

# A Clinical Comparative Study of Two Different Endometrial Cell Samplers for Evaluation of Endometrial Lesions by Cytopathological Diagnosis

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**Purpose:** Cytopathology detecting for endometrial cancer is becoming accepted, and Tao Brush is the most widely used sampler for endometrial cells. This study aims to compare the effectiveness between Li brushes and Tao brushes for the diagnosis of endometrial lesions and to evaluate the diagnostic accuracy of endometrial cytology compared with histology.

**Methods:** There were 109 patients needing dilation and curettage (D&C) and 21 patients needing hysterectomies included from November 2017 to April 2018. Every patient was sampled by Tao brush and Li brush before D&C or hysterectomy performed. The cytological results were compared based on the gold standard histological results of D&C or hysterectomy.

**Results:** The sensitivity of Li brush cytology for detecting endometrial cancer and atypical hyperplasia was estimated at 83.33%, specificity at 100%, positive predictive value (PPV) at 100%, and negative predictive value (NPV) at 98.02%, respectively. While for the Tao brush, it was 91.67% of sensitivity, 96.04% of specificity, 73.33% of PPV, and 98.98% of NPV, respectively. The kappa value was 0.767, which indicated a substantial agreement. Cytology by both two brushes had a lower insufficient sample rate (2.75% of Tao brush, 4.59% of Li brush) than did D&C (11.93%).

**Discussion:** Endometrial cytology is a reliable approach for evaluating endometrium with a lower insufficient sample rate. Cytology sampled by both Li brushes and Tao brushes has a high accuracy with histological diagnosis in detecting endometrial cancer and atypical hyperplasia. Combining social and economic benefits, the Li brush may be a better endometrial cell collector.

**Keywords:** Li brush, Tao brush, cytology, dilation and curettage, endometrial cancer

## Introduction

Endometrial malignant diseases are becoming the most common malignancy of the female genital tract in developed countries, with approximately 63,230 new endometrial cancer cases in the United States in 2018.<sup>1</sup> Though dilation and curettage (D&C) is the most common method for endometrial lesions diagnosis, less than half of the uterine cavity is curetted in 60% cases.<sup>2</sup> As an invasive procedure, it has risks of infection and perforation.<sup>3</sup> Therefore, endometrial cytology has been a research hotspot for evaluating endometrium.<sup>4</sup> In Japan, endometrial cytology is one of the most common effective tests for evaluating the endometrium.<sup>4,5</sup>

Since satisfactory sampling is one key to success in endometrial cytology, many kinds of endometrial samplers have been developed, such as Endoflower, the Tao brush, and Endocyte.<sup>6,7</sup> The Tao brush, approved by the US Food and Drug Administration (FDA),<sup>8</sup> is the most widely used disposable sheathed-brush device. Much research has showed that the Tao brush is highly accurate in detecting endometrial cancer, with a sensitivity of 100% and specificity of 96%.<sup>9</sup> However, the Tao brush is too expensive for patients in developing countries, and the price of Tao brush is almost 10 times the Li brush.

As a direct endometrial sampler device, the Li Brush is T-shaped (Patent, ZL.201420720356.8), similar to the cavity of the uterus, and more likely to harvest cells from all parts of the uterine cavity, especially the fundus and cornua. The plastic sheath protects samples from the cervical canal and vagina cells contamination.<sup>8,10</sup> The Li brush has been used in many provinces in China. Moreover, it is cost-effective, well tolerated, and easily performed. Because of these advantages, the Li brush is expected to become a favored device in endometrial disease evaluation.<sup>11</sup>

For further popularization of the Li brush, a random control clinical trial was launched after registering on Chinese Clinical Trial Registry (ChiCTR1800020281). The goal of this study was to compare the effectiveness between Li brushes and Tao brushes for the diagnosis of endometrial lesions and to evaluate the diagnostic accuracy of endometrial cytology compared with histology.

## Materials and Methods

### Patients

From November 2017 to April 2018, 130 patients participated in this trial in the First Affiliated Hospital of Xi'an Jiao Tong University. The inclusion criteria of the study were as follows: patients needing to undergo D&C (abnormal uterine bleeding during pre-/postmenopause, postmenopausal endometrial thickness > 5 mm, hypermenorrhea, prolonged menstrual bleeding and uterine prolapse) or hysterectomy (uterine leiomyoma, endometrial cancer and atypical hyperplasia). The exclusion criteria of the study were as follows: patients with fever or acute inflammation, pregnancy, cervical cancer, or hematologic system disease. The study was approved by the Institutional Review Board of the First Affiliated Hospital of Xi'an Jiao Tong University (IRB No. XJTUIAF2017LSK-100). Informed consent was obtained from all patients.

