Abstract. Human papillomavirus (HPV) is the necessary cause for cervical cancer development, and the interaction of HPV-E6 with p53 is known as the most important event in HPV-associated carcinogenesis. In vitro studies have suggested that HPV-E6 interacts more efficiently with the arginine (Arg) p53 variant at position 72 as it appears to be more susceptible to degradation through the ubiquitin proteasome pathway. However, few reports have corroborated this data, and the role of the p53 codon 72 polymorphism in the development of cervical cancer requires further elucidation. We performed a meta-analysis review of all studies published within European populations to summarize the overall risk of this polymorphism considering the influence of the geographical/ethnic location as an important factor in defining a genetic profile and the susceptibility for cervical cancer development. Our analysis revealed that the p53 Arg/Arg genotype does not seem to represent a risk marker for the development of cervical lesions in the majority of the European countries analysed. However, in countries with low incidence rates of cervical cancer, this polymorphism might represent a significant genetic marker.

Introduction

Cervical cancer is the second most common cancer in women worldwide, with 493,000 new cases and 273,000 deaths estimated in 2002 (1). In Europe, data from 2002, revealed a median age standardized rate (ASR) incidence of 12.9/100,000, varying from 4.3 in Finland to 27.4 in Serbia and Montenegro (Fig. 1). Even Western European countries, considered to be developed countries, have a median ASR incidence of 8.7/100,000.

The major cause accepted as necessary for the development of cervical cancer is the infection by certain types of a sexually transmitted agent, human papillomavirus (HPV), such as HPV-16 or -18 (group I carcinogens) (2-4). Nevertheless, HPV is not sufficient for cervical carcinogenesis, and several co-factors have been associated with tumoral progression, such as age at first sexual intercourse, number of sexual partners, parity (>3 children), tobacco and alcohol consumption, co-infection with other sexually transmitted agents, as well as immunologic and host genetic factors (2,5-8).

The essential mechanism of HPV carcinogenesis begins with the integration of its DNA into the host cell DNA, leading to constitutive expression of HPV proteins. Only high-risk HPV genotypes are capable of integration. However, when it occurs, it happens to be an incomplete integration, and the absence of the viral gene E2 introduces a phenotype modification on the host cell (9). The HPV viral gene E2 is responsible for the expression of HPV-E2 protein, which controls the expression of both HPV-E6 and HPV-E7 viral proteins that have the ability to promote genetic instability in cells leading to cell cycle regulation and malignant progression (10). HPV-E6 is a viral oncoprotein that cooperates with the cellular ubiquitin protein ligase E6-AP to bind p53 leading to its degradation through ubiquitin-dependent proteolysis (Fig. 2) (11,12).

The tumour suppressor protein p53 has three major functions: cell cycle arrest, DNA repair activation and regulation of apoptosis. p53 acts as ‘the guardian of the genome’ and when cells have vast or irreparable DNA damage, it activates cell cycle arrest and induces DNA repair or apoptosis, preventing the cells’ progression with genetic mutations (13). The functional inactivation of p53 by HPV-E6 seems to be equivalent to any mutation on TP53 that could affect p53 normal functions (14-17). This fact supports the importance of HPV in cell cycle regulation and malignant progression.

Genetic polymorphisms have been described as having an important role in cancer development (18-22). Matlashewsky et al described a polymorphism on exon 4 of...
the TP53 gene, corresponding to p53 codon 72, causing an amino acid replacement from arginine (Arg) into proline (Pro) due to a transversion G→C (23). Although there is no obvious impact of proline at this position (24), this polymorphism confers two different structural and functional forms of p53 (25,26), and it has been largely investigated for its association with different neoplasias such as cervical cancer (27-29), bladder cancer (30,31), colorectal cancer (32), breast cancer (33), nasopharyngeal cancer (21), ovarian carcinoma (34) and lung adenocarcinoma (35). Storey et al suggested that the Arg p53 variant is seven times more susceptible to HPV-E6 targeting than the Pro p53 variant,
and thus women with the Arg/Arg genotype have an increased risk for cervical cancer development (36-39). However, since the results of Storey et al, several studies have tried to corroborate this association, but the data remain controversial (29,40). Several authors have shown that this TP53 polymorphism is segregated differentially among different ethnic populations, the Arg allele being more common in Caucasian than in African or Asiatic populations (41-47). These findings require profound analysis to provide explanations for the differential susceptibility to cervical cancer development based on the genetic background of populations.

