# Expression of Telomerase and Infection of High Risk Human Papillpmavirus in Cervical Cancer

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ABSTRACT Objective: To investigate the effect and relationship between high risk human papillomavirus (HR-HPV) infection and telomerase expression in the development of cervical carcinoma. Methods: HPV DNA in cervical exfoliated cells was detected by second-generation hybird capture technology, then the expression of telomerase was evaluated by immunohistochemistry. Results: (1) The positive rate of telomerase in control group, cervical intraepithelial neoplasia(CIN) Ⅰ group, CIN Ⅱ group, CINⅢ group and cervical carcinoma group was 10.00 %, 16.67 %, 40.00 %, 70.00 % and 95.00 %, respectively. The positive rate of telomerase in cervical cancer was significantly higher than that in CINⅢ ($x^2$=4.329, P＝0.037). And the positive rate in CINⅢ was significantly higher than that in CIN Ⅱ ($x^2$=4.327, P＝0.038). And the positive rate in CIN Ⅱ was significantly higher than that in CIN Ⅰ ($x^2$=4.022, P＝0.045). (2) With the deterioration of carcinoma lesions, HR-HPV load and the positive rate of HPV infection increased gradually. The positive rate of HPV infection was significantly different between the cervical cancer group, CIN Ⅲ group and CIN Ⅱ group, CIN Ⅰ group and control group ($x^2$=29.501~7.414, P＜0.01). The high risk HPV load was significantly different between control group and the other groups (P＜0.05). (3) With the increase of the cervical lesion level, both the high-risk HPV detection rate and the telomerase positive expression rate increased , and there was an obvious correlation between the HPV infection and the telomerase expression (r＝0.943, P<0.01). Conclusion: High-risk type HPV infection and the expression of telomerase had an obvious correlation with the development of cervical intraepithelial neoplasia and cervical cancer, and might be a monitoring index to detect and predict cervical cancer.

Key words: Cervical Intraepithelial Neoplasia; Cervix Neoplasms; Immunohistochemistry; Telomerase; Human papilloma virus

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## Introduction

Recently the international agency for cancer research reported that cervical cancer is still the second commonest cancer worldwide. Eighty-three percent of these deaths occur in developing countries [1]. The incidence rate of cervical cancer has increased year by year and affects more and more young women in China. Cervical cancer is a multi-factorial disease. Telomerase activation has been shown to be an important event for immortalization and carcinogenesis. Telomerase activity and telomere length were important factors in the pathobiology of human tumor. Telomerase may be required for the long-term proliferation of tumours. Stabilisation of telomere lengths by activation of telomerase is thought to be the key mechanism of indefinite cell proliferation and immortalization. telomerase activation can reduce or prevent the loss of telomeres. Because telomerase is activated during the progression of cervical neoplasia, telomerase activity and expression of its components may represent valuable biomarkers for the diagnosis and prognosis of patients with cervical neoplasia [2]. And some studies have been carried out to evaluate telomerase as a possible HSIL and invasive cervical cancer marker, the detection of telomerase activity is useful for cytological screening of cervical lesions using cellular and tissue samples of uterine cervix [3]. In addition, molecular epidemiology studies have confirmed: HPV is responsible for the majority of cervical cancers. Integration of high oncogenic risk HPV types (HR-HPV) is considered to be a key event in the progression of CIN to invasive cancer[4,5]. Most genital HPV infections regress within two years and only a minority of women will develop persistent HPV infection that could eventually cause cervical intraepithelial neoplasia (CIN)[6]. Thus, it is essential to evaluate the association between viral load of high-risk HPV and cervical cancer and its precursors. Telomerase activation has been demonstrated to be a relatively early event during multistage carcinogenesis of various cancers[7]. In cervical cancer, HPV infection is considered to be the initiating event of carcinogenesis. In order to investigate the relationship between telomerase expression and HR-HPV infection in occurrence and development of cervical carcinoma, the telomerase expression was evaluated in cervical cancer in comparison with normal cervical tissue samples, and HPV DNA content in cervical exfoliated cells was detected.

## 1 Materials

### 1.1 Patients and Tissues samples

130 specimens from patients (mean age 40 years; rang 21-60 years) were retrieved from the Affiliated Hospital of Qingdao University Medical College (Shandong Province, China), between March 2010 and May 2011. The studied cases were distributed into the following groups: CIN Ⅰ 30 cases, CIN Ⅱ 30 cases, CINⅢ20

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cases and cervical carcinoma 20 cases (Ⅰa stage 10 cases, Ⅰb stage 5 cases, Ⅱa stage 3 cases, Ⅱb stage 2 cases), and normal cervical tissues 30 cases.All of them were confirmed by the pathologists. Before the surgery, HPV DNA content in cervical exfoliated cells was detected by second-generation hybird capture technology.

