

RESEARCH ARTICLE

Incidental Finding of Abnormal Cervical Pathology in Hysterectomy Specimens after Normal Preoperative Papanicolaou Smears in Thammasat University Hospital

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Abstract

Background: To investigate abnormal cervical histopathology (ACH) from hysterectomy specimens with normal preoperative Papanicolaou (Pap) smears. **Materials and Methods:** Medical records from May 2009 to April 2012 were retrospectively reviewed of subjects from whom hysterectomy specimens were taken in Thammasat University Hospital. All had normal preoperative Pap smears. ACH was the primary outcome. A p-value less than 0.05 was considered significant. A total of 483 subjects with an average age of 50.5 years were recruited. Benign cases of enlarged uterus and pelvic mass were present in 94% (430/483). Endometrial and ovarian cancer were found at 6.2 and 4.7%, respectively. In hysterectomy specimens there were 19 (4%) cases of ACH. Silent ACH with benign disease, endometrial and ovarian cancers were 1.2% (5/430), 33.3% (10/30) and 17.4% (4/23), respectively. The negative predictive value (NPV) and false negative rate of Pap smears were 96 and 4%, respectively. ACH in malignant cases were 27.9% (12/43) and 20% (2/10) in adequate (APS) and inadequate (IPS) Pap collection groups, respectively. ACH in benign condition were 0.68% (2/292) and 2.2% (3/138) in APS and IPS, respectively. ACH was more often found in hysterectomy specimens with indication of malignancy than benign conditions with statistical significance. One third of preoperative stage I endometrial cancer cases had cervical involvement. **Conclusions:** Silent ACH in normal preoperative Pap smear was 4%. Inadequate Pap smear collection is still the major problem in this study. Reducing inadequate Pap smear collection could reduce the false negative rate.

Keywords: Hysterectomy - normal Pap smear - cervical histopathology - false negative rate

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Introduction

Hysterectomy is the most common major non-Obstetrics operation undergone by women worldwide (Lin et al., 2012; Stang et al., 2012). It is a destructive surgery. Hysterectomy can be used to eradicate both malignant and non-malignant gynaecological diseases. Previous reports showed that hysterectomy rate for uterine leiomyoma was greater than all other indications combined, namely endometriosis, uterine prolapse and other minor conditions (Lin et al., 2012, Stang et al., 2012). Hysterectomy was the second most medical operation undergone in woman for medical reason, after cesarean sections in Obstetrics and Gynaecological operations in Thammasat University Hospital.

Preoperative preparation of hysterectomy included history taking, physical and pelvic examination and

laboratory investigation. Papanicolaou smear (Pap smear) was performed as a routine in a hysterectomy cases as well as in other gynaecological patients to exclude any cervical intraepithelial neoplasia (CIN) or malignancy (Howard et al., 2008). Internal medical records of Gynaecological Department at Thammasat University Hospital, Thailand showed incidence of nonmalignant hysterectomy at 818 in 1000 (2009-2012). Some post-operative pathologic results revealed abnormal tissues where as the original Pap smear reported no abnormality. No other report of similar finding was found locally. Frick et al work reported in 2010 also found the silent CIN 0.3 percent in patients who had hysterectomy due to reconstructive pelvic surgery (Frick et al., 2010). Incidental finding of silent CIN and cervical cancer were thus the topic of interest. The objective of this study was to investigate the correlation of normal pre-operative Pap smear and silent cervical histopathology

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Materials and Methods

This study was approved by Thammasat University Ethical Committee. Medical records were retrospectively reviewed. Subjects were women who underwent hysterectomy with normal preoperative Pap smear in Thammasat University Hospital between May 2009-April 2012. Women who had previously been diagnosed with abnormal Pap smears, precancerous and cervical cancers were excluded from this study. Medical records of women who underwent hysterectomy were collected. All cases had normal preoperative Pap smear. The subjects consisted of benign and malignant gynaecological conditions. Subjects underwent hysterectomy with/without ovarian removal per standard protocol. All uterine specimens were sent to Department of Pathology for pathological study. Demographic data and histopathologic results were collected. Abnormal cervical pathology in normal preoperative Pap smear was the primary outcome. A p-value of less than 0.05 was considered significant. SPSS 17.0 (SPSS Inc., Chicago, USA) was used for all statistical analysis. Descriptive statistics were used for demographic data. Chi-square or Fisher's exact test, where appropriated, was used to compare the difference between groups.