To the best knowledge of the authors, no previous study has reported the influence of geographical and ethnic location as an important factor in defining a genetic profile and the susceptibility for cervical cancer development. Therefore, we reviewed the literature in order to analyse the distribution of the TP53 genotypes among European populations and its association with the development of cervical cancer, using a meta-analysis study design to summarize the overall risk.

Materials and methods

Study selection. All studies included in this review were selected from a PUBMED database search with the words ‘tp53 polymorphism cervical cancer’ and were published between 1998 (date of the first study) and 2005. In order to compile a list of studies regarding these data, we examined the reference list from all the identified studies. Nevertheless, studies which were conducted with cervical adenocarcinomas were excluded from the study due to the distinctive aetiology and behaviour of this type of carcinoma.

The decision to perform a meta-analysis regarding the role of TP53 polymorphism in cervical cancer only within European populations was based on the evidence of differential segregation depending on ethnic group (45,46). A total of 27 case-control studies within European populations were selected and reviewed by the authors in order to evaluate the best approach for data analysis.

Study outcome. We reviewed the literature in order to analyse the role of the p53 codon 72 polymorphism in the development of pre-invasive and invasive cervical lesions, among European populations. If different types of lesions were considered in a study, the outcome was examined separately. Histological data from selected studies were adjusted to the Bethesda classification system: pre-invasive lesions of the cervix (CIN I, II and III) were designated as SIL, independently of being low grade (LGSIL) or high grade (HGSIL), and invasive lesions were designated as invasive cervical cancer (ICC).

Data extraction. To perform a more accurate analysis, despite the fact that some studies revealed the odds ratios (ORs) and respective 95% confidence intervals comparing the Arg/Arg genotype versus Arg/Pro or Pro/Pro, we calculated the adjusted ORs for all studies, taking into consideration the frequencies and Chi-square ($\chi^2$) data provided. The Arg/Pro and Pro/Pro genotypes were grouped and ORs were calculated assuming the Arg/Arg genotype as the risk factor, since the first evidence suggested a 6-fold increased risk of ICC development (37). We also considered the heterogeneity of the studies by taking into account their different characteristics, such as the source of samples (blood versus cervical specimen) and genotyping method [allele specific-polymerase chain reaction (AS-PCR) versus other methods] in a meta-regression.

Statistical analysis. We used computer software Review Manager (RevMan) version 4.2 for Windows (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003) to perform a meta-analysis and determine the overall ORs. The heterogeneity between studies was evaluated using $\chi^2$ analysis in order to determine the odds ratio (OR) and its 95% confidence interval (CI) for the association between the p53 codon 72 polymorphism and the development of either pre-invasive and invasive cervical lesions.

Results

The 27 studies published within European populations between 1998 and 2005, included in this review, analyse the role of the p53 codon 72 polymorphism in cervical cancer development among 12 different populations (Table I). It was clearly evident that the majority of studies were conducted in Italy with 7 studies, followed by the UK and Sweden with 4 studies each. Among the published studies, 3 considered exclusively pre-invasive cervical lesions, 10 considered invasive cervical lesions and 14 studies were conducted with both pre-invasive and invasive lesions. The number of cases and controls varied among the studies analysed, from 12 to 484 and 30 to 626, respectively. The total number of cases included in this meta-analysis was 3183 (1826 SIL and 1357 ICC) which were compared to a total of 3273 controls.

The majority of studies showed no statistical significant differences between cases and controls, suggesting no effect of the Arg/Arg genotype on the development of cervical lesions, although a few studies revealed an increased risk of development. Curiously, these findings were reported only in studies from 4 countries: Greece, Italy, the UK and Sweden; whereas studies from Greece and the UK showed the highest OR values (Table I).

We observed no significant differences when comparing the studies according to some heterogeneity factors, such as the origin of samples (blood or cervical specimen), or the genotyping method [allele specific-polymerase chain reaction (AS-PCR) or other method] (data not shown).

The data from selected studies were analysed according to the type of lesion, and were further studied according to the geographical distribution of the studies. The results from the meta-analysis of each outcome are presented in Figs. 3-6.

