EARLY SQUAMOUS CELL CARCINOMA OF THE CERVIX:
IMPLICATIONS FOR PREVENTION STRATEGIES

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ABSTRACT

The carcinoma of the cervix is the second most common cancer amongst women around the world, with its higher occurrence in developing nations. Solid clinical and experimental evidence showed that the high-risk (HR) types of human papilloma virus (HPV) assume a focal part in bringing about cervical cancer. It is generally acknowledged that the development of intrusive cervical cancer from intraepithelial neoplasia (cervical intraepithelial neoplasia [CIN] 1-2/3) includes molecular changes and in this manner is a preventable if identified and treated early. In the pathogenesis of cervical carcinoma there are three noteworthy segments, two of them identified with the role of human papillomaviruses (HPV). First, the impact of viral E6 and E7 proteins. Second, the reconciliation of viral DNA in chromosomal region. Some of these viral incorporations occur intermittently at particular chromosomal regions, for example, 8q24 and, both harboring HPV18 and HPV16. Also,thirdly, there are other intermittent genetic modifications which are not connected to HPV. Recurrent losses of heterogeneity (LOH) have been distinguished in chromosome regions 3p14–22, 4p16, 5p15, 6p21–22, 11q23, 17p13.3 without impact on p53,18q12–22 and 19q13, every one of them proposing the genetic alteration of tumor suppressor genes not yet recognized. Intermittent amplification has been mapped to 3q+ arm, with the common region in 3q24–28 in 90% of invasive carcinomas. The development of cervical carcinoma requires the successive recurrence and selection of a few genetic alterations. The distinguishing proof of the particular genes involved, and their connection with particular cancer properties and stages could enhance the comprehension and perhaps the management of cervical carcinoma.
In this way, a top to bottom comprehension of the apoptotic genes that control molecular mechanism in cervical cancer are of critical significance. Valuable targets for therapeutic treatment would be those that adjust apoptotic pathways in a way where the departure of HPV from reconnaissance by the host immune system is avoided. Such a methodology coordinated at the apoptotic genes may be helpful in the treatment of cervical carcinoma.

**KEYWORDS:** cervical carcinoma; genetic damage; papillomavirus; viral integration; LOH.

**INTRODUCTION**
Cervical cancer is a serious malady which influences women's wellbeing.\(^{[1-3]}\) It is the second most common cancer in women globally. More than 200,000 women kick the bucket from cervical cancer every year.\(^{[4-5]}\) China is tormented with one of the most astounding rates from cervical cancer on the planet, and it is six times higher than other developing nations. Cervical cancer is a perplexing ailment that outcomes from the interaction between gene mutation and various environmental factors.\(^{[6]}\) Epidemiological and research center based studies have distinguished that human papilloma virus (HPV) infection leads to cervical cancer (table:1). More than 90% instances of cervical cancer are brought on by HPV infection, and type 16 and 18 are the most widely recognized types.\(^{[7-11]}\)

<table>
<thead>
<tr>
<th>Table 1: Different grades of precursor lesions found in biopsy</th>
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<tr>
<td>Cervical Intraepithelial neoplasia I (CIN I)</td>
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<td>CIN II</td>
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<td>CIN III</td>
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<tr>
<td>Carcinoma in situ</td>
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<td>Invasive Carcinoma</td>
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**Histopathology**
All cancers must be microscopically confirmed.\(^{[12-15]}\) Cases ought to be delegated carcinomas of the cervix if the primary development is in the cervix.\(^{[16]}\) Every histologic type must be incorporated. The histopathology types are.
- Squamous cell carcinoma (keratinizing; non-keratinizing; verrucous).
- Endometrioid adenocarcinoma.
- Clear cell adenocarcinoma.
- Adeno-squamous carcinoma.
- Adenoid cystic carcinoma.
Small cell carcinoma.
- Undifferentiated carcinoma.

**Whereas Histopathological grades are as per the following**[17-19]
- GX: Grade can't be evaluated.
- G1: Well separated.
- G2: Moderately separated.
- G3: Poorly or undifferentiated.

At the point when surgery is the essential treatment, the histologic findings allow the case to have pathologic staging, as depicted previously. In this circumstance, the TNM classification may be utilized[20-23] (Figure: 1).

