

P53, HPV and Cervical Cancer

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Background

- **Cervical cancer risk factors**
- **Tumor suppressor gene p53**
- **Interaction between HPV and p53**
- **Prognostic factors of cervical cancer**

Cervical Cancer

- Worldwide about **500 000** women acquire cervical cancer annually.
- **75%-80%** are from developing countries.
- Cervical cancer has leading mortality rate in the world, every year around **300 000** women die of this disease.

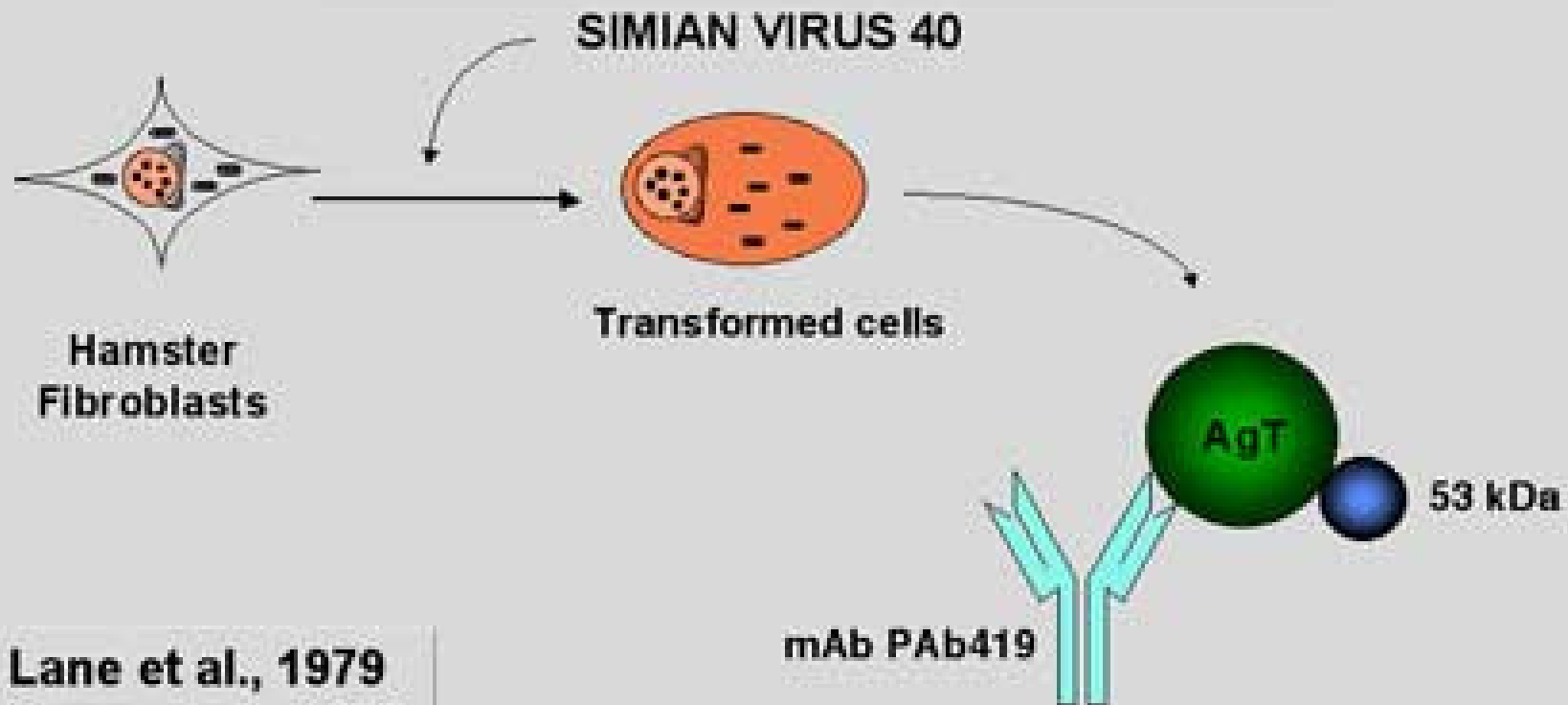
Risk Factors of Cervical Cancer

- HPV infection
- Multiple sex partners
- Smoking
- Oral contraceptives
- Family history
- **Molecular genetic factors: p53**

What is p53?

- **Discovery of tumor suppressor gene p53**
- **Structure and function**
- **Important transcription factor**

DISCOVERY OF p53 (I)



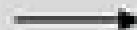
Lane et al., 1979
Kress et al., 1979
Linzer et al., 1979
Deleo et al., 1979

**Co-precipitation of SV40 large T Antigen
and a cellular protein of 53 kDa**

DISCOVERY OF p53 (II)

Rotter et al. 1979
Kress et al., 1979
Deleo et al., 1979

Transformed cells
(MetA, SVMK)

