



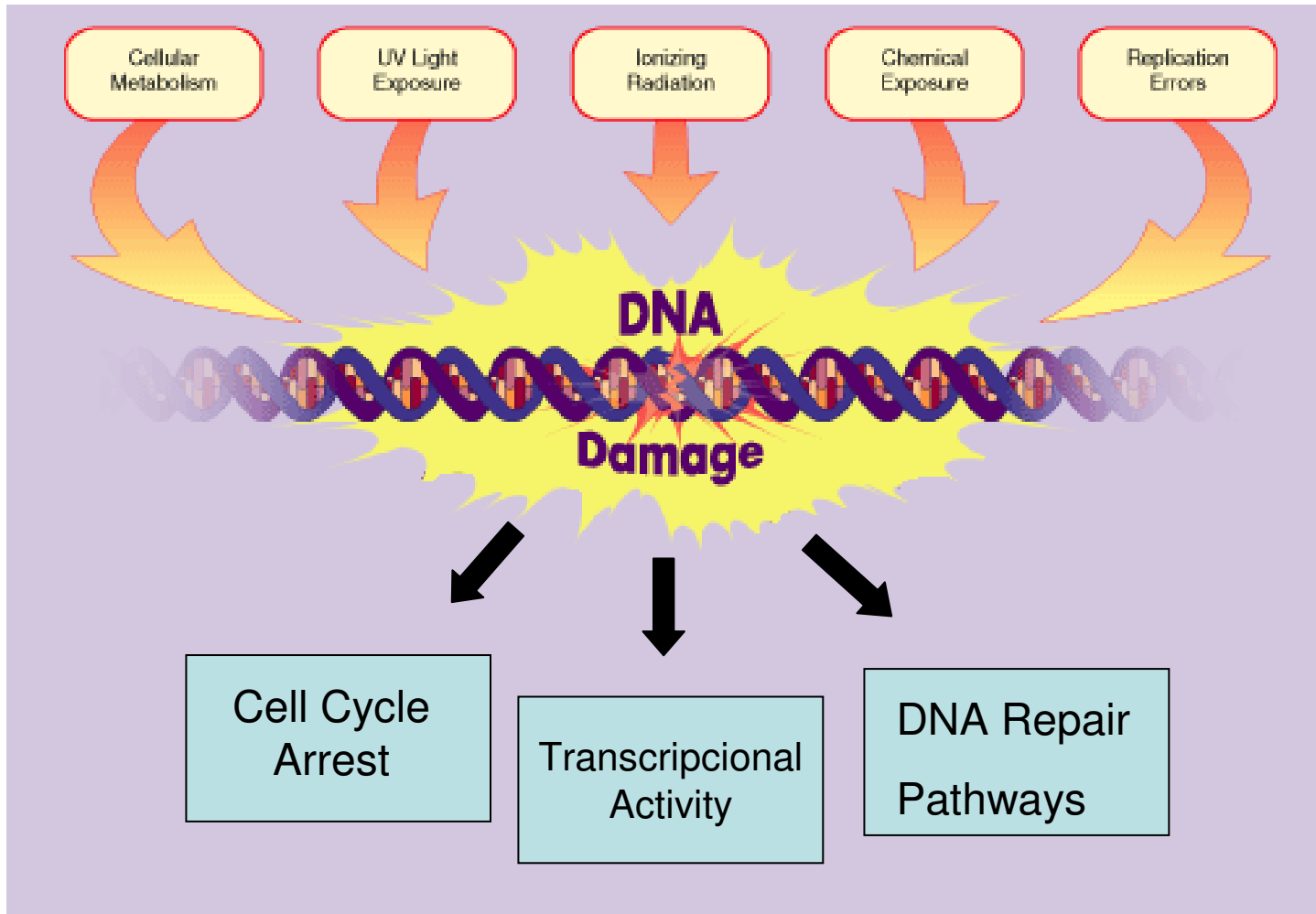
Laboratory of Experimental Oncology
School of Medicine - Universidade de São Paulo -
USP

