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CLINICAL ARTICLE

Risk factors for human papillomavirus persistence among women undergoing cold-knife conization for treatment of high-grade cervical intraepithelial neoplasia

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ABSTRACT

Objective: To investigate the risk factors potentially associated with high-risk human papillomavirus (HPV) persistence in women undergoing cold-knife conization (CKC) for treatment of high-grade cervical intraepithelial neoplasia (CIN). *Methods:* Medical records of women who underwent CKC for treatment of CIN 2/3 between 2007 and 2012 at a tertiary hospital in Ankara, Turkey, were retrospectively analyzed. Cases involving persistent HPV infection after 1 year of follow-up were identified. Using univariate and multivariate analyses, the impact of various factors such as patient age, menopausal status, parity, high-risk HPV type, excised cone dimensions (width, height, and depth), and surgical margin status on high-risk HPV persistence was assessed. *Results:* A total of 292 women underwent CKC for treatment of CIN 2/3 within the study period. After women with a subsequent diagnosis of cervical cancer, subsequent total hysterectomy, and inadequate follow-up data were eliminated, 113 women were eligible for final analysis. High-risk HPV persistence was detected in 24 (21.2%) women, and multivariate analysis revealed that patient age and cone depth were significant independent predictors ($P < 0.05$). *Conclusion:* High-risk HPV persistence may be encountered after CKC procedures. It is important to evaluate persistent HPV infections after treatment because affected women are at increased risk for disease persistence, recurrence, and progression.

1. Introduction

Despite the ongoing research and implementation of newer diagnostic techniques for early diagnosis, cervical cancer continues to be a major healthcare issue [1]. As of 2008, approximately 530 000 new cases were diagnosed worldwide, and approximately 275 000 deaths were due to cervical cancer [2]. The disease burden is especially prominent in low-resource countries. In Turkey, cervical cancer is the eighth most commonly diagnosed malignancy among women and the third most common gynecologic cancer, after ovarian and endometrial cancer [3]. According to Globocan 2008 data, 1443 new cases of cervical cancer were diagnosed and 556 mortalities occurred. The 5-year prevalence was 3998 cases [2].

Persistent infection with high-risk human papillomavirus (HPV) types is an almost-universal causal factor for the development of cervical premalignant lesions and invasive cancer [4]. HPV types are generally split into 2 groups according to their risk of association with malignancy. The most common high-risk types are generally considered to be HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, and -68. The most common low-risk types are considered to be HPV- 6, -11, -40, -42, -43, -44, -53, -54, -61, -72, -73, and -81. HPV-16 and HPV-18 are the most commonly found high-risk types and are associated with approximately 70% of all cases of cervical cancer (HPV-16 is isolated in approximately 50% of cases) [5].

Cervical intraepithelial neoplasia (CIN) 2/3 is the precursor of cervical cancer [6]. Before progression into invasive cancer, there is generally a relatively long time period in which HPV infection can be cleared by the immune system. In cases in which the immune system fails to clear HPV, a persistent high-risk HPV infection occurs, and the risk of developing CIN 3 (carcinoma in situ) and invasive cancer becomes significant.

Because of its persistent nature and high risk of progression to invasive cancer, high-grade CIN is commonly treated, rather than managed expectantly, when encountered. There are a number of treatment options for CIN, which can be broadly split into 2 categories: excision and ablation. Excisional treatments are generally referred to as conization procedures, whereby a cone-shaped biopsy specimen is excised from the cervix. Conization can be performed with either a scalpel (cold-knife conization [CKC]) or other energy modalities such as wire loop electrocautery (loop electrosurgical excision procedure [LEEP]) or laser. In Turkey, preference regarding these techniques is determined by institutional capabilities, patient condition, and surgeon experience.

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Cold-knife conization is a commonly used excisional treatment modality for CIN, although in many parts of the world it has been replaced by LEEP, which is a more feasible technique. Despite the fact that the premalignant lesion within the transformation zone is successfully extirpated with this procedure, women continue to carry risk for persistent infection with high-risk HPV, which increases the likelihood of disease recurrence [7,8]. Recurrence may be associated with progression to cervical cancer, so determining risks for HPV persistence might be useful for identifying women who carry a higher risk of disease recurrence. Following treatment with any of the techniques mentioned, a negative HPV test is a highly sensitive marker for reduced risk of recurrence [9].

The aim of the present study was to evaluate the possible risk factors associated with high-risk HPV persistence among Turkish women undergoing CKC for treatment of CIN 2/3.

2. Materials and methods

The present retrospective study was performed at the Department of Gynecologic Oncology at Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara, Turkey. The study institution is a large tertiary referral center for women's diseases and provides healthcare to patients from all over the country. Following scientific and ethical approval from the institutional review board, a retrospective analysis was performed on the department surgery database for women who underwent CKC for treatment of CIN 2/3 between January 1, 2007, and December 31, 2012. Owing to the retrospective study design, informed consent was not needed.

HPV DNA testing was routinely performed for all women during colposcopic evaluation of cervical cytologic abnormalities. Cervical brush specimens were collected in cell collection media (Cobas PCR; Roche Diagnostics, Indianapolis, IN, USA), and HPV DNA was purified with the MagNa Pure DNA Isolation Kit I on the MagNa Pure LC System (Roche Diagnostics). After nucleic acid isolation, all samples were analyzed via Linear Array HPV Genotyping Test (Roche Diagnostics) for polymerase chain reaction amplification of target DNA, followed by nucleic acid reverse hybridization for the simultaneous detection of high-risk HPV genotypes (HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68, and -82).

