■ ОБЗОРНЫЕ СТАТЬИ

E.I. CORTÉS-GUTIÉRREZ [1], M.I. DÁVILA-RODRÍGUEZ [1], R.M. CERDA-FLORES [2]

[1] Department of Genetics. Centro de Investigación Biomédica del Noreste, Instituto Mexicano del Seguro Social. Monterrey, México
[2] Facultad de Enfermería, Universidad Autónoma de Nuevo León. Monterrey, México
E-mail: elvacortes@cibinmty.net

CHROMOSOMAL DAMAGE AS PROGNOSIS MARKER IN CERVICAL CARCINOGENESIS

Cancer of the uterine cervix is the third most common cancer in women worldwide and the most common cancer among Mexican and Latin American women. Risk factors that have been associated with the development of cervical intraepithelial neoplasia suggest that Human Papillomavirus (HPV) types 16, 18, 31, and 33 entail a high risk of developing a malignancy of this type. The accumulation of genetic alterations allows the growth of neoplastic cells; chromosomal instability is an event that occurs in the precancerous stages. The candidate cancer risk biomarkers include cytogenetic endpoints, such as chromosomal aberrations, sister chromatid exchange, micronuclei, and the outcomes of comet assay and DNA breakage detection-fluorescence in situ hybridization. The patterns identified in these cytogenetic studies indicate that chromosomal instability is a transient and chromosomally unstable intermediate in the development of cervical lesions. In this context, the mechanisms that may underlie the progressive increase in genetic instability in these patients seem to be related directly to HPV infection. The studies discussed in this paper show that chromosomal instability may serve as a biomarker by predicting the progression of cervical intraepithelial neoplasia. Nevertheless, these results should be validated in larger, prospective studies.

Key words: *chromosomal instability, cervical cancer, biomarker.*

Introduction. Cancer of the uterine cervix is the third most common cancer in women worldwide and the most common cancer among Mexican and Latin American women [1]. Precancerous lesions of the cervix, commonly designated «dysplasia», present a complex problem of progression and regression because of their biological behavior. Dysplastic lesions of the cervix are morphologically classified into the following stages: mild cervical intraepithelial neoplasia (CIN 1), moderate (CIN 2), and severe (CIN 3). According to the Bethesda System for reporting cervical/vaginal cytological diagnoses [2], the lesions are classified as squamous intraepithelial lesions (SIL), which are either low-grade (LG-SIL), corresponding to human papillomavirus (HPV) infection and CIN 1, or high-grade (HG-SIL), corresponding to CIN 2 and CIN 3. Risk factors that have been associated with the development of CIN suggest that HPV types 16, 18, 31, and 33 entail a high risk of developing a malignancy of this type.

Considering that carcinogenesis is a complex stepwise process and that the accumulation of genetic alterations allows the growth of neoplastic cells, chromosomal instability is an event that occurs in the precancerous stages.

The development and validation of biomarkers that can anticipate the clinical diagnosis and suggest cancer prevention interventions in populations at risk are among the most promising strategies for cancer prevention. The candidate cancer risk biomarkers include cytogenetic endpoints, such as chromosomal aberrations [3], sister chromatid exchange (SCE) [4], micronuclei (MN) [5], and the outcomes of comet assay [6, 7] and DNA breakage detection-fluorescence in situ hybridization (DBD-FISH) [8].

Chromosomal aberrations. Numerical changes in specific chromosomes (aneusomy) can involve a gain (e.g., trisomy) or loss (e.g., monosomy) with respect to the normal condition (disomy). A misdivision gives rise to an amplification of the whole genome (polyploidy) [9] and structural anomalies (e.g., deletions, translocations, and isochromosomes).

Numerical or structural chromosomal anomalies, or a combination of the two, are related events that occur during the early stages and progression of cervical carcinogenesis [10, 11]. The numerical and/or structural deviations of some chromosomes (i.e., monosomy and polysomy of chromosomes 1, 3, and X) are routinely used as positive genetic biomarkers in the diagnosis of cervical cancer and prediction of disease progression

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[12–14]. Structural anomalies and numerical anomalies (aneusomy) of chromosome 1 have been described as the most frequent karyotypic changes in cervical cancer. It is possible that one or more of the tumor suppressor genes (PAX7, FBG3, ARH1, NEK2, RGL, and ARCH) located on chromosome 1 are involved in the development or progression of cervical cancer [15]. Aneusomy in chromosomes 1, 7, 8, 11, 17, and X have also been reported based on fluorescence in situ hybridization (FISH) and interphase cytogenetic findings [16–21]. In addition to the primary structural and numerical aberrations that are responsible for the initiation of carcinogenesis, new or secondary chromosomal abnormalities in the karyotype (e.g., stickiness, pulverization, chromatin extraction, chromatid gap, chromatid constriction, isochromatid break, endomitosis, and ring chromosomes) of a patient may appear as signaling a change usually to a more aggressive disorder [22]. An increased frequency of spontaneous chromosome aberrations was observed among patients with cervical precancerous lesions [23].

