

## Uterus: Carcinoma of the cervix (updated: old version not available)

### Classification

<b>Note</b>	squamous cell carcinoma (80%) adenocarcinoma (10%) adenoacanthoma (10%)
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### Clinics and Pathology

<b>Disease</b>	carcinoma of the cervix uteri; usually arises in the transitional zone between squamous and columnar cell epithelium
<b>Etiology</b>	infection with high-risk forms of the human papillomavirus (HPV) is established as the major factor: a secondary factor is cigarette smoking; recent evidence suggests that a polymorphic variant of the tumour suppressor P53 (p53Arg) may represent a risk factor for cervical carcinogenesis
<b>Epidemiology</b>	over 470,000 new cases are diagnosed annually worldwide
<b>Clinics</b>	haematuria
<b>Cytology</b>	cervical smears confirm the diagnosis of carcinoma or may reveal the presence of the disease in its preinvasive (preclinical) stage
<b>Pathology</b>	three grades of preinvasive carcinoma-in-situ (CIN) are recognised: I (which usually undergoes spontaneous resolution), II and III; carcinomas are staged as follows: IA: early invasive, not grossly visible; IB: usually grossly visible, but confined to the cervix; IIA: spread to the upper two thirds of the vagina only; IIB: lateral extension into the parametrium; IIIA: involvement of the lowest third of the vagina; IIIB: involvement of the pelvic side wall or hydronephrosis; IVA: bladder or rectal involvement; IVB: distant metastasis
<b>Treatment</b>	radiotherapy and/or surgery; late stages: radiotherapy supplemented by chemotherapy (e.g. cisplatin)
<b>Evolution</b>	preinvasive stage, detectable by cervical cytology, shows a peak incidence between 25 and 40 years; that of invasive cancer is 40-50 years, thus indicating that the preinvasive usually progresses to the invasive stage over a very prolonged period
<b>Prognosis</b>	preinvasive lesions are curable by local removal; stage I and early IIA cases may expect 80-90% five year survival; later cases show survival rates of 65-20% or less

## Cytogenetics

Note polyploidisation, with modes in the triploid region or above, is common, particularly in the preinvasive phase where it may be linked to the frequent spindle anomalies that result, for instance, in the "three group" metaphases seen in histological sections and chromosome preparations; structural changes are commonest in chromosomes 1, 3, 5, 11 and 17 where, except in chromosome 5, they most often result in short-arm deletions

Cytogenetics Morphological Chromosome 1: changes may also result in the acquisition of additional long-arm material (as is common in other types of carcinoma), e.g. in the form of a 1q isochromosome

Chromosome 3: additional material on 3q has been shown by comparative genomic hybridization (CGH) in 90% of carcinomas and this gain may occur at the point of transition from severe dysplasia to invasive carcinoma; recent studies suggest involvement of the hTR gene which encodes the RNA component of telomerase; loss of heterozygosity (LOH) studies indicate that there are two regions on 3p where tumour suppressor genes may be situated: at 3p14.2 (FHIT gene) and at 3q21, gene not yet identified

Chromosome 4: LOH studies suggest that at least two genes are important, at 4p16 and 4q21-35

Chromosome 5: an i(5p), often in two or more copies, is a frequent finding in cervical carcinomas, and this is consistent with CGH studies which show amplification of 5p, particularly in advanced stages

Chromosome 6: LOH studies show a high frequency of loss in the region 6p21.3-p25

Chromosome 11: possible gene loss on both chromosome arms are suggested by LOH studies, at 11p15 and 11q23; identities of the genes have yet to be determined

Chromosome 17: G-banding and LOH studies have shown the nonrandom loss of 17q, where the [P53](#) gene is situated (at 17p13.3); mutations or loss of this gene are, however, relatively infrequent compared with other types of tumour, perhaps because there is instead interaction between p53 protein and the HPV E6 viral gene in most carcinomas of the cervix; indeed, p53 appears to be more frequently mutated in HPV-negative tumours

Role of HPV: types 16 and 18 are associated with about 70% of cervical carcinomas (other high-risk types include 31, 33, 35, 39, 51, 52, and 56); these high-risk types are often demonstrable in the moderate and severe stages of preinvasive malignancy (CIN II and III); in these lesions they are commonly situated extrachromosomally while in carcinomas they are integrated into chromosomes at random locations, where they undergo disruption of the HPV E2 viral transcriptional regulatory protein; integration may thereby provide a selective advantage resulting in uncontrolled cellular proliferation leading to aneuploidy; it has recently been shown that a single finding of HPV DNA in a Pap smear from healthy women confers an increased risk of future

invasive carcinoma that is positive for the same type of virus. Another recent study suggests that integration of high-risk HPV DNA in cervical swabs or tissue removed from patients with CIN II or III strongly suggests that progression to carcinoma will occur

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