During follow-up after conization, all women were evaluated via cytology at 6 months, and cytology plus HPV DNA test at 12 months postoperatively. Colposcopy was performed when any of these tests showed an abnormality. Women with CIN 2/3 and a positive pre-conization HPV DNA test for high-risk types were included in the study. Exclusion criteria were subsequent diagnosis of invasive cervical cancer, subsequent total hysterectomy, and unavailability of required data. Patient age, menopausal status, parity, high-risk HPV type, excised tissue dimensions (width, height, and depth), and surgical margin positivity were recorded in each case.

Statistical analyses were performed with SPSS version 20.0 (IBM, Armonk, NY, USA). Continuous variables were expressed as mean ± SD, discrete variables as median (range), and categorical variables as number (percentage). The Kolmogorov–Smirnov test was used to assess normal data distribution. Univariate analyses to identify variables associated with HPV persistence were performed using χ^2, Fisher exact, Student *t*, and Mann–Whitney *U* tests, as appropriate. Correlations were assessed via Spearman correlation analysis. For multivariate analysis, possible factors identified in the univariate analyses were further entered into the logistic regression model to determine independent predictors of HPV persistence. The Hosmer–Lemeshow test was used to assess model fit. $P < 0.05$ was considered to be statistically significant.

3. Results

A total of 292 women underwent CKC at the study center for treatment of CIN 2/3 during the study period. Of these women, 217 (74.3%) were positive for high-risk HPV DNA. Nine women (4.1%) were excluded because of a subsequent diagnosis of invasive cervical cancer during follow-up, 44 (20.2%) because of definitive treatment with total hysterectomy, and 51 (23.5%) because of unavailability of follow-up data. The remaining 113 women were eligible for inclusion in the final analysis. Of these women, 81 (71.7%) had CIN 2 and 32 (28.3%) had CIN 3.

Mean patient age was 39.8 ± 10.9 years (range, 20–71 years). Eighty (70.8%) women were premenopausal and 33 (29.2%) were postmenopausal. Median gravidity and parity were 2 and 1, respectively. Twenty-one (18.6%) women were nulliparous and 92 (81.4%) had at least 1 prior delivery. None of the women had an immunosuppressive disorder such as HIV infection. Mean cone width, height, and depth were 29.2 ± 4.8 mm (range, 20–38 mm), 24.5 ± 6.3 mm (range, 5–35 mm), and 17.4 ± 4.6 mm (range, 10–35 mm), respectively. In 15 (13.3%) women, surgical margins were positive after the initial CKC procedure. Six of these women underwent a re-conization procedure; the other 9 were followed-up without further intervention.

Pre-conization frequencies of high-risk HPV DNA types are presented in Table 1. Post-conization persistence of high-risk HPV DNA was detected in 24 (21.2%) women: HPV-16 in 17 (70.8%) women; HPV-18 in 4 (16.6%) women; HPV-31 in 2 (8.3%) women; and HPV-45 in 1 (4.1%) woman. After colposcopic evaluation of the women with persistent HPV infection, CIN 1 was detected in 5 (20.8%) cases, CIN 2 was detected in 2 (8.3%) cases, and CIN 3 was detected in 1 (4.1%) case. No pathologic changes were found in 16 (66.6%) cases. Associations between HPV persistence and study parameters are presented in Table 2.

Mean patient ages of women with persistent HPV infection and those without persistent HPV infection were 35.2 ± 9.1 years and 41.02 ± 11.07 years, respectively ($P = 0.005$). Patient age was inversely correlated with HPV persistence (correlation coefficient = –0.26; $P = 0.005$). Mean cone width and height among women with persistent HPV infection and those without persistent HPV infection were 29.5 ± 5.02 mm vs 29.1 ± 4.8 mm and 24.2 ± 6.9 mm vs 24.6 ± 6.1 mm, respectively. Width and height of the cone specimen did not have a significant association with HPV persistence ($P > 0.05$). Mean cone depths among women with persistent HPV infection and those without persistent HPV infection were 13.9 ± 4.1 mm and 18.4 ± 4.2 mm, respectively ($P < 0.001$). Moreover, cone depth had a significant inverse correlation with HPV persistence (correlation coefficient = –0.442; $P < 0.001$).

We further compared women with pre-conization HPV-16 infection (n = 74) and women with pre-conization infection with other HPV types (n = 39) in terms of HPV persistence. HPV persistence was observed in 17 (23%) of the 74 women with HPV-16 infection, compared with 7 (17.9%) of the 39 women with other HPV infections ($P > 0.05$). Patient age (≤30 years vs >30 years), parity (nulliparous vs parous), and cone depth (<15 mm vs ≥15 mm) were included in the logistic regression analysis model. Patient age and cone depth were found to be significant predictors of HPV DNA persistence ($P < 0.05$) (Table 3).

Table 1
High-risk HPV DNA types detected pre- and post-treatment with cold-knife conization.[a]

HPV type	Pre-treatment	Post-treatment
HPV-16	74 (65.5)	17 (70.8)
HPV-18	10 (8.8)	4 (16.6)
HPV-31	12 (10.6)	2 (8.3)
HPV-33	6 (5.3)	0 (0.0)
HPV-45	6 (5.3)	1 (4.1)
HPV-51	5 (4.4)	0 (0.0)
Total	113 (100)	24 (100)

Abbreviation: HPV, human papillomavirus.
[a] Values are given as number (percentage).