Sister chromatid exchange (SCE) is a reciprocal exchange between sister chromatids. SCEs are generally visualized by exposing cells (in vitro or in vivo) to 5-bromodeoxyuridine for two cell cycles and allowing subsequent differential staining of sister chromatids. Exchanges are detected at switches in stained regions between sister chromatids. The molecular mechanisms underlying SCE are not known fully, but they occur after exposure to various genotoxic agents and are believed to indicate DNA damage [24]. The SCE phenomenon is widely used as a reliable indicator of chromosome (DNA) instability [25] and has been suggested as a preclinical marker for the breast cancer gene [26].

The performance of the SCE test to evaluate the genomic damage in patients with cervical carcinoma is more practical in cultured lymphocytes than in solid tumors because of the difficulties in obtaining surgical specimens. The use of lymphocytes is based on the assumption that there should be an association between the extent of chromosomal damage in lymphocytes and in tumor cells [27]. A significant increase of the number of SCEs was reported previously in patients with cancer of the uterine cervix [28–33]; however, other studies have not shown significant differences [34]. These results suggest that the frequency of SCE is higher in patients with cervical carcinoma than in controls, in studies with a statistical power of 0.80. It could be assumed that these patients show a certain amount of chromosome instability. This finding is in agreement with those reported by other authors [27–33]. High values of statistical power (0.99 to 1.00) were achieved in all references listed in Table I (computed by the authors using the Stata software) [34]. Conversely, Adhvaryu et al. [35] did not find that SCE was a significant marker in cervical cancer patients, possibly because of the low statistical power ($1 - \beta = 0.57$) in the experimental design.

SCEs are associated with cervical cancer. The inconsistency of the results of other studies might be attributable to the low statistical power in the experimental design of those studies; however, the usefulness of increased SCE levels as a preclinical marker to identify women at a high risk of developing cancer needs to be ascertained in follow-up studies of precancerous lesions with high levels of SCE.

Micronuclei. A micronucleus (MN) is formed by chromosomes or chromosome segments that fail to be incorporated in the nuclei during cell division. MN can be generated through various processes, i.e., chromosomal damage and chromosome loss (aneuploidy). During the past few decades, MN has generally been used as a biomarker of chromosomal damage, genome instability, and cancer risk, integrating acquired mutations and genetic susceptibility toward mutations [36]. Therefore, increased MN frequency is expected in preneoplastic conditions, which has been demonstrated [37–41]. The role of MN in various steps of carcinogenesis has been substantiated by investigators and it has clearly been shown that the level of baseline chromosome damage is much higher in untreated cancer patients than in cancer-free controls [42]. Therefore, MN scoring could be used as a biomarker to identify various preneoplastic conditions much earlier

Table 1. **Sister chromatid exchange frequencies in women with carcinoma of the uterine cervix in studies with various statistical powers [34]**

Author	N	SCE (X ± SD)	Statistical power
Mitra et al. [28]	13	10.05 ± 2.35 (C)*	0.99
	11	6.95 ± 1.53 (P)	
Murty et al. [29]	46	10.15 ± 2.49 (C)*	1.00
	43	7.55 ± 2.24 (P)	
Adhvaryu et al. [35]	13	9.68 ± 0.97 (C)	0.57
	13	8.91 ± 1.15 (P)	
Yokota et al. [32]	35	10.00 ± 1.80 (C)*	1.00
	18	7.60 ± 0.80 (P)	
Lukovic et al. [30]	21	8.92 ± 1.47 (C)*	0.99
	19	6.94 ± 1.00 (P)	
Dhillon et al. [31]	14	9.44 ± 1.27 (C)*	1.00
	20	6.09 ± 1.07 (P)	
Capalash et al. [33]	30	7.18 ± 1.23 (C)*	1.00
	15	4.68 ± 1.82 (P)	
Cortés-Gutiérrez et al. [34]	28	7.80 ± 1.05 (C)*	0.80
	28	6.98 ± 1.13 (P)	