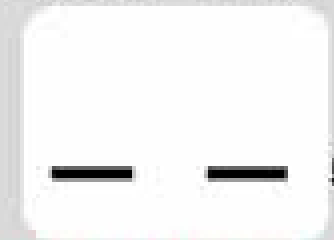


TUMOR



mouse sera

Met A SVMK

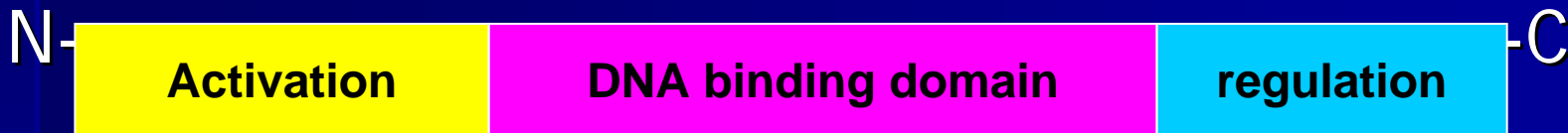


53 kDa

immunoprecipitation

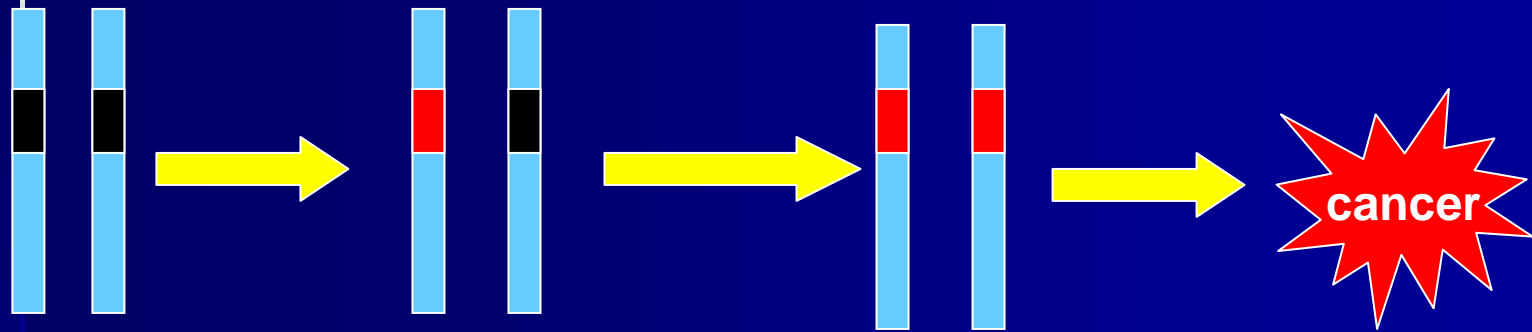
p53 Structure and function

- Located chromosome 17 p;



- 11 Exons, 393 Amino acids
- Molecular weight: 53 kd
- **Wild type:** tumor suppressor, apoptosis inducer
- **Mutant type:** loss of tumor suppress function, gain of oncogenic function (**oncogene**)