XPC polymorphisms play a role in tissue-specific carcinogenesis: a meta-analysis

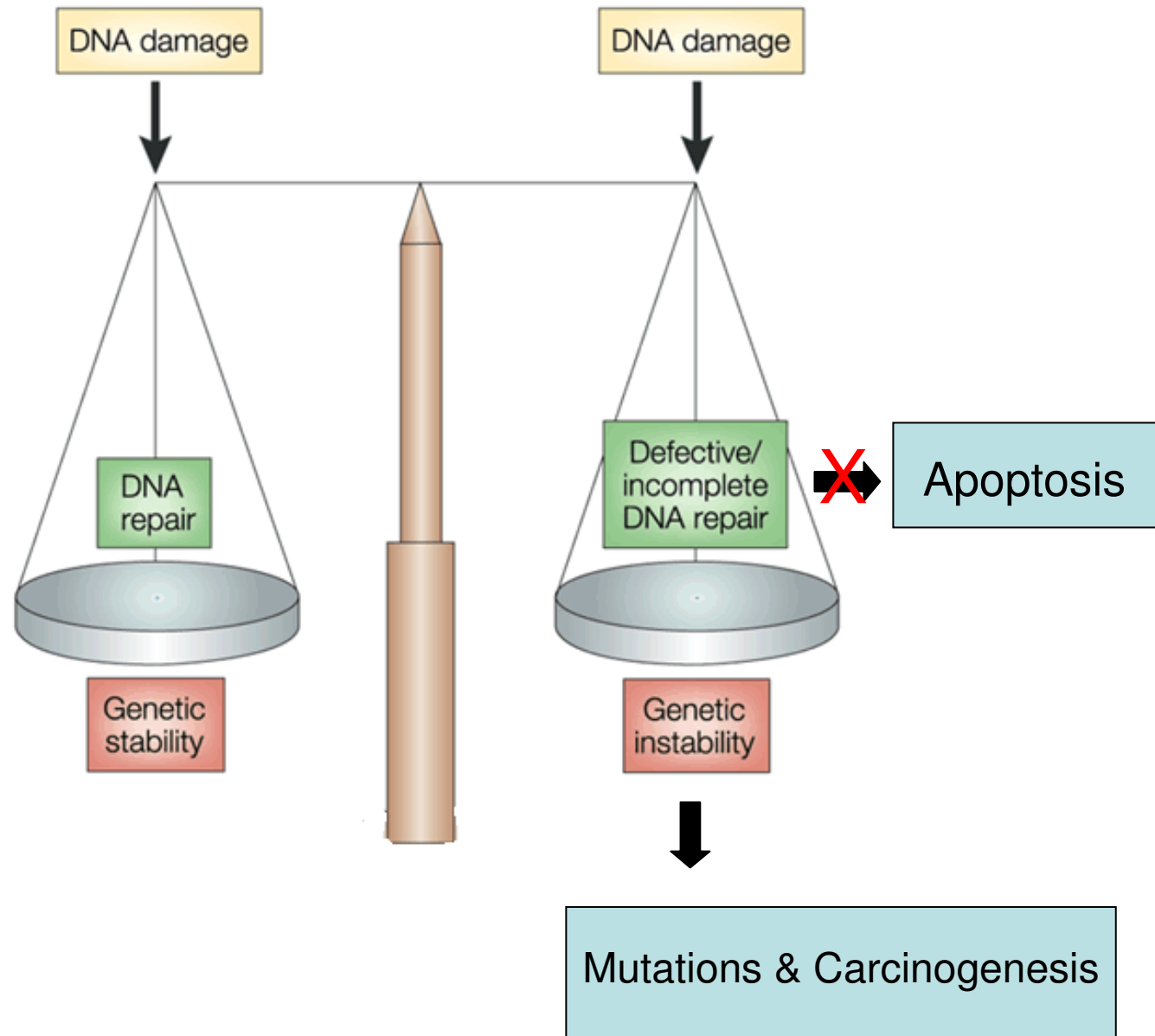
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DNA DAMAGE



