



A Review of Cervical Cancer Precursor Lesions and Recurrence after Treatment: What are the Real Risk Factors?

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Abstract

Objective: To evaluate the predictive factors that can influence recurrence of HSIL after treatment with LEEP or with cervical conization and show review from the literature the level of influence of each factor.

Methodology: We reviewed scientific publications after 2000 in PubMed, Web of Science, Scopus, LILACS databases to demonstrate factors that are related to the recurrence of HSIL after surgical treatment. To show the level of influence, the conditions were divided according to arbitrate convention: Indicative of evidence, lack of evidence and debatable.

Results: Factors that indicate increased risk of recurrence independent of importance scale were: Older age, HIV positive, HPV 16 presence, HPV viral load, glandular extension of the lesion, p16 and Ki-67 presence, depth of resection in conization, positivity of margins, number of quadrants involved by lesion, and non-HPV vaccination. Age at first sexual intercourse, use of oral contraceptives, parity, smoking, previous pregnancy, grade of intraepithelial neoplasia before conization and colposcopy gradation of the lesion did not show evidence of recurrence of the disease. The volume of the excised piece and the presence of other HPV oncogenic types no 16 or 18 had debatable evidence.

Conclusion: Factors that are indicative of recurrence of HSIL were: older age, HIV positive, HPV 16 presence, HPV viral load, glandular extension, conization depth, positivity of that markers p16 and Ki-67, positivity of margins, lesion included in multiple quadrants and not vaccinating against HPV. Patients who present some of these isolated factors or in association should be alert for a greater recurrence possibility.

Keywords: HSIL; Conization; LEEP; Recurrence; Cervical intraepithelial neoplasia

Introduction

Cervical carcinoma of the uterus is the second most common cancer among women in the world and the most common female cancer in developing areas [1]. An estimated 527,600 cervical cancer cases and 265,700 deaths occurred in 2012 worldwide [2]. Cervical carcinoma incidence is still very high and occurrence is estimated at about 16,340 new cases in 2016 according to the National Institute of Cancer in Brazil making it the third most common cancer and the fourth cause of death of women by cancer [3]. Human Papillomavirus (HPV) infection is the most important factor associated with development of premalignant cervical lesion [4]. Cytological cervical screening by Papanicolaou testing is the most widely used strategy for cervical cancer prevention worldwide. Achieving high coverage of the risk population is the most important factor to decrease the incidence and mortality of cervical cancer [5]. Until the 1960s, aggressive methods such as extensive conization or even hysterectomy were used to treat cervical intraepithelial neoplasms of any degree. The introduction of a more conservative outpatient approach such as destruction or excision of the abnormal transformation zone was an important advance. Excision of the Large Loop Transformation Zone (LLTZ) or Large Loop Excision of Transformation Zone (LLETZ) is a procedure that removes the entire transformation zone focusing only on the lesion and thus more economically, decreases surgical morbidity and risk for the future reproductive health [6]. The resection of the lesion through Loop Electrosurgical Excision Procedure (LEEP) or Large Loop Excision of the Cervical Transformation Zone (LLETZ) methods was widely used because it had

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some advantages: Ambulatory procedure performed under local anesthesia, low risk of complications, easy to perform, and provided learning. Initially the technique developed by René Cartier consisted only of the use of a handle to remove the transformation zone, but the use of the second handle, aiming at the removal of greater quantity of the canal, was introduced by Prendiville to cover the deeper lesions. The success rate for this treatment modality can reach rates of 98%, according to Prendiville [7-9]. Despite proper treatment a percentage of High-Grade Intraepithelial Lesions (HSIL) will recur, increasing the risk of progression to invasive carcinoma. This new treatment modality, that is less aggressive and with less tissue resection required calls for the evaluation of predictive factors of recurrence or persistence of the lesion [7-11].

The studies point too many factors related to recurrence, but present in the same time, a great diversity of results in relation to these factors involved in recurrence after treatment. There appears to be a direct relationship between high-risk-HPV persistence after treatment and the presence of residual lesions after conization, and consequently all factors related to then [7-11]. This study aims to evaluate the current evidence in the literature through overview regarding factors that are associated with the recurrence or persistence of high-grade intraepithelial lesion, to determine which variables are really important in clinical practice. Although there is no a score including the association of risk factors, the idea is to select the patients who deserve greater attention during follow up, based on current literature review.