Indications. N – number of patients studied; $P < 0.05$; C – control, P – patients, X ± SD – average ± standard deviation.

than the manifestations of clinical features and might specifically be exploited in the screening of high-risk populations for a specific type of cancer [43, 44]. For these reasons, the prevalence of MN in epithelial cells has been considered a potential tissue-specific indicator of cancer risk [43, 44]. Occasional studies have shown increased MN frequency in invasive cervical cancer and researchers have suggested that the MN score in exfoliated cervical cells may be an additional criterion for establishing cervical cancer risk [37, 45]. However, there are only a limited number of studies on MN scoring for the assessment of cervical cancer risk [37, 45] and on MN scoring in cervical preneoplastic and neoplastic conditions [11, 46]. Accordingly, an analysis of MN in

Table 2. **Micronuclei frequencies in women with cervical neoplasic lesions as reported in the literature**

Author	N	Diagnostic	No. cells studied	MN	Conclusion
Samanta et al. [55]	30 23	ASCUS CIN	30,000 23,000	2.87 ± 2.21* 8.35 ± 6.45	MN score may be helpful in identifying the true CIN cases that are mislabeled as ASCUS on cervical smear. In future, MN score can be used as an additional biomarker in cervical cancer screening
Samanta et al. [54]	40 40 30 38 22	Control Inflammatory ASC-US LG-SIL HG-SIL	40,000 40,000 30,000 38,000	1.05 ± 1.59* 0.42 ± 0.71 2.87 ± 2.21 4.74 ± 5.62 19.73 ± 17.18	MN scoring on the epithelial cells of cervix could be used as a biomarker in cancer screening. This is an easy, simple, reliable, reproducible and objective test and can be done on routinely stained smears
Aires et al. [53]	10 12 10 27	Control Inflammatory LG-SIL HG-SIL	20,000 24,000 20,000 54.000	3** 7 8 61	MN test and Papanicolaou test may be both utilized for screening women who are at risk of developing cervical cancer
Campos et al. [52]	35 10 25 16 15	Control Inflammatory CIN 1 CIN 2 CIN 3	35,000 10,000 25,000 16,000 15,000	1.3 ± 1.4* 7.2 ± 9.6 4.3 ± 4.3 10.6 ± 5.3 22.7 ± 11.9	The prevalence of MN in exfoliated uterine cervical cells was greater in the patients with one or more risk factors for cancer than in the patients without risk factors
Leal-Garza et al. [47]	10 10 10 10	Control LG-SIL HG-SIL Invasive	10,000 10,000 10,000 10,000	3.05* 7.1 9.7 14.0	A positive linear trend between the MN frequency and increased cervical cancer risk. After being validated, MN could be used as screening and annual PAP test and as part of cancer staging
Cerqueira et al. [51]	45 113 24 14 4	Control Inflammatory LG-SIL HG-SIL Cancer	145,388 345,235 65,171 43,086 10589	27** 166 38 47 14	MN testing would be helpful in monitoring smokers with cervical intraepithelial lesions
Chakrabarti et al. [50]	48 33 32 6	Control Inflammatory LG-SIL HG-SIL	24,000 16,500 16,00 300	1.91** 3.80 3.5 4.0	The rising frequency of MN in exfoliated cervical cells reflects a sustained mutagenesis in cervical epithelium

Indications. N – number of cells studied; ASCUS – Atypical Cells of Undetermined Significance; CIN – Cervical Intraepithelial Neoplasia; LG-SIL – low-grade squamous intraepithelial lesion; HG-SIL – high-grade squamous intraepithelial lesion. * Frequencies of MN/1000 cells. ** Frequencies of MN/100 cells.

peripheral blood lymphocytes (PBLs) revealed the presence of a correlation between MN frequency and grade of cervical lesions [47] and provided evidence that MN frequency in PBLs is a predictive biomarker of cancer risk within a population of healthy subjects [48].

The similarity between the level of chromosome damage in surrogate tissues, such as oral mucosa or PBLs, and the corresponding damage in cancer-prone tissues provided the rationale for the use of these biomarkers as markers of cancer risk [49].

Several studies reported an association between MN frequency and progression of precursor lesions of cervical cancer [46, 47, 50–54]; however, the elevation in the number of these structures in women with HG-SIL did not reach significance. Samanta et al. [55] reported a significant increase of MN in CIN lesions compared with Atypical Cells of Undetermined Significance (Table 2).