The meta-analysis revealed that the overall risk for ICC development was relatively low (OR, 1.27; 95% CI, 1.11-
Table I. Description of the characteristics of the studies regarding the p53 codon 72 polymorphism in cervical lesions.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Protocol</th>
<th>Source</th>
<th>Controls</th>
<th>Cases</th>
<th>P</th>
<th>OR</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storey et al, 1998 (37)</td>
<td>UK</td>
<td>AS-PCR</td>
<td>Tissue</td>
<td>41</td>
<td>36.6</td>
<td>&lt;0.001</td>
<td>5.70</td>
<td>1.98-16.41</td>
</tr>
<tr>
<td>Rosenthal et al, 1998 (40)</td>
<td>UK</td>
<td>AS-PCR</td>
<td>Tissue</td>
<td>246</td>
<td>63.0</td>
<td>0.233</td>
<td>0.69</td>
<td>0.37-1.27</td>
</tr>
<tr>
<td>Helland et al, 1998 (67)</td>
<td>Norway</td>
<td>PCR-RFLP</td>
<td>Blood</td>
<td>225</td>
<td>54.2</td>
<td>0.656</td>
<td>1.13</td>
<td>0.67-1.90</td>
</tr>
<tr>
<td>Heyes et al, 1998 (68)</td>
<td>Netherlands</td>
<td>AS-PCR</td>
<td>Tissue</td>
<td>158</td>
<td>57.0</td>
<td>0.326</td>
<td>1.56</td>
<td>0.64-3.84</td>
</tr>
<tr>
<td>Josefsson et al, 1998 (69)</td>
<td>Sweden</td>
<td>PCR-RFLP</td>
<td>Tissue</td>
<td>626</td>
<td>49.7</td>
<td>0.516</td>
<td>1.19</td>
<td>0.69-2.06</td>
</tr>
<tr>
<td>Zehbe et al, 1999 (39)</td>
<td>Sweden</td>
<td>PCR-SSCP</td>
<td>Tissue</td>
<td>40</td>
<td>52.5</td>
<td>0.028</td>
<td>3.32</td>
<td>1.11-9.92</td>
</tr>
<tr>
<td>Brady et al, 1999 (70)</td>
<td>UK</td>
<td>AS-PCR</td>
<td>Blood, tissue</td>
<td>74</td>
<td>58.1</td>
<td>0.138</td>
<td>1.64</td>
<td>0.85-3.14</td>
</tr>
<tr>
<td>Giannoudis et al, 1999 (71)</td>
<td>UK</td>
<td>AS-PCR</td>
<td>Tissue</td>
<td>30</td>
<td>56.7</td>
<td>0.598</td>
<td>1.29</td>
<td>0.50-3.34</td>
</tr>
<tr>
<td>Klæs et al, 1999 (72)</td>
<td>Germany</td>
<td>PCR-RFLP</td>
<td>Tissue</td>
<td>151</td>
<td>55.6</td>
<td>0.680</td>
<td>0.89</td>
<td>0.53-1.52</td>
</tr>
<tr>
<td>Tachezy et al, 1999 (73)</td>
<td>Czech Republic</td>
<td>AS-PCR</td>
<td>Blood, tissue</td>
<td>172</td>
<td>53.5</td>
<td>0.845</td>
<td>0.95</td>
<td>0.54-1.65</td>
</tr>
<tr>
<td>Bertorelle et al, 1999 (74)</td>
<td>Italy</td>
<td>AS-PCR</td>
<td>Blood, tissue</td>
<td>130</td>
<td>54.6</td>
<td>0.681</td>
<td>0.88</td>
<td>0.53-1.47</td>
</tr>
<tr>
<td>Szarka et al, 2000 (75)</td>
<td>Hungary</td>
<td>AS-PCR</td>
<td>Blood</td>
<td>87</td>
<td>60.0</td>
<td>0.630</td>
<td>1.17</td>
<td>0.60-2.28</td>
</tr>
<tr>
<td>Dybikowska et al, 2000 (76)</td>
<td>Poland</td>
<td>AS-PCR</td>
<td>Tissue</td>
<td>52</td>
<td>73.1</td>
<td>0.775</td>
<td>0.88</td>
<td>0.36-2.14</td>
</tr>
<tr>
<td>Tong et al, 2000 (77)</td>
<td>Austria</td>
<td>AS-PCR-Probe</td>
<td>Blood</td>
<td>133</td>
<td>62.4</td>
<td>0.206</td>
<td>0.72</td>
<td>0.43-1.20</td>
</tr>
<tr>
<td>Dokianakis et al, 2000 (49)</td>
<td>Greece</td>
<td>AS-PCR</td>
<td>Tissue</td>
<td>135</td>
<td>20.0</td>
<td>&lt;0.001</td>
<td>4.94</td>
<td>2.30-10.63</td>
</tr>
<tr>
<td>Agorastos et al 2000 (48)</td>
<td>Greece</td>
<td>AS-PCR</td>
<td>Tissue</td>
<td>30</td>
<td>20.0</td>
<td>0.003</td>
<td>8.00</td>
<td>1.79-35.74</td>
</tr>
</tbody>
</table>