Tumor suppressor gene



normal alleles

one allele mutated

**the second allele mutated
(loss of heterozygosity)**

cancer

Cell growth arrest
Or apoptosis

DNA repair

Gene stability

No cell growth arrest

Inefficient DNA repair

Gene instability

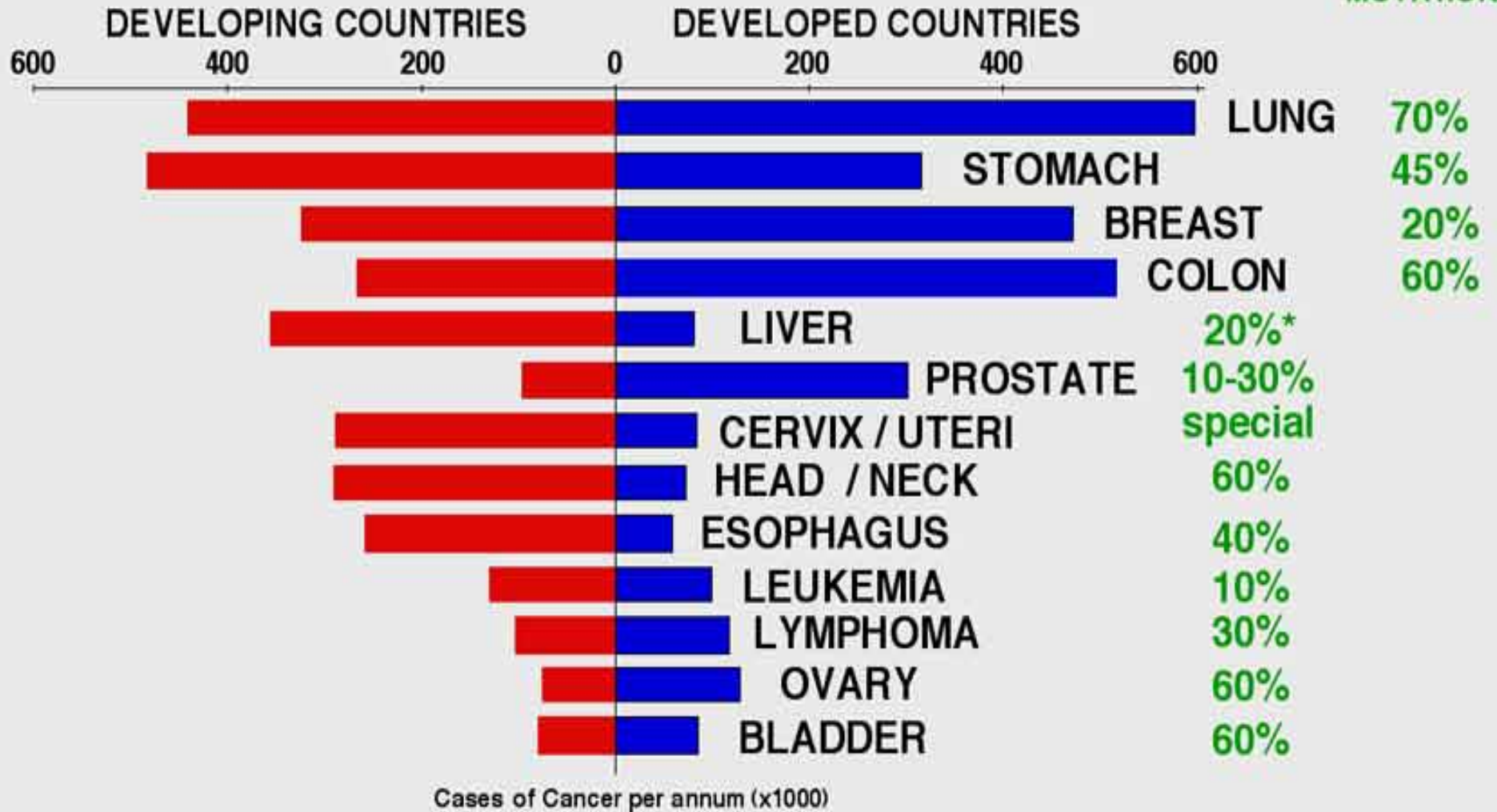
Malignant potential

P53 in Human Cancer

- The first p53 gene mutation in human cancer was described by Baker in 1989.
- It is estimated that **p53 mutations** are the most frequent genetic events in human cancers, accounting for more than **50%** of the human cancers.

WORLDWIDE DISTRIBUTION OF CANCERS AND p53 MUTATIONS

p53
MUTATIONS



NON MELANOMA SKIN 80%

Anatomy of p53 Mutations

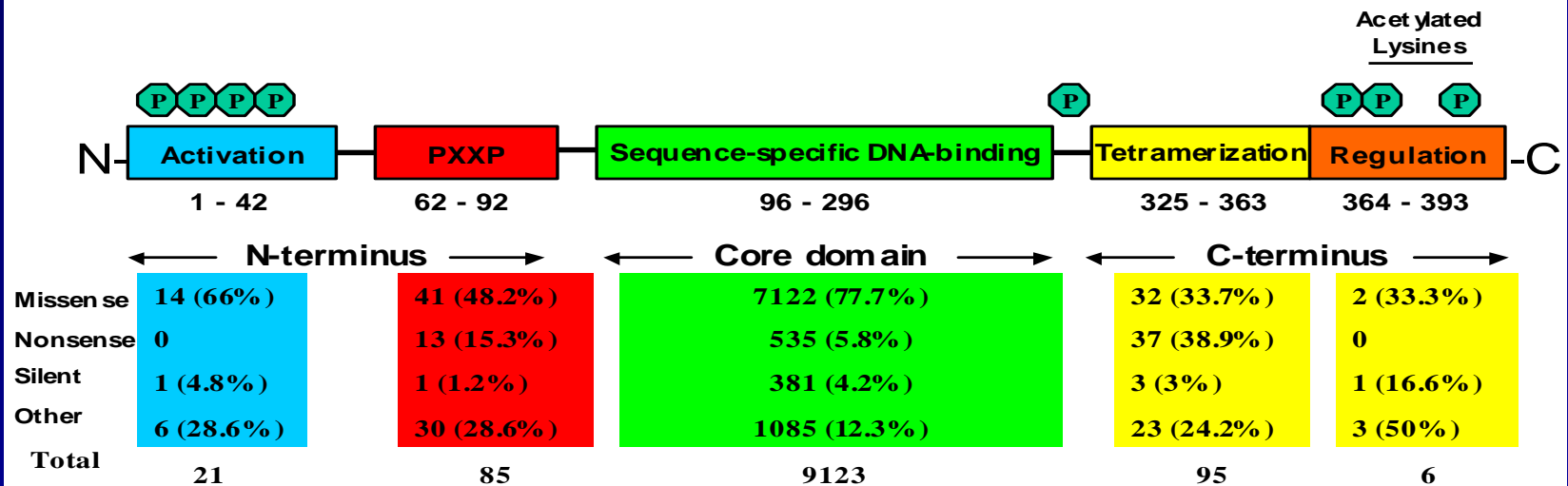


Fig. 1: Anatomy of p53 and the mutations in its coding sequence. p53 is a protein (393 amino acids) with the typical structure of a transcription factor: transcriptional regulatory region in the N-terminus, dimerization domain and regulatory regions in the C-terminus, central DNA binding domain that binds to consensus DNA motifs and provides the essential function for regulation of gene activation or repression. It is interesting to note that most known mutations in cancer affect the DNA binding domain. As you can see 90% of them are located in the central DNA binding domain. These results are based on the 10,000 mutations from the IARC database 1999.

