

# The relationship between expression of p53/bcl-2 and clinicopathological criteria in cervix squamous cell carcinomas

M. Bitiren<sup>1</sup>, M.D.; E. A. Cakmak<sup>2</sup>, Ph.D.; A. Gocmen<sup>3</sup>, M.D.;  
S. S. Inaloz<sup>4</sup>, Ph.D.; I. Sari<sup>5</sup>, M.D.; M. Karakok<sup>5</sup>, M.D.; A. Aydin<sup>5</sup>, M.D.

<sup>1</sup>Department of Pathology, University of Harran Faculty of Medicine, Sanliurfa

<sup>2</sup>Department of Medical Biology & Genetics; <sup>3</sup>Department of Gynecology & Obstetrics

<sup>4</sup>Department of Histology & Embryology; <sup>5</sup>Department of Pathology, University of Gaziantep Faculty of Medicine, Gaziantep (Turkey)

## Summary

**Objective:** Thirty cases with squamous carcinomas of cervix who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy were reviewed histopathologically.

**Materials and Methods:** The tissues were stained immunohistologically with p53 and bcl-2. Ten cases were selected as well differentiated (large cell keratinizing) carcinoma, ten cases moderately differentiated (large cell non keratinizing) carcinoma and ten cases poorly differentiated carcinoma (includes small cell squamous cell carcinoma).

**Results:** We observed 11 cases (36.6%) with bcl-2 and 13 cases (43.3%) with p53 positivity. P53 expression showed the opposite correlation to bcl-2 staining.

**Conclusion:** A decrease in bcl-2 reactivity and an increase in p53 positive staining was noted as the histological differentiation worsened.

**Key words:** p53; Bcl-2; Cervix squamous cell carcinomas.

## Introduction

Recently, many studies on the importance of genomic changes are being carried out. Tumorigenesis is considered to result from many progressive gene alterations as activation of oncogenes and inactivation of tumor suppressor genes take place. One of these genes is the bcl-2 oncogene, which codes proteins blocking apoptosis in pathological conditions. Bcl-2 acts as an inhibitor of apoptosis; it may prolong the survival of genetically altered cells. As a tumour suppressor gene, p53 induces apoptosis but a mutant p53 may inhibit it [1-3]

In this study, we aimed to examine the relationship between bcl-2 and p53 in invasive conventional squamous carcinoma of the cervix.

## Materials and Methods

Materials from 30 patients with squamous cell carcinomas of the cervix who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy were evaluated. The patients were gathered at Kayseri Obstetric Hospital and Medical Faculty of Harran University. The ages of the patients ranged from 45-70 years. Forty percent were between 50 and 60 years of age. Ten cases were selected as well differentiated (large cell keratinizing) carcinoma, ten cases moderately differentiated (large cell non keratinizing) carcinoma and ten cases poorly differentiated carcinoma (includes small cell squamous cell carcinoma). The most hyper cellular slides from each case (4-6 µ in thickness) were chosen from paraffin-embedded tumor tissues

and stained immunohistochemically using an avidin-biotin peroxidase method for p53 expression and bcl-2. Tonsillar tissue for bcl-2 and breast carcinoma tissue for p53, estrogen and progesterone were used as positive control slides; and normal skin was used as a negative control slide to determine the specificity of the immunohistochemical staining. Expression of bcl-2 (clone 124) and p53 (DO 7, monoclonal) in each differentiation of conventional squamous cell carcinoma was assessed to find out if there were any expression differences. More than 5% nuclear and cytoplasmic staining of tumor cells was accepted as positive for p53 and bcl-2, respectively.

## Results

Positive staining was detected in 11 of 30 women (36.6%) for bcl-2 and 13 (43.3%) for p53 (Tables 1 and 2); p53 expression showed the opposite correlation to bcl-2 staining. A decrease in bcl-2 reactivity and an increase in p53 positive staining were observed as the histological differentiation worsened (Table 2). There was a strong relationship between immunoreactivity of bcl-2 and progesterone/estrogen, and intensive staining was observed in low grade tumours and in premenopausal women with SCC (Table 1).

## Discussion

Generally, mutation of the p53 gene does not appear to be a common event in cervical carcinogenesis [4]; p53 point mutations in human cervical cancers have an inverse correlation with HPV infections. HPV unrelated carcinomas showed the highest incidence of p53 muta-

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Table 1. — Relationship between immunoreactivity and clinicopathological factors.

Clinicopathological features	bcl-2 immunoreactivity	p value
<i>Estrogen receptor</i>		
Positive	10/19 (52.6%)	p < 0.05
Negative	1/11 ( 9.9%)	
<i>Progesterone receptor</i>		
Positive	10/19 (52.6%)	p < 0.05
Negative	1/11 ( 9.9%)	
<i>p53</i>		
Positive	1/13 ( 7.6%)	p < 0.05
Negative	10/17 (58.8%)	
<i>Menopause status</i>		
Premenopause	5/8 (62.5%)	p > 0.05
Postmenopause	7/22 (31.8%)	

Table 2. — Relationship between bcl-2/p53 reactivity and histological grade.

Histological grade	bcl-2	p53
Low grade	7/10 (70%)	2/10 (20%)
Intermediate grade	3/10 (30%)	4/10 (40%)
High grade	1/10 (10%)	7/10 (70%)
p value	p < 0.005	p > 0.005

tions [5]. An attractive hypothesis is therefore that p53 is inactivated in cervical carcinoma, either by complex with HPV 16 protein (in HPV positive tumours), or by p53 gene mutations in those that are HPV negative. This has not, however, been a consistent finding and other researchers have shown that inactivation of the p53 gene by allelic loss or by point mutation is infrequent in cervical cancer, irrespective of the presence or absence of HPV infection [6-8]. Additionally, Crook and Vousden have identified p53 point mutations in metastases arising from HPV-positive cervical carcinomas suggesting that acquisition of p53 mutation may play a role in the progression of some HPV-associated primary cancers [9]. We did not investigate the incidence of HPV in our cases.

Bcl-2 expression has been observed more extensively in low grade than in high grade tumours [10-12]. Generally, an inverse relationship between bcl-2 and p53 expression has been reported. High grade tumour reactivity for p53 has been found to be strongly positive but for bcl-2 weakly positive [13]. For example, Lisboa *et al.* found positive staining of 14% in grade 1, 45% in grade 2 and 48% in grade 3 for p53 in invasive carcinoma of the breast [14]. Lee *et al.* found that bcl-2 immunoreactivity gradually decreased from grades 1 to 2 and demonstrated an inverse relationship between bcl-2 and p53 immunoreactivity [15].

Expression of estrogen and progesterone receptor immunoreactivity has been found in the majority of the breast carcinoma cases [16]. Bcl-2 is closely related to positive staining of estrogen and progesterone receptors in breast carcinoma cells and premenopausal status of patients [12, 17]. The results of our study of cervical SCC were similar to the literature on the breast.

The relationship between bcl-2/p53 and histological prognostic groups was examined in this study. As a result, expression of bcl-2 inhibited apoptosis, but did not stimulate cell proliferation. Bcl-2 positive staining was accompanied by good prognostic parameters such as low histological grade and absence of mutant p53 reactivity. Bcl-2 positive tumours appeared to have a better prognosis. However, further studies should be performed on larger patient groups to verify the value of bcl-2 as a prognostic factor for cervical SCC.

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Address reprint requests to:  
Prof. S. S. INALOZ, M.D.  
Gaziantep Universitesi Tip Fakultesi  
Histoloji & Embriyoloji AD  
Gaziantep (Turkey)