A recent study [56] provided strong evidence that MN frequency assessed in the PBLs of disease-free subjects is a good predictor of cancer death risk, as evaluated in a nested case-control study performed 14 years after the original recruitment.

In particular, the high reliability and low cost of the micronucleus assay has contributed to the worldwide success and adoption of this biomarker for in vitro and in vivo studies of genome damage in cervical neoplasia [57].

Comet assay. The comet or single-cell gel electrophoresis (SCGE) assay is now widely accepted as a standard method for the assessment of DNA damage in individual cells. It has been used in a wide variety of applications, including human biomonitoring, genotoxicology, and ecological monitoring, and as a tool to investigate DNA damage and repair in various cell types. It can be used to detect the DNA damage in individual cells and to assess the presence of double-stranded breaks, single-stranded breaks, and alkali-labile sites [6].The sensitivity of the SCGE assay and its ability to measure DNA damage in individual cells have rendered it a rapid tool that is useful in addressing a wide range of questions in biology, medicine, and genetic toxicology.

Several studies have shown that basal DNA damage is increased in PBLs of patients suffering from a variety of cancers, including head and neck, breast, renal, esophageal, bladder, ovarian, and lung cancer. The authors of many of these studies, as well as other studies, have also extracted PBLs from cancer patients (usually prior to radiotherapy or chemotherapy) and exposed them to DNA-damaging agents *in vitro*, to assess whether the susceptibility to DNA damage and subsequent repair capacity in these cells are significantly different from those observed in control samples [6].

A direct association between genomic damage in cervical epithelial cells and the progression of LG-SIL to HG-SIL has been demonstrated in two studies [58, 59]. The SCGE assay may serve as a novel tool to predict the fate of cervical dysplasia; however, further standardization and experimental validation studies are needed.

DNA breakage detection-fluorescence *in situ* hybridization (DBD-FISH). This technique is a new procedure that allows the cell-by-cell detection and quantification of DNA breakage in the whole genome or within specific DNA sequences. Cells embedded in an inert agarose matrix on a slide are lysed to remove membranes and proteins and the remaining nucleoids are subjected to controlled denaturation with an alkali. The alkali transforms DNA breaks into restricted single-stranded DNA (ssDNA) motifs, which can be detected via hybridization with specific or whole-genome fluorescent DNA probes. As the number of DNA breaks increases in a target region, so do the amounts of ssDNA produced and probes hybridized, resulting in a more intense FISH signal, which can be quantified using image analysis systems [60–62]. Moreover, the alkaline treatment may break the sugar-phosphate backbone at basic sites or at sites with deoxyribose damage, transforming these lesions into DNA breaks that are also converted into ssDNA. DNA damage levels may be a consequence of the torsional stress on DNA loops associated with tight chromatin packing, may vary among cell types in conventionally conformed genomes (e.g., sperm and lymphocytes) [63], and may change if the cell is under stress, such as in the presence of a viral infection.

DNA damage is a product of external stressors, which also act on the genome [64]. It may also be a consequence of the torsional stress on DNA loops that is associated with tight chromatin packing. Abundant damage has been found in the chromatin of condensed mitotic chromosomes [64]. In addition, the exposure of DNA to constant tension above a critical level leads to its unwinding [65]. Although the molecular biology and significance of constitutive DNA damage are not well understood, some observations support the idea that these genomic regions escape the normal DNA configuration and may be transient structural features of cells. Even under homeostatic cell conditions, the presence of DNA breakage may vary among cell types [63]. It is noteworthy that the applica-

Table 3. **Comparison of the integrated density (ID) after fluorescence densitometry, in cervical epithelial cells of control women, women with LG-SIL, and women with HG-SIL, as assessed using DBD–FISH [70]**

Group	N	Number of studied cells	ID (X ± SD)
Control	10	500	38 ^{E7} ± 70 $^{E7\ b,c}$
LG-SIL	10	500	926 ^{E7} ± 1926 $^{E7\ a,c}$
HG-SIL	10	500	4339 ^{E7} ± 3161 $^{E7\ a,b}$

Indications. N – number of cells studied; ID – fluorescence area × fluorescence intensity; [a] Different to control (p = 0.0001); [b] Different to LG-SIL (p = 0001); [c] Different to HG-SIL (p = 0.0001).

tion of a whole-genome probe to other somatic cells does not yield a homogeneous background DBD-FISH signal, as certain chromatin regions are more strongly labeled. In human leukocytes, the DBD-FISH areas with a more intense background visualized using a whole-genome probe corresponded to areas containing 5 bp satellite DNA sequences [66]. In mouse splenocytes, the background areas corresponded to repetitive DNA satellite sequences located in pericentromeric regions [67], whereas in Chinese hamster cells, they corresponded to pericentromeric interstitial telomeric-like DNA sequences [68]. Their presence is not limited to mammalian species, as they have also been found in insects [69].