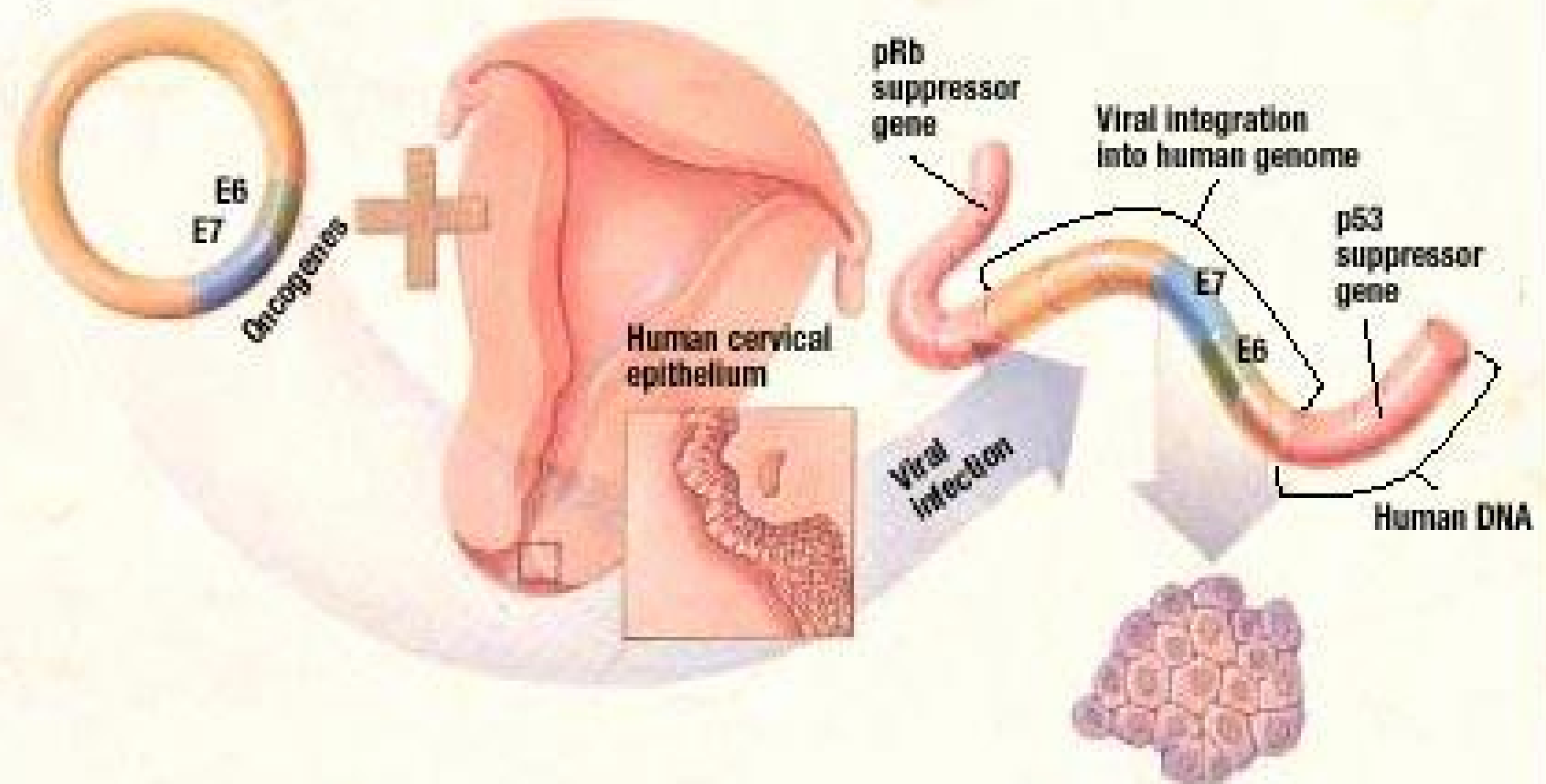
HPV and p53

Correlation ?