Methods

The search strategy used, since January 2006 to December 2016, was based on the following descriptors: ("Uterine Cervical Neoplasms" OR "Cervical Intraepithelial Neoplasia" OR "Intraepithelial lesion" OR "High Grade Squamous Intraepithelial Lesion") AND (Reoperation OR "Neoplasm Recurrence", Local "OR recurrence) AND ("risk factors" OR "depth height width" OR conization OR Smoking OR *Papillomaviridae* OR "human papillomavirus" OR "Papillomavirus Infections" OR HIV OR "Cyclin-Dependent Kinase Inhibitor p16" OR "depth of glandular crypts" OR "Endocervical Crypt Involvement" OR crypts OR crypt OR vaccine).

The way to choose the descriptors was made according to suggestions found in SCIENTIFIC SEARCH SITES. The bases selected were PubMed, Web of Science, Scopus and LILACS. Almost 3,000 (2,989) documents were included in the EndNote™ basic Reference Manager (Thomson Reuters). Data were refined as shown in Table 1. According to reviewing the literature, 19 variables that could potentially influence the recurrence rate were studied. These were classified into 4 groups: Conditions related to the host, virus, lesion and conditions related to treatment (Table 2). The analysis was limited to research articles only where systematic reviews and meta-analysis were excluded. Due to different methodologies from each study, the systematic review was not able to be done. Although each paper used a different number of patients and a different methodology to analyze the results, we decided to analyze all values arbitrating scores according to their conclusions. In the created scoring convention, it was defined that: When more than 80% of the studies were favorable and 20% were not favorable to the recurrence risk, that variable was classified as "Indicative of recurrence". In this way, when more than 80% of the studies showed that the factor did not influence the recurrence disease and 20% of the studies showed that it influenced the recurrence, the variable was classified as "Non-Indicative of

Table 1: Search Strategy of Studies Selection.

Data Base	Details from Search strategy
	("Uterine Cervical Neoplasms" OR "Cervical Intraepithelial Neoplasia" OR "Intraepithelial lesion" OR "high-grade squamous intraepithelial lesion") AND (Reoperation OR "Neoplasm Recurrence, Local" OR recurrence) AND ("risk factors" OR "depth height width" OR conization OR Smoking OR <i>Papillomaviridae</i> OR "human papillomavirus" OR "Papillomavirus Infections" OR HIV OR "Cyclin-Dependent Kinase Inhibitor p16" OR "depth of glandular crypts" OR "Endocervical Crypt Involvement" OR crypts OR crypt OR vaccine)
Medline/PubMed (via. National of Library in Medicine)	1,217 studies
Web of Science-Coleção Principal (Thomson Reuters Scientific)	351 studies
Scopus	1,385 studies
LILACS-Latin American and Caribbean Health Sciences Literature	36 studies
Total	2,989 studies
Duplicate work -EndNote™ verification	782 studies
Duplicate works-manual verification	491 studies
Journal before 2000 January	453 studies
Studies that were not related to the theme read the title and abstract	1,229 studies
Final corpus of the study	34 studies

recurrence". Finally, when the percentage was not according to this scale was classified as "debatable evidence". To demonstrate the importance from each risk factor, a table was organized with the data highlighted in different colors for better observation: Red, blue and green to demonstrate positive, negative and debatable evidence respectively (Table 6).

Results

In the last 10 years, the recurrence rates shown in the literature after treatment of CIN through resections (LEEP, LLETZ OR cold knife cone), had great variability interval of between 7% and 51.7%. Table 3 shows that among 15 studies including 4,078 cases, the mean recurrence rate was 15.7%. These studies show that one of the main factors associated with recurrence/persistence is residual presence of the lesion in the margins from conization. Therefore, due to the importance from this risk factor, we decided to review some particularities about the residual presence of the lesion in the margins and its recurrence/persistence rate. Table 4 shows five studies where the ecto and/or endocervical margins were available in the same sample and its relationship with recurrence rates of treated HSIL [12-24].

