these cases increased expression of Ki 67 and c-erbB-2, low PR (progesterone receptor) levels as well as aneuploidy have been found more frequently also. Identification of these genetic markers seemed to be useful in distinguishing patients with prognostically unfavorable EC [6].

Table 4a. Distribution of genotypes and allele frequencies of TP53 codon 72 gene polymorphism according to the EC risk factors: BMI

BMI	<24.99 kg/m^2 (n=32)		25-29.99 kg/m^2 (n=49)		>30 kg/m^2 (n=71)		Controls
	Number (%)	OR(95%CI)	Number (%)	OR(95%CI)	Number (%)	OR(95%CI)	Number (%)
Pro/Pro	14 (44%)	1.06 (0.44-2.57)	17 (35%)	0.66 (0.28-1.54)	30 (42%)	0.93 (0.45-1.94)	22 (44%)
Pro/Arg	9 (28%)	0.52 (0.19-1.31)	11 (22%)	0.51 (0.16-1.55)	19 (27%)	0.50 (0.23-1.09)	21 (42%)
Arg/Arg	9 (28%)	2.30 (0.76-7.21)	21 (43%)	4.81[b] (1.82-13.96)	22 (31%)	2.76[b] (1.12-7.55)	7 (14%)
Pro	37 (58%)	0.43 (0.14-1.31)	45 (46%)	0.21[b] (0.07-0.55)	79 (56%)	0.36[b] (0.13-0.90)	65 (65%)
Arg	27 (42%)	0.94 (0.39-2.30)	53 (54%)	1.52 (0.65-3.61)	63 (44%)	1.07 (0.52-2.23)	35 (35%)
χ^2	6.27[a]		12.71[a]		14.89[a]		

[a] p<0.05 as compared with Hardy-Weinberg distribution; [b] p<0.05 as compared with controls

Table 4b. Distribution of genotypes and allele frequencies of TP53 codon 72 gene polymorphism according to the EC risk factors: arterial hypertension

Arterial hypertension	yes (n=80)		no (n=72)		Controls
	Number (%)	OR(95%CI)	Number (%)	OR(95%CI)	Number (%)
Pro/Pro	32 (40%)	0.84 (0.41-1.72)	31 (43%)	0.98 (0.47-2.05)	22 (44%)
Pro/Arg	20 (25%)	0.47[b] (0.22-0.99)	19 (26%)	0.49 (0.22-1.06)	21 (42%)
Arg/Arg	28 (35%)	3.30[b] (1.38-8.84)	22 (31%)	2.69[b] (1.08-7.39)	7 (14%)
Pro	84 (52.5%)	0.30[b] (0.11-0.73)	81 (56%)	0.37[b] (0.14-0.92)	65 (65%)
Arg	76 (47.5%)	1.19 (0.58-2.43)	63 (54%)	1.02 (0.49-2.13)	35 (35%)
χ^2	20.16[a]		15.19[a]		

[a] p<0.05 as compared with Hardy-Weinberg distribution; [b] p<0.05 as compared with controls

Table 4c. Distribution of genotypes and allele frequencies of TP53 codon 72 gene polymorphism according to the EC risk factors: diabetes mellitus

Diabetes mellitus	yes (n=28)		no (n=124)		Controls
	Number (%)	OR(95%CI)	Number (%)	OR(95%CI)	Number (%)
Pro/Pro	13 (46%)	1.10 (0.43-2.80)	50 (40%)	0.86 (0.44-1.68)	22 (44%)
Pro/Arg	9 (32%)	0.65 (0.24-1.70)	30 (24%)	0.44[c] (0.22-0.89)	21 (42%)
Arg/Arg	6 (21%)	1.68 (0.49-5.65)	44 (36%)	3.38[c] (1.08-7.39)	7 (14%)
Pro	35 (52.5%)	0.60 (0.18-2.06)	130 (52%)	0.30[c] (0.11-0.68)	65 (65%)
Arg	21 (47.5%)	0.91 (0.36-2.31)	118 (48%)	1.16 (0.60-2.26)	35 (35%)
χ^2	2.77[b]		32.89[a]		

[a] $p<0.05$ as compared with Hardy-Weinberg distribution; [b] $p>0.05$ as compared with Hardy-Weinberg distribution; [c] $p<0.05$ as compared with controls

But whether such correlations are present with some specific TP53 polymorphisms remains somewhat obscure.