**Intermittent point mutations in cervical cancer**

There have been a few studies endeavoring to recognize mutations in gene understood to have point transformations in different cancers, including H-RAS, TP53, p16INK4A, p15INK4B RB and other cell cycle genes.[24] These were tested in both HPV positive and negative cells. The p15 and p16 genes, both on chromosome 9p21 and isolated by 25 kb, don't show mutations in Cervical cancer.[25-27] On the other hand, it is not known whether the p19ARF gene, which imparts exons to p16 and which seems, by all accounts, to be the reason for the phenotype beforehand ascribed to p16, is also influenced.[28]

**Neoadjuvant chemotherapy and surgery**

Hypothetical rationale for the utilization of neo adjuvant chemotherapy (NACT) incorporates the instigation of cancer shrinkage to encourage radical extraction, and a conceivable change in results over surgery alone.[29-30] There is additionally a plausibility of NACT sterilizing
nodes and parametria, accordingly decreasing risk factor for adjuvant treatment after surgery; then again, the safety and efficacy of neoadjuvant treatment in this circumstance is not known. Meta-analysis of individual patient information from randomized trials of neoadjuvant platinum-based chemotherapy preceding definitive surgery demonstrates that patients treated with NACT have preferred survival results over those treated with primary radiation alone, given at a moderately low measurements.\textsuperscript{[31-32]} NACT followed by surgery is regularly utilized in various countries, however its role is indeterminate as a survey of accessible literature recommends no advantage of NACT–surgery over forthright surgery in addition to adjuvant treatment. Ideal pathologic reaction, characterized as tenacious residual disease with under 3 mm of stromal intrusion in the surgical sample, is the most grounded indicator of freedom from local recurrence for subjects treated with NACT and surgery.

**Figure 2: Stages of IB1 and IB2 in cervical cancer**

A chemotherapy treatment of paclitaxel, ifosfamide, and cisplatin has higher reaction rates than ifosfamide and cisplatin for FIGO Stage IB\textsubscript{2} (figure 2), albeit not for Stage IIB. A measurably critical impact on general survival was not found, despite the fact that this study was inadequately fueled for general survival results.\textsuperscript{[33]} Surgery after NACT ought to comprise of radical hysterectomy and pelvic lymphadenectomy. Numerous patients randomized to NACT–surgery either were not able to continue with radical surgery after chemotherapy (40%) or required extra adjuvant treatment after surgery (26%). NACT–surgery ought to be deliberately considered in patients with large cancers or adenocarcinoma histology inferable from lower reaction rates.\textsuperscript{[34]} FIGO IIB and higher stages ought to be specially dealt with definitive chemo radiation treatment. NACT clouds the pathologic findings at the season of surgery, convoluting assessment of signs for adjuvant radiotherapy
with or without adjuvant chemotherapy. Signs for adjuvant treatment after primary surgery are regularly connected in the setting of NACT surgery.\textsuperscript{[35]}

**Cervical cancer amid pregnancy**

A multidisciplinary approach with contribution of obstetrician and neonatologist is prescribed to figure an ideal treatment approach for every individual situation. All management plans ought to incorporate full discussion with the women and her wishes must be regarded.\textsuperscript{[36]} In general, the management of cervical cancer in pregnant women follow the same standards as in non-pregnant women. Diagnoses made before 16–20 weeks of pregnancy are for the most part treated immediately with either surgery or chemo radiation owing a concern of impairment to patient survival with treatment delay.\textsuperscript{[37]} From the second trimester onwards, surgery and chemotherapy can be utilized in selected cases while safeguarding the pregnancy.\textsuperscript{[38–40]} In the event that the diagnosis is made after 20 weeks, treatment deferral has all the earmarks of being a possibility for Stages IA2 and IB1, with no clear impairment of prognosis compared with non-pregnant controls.\textsuperscript{[41]}

Treatment comprising of traditional cesarean delivery and radical hysterectomy is regularly attempted when a parity is reached between contending maternal and fetal wellbeing risks, as a rule not later than 34 weeks of pregnancy.\textsuperscript{[42–43]} For more propelled infection, it is not known whether treatment postponement will influence survival. In practice, the duration of the treatment delay ought to be affected by clinical stage and Histopathological findings of the cancer, gestational age at analysis, and the parent's desire in regards to their unborn kid\textsuperscript{44}. In the event that a treatment delay is planned in women with locally advanced disease neoadjuvant chemotherapy may be considered trying to forestall disease progression and a close clinical observation is mandatory.\textsuperscript{[43–46]}

**Closing Remarks**

HPV DNA testing has an enormous effect in both developed and developing nations considering the reproducibility and sensitivity of HPV tests. Further investigations are going ahead to contemplate if hr-HPV DNA testing should be possible as primary testing technique, in light of the fact that a negative HPV test outcome offers broadened time of safety over negative cytology results. Incorporation of hr-HPV tests in cervical screening program can build public awareness regarding hr-HPV and cervical cancer, which may prompt higher usage of prophylactic HPV immunization. In outline, latest advances in cervical cancer screening is one of the important multidimensional way to deal with the counteractive action
of cervical cancer. Notwithstanding usage of new screening methods, assessment of their adherence and accomplishment over time will augment the advantages of cervical cancer prevention strategies.

**Conflicts of Interest Statement**

The Authors declare no conflicts of interest.

**REFERENCES**


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