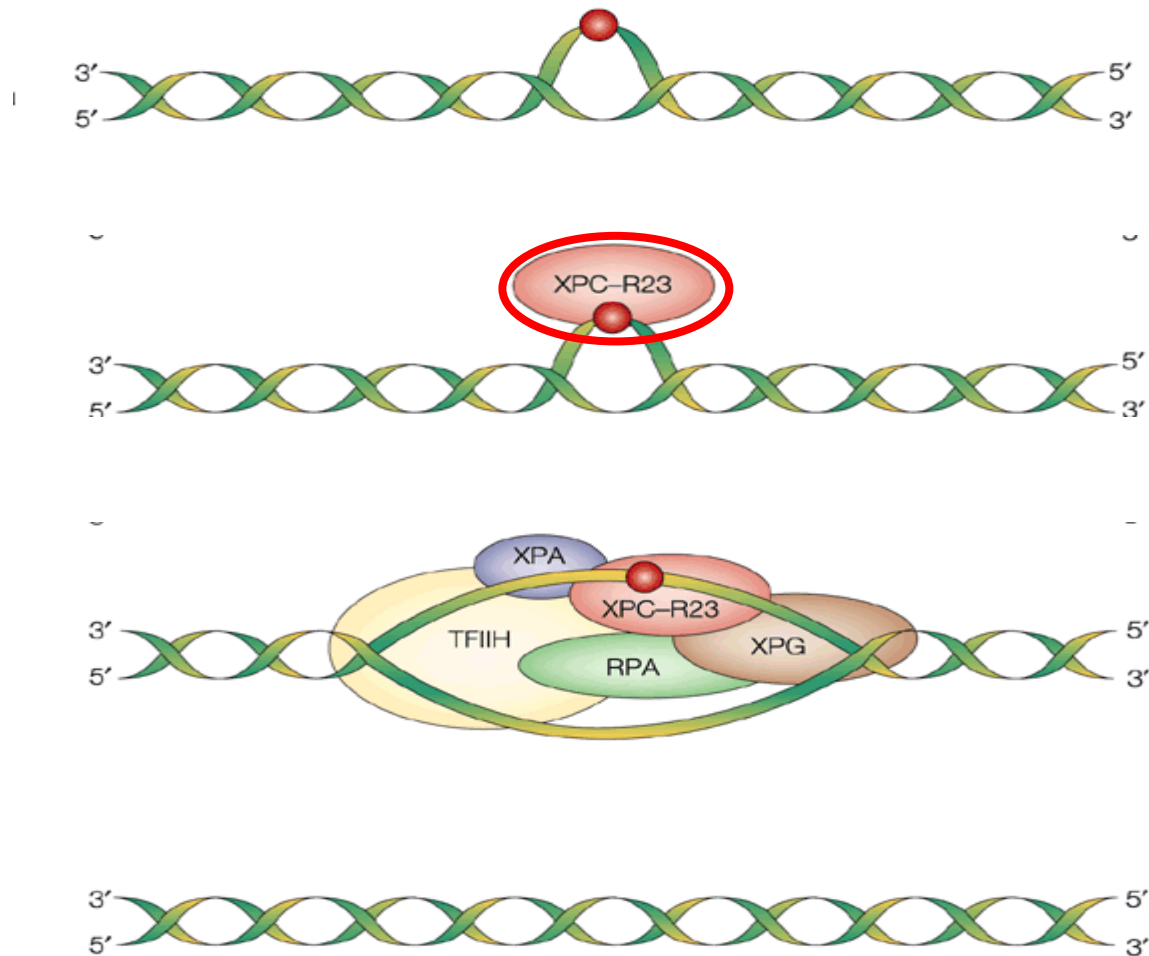
DNA DAMAGE X CANCER



DNA REPAIR PATHWAY

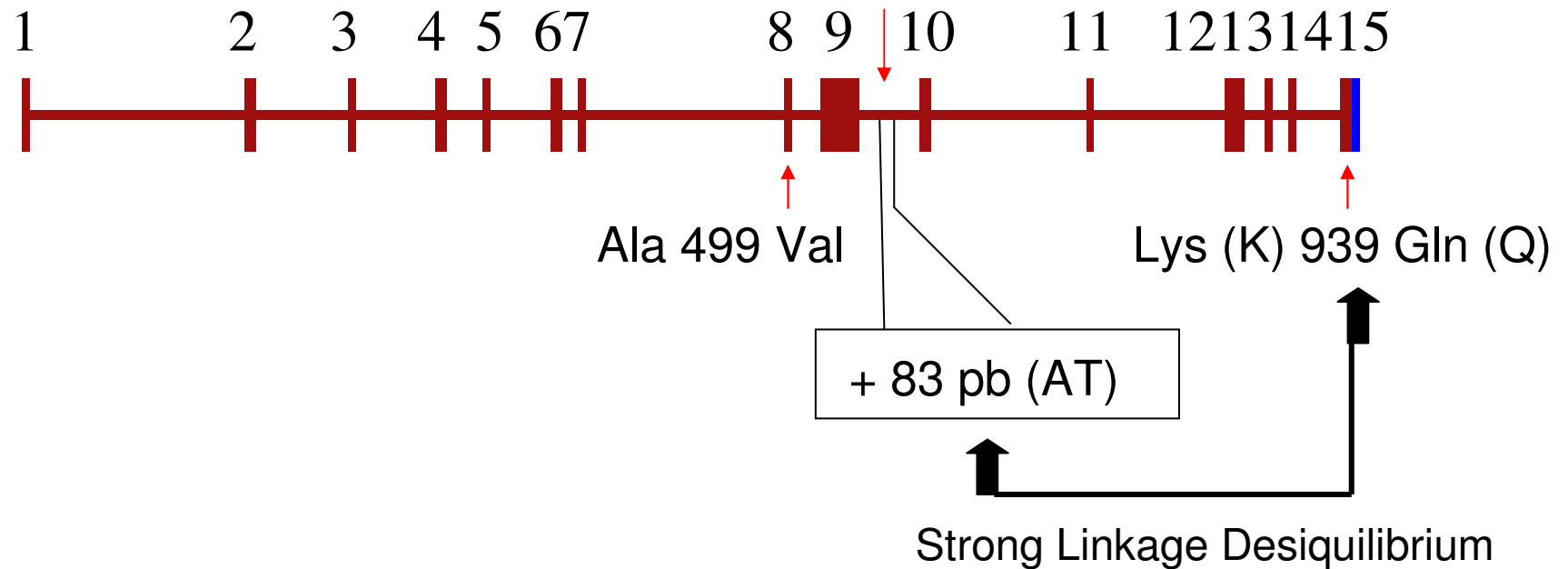
Nucleotide Excision Repair (NER)

