Cancer Epidemiology 39 (2015) 237–241

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

Random biopsy in colposcopy-negative quadrant is not effective in women with positive colposcopy in practice

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ARTICLE INFO

Article history:
Received 22 August 2014
Received in revised form 7 January 2015
Accepted 11 January 2015
Available online 12 February 2015

Keywords:
Colposcopy
Random biopsy
Colposcopic-directed biopsy
Cervical intraepithelial neoplasia

ABSTRACT

Aim: To assess the efficacy of random biopsy in diagnosing those high-grade squamous intraepithelial lesions or carcinomas (HSIL+) missed by colposcopy-directed biopsy, and to identify the scenarios of cervical cancer screening when random biopsy is necessary.
Patients/interventions: Data from 1997 women who participated in the Shanxi Province Cervical Cancer Screening Study I (SPOCCS I) were reviewed. Each woman received human papillomavirus (HPV) testing with the second-generation hybrid capture, liquid-based cytology, four-quadrant biopsy and endocervical curettage. The final diagnosis was based on the most severe pathological result obtained. The efficacy of random biopsy and colposcopy-directed biopsy was evaluated on the basis of the final pathological results.
Results: For women with severe cytological abnormalities (HSIL+) and negative colposcopy, the yield of HSIL+ diagnosed by random biopsy was 25%. On the other hand, the yield of HSIL+ diagnosed by random biopsies in the negative quadrant was no more than 4% when the colposcopy was positive, regardless of the cytological findings. For women with negative HPV, no HSIL+ was found by random biopsy. For women with severe cytological abnormalities (HSIL+) and positive HPV, the yield of HSIL+ diagnosed by random biopsy was 35% when colposcopy was negative. For women with low-grade intraepithelial lesion (LSIL) and positive HPV, the yield of HSIL+ diagnosed by random biopsy was 12.5% when colposcopy was negative.
Conclusion: Random biopsy is not effective in the negative quadrant in women with positive colposcopy, but should be performed in women with cytological HSIL+ but negative colposcopy, or in those with cytological LSIL or HGSL+ and positive HPV but negative colposcopy.

1. Introduction

The introduction of cervical screening – including cytological diagnosis, human papillomavirus (HPV) testing, and colposcopy with biopsy – has markedly reduced the number of deaths from cervical cancer in recent years [1,2]. It is generally agreed that women with cytological high-grade squamous intraepithelial lesion (HSIL) should be referred for colposcopy. Women with cytological low-grade intraepithelial lesions (LSILs) should also receive colposcopy after a single abnormal result. In women with cytological borderline changes, i.e. atypical squamous cells of undetermined significance (ASCUS), acceptable options include testing for high-risk HPV, repeat cervical cytology, and/or immediate colposcopy [3]. In colposcopy, acetic acid is applied to the cervix under magnification, the grade of lesion is assessed, and the lesion is biopsied under colposcopic guidance (colposcopy-directed biopsy) [4]. Colposcopic-directed biopsy is the most commonly used diagnostic method for high-grade squamous intraepithelial lesions or carcinoma (HSIL+) in cervical screening [5,6], while HSIL+ cases may be missed by colposcopy-directed biopsies when lesions are not obvious [7,8]. Based on the results of 364 HSIL+ cases, it was reported that 37.4% of HSIL+ cases were

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http://dx.doi.org/10.1016/j.canep.2015.01.008
1877-7821/

detected by random biopsy [9]. Another paper reported that colposcopy-directed biopsy augmented with random biopsy could markedly increase the yield of HSIL+, regardless of skill [10]. As a result, some authors recommend applying random biopsies to the squamocolumnar junction in practice if cytology is high-grade [9,11].

In current clinical practice, the improved sensitivity of cytological screening with the addition of HPV testing has led to increasing numbers of referrals for colposcopy. Is it necessary to perform random biopsy in every negative quadrant in colposcopy if cytology is high-grade? What is the best way to combine random biopsy with colposcopy-directed biopsy to detect more HSIL+ after triaging with cytology and/or HPV testing? Being the only study in which all participants received identical screening tests – including colposcopy, four-quadrant biopsies and endocervical curettage (ECC) – Shanxi Province Cervical Cancer Screening Study I (SPOCCS I) provided us with a unique opportunity to assess the efficacy of random biopsy in every quadrant in diagnosing HSIL+ in practice.

2. Subjects and methods

2.1. Subjects

Data from 1997 women who participated in SPOCCS I between June 1999 and July 1999 were reviewed. The Institutional Review Boards for human research subjects of the Cleveland Clinic Foundation and the Cancer Institute/Hospital of the Chinese Academy of Medical Sciences (CICAMS) approved this study. Non-pregnant women between the ages of 35 and 45 with no history of cervical screening, pelvic radiation, or hysterectomy were eligible. Only women who voluntarily signed the informed consent after the doctors explained the study procedure and potential side effects in detail were enrolled in our study. All women were screened for cervical lesions/neoplasia. Each woman underwent cervical screening with cytological analysis and visual inspection with acetic acid (VIA). Physicians gathered cervical samples for HPV DNA tests and liquid-based cytology. Colposcopy was performed on every woman and biopsy was performed in every quadrant. An ECC was also done on every patient.