Fonseca et al. [6,15] studies show that rates of endo and ectocervical compromised margins have equal percentages. Chikawaza et al. [17] showed that the ectocervical margin was the most affected. The studies by Fu et al. [14], Chikawaza et al. [17], and Lubrano et al. [23] reported that the endocervical margin was the most compromised. Observing the mean number of margins involved, the internal one tends to show a greater chance of recurrence (Table 5). Table 6 objectively evaluated

Table 2: Factors related to the host, virus, lesion and treatment (19 variables studied).

Conditions	Variables
Host	Age
	HIV
	Tabagism
	Age at first sexual intercourse
	Use of oral contraceptives
	Parity
	Previous pregnancy
Virus	HPV 16
	HPV viral load
	p16 and Ki-67
	Other HPV oncogenic types no 16/18
Lesion	Colposcopy gradation of the lesion
	Lesion grade before LEEP/LLETZ/Conization (LSIL, HSIL, atypical squamous cell)
	Glandular extension of the lesion
	Lesion included in multiples quadrants
Treatment	Depth of conization
	Positive margins
	HPV vaccination
	Cone volume

the factors that may be associated with recurrence. In these 34 studies, only the recurrence rate is debugged. Such data can be seen in each of the studies in isolation or in association.

In summary, Table 7 shows the main product of this review where the risk factors correlate with an indicative trend, no indicative trend or debatable evidence.

Discussion

Factors associated with residual/recurrent disease of cervical

intraepithelial neoplasia need to be better characterized through a review of the literature. In a review of this topic, Kang et al. [25] reported that recurrent/residual disease after LEEP ranges from 5% to 30%, requiring follow-up or re-treatment once the lesion is identified. Evidence suggests that cone wedge involvement is one of the major predictors of recurrence failure. Lima et al. [26] attribute both the ectocervical and the endocervical margins to the association with the persistence of the disease. Some authors attribute this correlation only to the ectocervical margin and still others attribute it to the endocervical margin [20,27-29].

Previous research by these authors identified a similar rate of recurrence for ectocervical and endocervical margins compromised, 27% and 33%, respectively [6]. Therefore, details of the technique should be revised during resection of the lesions to obtain the free margins. The operator must use a loop that is larger than the lesion (s) and the processing zone must be fully identified and excised. The depth of the loop must be at least 5 mm (height of the cable to the furthest part of the wire). Often, an oval diathermy loop of 2.0 cm × 0.8 cm is used. If an injury occupies the endocervical canal so that it can barely be excised with the depth of the usual single layer passage described above, a two-layer excision method may be used. Most of the lesions occupying the cervical canal usually extend to a depth of up to 1 cm [30].

In general, the ectocervical portion of the lesion extending into the endocervical canal can be excised with a large oval loop (2.0 cm × 0.8 cm). The remainder of the tissue in the endocervical canal can be excised with a smaller loop, usually square and measuring 1.0 cm × 1.0 cm. However, care must be taken not to go deeper than necessary. This type of excision can penetrate up to 1.6 cm in the endocervical canal [30].

We found, among 2,427 cases of LEEP, that when excised less than 1.25 cm of the endocervical canal, the recurrence rate increased in a significative way (2,5 times)*.

In relation to margins involvement, this may be due by inadequate technique or be caused by the greater extension of lesions. And the

Table 3: Recurrence rates of HSIL after conical resections, according to recent studies (2006 to 2016).