- UV- induced lesions
- Chemical Carcinogens
- Intrastrand lesions
- DNA bulky adducts



Nature Reviews | Cancer

XPC GENE AND ITS POLYMORPHISMS



“Polymorphisms in XPC gene have been analyzed in case-control studies to assess the cancer risk attributed to these variants, but results are conflicting”

XPC POLYMORPHISMS X CANCER

- Meta-Analysis

Data Extraction: Search in Pubmed database

Eligibility: Original papers, unrelated studies, genotype frequency and HWE

Data Collected: Sociodemographic, ethnicity and genetic informations

Polymorphisms analyzed: A499V and XPC K9393Q

Summary Odds Ratio (OR), obtained using fixed-effects (Mantel-Haenszel method). Random-effects for heterogeneity pool samples

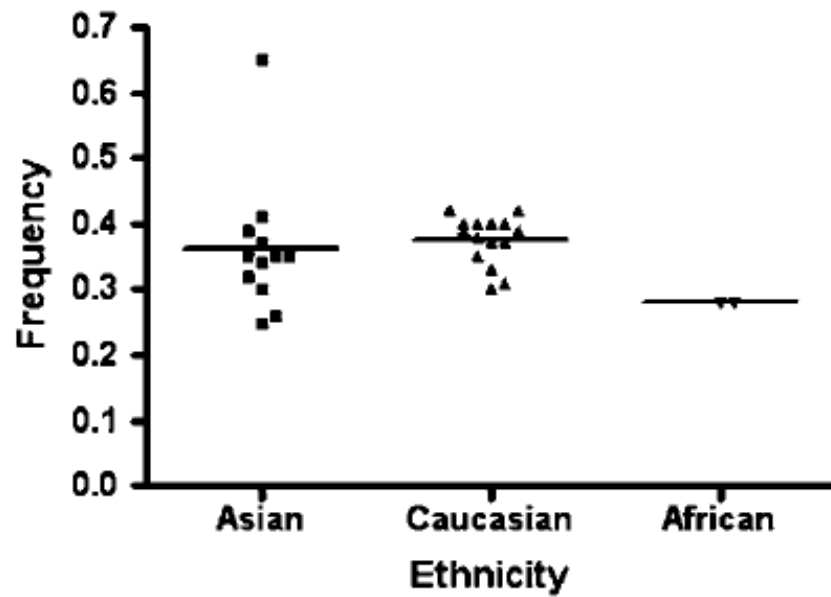
Publication Bias verified by funnel plot and Egger's test

