P53 Codon 72 and Endometrium Cancer

F. Gloria-Bottini[1,*], M. Nicotra[2], C. Spina[1], P.L. Benedetti-Panici[2], P. Saccucci[1], A. Neri[1], A. Magrini[1] and E. Bottini[1]

[1]*Department of Biomedicine and Prevention, University of Rome, Tor Vergata, Rome, Italy*

[2]*Department of Gynaecologic, Obstetric and Urologic Sciences, University of Rome La Sapienza, Rome, Italy*

Abstract: *Background*: The possible role p53 codon 72 in endometrium cancer has been investigated in several human populations: a positive association with the Pro variant has been observed in Asiatic but not in Caucasian populations. We reasoned that polymorphisms associated with endometrium cancer may interact with p53 codon 72 influencing the degree of association between this polymorphism and cancer.

Methods: Sixty nine women admitted to the hospital for endometrium cancer and 473 healthy subjects were studied in the White population of Rome. Verbal consent was obtained from these subjects to participate to the study that was approved by the Department. P53 codon 72, ADA_1, ADA_6 and PTPN22 genotypes were determined by DNA analysis Statistical analysis were performed by using commercial software (SPSS).

Results: The joint genotype carrying the *Pro allele of p53 codon 72and the ADA_1*2 allele, the joint genotype carrying the *Pro allele and ADA_6 *1 allele and the joint genotype carrying the *Pro allele and *C/*C genotype of PTPN22 show a proportion greater in cancer than in controls. The proportion of *Pro allele carriers in endometrium cancer shows a positive correlation (p=0.019) with the number of genetic factors considered i.e. ADA_1,ADA_6, PTPN22.

Conclusion: Our data suggest that the strength of association between the disease and p53 codon 72 depends on other genetic factors. Thus the different patterns of association between p53 codon 72 and endometrium cancer observed among human populations could be at least in part related to differences in allelic frequencies of these genetic factors.

Keywords: Endometrium cancer, p53 codon 72, ADA_1, ADA_6, PTPN22.

INTRODUCTION

p53 codon 72 is a polymorphic site within the p53 gene. The nucleotide substitution at this codon results in the presence of arginine or proline in the aminoacid sequence of protein. Proline (Pro) variant is a strong transcriptional activator while arginine (Arg) variant is a strong apoptosis inducer [1].

In the last decade the possible association of endometrium cancer with p53 polymorphism codon 72 has been investigated in several human populations. A positive association with the Pro variant has been observed in Korean and other Asiatic populations but not in Caucasian populations [2-6]. In Japanese women a positive association has been found with Arg variant [7].

We reasoned that polymorphisms associated with endometrium cancer may interact with p53 codon 72 influencing the degree of association between this polymorphism and cancer, thus contributing to explain the differences observed among human populations. Therefore we have studied the effect of ADA gene polymorphisms previously found associated with endometrium cancer [8] on the strength of association between p53 codon 72 and this cancer. In addition PTPN22 polymorphism was also studied.

The adenosine deaminase (ADA) structural gene is composed by 12 exons spanning about 32 Kb of DNA on chromosome 20q13.11 [9]. Several differences among normal sequences have been observed in both coding and intronic regions [10]. Exons are coding regions separated by non coding regions. Adenosine deaminase irreversibly deaminases adenosine to inosine contributing to regulate the concentration of adenosine in body fluid.

Adenosine exerts an important role in the regulation of glucose metabolism and immunological functions. Adenosine increases insulin sensitivity in adipocytes [11,13] and decreases insulin sensitivity in muscle fibers [14,15]. Decreased concentration of adenosine weakens T cell while high concentration increases the activity of adenosine receptors strengthening T cell activation [16,17]. ADA is present on the surface of many cell types acting as ecto-enzyme [18]. In the present paper we have studied two intragenic ADA polymorphisms localized respectively on exon 1, ADA_1 (Taq1 site nt 4050-4053), and on exon 6 ADA_6 (MluNI site nt 31230-31235) [10]. The polymorphic site on exon 1 corresponds to the biochemical polymorphism discovered by Spencer *et al.* [19] characterized by the presence of two common alleles ADA_1*1 and ADA_1*2.

*Address correspondence to this author at the Department of Biomedicine and Prevention, University of Rome Tor Vergata, Via Montpellier, 1, 00123 Rome, Italy; Tel: +39 06 30889514; E-mail: gloria@med.uniroma2.it

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Lyp is a protein tyrosine phosphatase expressed mainly in lymphoid tissue. It is encoded by the protein tyrosine phosphatase non receptor type 22 (PTPN22) gene. The gene is located on the short arm of chromosome 1 and encodes a protein of 807 aminoacids that influences the responsivity of T and B cell receptors. The gene shows a polymorphism C/T at +1858 resulting in the variant W620 associated with autoimmune diseases [20]. Therefore there are two alleles *C 1858 (encoding the normal R620 variant) and *T 1858 (encoding W620 variant), correspondingly there are three genotypes C/C,C/T and T/T. PTPN22 is associated with Type 1 Diabetes, Rheumatoid Arthritis, Lupus Erythematosus and other autoimmune diseases.