Cortés-Gutiérrez et al. [70] reported that LG-SIL patients exhibited a hybridization signal that was 20 times greater than the signal observed in control individuals, which reflected the basal level of DNA damage detected, and that HG-SIL patients exhibited a hybridization signal that was 100 times greater than the basal control signal (Table 3).

The DBD-FISH technique is easily applicable to cervical scrapings and provides prompt results that are easy to interpret; however, these results need to be validated in larger prospective studies.

Genomic instability in cervical cancer. The possible mechanisms that may explain the progressive increase of DNA damage in patients with cervical neoplasia include: 1) metabolic stress due to tumor growth; 2) a «clastogenic» product released by tumor cells; 3) micronutrient deficiencies, such as folate and vitamin B12 deficiencies [71, 72], and HPV infection. HPV DNA can be detected in 95–100 % of cervical cancer specimens and it has been called a «necessary cause» of cervical cancer [4, 73]. Alvarez-Rosero et al. [74] observed a correlation between the presence of high-risk HPV infection in cervical cells and the induction of genomic instability (chromosomal aberrations) in lymphocytes. Similarly, Cortés-Gutiérrez et al. [75] reported that women with HPV infection had a higher MN frequency in cervical cells. A chromosomal profile of high-grade cervical intraepithelial neoplasia was related to duration of preceding high-risk HPV infection [76].

Mechanistically, chromosome breakage in HPV-oncoprotein-expressing cells probably increases the cellular susceptibility to DNA damage or the defective repair

Table 4. **Classic cytogenetic tests as candidate biomarkers of cervical cancer risk**

Cytogenetic test	Sample (tissue)	Advantages	Limitations	Validations
Chromosomal abnormalities	Lymphocytes	Indicator chromosomal instability	Required cellular culture Laborious results interpretation	Inconsistency of the results [10–23]
SCE	Lymphocytes	Sensible indicator chromosomal instability	Required cellular culture Laborious results interpretation	The inconsistency of the results [28–34]
MN	Lymphocytes	Easy, simple, reliable, reproducible, objective, and low cost	Required cellular culture	Strong evidence of good predictor of cancer death risk [56] Taking into account the role of possible confounders and effect modifiers
	Cervical epithelium	No required cellular culture Easy, simple, reliable, reproducible, objective, and low cost	Limited number of studies in cervical preneoplastic lesions [11, 37, 45, 46]	Consistency of results Validation and detailed follow up studies are required
Comet assay	Lymphocytes	Sensitive, rapid and versatile	Required fluorescence equipment.	Experimental validation, standardization and interpretation are needed
	Cervical epithelium	Sensitive, rapid and versatile. No required cellular culture	Few studied in dysplasias [58, 59]	Validation and detailed follow up studies are required

of DNA damage as a consequence of reduced p53 or pRB function [77]. The HPV-16 E7 oncoprotein induces centrosome abnormalities, thereby disrupting mitotic fidelity and increasing the risk for chromosome missegregation and aneuploidy. In addition, expression of the high-risk HPV E7 oncoprotein stimulates DNA replication stress, which is a potential source of DNA breakage and structural chromosomal instability [78, 79]. Unrepaired, broken DNA can promote gene translocations or gene amplifications/deletions, which may provide a growth advantage to cells through gain of oncogenes or loss of tumor suppressors. This chromosomal instability may promote the development of cells with numerical and structural aberrations in chromosomes 1, 3, 5, 11, and 17 [12, 74, 80], which are critical factor for cervical carcinoma development and malignant progression [12, 13].

Several lines of evidence show that expression of HPV-16 E6 and E7 can independently induce structural chromosomal instability using the comet assay [77].