### 1.2 Methods

**1.2.1 Hybrid capture HPV DNA test** The Digene High-Risk HPV DNA Test Hybrid Captures II (Digene Corporation, Gaithersburg, MD, USA) was performed on liquid based cytology specimens. The RNA probe mix for the detection of high risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 was used according to the manufacturer's instructions. Signal amplification is based on immunocapture of DNA/RNA hybrids and subsequent EIA with a chemiluminescent reporter system. The results are given as relative light unit (RLU) ratio. As the RLU ratio is the ratio of light emitted by the specimen to the light emitted from the mean RLU of triplicate positive control specimens containing 1 pg/mL of HPV DNA (5000 copies of HPV genome). So it is a semiquantitative estimate of viral load in the specimen.

**1.2.2 Immunohistochemistry for telomerase** The expression of telomerase was detected by immunohistochemical technique. Organization specimens were fixed with 4 % formaldehyde and rinsed with PBS before embedding in paraffin. Serial 3-μm-thick cryosections were cut by an ultramicrotome and mounted on gelatin-covered slides for immunohistochemical analysis. The primary rabbit anti-telomerase catalytic subunit (dilution 1: 200; Beijing bo orson biological technology Co, LTD)were applied and placed in an incubator with 37 ℃ for 90 minutes. Sections were then washed 3 times for 5 minutes in PBS and incubated for 30 minutes with the secondary antibodies (PV-6000 universal kit (Zhongshan Goldenbridge Biotechnology Com. Ltd, Beijing, China), Diaminobenzidine tetrachloride (Zhongshan Goldenbridge Biotechnology Com. Ltd, Beijing, China) was used as the chromogen. All incubations were carried out in a humidified chamber at 37 ℃. After counterstaining with hematoxylin-eosin, sections were evaluated by light microscopy. Positive immunostaining with the antibody was detected in the nuclei of tumor cells and showed brown staining.

**1.2.3 Immunohistochemical quantification of staining with anti-telomerase** Ten powerful microscope fields were randomly selected and 100 tumor cells in each field were counted by two specialist gynecological histopathologists who had no knowledge of the patients, family histories or the results of mutation analysis. The distribution of the immunoreactive cells was classified according to the following scale: negative=<5 %; positive=>5 % to <10 %; ++=between 10 % and 50 %; +++=>50 %. In the case of telomerase, any nuclear staining was interpreted as positive and considered overexpression or abnormal expression. Moreover, we estimated staining intensity and scored as follows: low, moderate, or high. All tissue microarrays were evaluated first by an observer and later by an experienced pathologist without knowledge of clinical data.

### 1.3 Statistical Analysis

All statistical calculations were carried out by SPSS 17.0 statistical software. The results were compared by the chi-square test. Pearson's method was used for correlation analysis. $P<0.05$ was considered as statistically significant.

## 2 Results

### 2.1 The expression of telomerase in cervical intraepithelial neoplasia and cervical cancer tissues

The positive rate of telomerase in control group, CINⅠ group, CINⅡ group, CINⅢ group and cervical carcinoma group was 10.00 %, 16.67 %, 40.00 %, 70.00 % and 95.00 %, respectively. With the increase of the cervical lesions level, the expression of telomerase increased. A representative sample of the staining patterns observed in epithelial normal cervix, CINⅢ and cervical cancer was presented in Fig.1, Fig.2 and Fig.3. The positive rate of telomerase in cervical cancer was significantly higher than that in CINⅢ ($x^2=4.329$, $P=0.037$). And the positive rate in CINⅢ was significantly higher than that in CINⅡ ($x^2=4.327$, $P=0.038$). And that in CINⅡ was significantly higher than that in CINⅠ ($x^2=4.022$, $P=0.045$). However, there was no difference between CINⅠ group and control group($P>0.05$)(Table 1).