CI = confidence interval; %A/A = percentage of the A allele.
Table I. Continued.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Protocol</th>
<th>Source</th>
<th>Controls n</th>
<th>%A/A</th>
<th>Cases n</th>
<th>%A/A</th>
<th>Type</th>
<th>P</th>
<th>OR</th>
<th>CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenti et al, 2000 (53)</td>
<td>Italy</td>
<td>AS-PCR</td>
<td>Tissue</td>
<td>140</td>
<td>61.4</td>
<td>64</td>
<td>53.1</td>
<td>ICC</td>
<td>0.264</td>
<td>0.71</td>
<td>0.39-1.29</td>
</tr>
<tr>
<td>van Dun et al, 2000 (78)</td>
<td>Netherlands</td>
<td>AS-PCR</td>
<td>Tissue</td>
<td>86</td>
<td>57.0</td>
<td>71</td>
<td>62.0</td>
<td>ICC</td>
<td>0.526</td>
<td>1.23</td>
<td>0.65-2.34</td>
</tr>
<tr>
<td>Zehbe et al, 2001 (50)</td>
<td>Sweden</td>
<td>PCR-SSCP</td>
<td>Tissue</td>
<td>188</td>
<td>47.3</td>
<td>72</td>
<td>63.9</td>
<td>ICC</td>
<td>0.0017</td>
<td>1.97</td>
<td>1.12-3.44</td>
</tr>
<tr>
<td>Zehbe et al, 2001 (50)</td>
<td>Italy</td>
<td>PCR-SSCP</td>
<td>Tissue</td>
<td>40</td>
<td>52.5</td>
<td>43</td>
<td>76.7</td>
<td>ICC</td>
<td>0.020</td>
<td>2.99</td>
<td>1.17-7.65</td>
</tr>
<tr>
<td>Rezza et al, 2001 (79)</td>
<td>Italy</td>
<td>PCR-RFLP</td>
<td>Tissue</td>
<td>172</td>
<td>50.0</td>
<td>71</td>
<td>49.3</td>
<td>SIL</td>
<td>0.920</td>
<td>0.97</td>
<td>0.56-1.69</td>
</tr>
<tr>
<td>Gustafsson et al, 2001 (80)</td>
<td>Sweden</td>
<td>Pyrosequence</td>
<td>Tissue</td>
<td>36</td>
<td>50.0</td>
<td>20</td>
<td>60.0</td>
<td>ICC</td>
<td>0.472</td>
<td>1.50</td>
<td>0.43-5.27</td>
</tr>
<tr>
<td>Humbey et al, 2002 (52)</td>
<td>France</td>
<td>PCR-DGGE</td>
<td>Tissue</td>
<td>50</td>
<td>52.0</td>
<td>68</td>
<td>45.6</td>
<td>SIL</td>
<td>0.491</td>
<td>0.77</td>
<td>0.37-1.61</td>
</tr>
<tr>
<td>Cenci et al, 2003 (51)</td>
<td>Italy</td>
<td>AS-PCR</td>
<td>Tissue</td>
<td>50</td>
<td>46.0</td>
<td>30</td>
<td>46.0</td>
<td>ICC</td>
<td>0.954</td>
<td>1.03</td>
<td>0.38-2.18</td>
</tr>
<tr>
<td>Comar et al, 2004 (81)</td>
<td>Italy</td>
<td>PCR-Probe</td>
<td>Tissue</td>
<td>76</td>
<td>60.5</td>
<td>23</td>
<td>52.2</td>
<td>ICC</td>
<td>0.476</td>
<td>0.71</td>
<td>0.28-1.82</td>
</tr>
<tr>
<td>Santos et al, 2005 (29)</td>
<td>Portugal</td>
<td>AS-PCR</td>
<td>Blood</td>
<td>145</td>
<td>63.4</td>
<td>164</td>
<td>67.1</td>
<td>ICC</td>
<td>0.504</td>
<td>1.17</td>
<td>0.73-1.88</td>
</tr>
</tbody>
</table>

*aThese two studies used the same control group but different methodologies. bThe results from the controls were the same as a previous study from Zehbe et al, 2001. ICC, invasive cervical cancer; SIL, squamous intraepithelial lesions; P, Pearson Chi-square; OR, odds ratio; CI, confidence interval.
and moreover, in the case of SIL development the overall risk is approximately null (OR, 0.97; 95% CI, 0.85-1.10) (Fig. 5).

