Summary
SUMMARY

The aim of this research was to analyse the prevalence of HPV subtypes and its significant role in the molecular pathogenesis of cervical cancer in Chennai, South India. Considerable importance was given to the understanding of the molecular pathology of HPV infection in cervical carcinogenesis. Thus, the involvement of certain co-factors of host cell and their interactions with HPV infection have been investigated in this study.

Sixtysix percent of the study population including normal subjects analysed using sensitive PCR technique with type specific primers, were found to be infected with HPV subtypes 6,11,16 and 18. Interestingly, 90% of the invasive cervical carcinoma cases (54/60) were found to be infected with high-risk subtypes (HPV 16/18) alone. Besides, 75% of cervical cancer cases of different histopathologic grades were positive for HPV infection. Thus, high-risk HPV infection could be the key etiologic factor leading to cervical carcinogenesis in Chennai, South India.

This study using PCR technique has identified the high-risk subtype HPV 16 as the predominant one with a prevalence of 78.3% of the study population in Chennai.

This risk of HPV infection to develop cervical cancer has been estimated by statistical analysis and the odds ratio was found to be 62 with a relative risk of 17.82. This risk estimation is very much close to the estimation reported recently (Krishnan Nair, 1999).
The frequency of infection with low-risk subtypes HPV 6/11 found in cervical intraepithelial lesions was not seen in invasive cancer, which is in good agreement with Hines et al. (1995). This suggests the involvement of low-risk HPV subtypes in benign premalignant lesions with lower oncogenic potential and such lesions can be regressed upon treatment.

A very good positive correlation also was observed for high-risk HPV 16/18 infection with cervical cancer progression in the present study, which indicates the strong association of high-risk HPV infection with higher oncogenic potency in cervical cancer in Chennai, South India. So, priority should be given for the eradication of HPV infection so as to control cervical cancer.

HPV infection has been shown to interrupt both the process of apoptosis and cell proliferation of normal cell cycle. This interruption can be mediated through certain cellular oncogenes like, tumour suppressor gene p53, apoptosis promoter gene bax, anti-apoptotic proto-oncogene bcl-2 etc., and factors involved in cell proliferation like PCNA.

An abnormal nuclear expression of tumour suppressor protein p53 was observed using immunocytochemistry in cervical cancer biopsies but not in normal subjects. The intensity of its immunoreactivity also was positively correlated with the histopathologic progression and HPV status of cervical cancer.
An anti-apoptotic protein bcl-2 also has been shown to be abnormally expressed in the cytoplasm of cervical cancer biopsies on immunocytochemical analysis, with a highly significant correlation with histopathologic progression.

The cell proliferation status was assessed in terms of PCNA by immunocytochemistry using anti-PCNA monoclonal antibody. An over-expression of nuclear PCNA was observed in cervical cancer throughout the epithelium, whereas the immunoreactivity was limited to the basal layer alone in the case of normal biopsies. The intensity of PCNA immunoreactivity was positively correlated with the histopathologic progression of cervical cancer.

This study thus indicates that the above-said apoptosis regulatory proteins and proliferation marker are serially modulated in cervical cancer progression. We have also indicated a strong positive correlation between the modulated expression of these cellular oncogenic factors and HPV infection status. This depicts that the modulation of cellular factors may be brought about by the high-risk HPV infection.

Finally, the present study was focused on the complex interlinked process responsible for cervical carcinogenesis and its progression. Cancer is a result of disturbance of interregulated cell cycle of a normal cell and the understanding of which may provide an important information about the mechanism of carcinogenesis.
In extention to the present study we have also analysed the role of all-trans-retinoic acid (ATRA) in HPV-induced cervical lesions in limited number of cases and controls. The results suggest that the decreased serum level of ATRA may have major influence on HPV infection and progression to cervical cancer.

In conclusion, we found high-risk HPV to be the strongest risk determinant of cervical cancer, particularly in Chennai, South India. The complex formation of oncoproteins of high-risk HPV subtypes with normal p53 protein leads to the inactivation of p53 protein which in turn may release the repressive action of p53 on bcl-2 protein. This may be the reason for the co-overexpression of the functionally antagonistic proteins p53 and bcl-2 in cervical cancer. It is also important to note that the PCNA overexpression may be the direct effect of HPV upon induction of cell growth signals. The mechanism of HPV-induced cervical carcinogenesis proposed in the present study is schematically represented in Fig.20.

The cervical cancer incidence can be reduced by effective screening program using PCR technique and by developing a vaccine against particular high-risk HPV subtype 16. The understanding of molecular pathogenesis of HPV infection may also help to improve the therapeutic approaches.
Fig. 20  Role of p53, bcl-2 and PCNA in Normal Cell Cycle and its Altered Function in Pathologic Conditions of HPV Induced Cervical Carcinogenesis

Normal Cell Cycle

EGF

Normal EGF Activity

Normal cell

Cell cycle with genetic damage

Genotoxic stress signals

Cell growth signals

Cell Growth genes

Proapoptotic genes

p53

Cell cycle arrest genes

DNA repair genes

Apoptosis regulators

Bax

bcl -2

Cell death effectors

Unrepaired cell cycle

Cell cycle arresting proteins

Cell cycle arrest at G1 → S and G2 → M

Gene repair system

Cell cycle progression by growth signals

Repaired Normal Cell cycle

Normal cell growth

Normal PCNA expression

Apoptosis

Normal cell growth events

Normal cell