## Sample Collection

All participants were numbered randomly. Before D&C or hysterectomy, the odd-numbered group was sampled by Tao brush first and then Li brush, while the even-numbered group was sampled in the reverse order. The procedures followed the steps in Figure 1, referring to the study of Han et al.<sup>11</sup>

Endometrial cells sampled by Tao brush (Cook Incorporated, USA, J-ES-090500) and Li brush (Xi'an Meijiagia Bio-Technologies Co. Ltd., China, 20152660054) from every patient were labeled differently. Only the operating doctor knew the tags and their corresponding variables. The following patient-related variables were obtained from their records: name, age, and chief complaint. After cytological collection, the patient underwent D&C or hysterectomy.

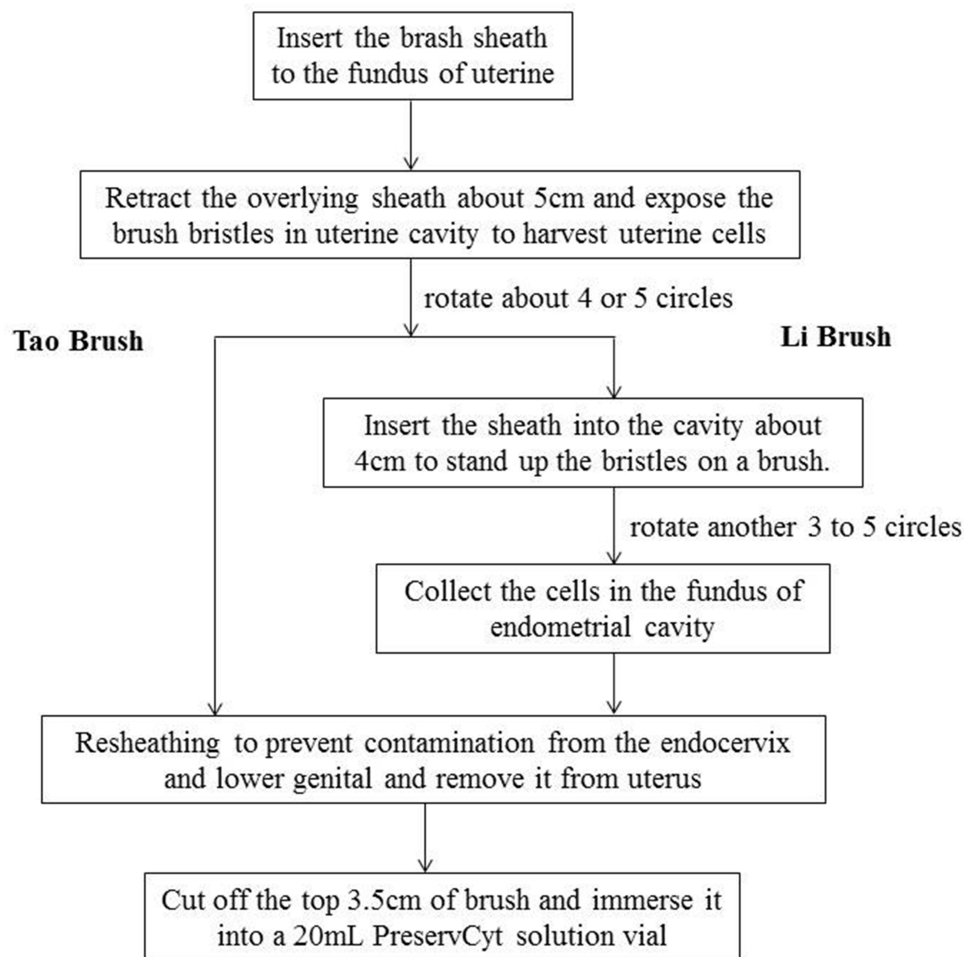
## Cytopathological and Histopathologic Diagnosis

Both cytological and histological diagnoses were blindly made by two pathologists. The negative results included secretory endometrium, atrophic endometrium, mixed endometrium, and hyperplasia without atypia. Positive results included endometrial hyperplasia with atypia and endometrial carcinoma.