By merging studies by country origin and analysing data according to geographical distribution using longitude, it was observed that the majority of the studies did not show an increased risk for the development of ICC and, in the case of SIL, data pointed somehow to a protective role of the TP53 Arg/Arg genotype. Furthermore, the individual meta-analysis for countries with more than one published study revealed that only Italy and the UK had statistically significant results (P=0.050 and P=0.007, respectively) for ICC development, whereas for SIL none of the countries had significant results. These results emphasize the fact that since the results of Storey et al, few studies revealed a significant increased risk for Arg/Arg genotype carriers for the development of either SIL or ICC, but the implication of this polymorphism remains unexplained.

Discussion

In vitro studies suggest that HPV-E6 protein binds more efficiently to the Arg p53 variant at position 72, than to the Pro p53 variant, increasing its degradation through the ubiquitin proteasome pathway (15,17). Without functional p53, cell cycle deregulation occurs and cells start to proliferate without control leading to the development of neoplastic cells.

Storey et al made the first effort to show the role of the p53 codon 72 polymorphism in cancer development, emphasizing that the Arg/Arg genotype increased the risk of cervical cancer development by ~6-fold (37). Since then, and despite all the criticism about the reduced number of samples of this study, the Arg/Arg genotype has been suggested as a potential susceptibility marker for cervical cancer development. Several other studies were conducted in numerous countries worldwide, and despite some that supported the findings of Storey et al (39,48-50), the great majority did not corroborate them suggesting that the Arg/Arg genotype had no evidence for an increasing susceptibility for the development of cervical cancer (29,40,51-53). This controversy has already led to an increasing number of reviews about the role of this polymorphism. However, as far as the authors are concerned, no study has reported the influence of the geographical and ethnic location as an important factor in the definition of genetic profile and susceptibility for cervical cancer development (27,28,54). Among the several reports that attempted to explain the role of the TP53 polymorphism in cervical cancer many aspects were not considered that might have interfered in the analysis. Makni et al made the first effort to study the
accuracy of the results in different laboratories, suggesting that the protocol selected for the allelic discrimination and the source of the sample (blood or tissue) were extremely important in the analysis and could represent biased results (55). Therefore, we considered these characteristics among the studies in the European countries here resumed, and we observed that the greatest majority used allele-specific polymerase chain reaction (AS-PCR) as protocol, and tissues as samples. Although the use of blood samples would reduce the possible misclassification due to mutations and loss of heterozygosis (LOH) present in the local tumor as a consequence of neoplastic changes, the use of tissues is still accepted. Nevertheless, the use of another sample source or protocol did not have a direct implication on the accuracy of the results (54).

Another important factor that must be taken into consideration due to its possible interference with the analysis is the number of cases and controls. Most studies...
frequently use a reduced number of samples, thus many do not achieve statistically significant results. In this review, we observed that several studies used a reduced number of cases and controls; therefore without a large range of samples it was not possible, even with statistical analysis, to accurately reach overall conclusions for the population. To increase the accuracy of the studies, we suggested that the number of cases should be >100, so the sample could be representative, and that the controls should be at least equal or double. This condition was not observed in any of the studies analysed here, but this was somehow understandable due to difficulties in the selection and collection of samples from either cases or controls.

Table I shows the data collected from all published studies, and it is evident that a few studies revealed significantly higher frequencies of the Arg/Arg genotype in the cases analysed than in the controls, revealing an increased risk for invasive cervical cancer. Similar results were observed for the development of pre-invasive lesions of the cervix (SIL).

Table I also reveals that, despite their high ORs, the studies from the UK, Italy, Greece and Sweden should be analysed more carefully.

From the five studies made in the UK, only one, and the first to be known, showed statistically significant association (37). Nevertheless, this study was conducted using a reduced number of samples and it revealed a large confidence interval. As a result, we believe that the study of Storey et al might not have been the most representative study for this population. Among the seven studies from Italy, only two suggested an increased risk of developing cervical cancer in individuals carrying the Arg/Arg genotype. Similar results were observed for the development of pre-invasive lesions of the cervix (SIL).