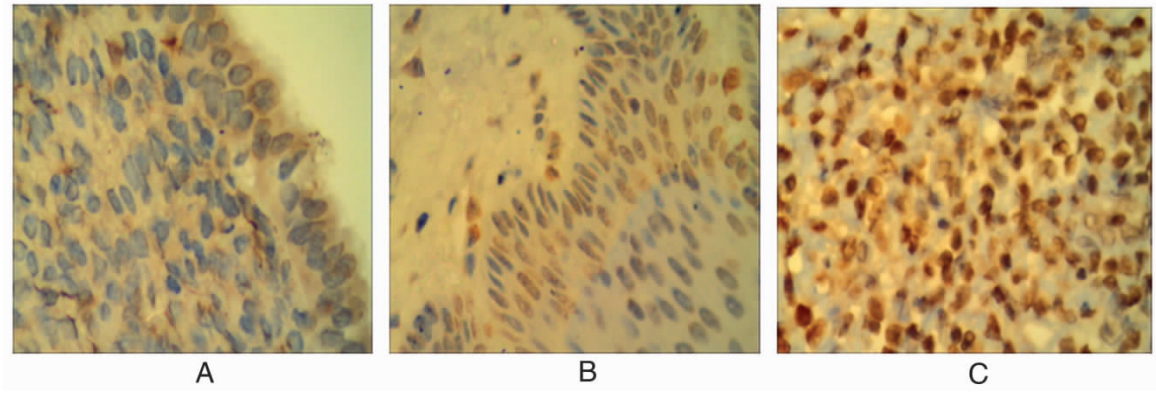


Fig.1 A The expression of telomerase in epithelial normal cervix. B The expression of telomerase in CINⅢ. C The expression of telomerase in cervical cancer. (magnification, × 400)

Table 1 Expression of telomerase in different cervical lesions

| Pathological type | Cases | Expression of telomerase activity | | | |
|---|---|---|---|---|---|
| | | Low positive | Moderate | High positive | Positive rate (%) |
| Controls | 30 | 3 | 0 | 0 | 10.00 |
| CIN Ⅰ | 30 | 3 | 2 | 0 | 16.67 |
| CIN Ⅱ | 30 | 8 | 4 | 0 | 40.00 |
| CINⅢ | 20 | 5 | 5 | 4 | 70.00 |
| Cervical cancer | 20 | 6 | 8 | 5 | 95.00 |

**2.2 Relationship between HR-HPV infection and different cervical lesions**

The positive rate of HPV infection was significantly different between cervical cancer group, CIN Ⅲ group and CIN Ⅱ group, CIN Ⅰ group and control group ($x^2$=29.501~7.414, P＜0.01). The higher the cervical lesion stage, the higher positive rate of HPV infection ($x^2$=48.981, P<0.01). The positive rate of HPV infection was not significantly different (P＞0.05) among control group and CIN Ⅰ group, CIN Ⅲ group and cervical carcinoma group. The high risk HPV load was significantly different among control group, CIN Ⅰ group, CIN Ⅱ group, CIN Ⅲ group and cervical carcinoma group(P＜0.05). HR-HPV load in CIN Ⅰ group was significantly higher than that in CIN Ⅱ group, CIN Ⅲ group and cervical carcinoma group (P＜0.05). But there was no significant difference among CIN Ⅱ group, CIN Ⅲ group and cervical carcinoma group(P＞0.05)(Table 2).

Table 2 Relationship between HR-HPV infection and different cervical lesions

| Pathological type | Cases | HPV | | |
|---|---|---|---|---|
| | | Positive[cases,(rate%)] | Load (pg/mL) | |
| | | | Median (M) | Inter-quartile range (Q) |
| Controls | 30 | 5 (16.67) | 2.56 | 4.65~1.32 |
| CIN Ⅰ | 30 | 8 (26.67) | 11.56 | 40.56~3.15 |
| CIN Ⅱ | 30 | 6 (53.33) | 150.43 | 521.45~4.20 |
| CINⅢ | 20 | 18 (90.00) | 162.86 | 664.59~20.80 |
| Cervical cancer | 20 | 19 (95.00) | 355.43 | 1084.77~116.50 |

**2.3 Correlation between HR-HPV infection and telomerase expression**

By Pearson's method, with increasing of the cervical lesions level, HR-HPV detection rates and telomerase positive expression rates increased in turn, and there was an obvious correlation (r＝0.943, P<0.01). 19 cervical cancer cases were positive of HR-HPV which were also positive for telomerase (Expression rate 100.00 %), and 18 CINⅢ cases were positive of HR-HPV which were 12 cases positive for telomerase (Expression rate 66.67 %);16 CIN Ⅱ cases were positive of HR-HPV which were 7 cases positive for telomerase (Expression rate 43.75 %); 8 CIN Ⅰ cases were positive of HR-HPV which were 2 cases positive for telomerase (Expression rate 25.00 %). It was shown that telomerase was mainly found in the cases with HPV infection, and had a tight correlation with high grade CIN. In addition, 77.5 % of CIN Ⅲ and cervical cancer (31 out of 40) was positive for HPV and telomerase, but 15.00 % (6 out of 40) was positive for HPV alone and 5.00 %(2 out of 40)were positive for HPV alone (Table 3).