"Insufficient" was considered as a histological diagnosis for slides with a scarcity of endometrial tissue or with severe fragmentations. For cytological diagnosis, "insufficient" was considered when the evaluable endometrial clusters were <10 in child-bearing women or <5 in postmenopausal women.<sup>7</sup>

## Statistics

The data of 130 patients were extracted from their medical records. Normally distributed data were expressed as mean  $\pm$  standard deviation, and non-normally distributed data were expressed as median (first quartile to third quartile). The diagnostic accuracy of the two brushes was analyzed using true positive (TP), false positive (FP), false negative (FN), true negative (TN), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The analysis was carried out by SPSS22.0 statistical software. The inter-rater agreement of the Li brush and Tao brush in diagnosing endometrial lesions was measured by Cohen's kappa coefficient. Qualitative values were analyzed by Chi-square test. *T*-test was used in numerical variables. Logistic regression analysis was used to investigate risk factors of insufficient specimens



**Figure 1** Sampling flow diagram.

of D&C.  $P < 0.05$  showed the significant statistical difference.

## Results

There were 130 patients involved in this trial: 21 from the Inpatient Department (hysterectomy) and 109 from the Outpatient Department (D&C). The patients' characteristics are showed in Table 1. Eleven of the 130 patients were histologically diagnosed with endometrial cancer, and seven of these 11 patients with cancer were postmenopausal. The average age in the cancer group was  $54.9 \pm 8.3$ , and in the non-cancer group, it was  $47.0 \pm 9.6$  ( $P = 0.009$ ). The menarche age in the cancer and non-cancer groups was  $14.5 \pm 2.0$  and  $14.6 \pm 1.8$ , respectively ( $P = 0.919$ ). The body mass index (BMI) was  $23.2 \pm 2.8 \text{ kg/m}^2$  in the cancer group and  $23.6 \pm 3.4 \text{ kg/m}^2$  in the non-cancer group ( $P=0.685$ ). The first three chief complains of these 130 patients were postmenopausal uterine bleeding (21/119 in the non-cancer group; 7/11 in the cancer group), abnormal

uterine bleeding (25/119 in the non-cancer group; 2/11 in the cancer group), and hypermenorrhea (31/119 in the non-cancer group; 2/11 in the cancer group).

Out of all 130 patients, 13 patients had no histological diagnosis (all sampled by D&C) for insufficient samples; however, these 13 patients were all diagnosed by cytology sampled by both the Li brush and Tao brush. Three of the patients gave insufficient specimens sampled by both the Li brush and Tao brush. Two of the patients gave insufficient specimens sampled by the Li brush alone. All five patients with inadequate cytological reports were outpatients, and their matched histological samples were collected by D&C. Thus, except for 21 patients with postoperative pathological diagnosis, the insufficient sample rate was 2.75% of the Tao brush, 4.59% of the Li brush, and 11.93% of D&C, respectively.

The comparison of histological and cytological diagnoses and the diagnostic accuracy of the Tao brush and Li brush for detecting endometrial cancer and atypical

**Table 1** Characteristics of Patients with or Without Endometrial Cancer

	Non-Cancer Group	Cancer Group	P value
patient number	119	11	0.006
post-menopause	29	7	
pre-menopause	90	4	
age (years old)	47.0±9.6	54.9±8.3	0.009
menarche (years old)	14.6±1.8	14.5±2.0	0.919
BMI (kg/m <sup>2</sup> )	23.6±3.4	23.2±2.8	0.685
Parity	1.6±0.9	1.8±1.1	0.384
Complains			
Post-menopausal uterine bleeding	21	7	
Abnormal uterine bleeding	25	2	
Hypermenorrhea	31	2	
Prolonged menstrual bleeding	16		
Heavy menstrual bleeding	6		
Uterine leiomyoma	6		
Thicken endometrium under ultrasound	4		
Uterine prolapse	3		
Others	7		

**Abbreviation:** BMI, body mass index.

hyperplasia are presented in Tables 2 and 3, respectively. The sensitivity of the Tao brush and Li brush was 91.67% and 83.33%, respectively. The specificity of the Tao brush was 96.04% and the Li brush was 100.00%. The Tao brush had a diagnostic accuracy in PPV of 73.33% and NPV of 98.98%, while Li Brush was 100.00% and 98.02%, respectively. The comparison of cytological diagnosis between the Tao brush and Li brush is shown in Table 4. The kappa value was 0.767, which indicates a substantial agreement between these two brushes.