From the five studies made in the UK, only one, and the first to be known, showed statistically significant association (37). Nevertheless, this study was conducted using a reduced number of samples and it revealed a large confidence interval. As a result, we believe that the study of Storey et al might not have been the most representative study for this population. Among the seven studies from Italy, only two suggested an increased risk of developing cervical cancer in individuals carrying the Arg/Arg genotype. Similar results were observed for the development of pre-invasive lesions of the cervix (SIL).

Table I also reveals that, despite their high ORs, the studies from the UK, Italy, Greece and Sweden should be analysed more carefully.

The data from the meta-analysis presented in Fig. 3 confirmed the first evidence that an increased risk for ICC development could be found only in studies from Greece, Italy, the UK and Sweden. Although the overall analysis provided a statistically significant association between the Arg/Arg genotype and ICC development (P<0.001) the overall risk was not significant (OR, 1.27; 95% CI, 1.11-1.46). By merging studies from each country (Fig. 4) we observed that, despite Italy and the UK having statistically significant results (P=0.050 and P=0.007), respectively for ICC development, only Sweden and Greece had results that deviated from the other countries. With this analysis we summarized all data regarding the association between the TP53 Arg/Arg genotype and the development of ICC in European populations. Our data point to an overall risk for Europe of ~1.2-fold, which does not provide a strong association of this genotype as a susceptibility marker for ICC development as it was first suggested by previously published data.
The same analysis was performed for SIL development, and the data revealed that only studies from Greece, the UK and one from Sweden revealed an increased risk (Fig. 5). Despite the first evidence, individual meta-analysis for countries with more than one published study revealed that there were no countries with significant results for SIL development. Despite that the meta-analysis did not provide statistically significant results (P=0.170), it did suggest that the Arg/Arg genotype might not have an influence on the development of SIL (OR, 0.97; 95% CI, 0.85-1.10) (Fig. 6). Our analysis summarized all the data from European countries and indicated that the Arg/Arg genotype does not represent a risk marker for SIL development.

It is extremely important to mention that, although our meta-analysis revealed an overall risk for invasive cervical cancer development in Europe of ~1.27 fold, we believe that the studies from Greece, two studies from both Sweden and Italy, and the one from Storey et al have introduced deviating factors in the analysis. In fact, if we do not consider these studies in the analysis, due to their different frequencies, the overall risk would be 1.02 (95% CI, 0.89-1.10). As we stated before, if we take into consideration that these countries have low incidence rates of ICC, there might be evidence that this polymorphism represents a susceptibility marker in countries with low incidences, but not in all populations (43,56,57).

This fact supports the need of more meta-analysis reviews within this subject to allow a better explanation of the role of the p53 codon 72 polymorphism in cancer development. Summarizing the meta-analysis, this original study emphasizes the evidence of the most recently published studies worldwide revealing no association of the TP53 polymorphism with the development of any modification on cervix epithelium (54,55,58-66).

Another notable finding from our review was the comparison of the Arg/Arg genotype frequency among the controls of the different studies (Fig. 7). By analysing the frequencies considering the longitude of each country represented by its capital, we observed that central European countries had similar frequencies of the Arg/Arg genotype (52-62%), while the countries at the edges showed some differences in the frequency. Additionally and despite the fact that Portugal and Sweden had slightly different frequencies compared to the others, 63.4 and 49.0% respectively, countries from the Eastern edge such as Poland and Greece showed the largest differences. While Poland showed a significantly higher frequency of the Arg/Arg genotype (73.1%), Greek studies revealed a frequency among the control population of only 20%, which is significantly different compared to the others. By analysing the data from Greece we observed that the studies used a reduced number of controls, and thus this might have biased the presented data.

Hence, several authors have studied the ethnic variations of the TP53 polymorphism worldwide, showing that the Arg allele is more common in Caucasian than in African and Asiatic populations (41-47,58). Beckman et al conducted a noteworthy study regarding the potential natural selection of p53 during intrauterine development and suggest that this p53 codon 72 polymorphism might balance natural selection (41).

This is the first review that reports geographical location as an important marker in the population genetic background for the influence of the p53 codon 72 polymorphism. Despite the laboratory differences and methodologies, our data indicates that the Arg/Arg genotype does not represent a susceptibility risk marker for the development of any cervical lesion in most of the countries of Europe, although in countries with low incidence rates of ICC this polymorphism might represent a significant genetic marker (43,44,56,57). Furthermore, future investigations are required with appropriate attention to the design and methodological issues, mainly by considering larger study samples.

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References