MATERIAL AND METHODS

We have studied 69 women admitted to the hospital for endometrium cancer and 473 healthy subjects of comparable age without cancer from the White population of Rome. Clinical and demographic data of these women have been reported in a previous study [8]. Verbal informed consent was obtained from these subjects to participate to the study that was approved by the Department.

P53 codon 72, ADA_1, ADA_6 and PTPN22 genotypes were determined by DNA analysis as previously described [21-23]. In some women it was not possible to determine all genotypes (see Table **1**). Statistical analyses were performed by using commercial software (SPSS) [24].

RESULTS

Table **1** shows the proportion of the joint genotypes of p53 codon 72 with PTPN22, ADA_1 and ADA_6 in endometrium cancer and in controls. A statistically significant difference between cancer and controls is observed for the joint genotype carrying the *Pro allele and ADA_1*2 allele and for the joint genotype carrying the *Pro allele and ADA_6*1 allele. Both these joint genotypes are more frequent in cancer than in controls. The difference between cancer and controls for the joint genotype carrying the *Pro allele and *C/*C genotype of PTPN22, that is more frequent in cancer, is relevant but does not reach the standard level of statistical significance.

Figure **1** shows the relationship between the proportion of *Pro allele carriers in endometrium cancer and the number of genetic factors considered, i.e. PTPN22, ADA_1 and ADA_6. There is a statistically significant correlation (p=0.019) pointing to an additive affect of the three polymorphisms on the strength of the association between *Pro allele and endometrium cancer. Such association is lacking in healthy subjects (p=0.855-data not shown). The correlation is statistically significant in patients with cancer grade ≤ 2 only suggesting that in patients with higher grade other stronger factors overshadow the effect of the polymorphisms considered.

DISCUSSION

Genetic interactions, both cooperative and epistatic, are common and have an important role in the susceptibility to diseases. Our data support the multifactorial origin of endometrial cancer and suggest that the strength of association between the disease and p53 codon 72 depends on other genetic factors. Thus the different patterns of association between p53 codon 72 and endometrium cancer observed among human populations could be related to differences in allelic frequencies of these genetic factors.

Table 1: Proportion of the Joint Genotype of p53 Codon 72 with PTPN22, ADA2 and ADA6

	Endometrium cancer		Controls			
	%	Total n°	%	Total n°		
PTPN22 Carriers of *Pro allele and *C/*C genotype of PTPN22	52.2%	69	44.0%	473	Chi-square test of independence p=0.250	
					O.R.	1.40
					95%C.I.	0.81- 2.33
ADA1 Carriers of *Pro allele and carriers of ADA_1*2 allele	16.4%	67	5.1%	469	Chi-square test of independence p=0.001	
					O.R.	3.64
					95%C.I.	1.58- 8.29
ADA6 Carriers of *Pro allele and carriers of ADA_6*1 allele	23.5%	68	13.0%	445	Chi-square test of independence p=0.035	
					O.R.	2.05
					95%C.I.	1.05- 3.99

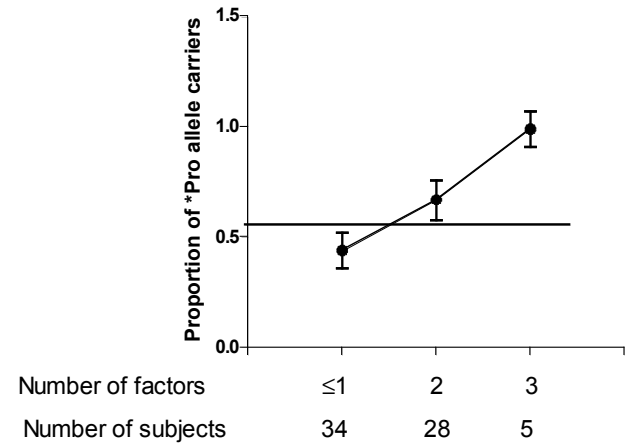

Figure 1: The relationship between the number of factors considered (*C/*C genotype of PTPN22, ADA_1*2 allele carrier, ADA_6*1 allele carrier) and the proportion of *Pro allele carriers in endometrium cancer. The horizontal line corresponds to the proportion of *Pro allele carriers in the general population.

All subjects	Linear correlation, p=0.019
Cancer grade >2	Linear correlation, p=0.396
Cancer grade ≤2	Linear correlation, p=0.017

ADA_1 is a polymorphic site that controls ADA activity and in turn adenosine concentration. Carriers of ADA_1*2 allele show a lower activity [19] and an increased concentration of adenosine. Since this substance inhibits the immune response an increase of its concentration could contribute to immune evasion by tumor cells [25].

At present it is not known whether ADA_6 polymorphism contributes with ADA_1 to the control of ADA enzymatic activity. This site could be directly or indirectly involved in other functions of ADA molecule as ecto enzyme [11]. Further studies in this area could be rewarding.

The polymorphic systems considered are involved in immunologic functions suggesting an important role of immune mechanism in the susceptibility to endometrium cancer.

The limitation of the study is represented by the relatively small number of the subjects examined.

CONFLICT OF INTEREST

None conflict of interest.

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