Results

In this study, there were 483 patients aged between 33-79 years old (average 50.5 years). The demographic data showing age, occupation, marital status and medical financial support were shown in Table 1. Ninety five percent of cases were older than 40 years old. Half of cases were housewives and paid their own medical expenses.

Four hundred and eighty three cases were enrolled in this study. All cases had normal preoperative Pap smear. Ninety eight percent was conventional Pap smear. The number of benign condition was 430 cases. Benign cases were enlarged uterus (94%) mainly (myoma and adenomyosis) and pelvic mass. Endometrial and ovarian cancer were found at 6.2 percent and 4.7 percent, respectively. From hysterectomy specimen, there were

Table 1. Demographic Data of Patients

Characteristics	%(n=483)	
Age (years)	<40	4.3(21)
	≥40	95.7(462)
Occupation	Household	44.72(16)
	Agriculturist	2.9(14)
	Merchandise	9.5(46)
	Self employee	21.3(103)
	Government officer	21.5(104)
Marital	Marriage	64.6(312)
	Single	23.8(115)
	Divorce	11.6(56)
Welfare	Cash	53.0(256)
	Reimburse	29.8(144)
	National Health Security	11.2(54)
	Social Security	6.0(29)

*Reimburse: Expense reimbursement from the original affiliation

19(4%) cases of abnormal cervical pathology as shown in Figure 1. Silent abnormal cervical pathology of benign disease (myoma uteri, adenomyosis and benign ovarian cysts, etc.), endometrial and ovarian cancers were 1.2 (5/430), 33.3 (10/30) and 17.4 (4/23) percent, respectively. In this study, negative predictive value (NPV) and false negative of Pap smear were 96 and 4 percent, respectively.

Table 2 showed correlation between cervical histopathology and Pap specimen adequacy in benign and malignant conditions. From 483 hysterectomy specimens, two-third of preoperative Pap smear had specimen adequacy for evaluation. Dividing out the patients by specimen adequacy, there were adequate and inadequate Pap smear specimens for evaluation (APS and IPS, respectively). Of 335 APS, abnormal cervical histopathology (ACH) was 4 percent (14/335). ACH of benign and malignant disease in APS were 0.68 (2/292) and 27.9 (12/43) percent, respectively. The difference had statistical value at $p \leq 0.05$. Of 148 IPS, ACH was 3.4 percent (5/148). ACH of benign and malignant disease in IPS were 2.2 (3/138) and 20 (2/10) percent, respectively. The difference was statistically significant at $p \leq 0.05$.

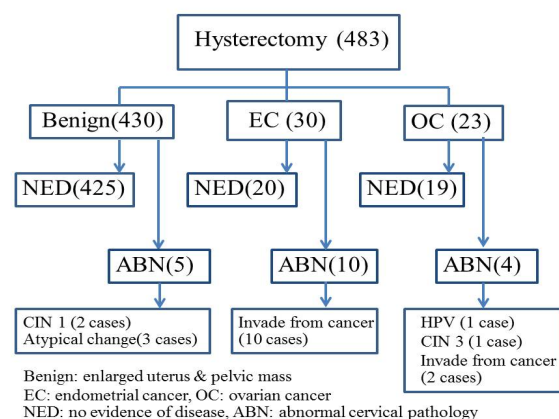


Figure 1. Algorithm of Study

Table 2. Correlation of Cervical Histopathology and Adequacy of Pap specimen in Benign and Malignant Conditions

Final diagnosis	Cervical histopathology		
	Negative	Positive	p value
Adequate Pap specimen	321	14	<0.05
Benign	290	2	
Malignant	31	12	
Inadequate Pap specimen	143	5	<0.05
Benign	135	3	
Malignant	8	2	