2.2. Liquid-based cytology and HPV testing

Specimens for HPV testing were obtained from the endocervix with a conical-shaped brush placed high in the vagina and rotated three to four times. The conical brushes were placed into a liquid medium and tested for a mixture of 13 intermediate- and high-risk types of HPV (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 5658, 59 and 68) with the second-generation hybrid capture microplate-based HPV test (HC2 test, Digene, Corp.). A cutoff value of 1.0 pg HPV DNA was regarded as positive.

Specimens for liquid-based cytology were obtained with a plastic spatula and an endocervical brush and placed in transport medium. Liquid-based cytology was prepared via the ThinPrep method (CytycCorp., Boxborough, MA) and interpreted using the Bethesda classification system by cytopathologists who were blinded to the results of the screening tests from the Cancer Institute and Hospital in Beijing. Cytopathologists at the Cleveland Clinic reviewed all abnormal slides and 5% of the normal slides. No significant differences in diagnoses were seen between the Beijing and the Cleveland Clinics.

2.3. Colposcopy and biopsy

Gynecological oncologists performed all colposcopies and biopsies. Colposcopies were considered satisfactory if the entire squamocolumnar junction was seen. The cervix was divided visually into four quadrants by lines drawn from 12 to 6 o'clock and from 3 to 9 o'clock positions. Each quadrant of the cervix was graded separately as negative (no lesions seen), low-grade squamous intraepithelial lesion (LSIL) suggestive of HPV or cervical intraepithelial neoplasia 1 (CIN1), high-grade squamous intraepithelial lesion (HSIL) suggestive of intraepithelial neoplasia 2 or 3 (CIN2 or 3), or invasive cervical cancer (ICC). All abnormalities diagnosed by colposcopy were biopsied. If colposcopic examination showed no lesions in any quadrant, a random biopsy was obtained at the squamocolumnar junction in four quadrants at the 2, 4, 8, or 10 o'clock positions, respectively. It was acceptable to take more than one biopsy per quadrant depending on the colposcopic impression. Unlike traditional biopsy forceps with 5-mm jaws, all biopsies were performed with a bronchoscopy biopsy instrument that has 2-mm jaws and is virtually painless for most patients. ECC was also performed on every patient with a Kevorkian curette.

2.4. Pathological diagnosis

The histological diagnosis was based on the consensus of two gynecological pathologists of the Cancer Institute and Hospital in Beijing who independently reviewed every biopsy. In specimens with discordant diagnoses, the final diagnosis was based on the majority assessment after a third gynecological pathologist examined the specimen. The pathologists were not aware of the results of any of the other tests. The final diagnosis was based on the most severe biopsy result obtained (i.e. colposcopy-directed, random, or ECC). The biopsies were also sent to the Cleveland Clinic for a similar review. No significant differences in diagnoses were found between the Beijing and the Cleveland Clinics.

2.5. Statistical analysis

Statistical analyses were performed using SAS software (SAS Institute, Cary, NC). All continuous variables were tested for normal distribution and presented by mean $\pm$ standard deviation. Sample proportions and corresponding 95% Clopper–Pearson confidence intervals (95%CI) were estimated under binomial assumption. Comparisons between proportions were analyzed using the Fisher exact test. All tests were two-sided, and p-values <0.05 were considered to be statistically significant.

3. Results

3.1. Participant characteristics

The mean age of participants was 39.1 ± 3.16 years. The mean number of pregnancies was 3.1 ± 1.27 and the mean number of births was 2.6 ± 0.93. Among the 1997 women, 98.5% were currently married, 93.3% had never smoked, and 0.3% had a history of condyloma. Of the enrolled 1997 women, 1784 (89.3%) were negative for squamous intraepithelial lesion, 127 (6.4%) had LSIL (CIN1), 74 (3.8%) had HSIL (43 CIN2 and 31 CIN3), and 12 (0.6%) had ICC. Therefore, 4.3% (86 of 1997) had HSIL+. Of these 86 HSIL+ cases, 74.4% (28 CIN2, 24 CIN3 and 12 ICC) were diagnosed by colposcopy-directed biopsy, 20.9% (14 CIN2 and 4 CIN3) were diagnosed by random biopsy, and 4.7% (one CIN2 and three CIN3) were diagnosed by ECC alone. In order to analyze the efficacy of biopsy, four HSIL+ cases found by ECC alone were excluded from this paper.

3.2. Efficacy of colposcopy-directed biopsies and random biopsies and correlation with results of cytology (ThinPrep Pap)

Of the ThinPrep Pap smears, four were unsatisfactory, 1480 were negative, 314 were ASCUS, 91 were LSIL, 96 were HSIL,