FIGURE 2

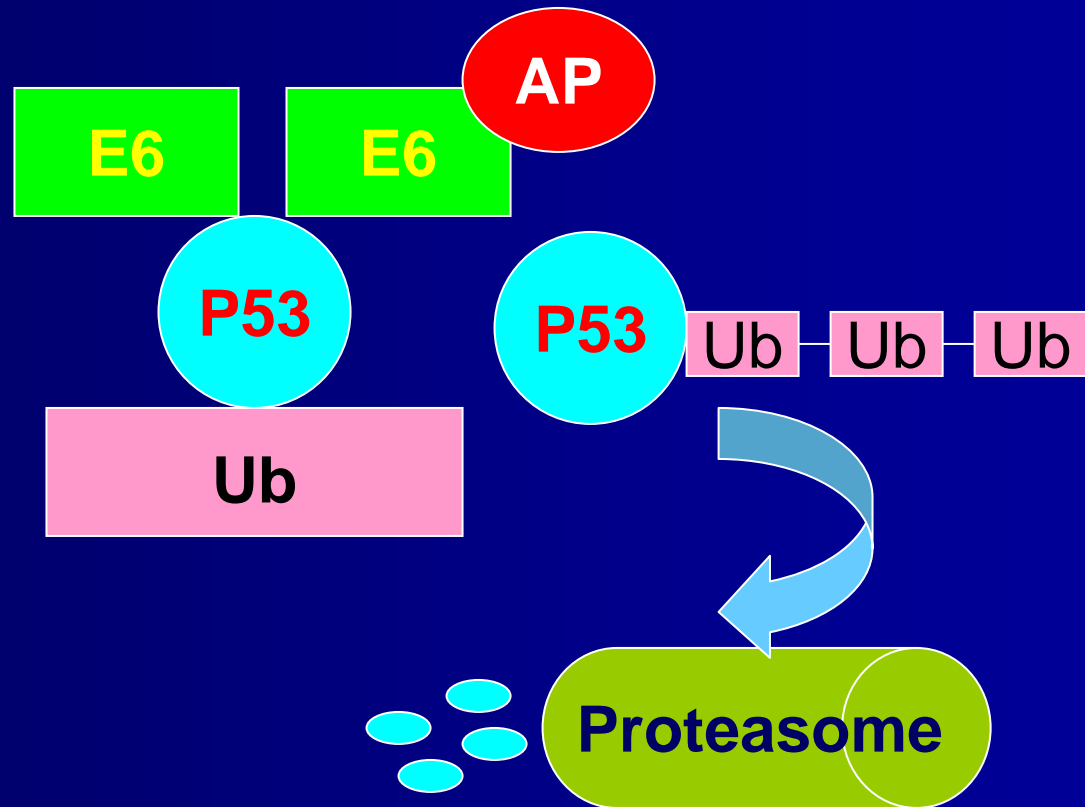
Viral oncogenes and cellular tumor suppressor genes in cervical cancer

Circular double-stranded
HPV 16 genome



E6 and E7 block tumor suppressor gene products p53 and pRb, leading to cell proliferation and tumor formation.

Degradation of p53 by E6



E6-AP :E6 associated protein

Ub: Ubiquitin

Prognostic Factors

- Tumor histologic type
- Low grade differentiation
- Parametrial infiltration
- Lymph node metastases
- HPV
- **P53 ?**

Objectives

- To analyse data about of p53 mutation LOH of p53 and p53 polymorphism in cervical cancer
- To investigate the correlation of p53 mutation and HPV infection in cervical cancer
- To evaluate whether p53 can be a prognostic factor in this malignancy

Methodology

- Electronic search, MEDLINE from 1989 to March 2004.
- World Health Organization (WHO)
- International Agency for Research on Cancer (IARC): p53 database

Key Words (MeSH):

- Cervical cancer/carcinoma, p53 mutation, HPV, LOH, p53 polymorphism

Exclusion Criteria

- Technical papers without original data.
- Letters and those that did not address cervical cancer or p53 mutation.
- Those data only containing results from cell line studies.
- Papers that did not measure HPV and p53 mutation as the reference standard.

Methods Commonly used to Detect p53 Alterations

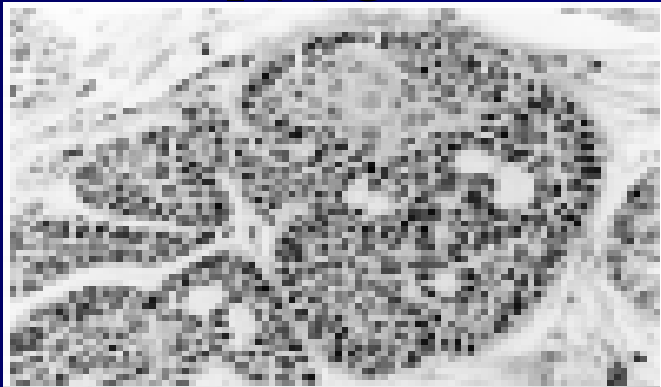
- Immunohistochemistry (IHC)
- Single-Strand Conformation Polymorphism (SSCP)
- PCR based methods to analyse LOH of p53 located in 17p13 and polymorphism in p53.