RESULTS

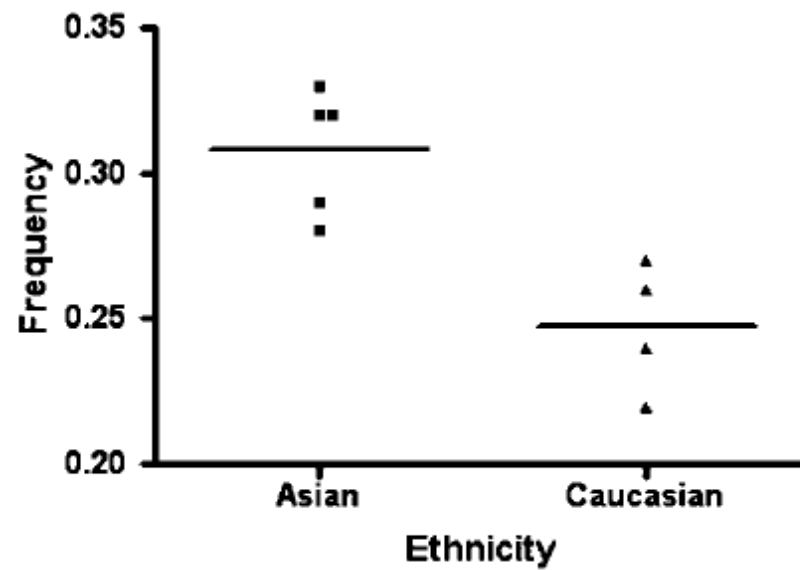
Meta-analysis based in 33 studies

XPC polymorphism frequency X Ethnicity

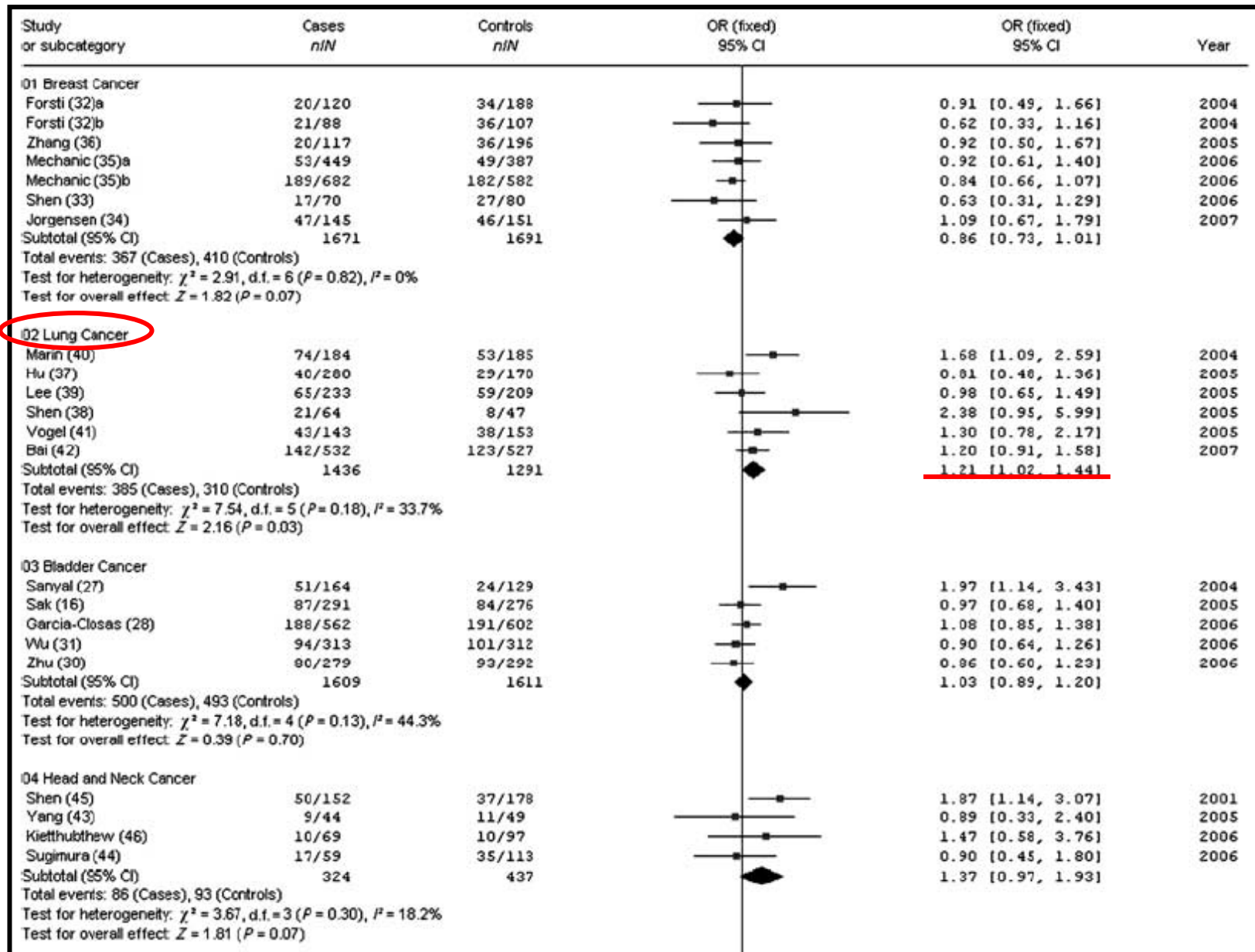
a Allele frequencies XPC of 939^{Gln} among controls