## Discussion

In developed countries, endometrial cancer is now the most prevalent cancer of the female genital tract, and it accounts for nearly 50% of all new cancer cases of the genital tract system.<sup>12</sup> D&C, as the traditional gold standard to evaluate the endometrium, is painful and expensive and requires anesthesia.<sup>13–15</sup> The biggest problem for pathologists is the high inadequacy rate of D&C, which is affected by many factors such as a patient's age, parity, endometrial thickness, samplers, and the surgeon's

**Table 2** Comparison of Histology and Cytology Diagnosis by Tao Brush and Li Brush

		Histology		Total
		Positive	Negative	
cytology by Tao Brush	Positive	11	4	15
	Negative	1	97	98
	Total	12	101	113
cytology by Li Brush	Positive	10	0	10
	Negative	2	99	101
	Total	12	99	111

**Table 3** Diagnostic Accuracy of Tao Brush and Li Brush

	Se (%)	Sp (%)	FN (%)	FP (%)	PPV (%)	NPV (%)
Tao Brush	91.67	96.04	8.33	3.96	73.33	98.98
Li Brush	83.33	100	16.67	0	100	98.02

**Abbreviations:** Se, sensitivity; Sp, specificity; FN, false negative; FP, false positive; PPV, positive prediction value; NPV, negative prediction value.

technique.<sup>16</sup> Dina et al analyzed 17,522 endometrial samples, and the insufficiency rate in curettage was 6.4% (810/12,745), while in endometrial biopsy it was 6.5% (310/4,777). In groups of patients under 40 years old (3,454 cases), 40 to 59 years old (11,838 cases), and 60 years and older (2,230 cases), the insufficient rate was 2.7%, 5.8%, and 14.6%, respectively.<sup>17</sup>

Pipelle is also a widely used biopsy apparatus to evaluate endometrium.<sup>18</sup> It is safe and easily performed. Meanwhile, it has a high concordance rate with D&C/hysteroscopy/hysterectomy in diagnosis of endometrial cancer.<sup>19</sup> However, blind random point sampling results in a high insufficient rate.<sup>20</sup>

Hysteroscopic guided biopsy is the most reliable procedure to evaluate endometrial lesions.<sup>21</sup> It has a high accuracy in the diagnosis of not only endometrial cancer but also endometrial hyperplasia, especially when using the “grasp technique”.<sup>22,23</sup> Senior operators showed a more accurate prediction in endometrial hyperplasia following the morphological criteria.<sup>23</sup> But hysteroscopy is expensive and difficult to perform. What's more, it could not be performed in asymptomatic women for endometrial cancer screening.

Endometrial cytology seems to have a high consistency with histopathology results and could be used to evaluate endometrial diseases.<sup>5,11</sup> It is safe, minimally invasive, and

**Table 4** Comparison of Cytology Diagnosis of Tao Brush and Li Brush

		Tao Brush						Total
		Atrophy	Secretory	Mixed Endometrium	Hyperplasia	Atypical Hyperplasia	Cancer	
Li Brush	Atrophy	14	0	0	3	0	0	17
	Secretory	0	4	0	0	1	0	5
	Mixed endometrium	0	0	5	4	0	0	9
	Hyperplasia	1	0	2	78	2	1	84
	Atypical hyperplasia	0	0	0	0	1	0	1
	Cancer	0	0	0	0	1	8	9
	Total	15	4	7	85	5	9	125

**Note:** mixed endometrium refer to mix of secretory and hyperplasia endometrium.

easily preformed.<sup>24</sup> Fujiwara et al<sup>5</sup> analyzed 1,441 endometrial cancer cases and 1,361 control cases. Endometrial cytology detected cancer in 1,279 (916 positive and 363 suspicious) cases, sampled by Soft Cyto sampler/Endocyte sampler/Honest Uterine Brush sampler, with a sensitivity (positive plus suspicious cases) of 88.8% and a specificity of 98.5%. Yang et al<sup>7</sup> sampled 1,672 patients using SAP-1 device and reported the diagnostic accuracy of liquid-based endometrial cytology for atypical hyperplasia and endometrial cancer was 86.1%. The sensitivity and specificity were estimated at 70.3% and 88.5%, respectively. The PPV and NPV were 48.0% and 95.2%, respectively. Consecutive endometrial cytological samples obtained in 13 Japanese hospitals showed the unsatisfactory specimen rate was 5.5% (557/10,152),<sup>25</sup> which was lower than in histological specimens.