Methods used to detect p53 mutation

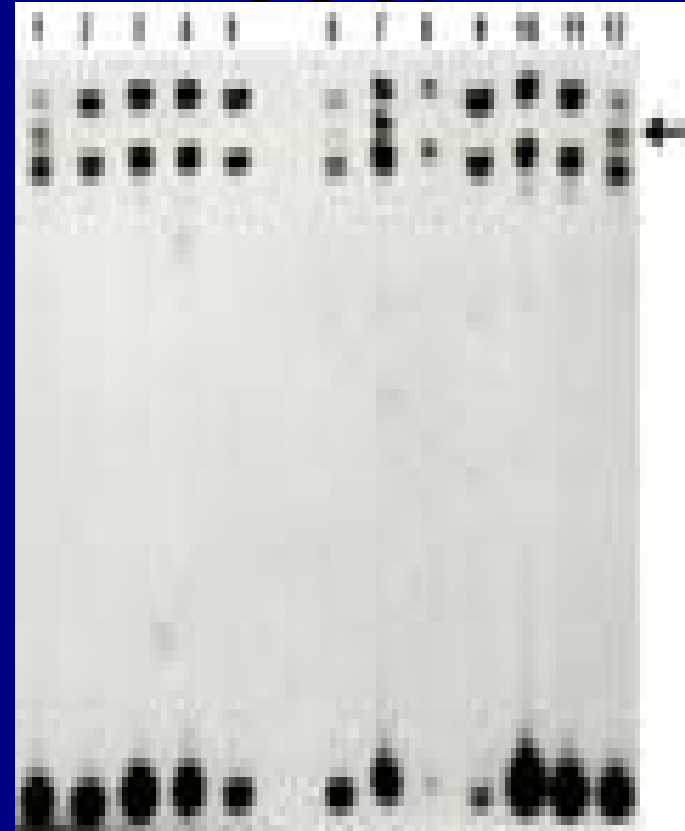
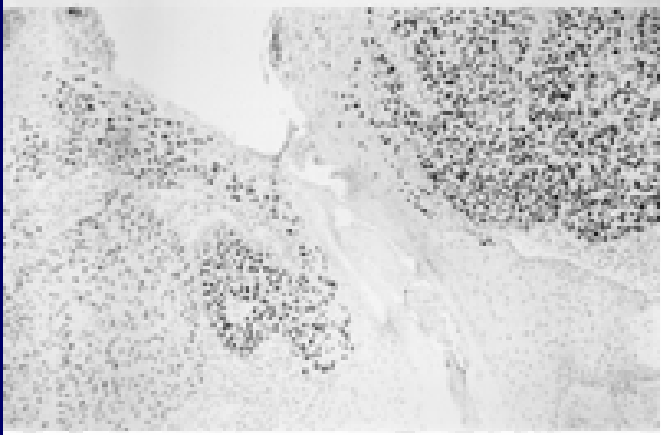
IHC