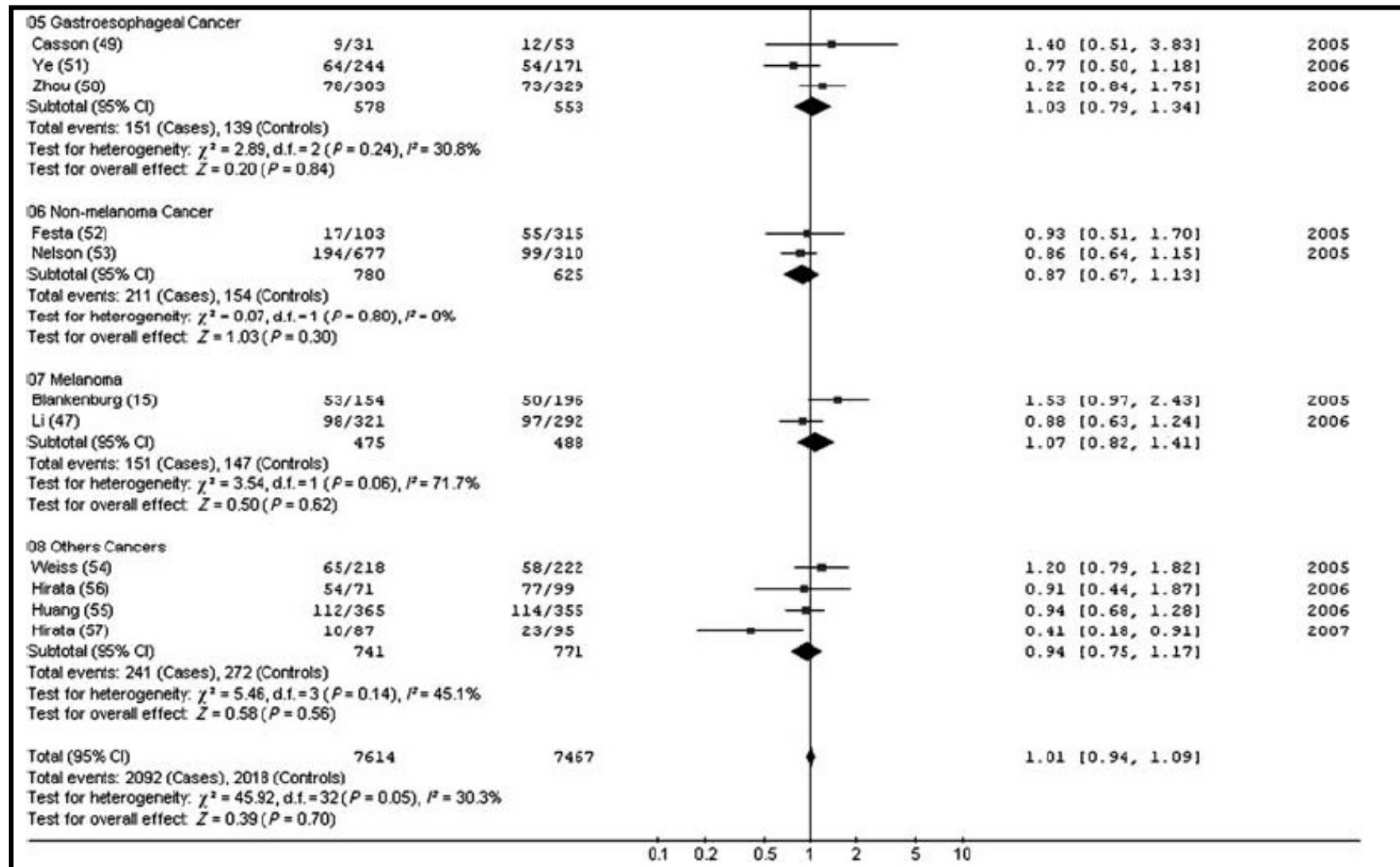
b Allele frequencies of 499^{Val} among controls