A variety of cytologic samplers have been developed, such as the Tao brush, Uterobrush, Li brush, Cytobrush, Endoflower, and SAP-1 sampler.<sup>6,7</sup> The Tao brush, as a widely used endometrial brush, has a low inadequacy rate, a high sensitivity of 100%, and a specificity of 96% in the diagnosis of atypical hyperplasia or endometrial carcinoma.<sup>9</sup> Abdelazim et al<sup>26</sup> compared the diagnostic accuracy between the Tao brush and D&C in 220 women with abnormal uterine bleeding, and results showed that the Tao brush had a high accuracy for diagnosing endometrial carcinoma with a sensitivity of 100%, a specificity of 100%, predictive values of 100%, and a high adequacy rate of 98.2%.

However, the Tao brush is very expensive and is hard to get in many countries like populous China. As a similar direct endometrial sampler device, the Li brush is much cheaper. It consists of four parts: the brush head, the pipe core, the sheath,

and the handle. Compared with the Tao brush and other samplers, the Li brush is designed as an inverted cone: it is T-shaped, which is similar in shape to the uterine cavity. Theoretically, because of its shape, it can harvest more endometrial cells, especially cells in the uterine horns and the fundus when operators stand up the bristles of the brush. The sheath successfully protects endometrial cells from cervical or vaginal contamination. Meanwhile, the material is soft and causes little damage to the endometrium.<sup>8,10</sup> The Li brush had been used in many provinces in China. It is cost-effective, well tolerated, and easily performed. Han et al<sup>11</sup> enrolled 271 women undergoing endometrial cytology sampling by Li brush before hysterectomy and showed that the sensitivity and specificity of cytology compared with postoperative histological results were 92.73% and 98.15%, respectively. The PPV and NPV were 92.73% and 98.15%, respectively.

Taking the endometrial histological results as the gold standard, our results showed that endometrial cytology by both Li brush and Tao brush had a really high specificity and sensitivity for the diagnosis of endometrial cancer and atypical hyperplasia. Cytological diagnosis sampled by Li brush and Tao brush had a high accuracy with histological diagnosis in detecting endometrial cancer and atypical hyperplasia. In our study of histologically confirmed cases, the sensitivity of Li brush cytology for detecting endometrial cancer and atypical hyperplasia was estimated at 83.33%, specificity at 100%, PPV at 100%, and NPV at 98.02%, respectively. While for Tao brush, the values were 91.67% of sensitivity, 96.04% of specificity, 73.33% of PPV, and 98.98% of NPV, respectively. The kappa value was 0.767, which indicated a substantial agreement. Also, samples collected by both Li brush and Tao brush had a lower insufficient sample rate (2.75% of Tao brush,

4.59% of Li brush) than did D&C (11.93%). The similarity and the insufficiency were also comparable when both Li brush and Tao brush were used.

Our comparative analysis showed a high diagnostic accordance between the two brushes in evaluating endometrial lesions, and a high accuracy between endometrial cytological and histological diagnosis. However, there are some limitations: 1) Our sample is small. We had tried hard to enlarge our sample size, but no supplier of Tao brush could be found in China after the original supplier quit. 2) Out of 109 patients undergoing D&C, there are 13 histological specimens considered as “insufficient”. Univariate regression analysis showed menopause and endometrial cavity fluid were risk factors of insufficient specimens ([Supplementary Table 1](#)), while parity and endometrial thickness were not. Bigger sample size is needed to verify these risk factors.

## Conclusion

Our study showed the endometrial cytology is a reliable method for evaluating endometrium, with a lower insufficient sample rate. Also, cytology sampled by both Li brush and Tao brush has a high accuracy with histological diagnosis in detecting endometrial cancer and atypical hyperplasia. Combining social and economic benefits, the Li brush may be a better endometrial cell collector.

## Ethical Approval

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. And it was approved by the Institutional Review Board of the First Affiliated Hospital of Xi'an Jiao Tong University (IRB No. XJTUIAF2017LSK-100). Informed consent was obtained from all patients.

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## Disclosure

The authors declare no conflict of interest.

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