SSCP

Cxad

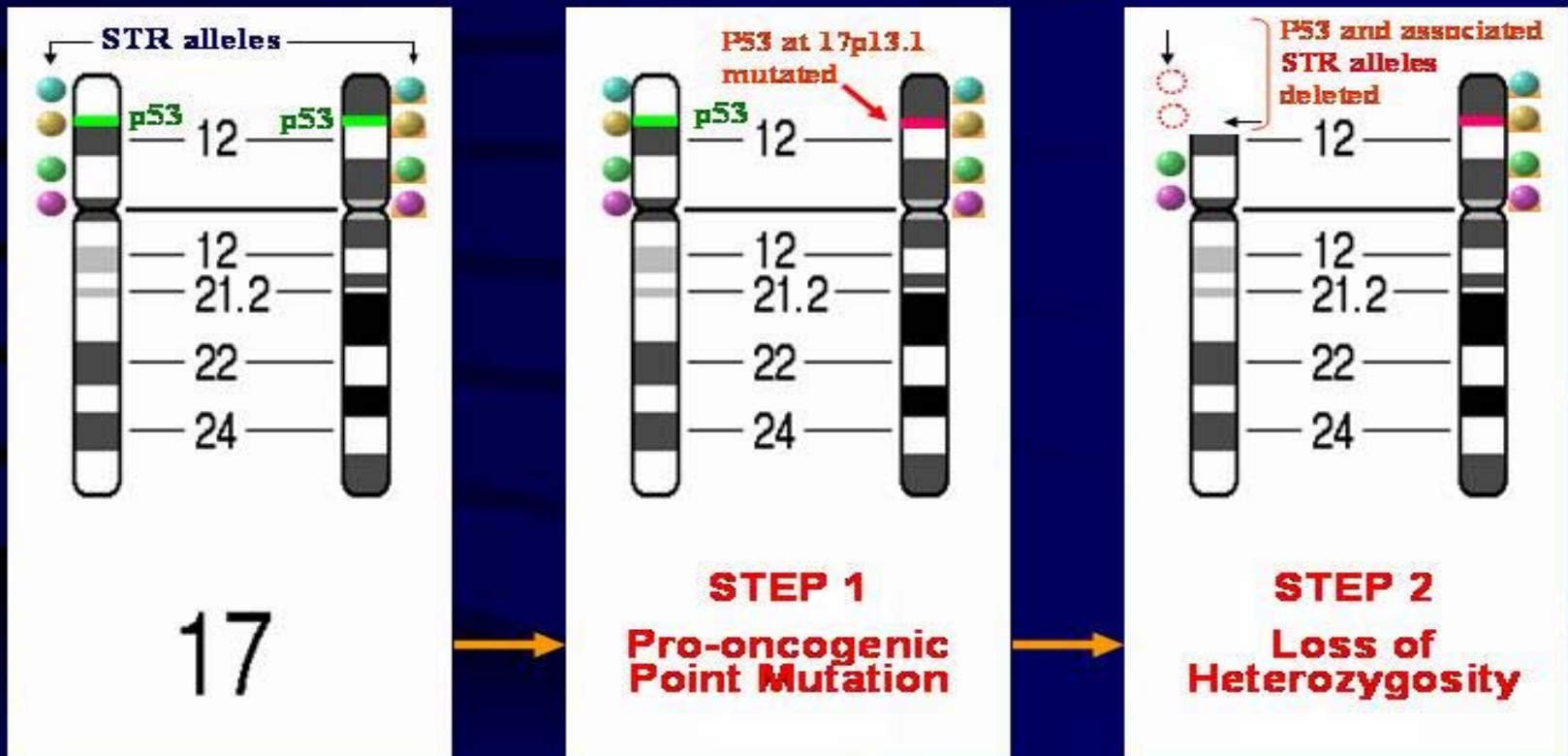


SCC



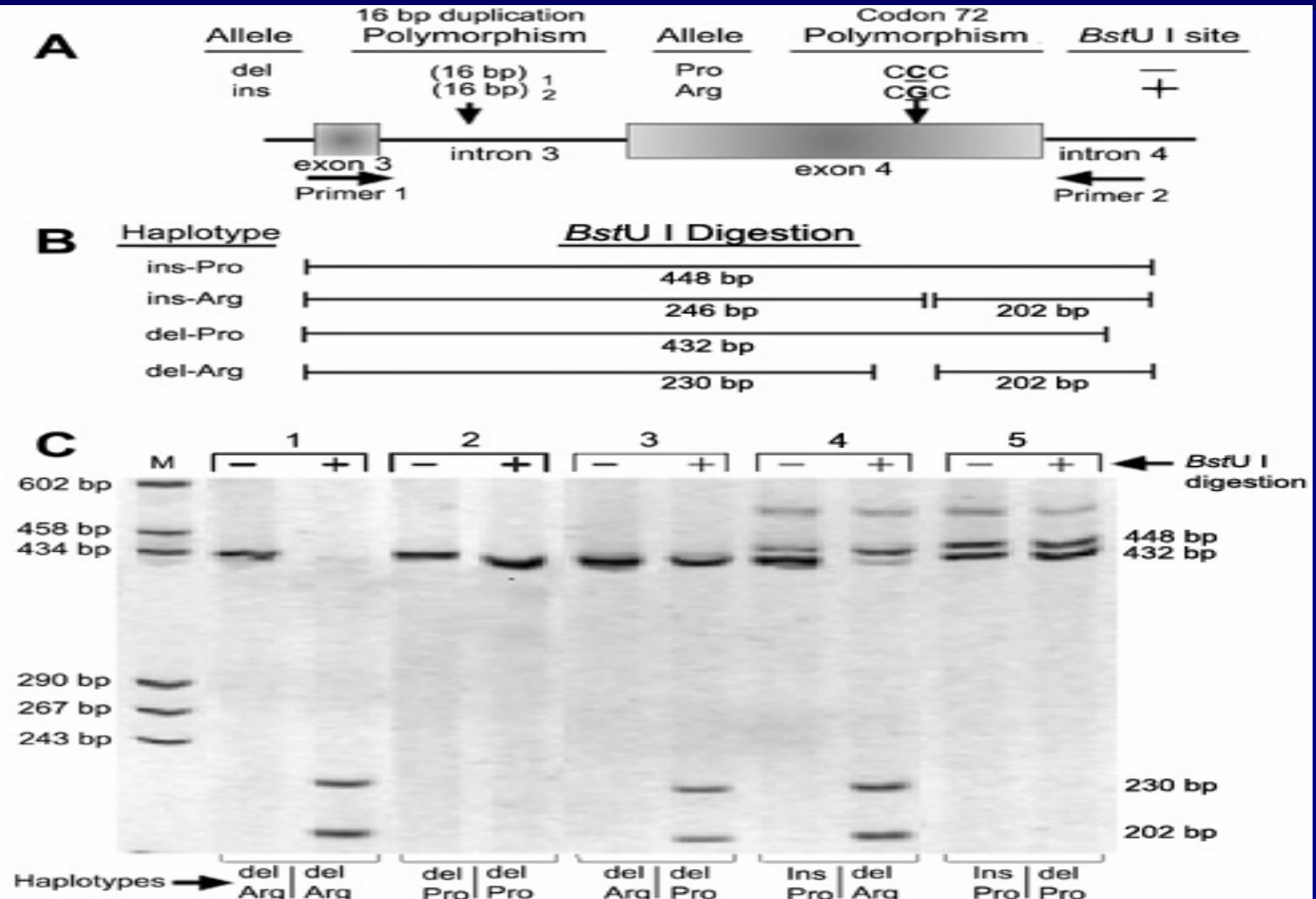
Loss of heterozygosity (LOH)

LOH in Knudson's "Double-Hit" Tumorigenesis Model



Li-Fraumeni Syndrome:
germline p53 mutation

p53 polymorphism



Results

- **P53 mutation in cervical cancer**
- **Correlation between p53 mutation and HPV**
- **Correlation between p53 mutation and radiotherapy**
- **LOH of p53**
- **P53 polymorphism**
- **Prognosis evaluation**

Prevalence of p53 Mutation in Cervical Cancer (SSCP)