The induction of chromosomal instability is an emerging topic in viral tumorigenesis in humans and is associated with high-risk HPV [81], hepatitis B virus [82], Kaposi's sarcoma herpesvirus [83], and human T-cell leukemia virus type 1 (HTLV-1) [84]. The level of DNA damage in the genome as a structural feature of the chromatin may be unbalanced after exposure of cells to stress, such as a viral infection. Several studies have reported changes in chromatin organization during carcinogenesis and the subsequent association of distorted DNA-binding proteins with the nuclear matrix, which may have a functional role in chromatin organization and gene regulation [85]. An increase in the incidence of DNA single breakage (dsb), which is mediated by Ku70 depletion, is associated with HPV-16 episomal loss in cervical keratinocytes and with a new integration event. Normal levels of host DNA repair proteins, including Ku70, may protect against such events by preventing the generation of host dsb and linearized viruses. Interestingly, the HPV-16 E7 protein may play a direct role in inducing integration by interference with the nonhomologous end joining (NHEJ) pathway. Expression of HPV-16 E7 in the HPV-negative cervical keratinocyte cell line C33A resulted in the upregulation of the Ku70-binding protein [86], which may interfere with normal NHEJ and increase the frequency of dsb. Despite the well known function of HPV-16 E7 to induce DNA damage, the precise source of DNA double strand breaks remains poorly understood.

Clinical significance. From a clinical perspective, the presence of chromosomal instability may help distinguish patients with clinically significant cervical lesions from those who have insignificant lesions, thus discriminating lesions (Table 4). The ease and low cost of the detection of MN may allow its use as a prognostic indicator during the planning and validation of programs for cancer monitoring and prevention. In brief, MN scoring on the epithelial cells of the cervix could be used as a biomarker in cancer screening. This is an easy, simple, reliable, reproducible, and objective test that can be performed on routine stained smears.

Further investigations are required to confirm and validate the results of chromosomal abnormalities, SCE, and comet assay. Moreover, the results of DBD-FISH are preliminary.

Conclusions and future directions. Cervical cancer is the corollary of a long process that has its onset in LG-SIL and HG-SIL precursor lesions. Vaccination against HPV infection and periodical Papanicolaou cervical cytological screening are effective measures for preventing cervical cancer. Despite the effectiveness of Papanicolaou examinations, the detection of chromosomal instability as an early biomarker of cervical cancer risk should be improved, to reduce the incidence of cervical cancer. Additional research is needed, not only to gain better insight into the association between the frequency of MN and cancer, but also to evaluate the benefits of including biomarkers of cancer risk in the surveillance of populations at increased environmental or genetic risk. The former goal is easier to achieve, and plans already exist within the framework of the HUMN project for increasing the size of the study group, both by including new national cohorts and by extending the length of the follow-up period for those cohorts currently included in the study. The latter goal implies an improved understanding of the association between chromosome instability and cervical cancer. In particular, the consideration of the role of possible confounders and effect modifiers, such as diet, oxidative stress, and genetic polymorphisms, would be desirable before the routine application of these biomarkers in population studies aimed at estimating the risk of cancer.

E.I. Cortés-Gutiérrez, M.I. Dávila-Rodríguez, R.M. Cerda-Flores

ХРОМОСОМНЫЕ ПОВРЕЖДЕНИЯ КАК ПРОГНОЗНЫЕ МАРКЕРЫ КАРЦЕНОГЕНЕЗА ШЕЙКИ МАТКИ

Рак шейки матки является третьим по распространенности в мире типов рака у женщин и наиболее часто встречающимся у женщин Мексики и Латинской Америки. Факторы риска, связанные с развитием интраэпителиальной цервикальной неоплазии, предполагают, что папилломавирус человека (HPV) типов 16, 18, 31 и 33 влечет за собой высокий риск развития опухолей этого типа. Накопление генетических изменений делает возможным рост опухолевых клеток; хромосомная нестабильность является событием, которое предшествует предраковым стадиям. Возможные биомаркеры риска опухоли включают цитогенетические критерии, такие как хромосомные аберрации, обмен сестринских хроматид, микроядра, и заканчиваются Comet-анализом и

детекцией поломок ДНК с помощью флюоресцентной гибридизации *in situ*. Образцы, идентифицированные в таких цитогенетических исследованиях, показывают, что хромосомная нестабильность является транзиентным промежуточным звеном в развитии цервикальных нарушений. В этой связи механизмы, которые могут лежать в основе прогрессирующей генетической нестабильности у таких пациентов, кажутся непосредственно связанными с инфекцией HPV. Настоящее исследование показывает, что хромосомная нестабильность может служить биомаркером для предсказания развития интраэпителиальной цервикальной неоплазии, тем не менее эти результаты должны быть оценены в более масштабных исследованиях.

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