Author	Year/local	Journal	Number of cases	Recurrence rate
Zhu et al. [10]	2015, China	BMC Cancer	238	27 (11.3%)
Pirtea et al. [11]	2016, Romania	BMC Surgery	110	22 (20%)
Lodi et al. [12]	2011, Brazil	Arch Gynecol Obstet	138	33 (23.9%)
Leite et al. [13]	2016, Brazil	Rev Bras Ginecol Obstet	86	17 (19.7%)
Fu et al. [14]	2015, China	Therapeutics and Clinical Risk Management	145	47 (32.4%)
Fonseca et al. [15]	2011, Brazil	Rev Bras. Ginecol. Obstet.	491	72 (14.6%)
Lu et al. [16]	2006, Taiwan	Obstetrics & Gynecology	449	64 (14.2%)
Chikawaka et al. [17]	2016, Japan	Japan Society of Obstetrics and Gynecology	178	32 (17.9%)
Serati et al. [18]	2012, Italy	European Journal of Obstetrics & Gynecology and Reproductive Biology	282	64 (22.7%)
Lima et al. [19]	2006, Brazil	Rev. Bras. Ginecol Obstet	201	40 (19.9%)
Kietpeerakool et al. [20]	2007, Thailand	Journal Obstet. Gynaecol	85	44 (51.7%)
Xi et al. [21]	2007, EUA	Journal Infected Disease	201	20 (10%)
Kreimer et al. [22]	2006, EUA	Cancer Epidemiol Biomarkers Prev	485	34 (7%)
Lubrano et al. [23]	2011, Spain	European Journal of Obstetrics & Gynecology and Reproductive Biology	637	88 (13.9%)
Lequevaque et al. [24]	2010, Mexico	Europe Journal Surg Oncol	352	37 (10.5%)
Total	2006 to 2016		4.078 cases	641 (15.7%)

Table 4: Rate of positive margins of the conization product for resection of cervical cancer precursor lesions by the LEEP technique related with rate of recurrence/persistence.

Author	Year	Number of cases	Positive ectocervical margin percentage (N%/ recurrence or persistence rate (N%))	Positive endocervical margin percentage (N%/ recurrence or persistence rate (N%))	Both margins positive percentage, (N%)/ recurrence or persistence rate (N%)
Fonseca et al. [6]	2016	262	15 (6%)/4 (26.6%)	15 (6%)/5 (33.3%)	1 (0.4 %)/1(100%)
Fu et al. [14]	2015	145	47 (32.4%)/11 (23.4%)	81 (55.9%)/31 (38.3%)	17 (11.7%)/5 (29.4%)
Fonseca et al. [15]	2011	103	12 (11.6%)/8 (67%)	9 (8.7%)/9 (100%)	3 (2.9%)/3 (100%)
Chikawawa et al. [17]	2016	178	28 (16%)/10 (35,7%)	10 (5,6%)/3 (30%)	6 (3.4%)/2 (33.3%)
Lubrano et al. [23]	2011	637	58 (9.1%)/11 (28.9%)	68 (10.6%)/20 (29.4%)	11/(27.3%)/3 (27.3%)
Total	2011-2016	1.325	102 (14.8%)/33 (32.3%)	115 (16.7%)/48 (41.7%)	27 (3.9%)/11 (40.7%)

Table 5: Percentage of recurrence rate in relation to ecto and endocervical margins compromised.

Author	Ectocervical margin (%)	Endocervical margin (%)	p value
Fonseca et al. [6]	26.6	33.3	<0.0001
Fu et al. [14]	23.4	38.3	<0.05
Fonseca et al. [15]	67	100	<0.001
Chikazawa et al. [17]	35.7	30	<0.05
Lubrano et al. [23]	28,9	29,4	<0.001

Table 6: Number of studies evaluated in relation to risk factors for recurrence in descending order of citations.

Variable searched	Total no. of studies	No. of studies with positive evidence	No. of studies with negative evidence
1-Age	15	10	5
2-Positive margins	14	10	4
3-Glandular extension of the lesion	11	8	3
4-Severity of the lesion	10	3	7
5-Parity	8	2	6
6-HPV 16 presence	7	5	2
7-Tabagism	6	2	4
8-HIV positive	4	3	1
9-Age at first sexual intercourse	4	0	4
10-Conization depth	4	3	1
11-HPV viral load	4	3	1
12-Colposcopy gradation of the lesion HPV viral load	3	0	3
13-HPV vaccine	3	2	1
14-Lesion included in multiples quadrants	3	3	0
15-Use of oral contraceptives	3	0	3
16-Other HPV oncogenic types no 16/18	2	1	1
17-Cone volume	2	1	1
18-Previous pregnancy	2	0	2
19-p16 e Ki-67	1	1	0