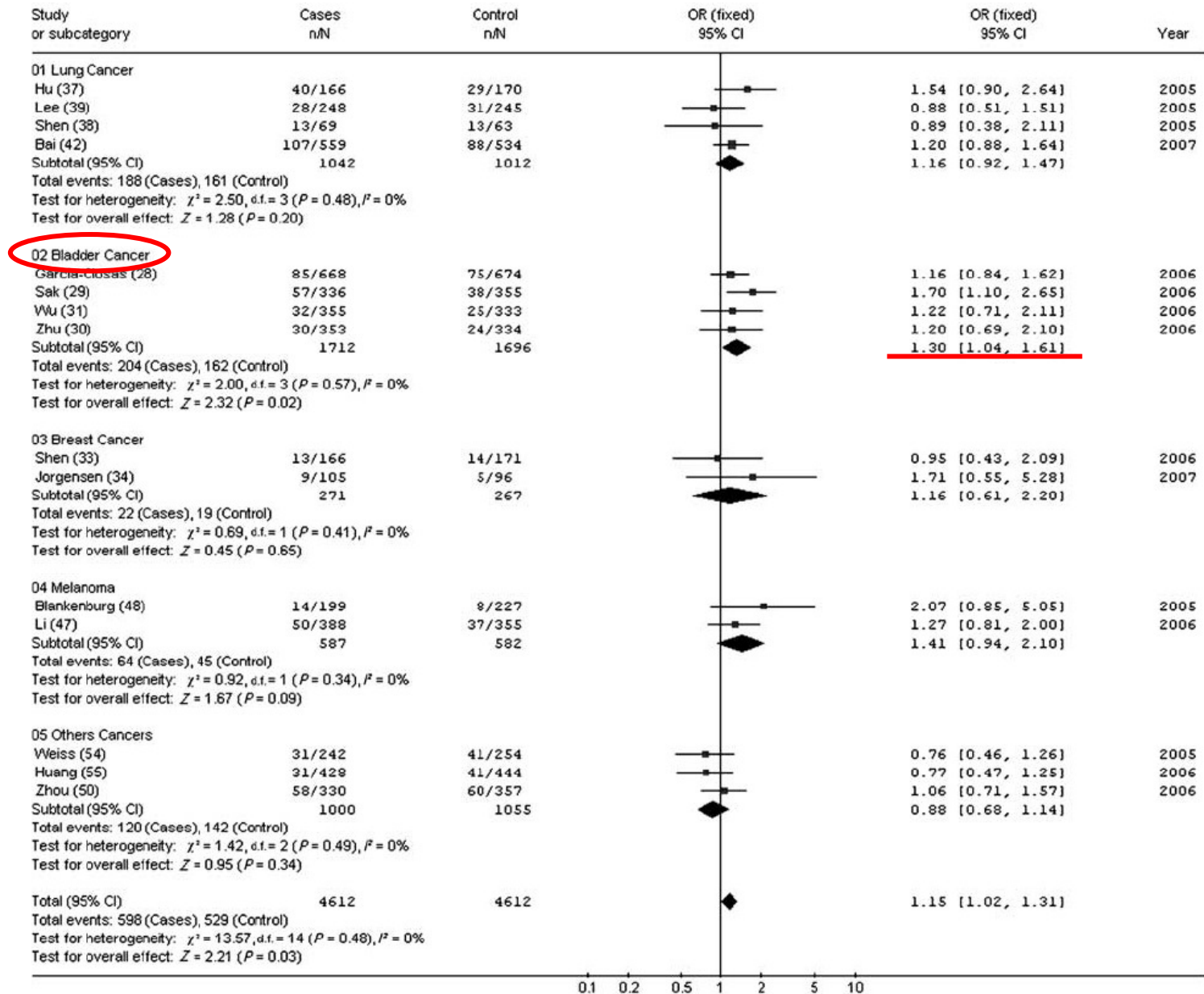
XPC 939Q allele X Cancer



XPC 939Q allele X Cancer



XPC 499V allele X Cancer



Contribution of heterozygous in Cancer susceptibility

XPC K939Q

| <i>XPC Lys939Gln</i> Tumor site | No. of studies | Cases n/N | Controls n/N | KK + KQ vs QQ | | KK vs KQ + QQ | |
|------------------------------------|----------------|--------------|-----------------|-------------------------------------|--------------|-----------------|-------------------------------|
| | | | | Genetic model recessive | Cases n/N | Controls n/N | Genetic model dominant |
| Breast | 7 | 367/3073 | 410/3048 | 0.87 (0.74–1.01) [£] | 1769/3073 | 1770/3048 | 0.97 (0.87–1.07) |
| Lung | 6 | 401/2580 | 331/2604 | <u>1.30 (1.11–1.53)[§]</u> | 1608/2580 | 1598/2604 | 1.05 (0.93–1.17) |
| Bladder | 5 | 500/3130 | 493/3095 | 1.01 (0.88–1.15) | 2021/3130 | 2037/3095 | 0.95 (0.86–1.05) |
| Head and neck | 4 | 204/1417 | 207/1652 | 1.29 (0.94–1.77) | 867/1417 | 993/1652 | 1.14 (0.92–1.42) |
| Gastroesophageal | 3 | 196/1435 | 212/1622 | 0.97 (0.75–1.24) | 882/1435 | 952/1622 | 1.10 (0.92–1.31) |
| Nonmelanoma | 2 | 211/1501 | 154/1158 | 0.89 (0.70–1.14) | 932/1501 | 685/1158 | 0.97 (0.81–1.15) |
| Melanoma | 2 | 151/896 | 147/976 | 1.14 (0.89–1.46) | 572/896 | 635/976 | 0.99 (0.66–1.48) ^b |
| Other sites | 4 | 241/1313 | 272/1432 | 1.04 (0.85–1.27) ^b | 813/1313 | 933/1432 | 0.91 (0.77–1.06) |
| Total | 33 | 2271/15345 | 2226/15587 | 1.03 (0.97–1.11) ^b | 9649/15345 | 9603/15587 | 0.99 (0.94–1.04) |