Table 3 Correlation between HR-HPV infection and telomerase expression

| Items controls | CIN Ⅰ | CIN Ⅱ | CINⅢ | Cervical | Cancer |
|---|---|---|---|---|---|
| HPV-/telomerase- | 22 | 19 | 9 | 0 | 1 |
| HPV+/telomerase- | 5 | 6 | 9 | 6 | 0 |
| HPV-/telomerase+ | 3 | 3 | 5 | 2 | 0 |
| HPV+/telomerase+ | 0(00.00) | 2(25.00) | 7(43.75) | 12(66.67) | 19(100.00) |
| Total | 30 | 30 | 30 | 20 | 20 |

## 3 Discussion

### 3.1 Significance of telomerase in cervical lesions in different degrees

Recent observations support the concept that activation of telomerase is a critical step in cellular immortalisation and cancer. They play an important role in genomic integrity and stability by preventing the recognition of chromosomal ends as double-stranded DNA breaks. Most normal tissues of somatic Origin exhibit low or no telomerase activity, but germline cells, differentiated cells and tumour cells have elevated or detected levels of telomerase activity and have long or stable telomeres [8]. The previous studies showed that increased levels of telomerase activity have been detected in invasive cervical carcinomas, as well as in high grade cervical dysplasias [9]. Most normal cervical tissues and low-grade CIN lesions were devoid of detectable hTERT mRNA and telomerase activity [10]. In the experimental results, the positive rates of telomerase in cervical cancer and CINⅢ were significantly higher than those in CINⅡ, CINⅠ and controls. There were low level expression of telomerase in CINⅡ and CINⅠ (40.00 %、16.67 %), These results indicated that telomerase did not activate or had not high activation in the early of CIN. Cervical cancers exhibit high telomerase activity irrespective of histopathology grading but the intensity/level of telomerase activity increased with the clinical progression of the disease. The presence of telomerase activity in the preneoplastic cervical tissues indicates that telomerase is activated early in the course of cervical carcinogenesis and may be a vital constituent of malignant progression. These findings are in accordance with earlier reports[11].

### 3.2 Relationship between HR-HPV infection and cervical cancer

International cancer research center (IARC 1995) seminar clearly put that HR-HPV infection is the major risk factor of cervical cancers. HR-HPV infections were considered as the most common causal factor and reported in more than 90 % of cervical cancers[12]. The studies showed that relationship between HR-HPV infection and cervical intraepithelial neoplasia was statistically significant. Especially the positive rates of HR-HPV and HR-HPV load in cervical cancers and CINⅢ were significantly higher than that in CINⅠ and controls. Our studies suggest that high-risk HPV persistent infection is an important factor in the process of cervical cancer progress. HR-HPV testing has an important value to predict the happen of cervical cancers.

In addition, HCⅡ was used to detect HR-HPV load. In this study, the high risk HPV load in cervical cancer and CINⅢ/Ⅱ group were significantly different from the CINⅠ and controls. It was shown that a high viral load was a risk factor not only for the development of CIS but also for invasive cancer. Studies have confirmed that increasing HPV DNA load played an role in promoting the occurrence and development of cervical carcinoma[13]. The developing cervical cancer precursors were associated with elevated high-risk HPV viral load[14]. With the deterioration of cervical lesions, the high risk HPV load increased. The clinical measurement of viral load may help to identify HPV-positive women in greater risk of developing moderate or severe dysplasia, but its greatest value is to predict the initiation of the dysplastic process. Recent studies have suggested a high correlation between HR-HPV viral load (notably HPV-16) and high-grade squamous-cell intraepithelial lesions [15,16]. This study was in accordance with these reports. Therefore, HPV viral load may be predictive of future risk of high grade CIN. Most studies also reported that HPV load was an ancillary marker for persistent HPV infection.