In the present study we found that Arg/Arg genotype of TP53 codon 72 polymorphism is connected with increased risk of EC, whereas Pro/Arg genotype and the Pro allele are associated with decreased risk. We also observed some correlations of TP53 Arg72Pro with stage II (S II) and grade 2 (G 2) of EC. Moreover, two of the three evaluated EC risk factors – obesity and arterial hypertension, but not DM – appeared to have an influence on this polymorphism distribution.

Japanese scientists in this year's publication evaluated the impact of TP53 Arg72Pro, MDM2 SNP309, p21 codon 31, ESR1 PvuII and XbaI on EC risk in a group of 125 cancer patients and in a control group (n=200). None of the studied polymorphisms alone was associated with increased EC risk (MDM2 SNP309 GG genotype slightly increased this risk, but non-significantly). Only combination of TP53 codon 72 Arg/Arg and SNP309 GG + TG significantly enhanced the cancer risk – OR=2.53 (95%CI=1.03-6.21; p=0.04) [11]; so, these findings are in part supported by our own results. This group of researchers in their previous report showed that the ER/MDM2/p53/p21 pathway plays an essential role in carcinogenesis of EC [8].

Also very interesting is a Greek report on gene expression in EC – two of them, TP53 and PTEN (phosphatase and tensin homolog deleted on chromosome 10 or MMAC1 – mutated in multiple advanced cancers 1) were evaluated here in the context of EC grading and staging. This five-year study was carried out in a group of 61 women: 49 (80.32%) with type I and 12 (19.67%) with type II EC. In the type I EC group (mean age 62.5 years) with increasing grading the enhanced expression of TP53 and decreased expression of PTEN were observed: in G1 – 18.2% and 81.8% of patients respectively, in G2 – 17.3% and 73.91%, in G3 – 50% and 0%. In the group with type II EC (mean age 76 years) expression of TP53 was found in almost all patients (91.66%), with expression of PTEN diagnosed only in two cases (16.66%). Two conclusions were drawn on this basis: 1/Immunoexpression of TP53 and PTEN is helpful in both diagnostics and therapy of various types of EC, and 2/TP53 and PTEN are prognostic markers for these kinds of neoplasms [2].

Two meta-analyses linking TP53 polymorphism and EC are available nowadays, both of Chinese origin. The first one comes from Kunming (Yunnan, China), included 9 studies (with 829 EC cases and 1387 controls) and is not in conformity with our own results: none of the variant genotypes under evaluation were correlated with the risk of EC in any of the presented genetic models (additive model: OR=1.027, 95%CI=0.893-1.18; recessive model: OR=1.099, 95%CI=0.802-1.507; dominant model: OR=1.013, 95%CI=0.842-1.2190). The authors therefore suggested that TP53 codon 72 polymorphism is not associated with increased risk of EC, although they recommended further studies with larger numbers of participants [10].

The results of the second meta-analysis differ from the previous one. The authors retrieved 10 case-control studies with a total of 917 EC patients and 1680 controls: Pro allele and Pro carrier (Arg/Pro and Pro/Pro) of TP53 codon 72 polymorphism were here significantly related with the risk of EC (OR=1.25, 95%CI=1.10-1.41 and OR=1.34, 95%CI=1.12-1.59, respectively) [4].

To sum up, we can conclude that evaluation of TP53 codon 72 polymorphism in EC patients may have prognostic value and may be useful for the prophylaxis of this carcinoma as well.

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