XPC Ala499Val XPC A499V

| Tumor site | | Cases n/N | Controls n/N | AA + AV vs VV | | AA vs AV + VV | |
|-------------|----|--------------|-----------------|-------------------------------------|--------------|-----------------|-------------------------------|
| | | | | Recessive | Cases n/N | Controls n/N | Dominant |
| Lung | 4 | 188/1862 | 161/1854 | 1.18 (0.95–1.47) | 10088/1862 | 1003/1854 | 1.00 (0.88–1.14) |
| Bladder | 4 | 204/2765 | 162/2813 | <u>1.32 (1.06–1.63)[§]</u> | 1255/2765 | 1254/2813 | 1.04 (0.93–1.15) |
| Breast | 2 | 22/408 | 19/426 | 1.23 (0.65–2.30) | 159/408 | 178/426 | 0.89 (0.68–1.18) |
| Melanoma | 2 | 64/896 | 45/8221 | 1.37 (0.92–2.04) | 373/896 | 439/8221 | 0.86 (0.72–1.03) |
| Other sites | 3 | 120/1672 | 142/1703 | 0.85 (0.66–1.09) | 792/1672 | 790/1703 | 1.03 (0.90–1.18) ^b |
| Total | 15 | 598/7603 | 529/7618 | 1.15 (1.02–1.30) [§] | 3587/7603 | 3664/7618 | 1.00 (0.93–1.06) |

XPC Polymorphisms X Tumor site X Ethnicity

| <i>XPC Lys939Gln</i> <i>Ethnicity</i> | <i>No. of studies</i> | <i>Homozygous analysis</i> <i>Lys/Lys vs Gln/Gln</i> | <i>Genetic models</i> | |
|--|-----------------------|---|-------------------------------------|------------------|
| | | | <i>Recessive</i> | <i>Dominant</i> |
| Asian | 11 | 1.11 (0.95–1.30) | 1.13 (0.98–1.30) | 1.01 (0.92–1.12) |
| Caucasian | 12 | 1.04 (0.88–1.24) ^b | 1.02 (0.87–1.19) ^b | 1.05 (0.97–1.14) |
| Mixed ethnicity | 10 | 0.98 (0.86–1.11) | 1.01 (0.90–1.14) | 0.95 (0.87–1.04) |
| <i>Asian</i> | | | | |
| <u>Lung cancer</u> | 4 | <u>1.23 (1.00–1.51)[£]</u> | <u>1.26 (1.04–1.52)[§]</u> | 1.02 (0.89–1.16) |
| <u>Head and neck</u> | 3 | <u>1.02 (0.63–1.66)</u> | <u>1.07 (0.68–1.68)</u> | 0.91 (0.68–1.23) |
| <i>Caucasian</i> | | | | |
| Bladder | 3 | 1.09 (0.90–1.32) | 1.08 (0.76–1.54) ^b | 1.12 (0.98–1.28) |
| <i>XPC Ala499Val</i> | | <i>Ala/Ala vs Val/Val</i> | <i>Recessive</i> | <i>Dominant</i> |
| <i>Ethnicity</i> | | | | |
| Asian | 5 | 1.09 (0.84–1.42) | 1.02 (0.79–1.31) | 1.10 (0.95–1.28) |
| Caucasian | 4 | 1.25 (0.99–1.57) | 1.24 (0.99–1.55) | 0.95 (0.85–1.06) |
| Mixed ethnicity | 6 | 1.05 (0.83–1.31) | 1.13 (0.91–1.41) | 0.98 (0.88–1.09) |
| <i>Asian</i> | | | | |
| Lung cancer | 4 | 1.16 (0.92–1.47) | 1.18 (0.95–1.47) | 1.02 (0.88–1.14) |

CONCLUSIONS

1- XPC may play a role in lung carcinogenesis

- Contribution of K939Q polymorphism

...more evidences:

- * Hypermethylation of XPC in lung cancer samples (Wu et al., 2007)
- * XPC KO mouse leads to lung carcinogenesis (Hollander et al., 2005)
- * Increased lung cancer incidence in XPC mutant mouse (Cheo et al., 1999)

2- XPC may play a role in bladder carcinogenesis

- Contribution of A499V polymorphism

- * Low expression of XPC contribute to bladder carcinogenesis and progression (Chen et al. 2007)



ARTICLE

XPC polymorphisms play a role in tissue-specific carcinogenesis: a meta-analysis

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