References	Prevalence of p53	References	Prevalence of p53
■ Borresen AL et al. 1992	2.17	■ Kim JW et al. 1997	1.47
■ Fujita M et al. 1992	3.33	■ Ngan HY et al. 1997	2.0
■ Crook Tet al. 1992	10.71	■ Helland A et al. 1998	42.11
■ Paquette RL et al. 1993	3.57	■ Tenti P et al. 1998	13.51
■ Helland A et al.1993	2.17	■ Gostout B et al. 1998	4.0
■ Kessis TD et al.1993	3.45	■ Munirajan AK, 1998	9.0
■ Busby-Earle RM et al.1994	2.13	■ Limpai boon T et al. 2000	11.76
■ Miwa K et al.1995	5.13	■ Pinheiro NA et al. 2001	3.28
■ Ikenberg H et al.1995	4.65	■ Harima Y et al. 2001	10.77
■ Kim KH et al.1995	10.94	■ Denk C et al. 2001	5.56
■ Milde-Langosch K, et al. 1995	7.8	■ Ishikawa H, et al. 2001	26.9

Association between p53 Mutation and HPV Infection in Cervical Cancer (SSCP)

References	Cases	Prevalence of p53(%)	Prevalence of HPV (%)	P53 and HPV correlation
Ishikawa H, et al. 2001	52	26.9	76.9	positive related
Helland A, et al. 1998	365	42	76.5	negative related
Munirajan AK, et al. 1998	43	9	70	not related
Milde-Langosch K, et al. 1995	51	7.8	80.4	not related
Kim KH, et al. 1995	64	15.6	67.2	not related

Correlation between p53 Expression and Prognosis in Cervical Cancer (IHC)

References	Cases	P53 Prevalence (%)	Related with prognosis
Gitsch G, 1992	43	46.5	not related
Oka K, 1993	192	25.5	not related
Kainz C, 1995	109	20.2	not related
Benjamin I, 1996	132	44	not related
Kersemaekers AM, 1999	136	32	not related
Horn LC, 2001	114	63.8	not related
Ngan HY, 2001	57	25.2	not related
Haensgen G, 2001	70	85.7	not related
Total	853	46.0%	

Correlation between p53 expression and prognosis in cervical cancer (IHC)

References	Cases	P53 Prevalence (%)	Related with prognosis
Tsuda H, 1995	26	46	related
Bremer GC, 1995	156	30.2	related
Raju GC, 1996	119	58	related
Waggoner SE, 1996	21	67	related
Uchiyama M, 1997	32	34	related
Carrilho C, 2003	45	50	related
Total	399	47.80%	

Correlation between p53 and Radiotherapy

■	References	Cases	Prevalence of p53	relation with radiotherapy
■				
■	Oka K 2000	202	52.1	related
■	Mukherjee G 2001	78	34	related
■	Jain D 2003	76	53.9	related
■	Rajkumar T 1998	40	10	related
■	Ebara T 1996	46	63	not related
■	Nakano T 1998	64	84.6	not related

LOH of p53 in Cervical Cancer

■	References	Cases	Prevalence of LOH	LOH and prognosis
■	Atkin NB 1990	43	17	
■	Kinoshita M 1994	11	36.4	
■	Busby-Earle RM 1994	20	15	
■	Mitra AB 1994	17	41.2	
■	Park SY 1995	26	40	
■	Wistuba I 1996	12	50	
■	Mullochandov MR 1996	38	15	
■	Kim JW 1997	55	5.5	
■	Southern SA 1997	25	36	
■	Kersemaekers AMF 1998	64	38	
■	Harima Y 2001	65	33.8	related
■	Helland A 2000	79	18	related

P53 Polymorphism in Cervical Cancer

- Pillai MR, India, 2002
- Cervical cancer (Cxca): 232
- Control: 198
-

	Cxca (%)	Control (%)
■ Arg/Arg	20.2	18.5
■ Pro/Arg	48.4	51.3
■ Pro/Pro	31.4	30.2

- No correlation with HPV.

P53 polymorphism in Cervical cancer and its precursor

- Nishikawa A, Japan, 2000
- Cervical cancer (Cxca): 87
- CIN: 28
-

	Cxca(%)	CIN (%)
■ Arg/Arg	44.8	39.3
■ Pro/Arg	42.5	35.7
■ Pro/Pro	10.3	21.4

- No correlation with HPV and prognosis.

P53 Polymorphism in Cervical Cancer

- Hernadi Z, Hungary, 2003
- metastases nodes VS non-metastases nodes

■		nodes(+) (%)	nodes(-) (%)
■	Arg/Arg	54.5	67.9
■	Pro/Arg	45.5	21.4
■	Pro/Pro	9.1	7.1

- No correlation with HPV.

Summary of Results

- The tumor suppressor gene p53 mutations were found to be uncommon in cervical cancer.
- The correlation between p53 mutation and HPV infection is controversial.
- LOH of p53 has also been found in cervical cancers and related to the progression of this malignancy, but not related with HPV status.
- The p53 polymorphism failed to be an individual risk factor in predicting the outcome of patients with cervical cancer.

Conclusion

- **Understanding the behaviour of p53 alterations, and analysing it thoroughly for each patient, could allow us to develop sound correlations between p53 status and patient outcome.**

Conclusion-2

- **Epidemiological surveys should be undertaken in larger populations and in different geographical regions.**

Postgraduate Research Training in Reproductive Health in China 2004



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