technique chooses to treatment need to take into account. On age, the great majority ever that being ≥ 35 years is an important risk factor for predicting the risk of residual or recurrent lesion, however; Lodi et al. concluded that age is not a significant factor for recurrence of the disease in women infected with HIV. Nam et al. [31] cited that age, parity, cytology gradation prior to conization, lesion gradation on histology were not significant for HPV persistence in patients with negative margins. The number of quadrants involved (≥ 2) is a factor for recurrence of the disease as shown by the research of Lu et al. [16], Kietpeerakool et al. [20] and Kawano et al. [32].

Nam et al. [31] also demonstrated that HPV persistence increase

with HPV 16 presence compared to other types of HPV ($p=0.021$) can be considered as a risk factor. Kang et al. [25] evaluated 748 patients after LEEP; 360 women received the quadrivalent HPV vaccine and 377 did not receive the vaccine and concluded that the group of non-vaccinated patients after LEEP had a high recurrence of the disease than the unvaccinated (8.5% and 2.5% respectively). Similar data has been described for the bivalent vaccine as described in the study by Garland et al. [33] who demonstrated that women who underwent conization after receiving the bivalent vaccine continue to benefit from reduced risk of developing subsequent lesion. Glandular extension is another factor that shows positive evidence for recurrence of the disease. Kodampur et al. [34] concluded that

Table 7: Factors associated with the host, virus, lesion and treatment in relation to recurrence/persistence (19 variables studied).

Condition	Recurrence indicatives	Not indicative of recurrence	Debatable evidence
Host	-Older age	-Tabagism	
	-HIV presence	-Age at first sexual intercourse	
		-Use of oral contraceptives	
		-Parity	
		-Previous pregnancy	
Virus	-HPV 16 presence		-Other oncogenic HPV types no 16/18
	-HPV viral load		
	-p16 e Ki-67		
Lesion	-Glandular extension of the lesion	-Colposcopy gradation of the lesion; degree	
	-Lesion included in multiples quadrants	-Lesion grade before LEEP/LLETZ/conization (LSIL, HSIL, atypical squamous cell)	
Treatment	-Conization depth		-Cone volume
	-Positive margins		
	-Do not vaccinate against HPV		

the presence of crypt involvement after LLETZ increased the risk of recurrence and the need to repeat treatment by 2.67-fold despite complete margin excision. Paraskevaidis et al. [35] demonstrated that glandular extension presence affected 71% of the patients despite the free margins. Most studies related that increase in recurrence of HSIL when the viral load is >100 RLU (relative light units) [14,31,36,37]. However Willians et al. [36] concluded that a single measure of HPV viral load cannot be considered a clinically useful biomarker. Number of sexual partners, age at first sexual intercourse, parity and use of oral contraceptives are shown to have negative evidence regarding the risk of persistent/recurrent HPV [12,16,26,32,37,38]. Papoutsis et al. [39] showed that high-grade cytology recurrence was reduced significantly if more 1.9 cm³ of the cervix was removed. Nevertheless, Fonseca et al. [15] study did not correlate the size of the uterine volume removed with recurrence of disease.

In the limitations of the study, we noted that due to diversity of methodologies of each study, the statistical analysis wasn't done. The methodology was conducted direct to comparing each risk factor and, in each study, we believe that considering the arbitrated relevance score, where 80% of them as conclusive, lead us to the interpretation that the analysis may have relevance in the clinical follow-up. We concluded that factors indicative of recurrence of HSIL were: Older age, HIV positive, HPV 16 presence, HPV viral load, glandular extension of the lesion, conization depth, positivity of markers p16 and Ki-67, positivity of margins, lesion included in multiple quadrants and lack of vaccinating against HPV.

As a contribution, this review brings perspectives that new studies can build a score where, depending on the valuation of each risk factor involved, it is possible to predict the chance of recurrence after conical resections of the cervix, decreasing the risk of cervical carcinoma.

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