### 3.3 Relationship between telomerase activity, HR-HPV infection and cervical intraepithelial neoplasia

Statistics showed that 80 % of women naturally infected the virus, but because of their own immunity, some women had persistent infections. The number of HPV infections is significantly increasing in the developing world. These infections can lead to abnormal cell growth; After 10 to 20 years, persistent infection (if not detected and treated) can develop into cervical cancer. According to the World Health Organization (WHO) statistics, there are approximately 500,000 new cases registered each year out of which 250,000 cases are fatal. This alarming situation in the coming years for papillomaviruses has lead molecular virologists world wide to go deep into pathogenesis and bring out solutions to its therapeutic potential [17]. The two proteins which play a significant role in onset of this malignancy are E6 and E7 proteins and their expression has been seen in the cell lines [18]. When HPV infected the human body, HPVs encode E6 and E7 oncoproteins, multifunctional immortalizing and growth-promoting proteins, that bind to and inactivate the tumor suppressor proteins p53 and PRb [19]. The inactivation of these tumor suppressor genes through high-risk HPVs results in uncontrolled cellular proliferation of the host cell. There is a strong relationship between telomerase activation and HPV infection. Telomerase is maintaining telomere length of a kind of reverse transcriptase, and telomerase activation is a critical step in cellular immortalisation and cancer. HPV has been found to activate telomerase with its E6 oncoprotein [20]. There seems to be a clear association between telomerase activity and HR-HPV status in the development of cancer. In this study, from different grades of cervical dysplasia to invasive cervical cancer, high-risk HPV infection and the telomerase activity have obvious correlation ($r=0.943$, $P<0.01$), and expression of both increased in turn. The positive rates of telomerase activity were 60.61 % in HPV positive and 20.31 % in HPV negative, compared results were significantly different ($\chi^2=21.846$, $P<0.01$). This showed that telomerase activation was mainly found in the cases with HPV infection, and had a tight correlation with high grade CIN. 20 cases in cervical carcinoma, HR-HPV infection in 19 cervical scrapes which

were expression of telomerase activity (expression rate 100 %). HR-HPV infection in 8 CIN Ⅰ scrapes which were only 2 cases tissues of telomerase activity. It suggests that those early lesions infected with high risk HPV could be induced to progress because of induction of telomerase activity by their E6 oncoprotein. In carcinoma early, high-risk pattern has not yet been HPV infection with telomerase activation, along with the increase of pathological damage, both gradually consistent. Snijder's[21] research considered that HPV infection earlier than the genes for telomerase level rise, is the cause of telomerase activation. In addition, 77.5 % of CINⅢ and cervical cancer (31 out of 40) was positive for HPV and telomerase, but 15.00 % (6 out of 40) was positive for HPV alone and 5.00 %(2 out of 40)were positive for HPV alone. To better understand the capacity for different methods to evaluate high-grade cervical lesions and invasive cancers. The capacity of telomerase, in combination with high-risk HPV DNA, was used to identify histological CINⅢ or cervical cancer patients.

In summary, the relationship between HR-HPV infection and telomerase activity plays an important role in occurrence and development of cervical carcinoma. Telomerase activation is a relatively early-stage event in cervical carcinogenesis, and this activation is associated with the initiation and progression of cervical lesions. Detection of telomerase activity may serve as a tool for reliable diagnosis and prognosis of cervical neoplasias along with HPV testing.

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# 宫颈癌中端粒酶的表达和高危型人乳头瘤病毒感染

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**摘要** 目的:研究不同程度子宫颈病变中高危型人乳头瘤病毒 HR-HPV 感染和端粒酶活性的表达,以探讨两者在宫颈癌及宫颈上皮内瘤变中的作用及相关性。方法:采用第二代杂交捕获技术检测宫颈脱落细胞 HPV-DNA 含量,并用免疫组织化学 EnVision 二步法检测宫颈组织标本中端粒酶的表达。结果:(1) 端粒酶阳性表达率在对照组、CINⅠ、CINⅡ、CINⅢ和宫颈癌组分别为 10.00%、16.67%、40.00%、70.00%、95.00%,宫颈癌组高于 CINⅢ,CINⅢ高于 CINⅡ,CINⅡ高于 CINⅠ,差异均有统计学意义($\chi^2$=4.329,P=0.037;$\chi^2$=4.327,P=0.038;$\chi^2$=4.022,P=0.045)。(2) 随着宫颈病变级别的增加,高危型 HPV 的阳性率和病毒负荷量均增高。高危型 HPV 的阳性率在宫颈癌和 CINⅢ组明显高于对照组、CINⅠ及 CINⅡ($\chi^2$=29.501~7.414,P<0.01)。高危型 HPV 的病毒负荷量在对照组与其他 4 组比较,差异均有统计学意义(P<0.05);CINⅠ组分别与 CINⅡ、CINⅢ及宫颈癌组比较差异均有统计学意义(P<0.05)。(3) 随着宫颈病变级别的增加,高危型 HPV 的阳性率和端粒酶阳性表达率依次递增,两者有明显的相关性(r=0.943,P<0.01)。结论:高危型 HPV 感染和端粒酶活性均与宫颈癌前病变及宫颈癌的发生发展密切相关,有望作为子宫颈癌前病变和宫颈癌筛查的监测指标。

**关键词**:宫颈上皮内瘤变;宫颈肿瘤;免疫组化;端粒;末端转移酶;人乳头瘤病毒

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