TP53 codon 72 polymorphism and cervical cancer: a pooled analysis of individual data from 49 studies


CRD summary
This review investigated the association between the TP53 codon 72 polymorphism and cervical cancer. It reported no association when the analysis was restricted to methodologically sound studies, concluding that the increased risks seen in some studies were probably due to methodological errors. Limitations in the reporting of the review methods make it difficult to determine the reliability of this conclusion.

Authors' objectives
To establish whether there is an association between the polymorphism at codon 72 of the tumour protein 53 (TP53) tumour-suppressor gene and cervical cancer.

Searching
PubMed, EMBASE and Current Contents databases were searched for relevant studies published up to 2007 in any language. No search terms were reported. The internet was searched for relevant unpublished data.

Study selection
Inclusion appeared to be restricted to studies of the TP53 polymorphism and cervical cancer. The authors did not state how many reviewers performed the selection.

Included studies were conducted in Norway, Costa Rica, UK, Germany, China, Hungary, Czech Republic, Greece, Poland, USA, Japan, Italy, Netherlands, Korea, Peru, Sweden, Israel, India, France, South Africa, Mexico, Argentina, Brazil, Thailand, Taiwan, and Lithuania. The material used for assessment of the TP53 genotype included: tumour tissue (for cases, not controls), exfoliated cervical cells, white blood cells, and mixed sources.

Assessment of study quality
Study quality was assessed using four criteria: Hardy-Weinberg equilibrium among controls (yes/no), study type (epidemiological/non-epidemiological), study size (greater or fewer than 200 participants), and source of material used to determine the TP53 genotype (white blood cells/exfoliated cells/tumour tissue).

Data extraction
Study authors or principal investigators were contacted to obtain individual patient data. Histologically confirmed cases of invasive cancer were recorded as squamous-cell carcinoma, adenocarcinoma, adenosquamous carcinoma, and unknown types. Histologically or cytologically confirmed high-grade lesions included high-grade squamous intra-epithelial lesions and cervical intra-epithelial lesions grades two and three. Low-grade lesions consisted of low-grade squamous intra-epithelial lesions and cervical intra-epithelial lesions grade one. Only those controls confirmed by negative cytology were included, and men, girls under 15, and participants with unknown TP53 status or unclear case or control status were excluded.

The TP53 codon 72 genotype was analysed as a single variable with three categories: arginine homozygotes, proline homozygotes, and heterozygotes.

Methods of synthesis
Pooled estimates and 95% confidence intervals (CIs) were calculated by logistic regression. The three categories of genotype were dichotomised and odds ratios (ORs) were calculated for each of the various comparisons. The study population was stratified by tumour and cervical history, human papillomavirus status, ethnic group, and each of the
study quality criteria. Studies or individual women with missing information were included by generating a "missing" category for the variable. Sensitivity analyses were conducted based on the completeness of data, Hardy-Weinberg equilibrium, study design, and source of material used to determine the genotype. The Wald $\chi^2$ test was used to determine the statistical significance of the effect between genotypes, and the Bonferroni method was used to account for multiple testing in subgroup analyses.

Publication bias was assessed using Egger's test.

**Results of the review**

Valid individual patient data were obtained from a total of 49 studies (n=15,834 participants). There was statistically significant publication bias for the comparison of arginine homozygotes and heterozygotes (p=0.008).

For invasive cervical cancer, the odds ratio was 1.22 (95% CI 1.08 to 1.39) for arginine homozygotes versus heterozygotes and 1.13 (95% CI 0.94 to 1.35) for arginine homozygotes versus proline homozygotes. For squamous cervical cancer, the odds ratio was 1.19 (95% CI 1.03 to 1.36) for arginine homozygotes versus heterozygotes and 1.17 (95% CI 0.95 to 1.43) for arginine homozygotes versus proline homozygotes.

For arginine homozygosity versus heterozygosity, significant excess risks were found for non-epidemiological studies (OR 1.35, 95% CI 1.15 to 1.58), studies where controls were not in Hardy-Weinberg equilibrium (OR 1.71, 95% CI 1.21 to 2.42), and studies that determined the genotype from tumour tissue (OR 1.39, 95% CI 1.13 to 1.73). No significant differences were found between arginine homozygosity and heterozygosity among the pooled epidemiological studies, nor studies that determined the genotype from white blood cells.

**Authors' conclusions**

No association was found between TP53 codon 72 polymorphism and cervical cancer when the analysis was restricted to methodologically sound studies. The increased risks seen in some studies were probably due to errors in the methods, rather than to biological or clinical factors.

**CRD commentary**

This review was based on a question which was very broadly defined in terms of the prognostic factor, participants, and outcomes of interest. There were no language restrictions, but details of the search for relevant studies were limited, and there was evidence to suggest that there was publication bias among the included studies. Attempts were made to identify studies of greater methodological quality, but the authors did not give details of how the validity of individual patient data was assured, nor how the errors and bias were minimised throughout the review process. They acknowledged other limitations, such as the lack of data on risk factors, such as smoking, oral contraceptive use and parity.

The authors' conclusions follow from the evidence presented, but the limitations in reporting make it difficult to determine the reliability of these conclusions.

**Implications of the review for practice and research**

The authors did not state any implications for research nor practice.

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