*Malignant: endometrial and ovarian cancer, Benign: non-cancer diseases; Negative: no evidence of disease, Positive: abnormal cervical pathology

Table 3. Correlation of Cervical Histopathology and Final Diagnosis between Benign and Malignant Conditions

Final diagnosis	Cervical histopathology			p value
	Negative	Positive	Total	
Benign	425	5	430	<0.01
Malignant	39	14	53	<0.01
Total	464	19	483	

*Malignant: endometrial and ovarian cancer, Benign: non-cancer diseases; Negative: no evidence of disease, Positive: abnormal cervical pathology

Overall patients who underwent hysterectomy, 430 and 53 cases were diagnosed with benign and malignant condition, respectively. ACH was found 1.2(5/430) and 26(14/53) percent in benign and malignant cases, respectively as shown in Table 3. The difference was statistical significant at $p \leq 0.05$.

Discussion

This present study was conducted from retrospective medical chart review. All subjects in this study undergone hysterectomy with preoperative normal Pap smears. Most of them age over 40 years old.

Some limitations of this study should be considered in assessing its results. The data was retrospectively obtained from routine clinical records. This caused some important information not to be available which was the common weakness of a retrospective studies (Kim et al., 2011).

From the investigation we found 4 percent false negative of ACH in normal Pap smear. Inadequate Pap smear collection was a major problem.

In this study, rate of specimens inadequacy for evaluation was 30.6 percent (148/483). This percentage was higher than other studies (Bhaumik et al., 2004). Bhaumik's work found that an inadequacy of Pap smear collection rate in fourth attempt of Pap smears collection after three consecutive inadequate smear collection was 13.5 percent (36/266).

Silent cervical pathology in this study was 4% (19/483). Bhaumik's work in 2004 found that silent cervical pathology varied from 11.5% to 19.1% among inadequate Pap smear collection (Bhaumik et al., 2004). UK guideline recommended colposcopy after three consecutive inadequate Pap smear collection rather than the fourth Pap smear collection (Bhaumik et al., 2004).

However the gold standard in Bhaumik's study was colposcopic directed biopsy while current study used hysterectomy specimens. Bhaumik's study conducted on three consecutive inadequate Pap smear collection while this work employed a single negative result Pap smear prior to the operation. Any methods to reduce inadequate Pap smear collection should provide to decrease the false negative and to increase NPV such as liquid based cytology. Repeated Pap smear would not be the solution of inadequate Pap smear collection reduction.

False negative result of Pap smear in this study caused by poor technique of specimens collection, which could range from too thick spread cell on slide, numerous artifact on slide and some error of Pap smear staining process as mentioned in previous literature (Lee et al., 2009). This could be explained by variation performance of Pap smear collectors ranging from medical students to gynecological residents and gynecological specialist. Pap smear specimen collection technique was integrated in our medical school years but practice during those early years was not intensive. None were taught to evaluate the adequacy of their slide preparation technique. However, in years of Obstetrics and Gynaecology residency training programs, the more Pap smear specimen collection and the more Obstetrics and Gynaecology related procedures learning were performed. Competency to collect an

adequate specimen did not seem to increase in any Obstetrics and Gynaecology residents.

Literature reviews of Gynaecology related procedures between 2009-2014 found report of neither false negative Pap smear nor Pap smear inadequacy. Our effort to evaluate our false negative statistic found that our outcome within the range of what had been reported in the past (Lee et al., 2009). Inadequacy found pointed out that any improvement assure in Pap smear procedure by attending physicians will give higher in the Pap smear outcome.

In this study, 97 percent of cases underwent conventional Pap smears. One third of cases was IPS group. Liquid-based cytology (LBC) show an overall improvement in sample collection and processing, reduce artifacts that interfere in diagnosis (Hoda et al., 2013). Chen's work in 2012 from China found that silent cervical pathology were 5.66% and 2.6% in conventional and liquid-based Pap smear, respectively (Chen et al., 2012). Increasing of LBC usage may be benefit for reduction of inadequacy of Pap specimen collection and false negative rate.

Negative predictive value (NPV) in this investigation was 96 percent (464/483). NPV of adequacy of specimen collection group was 95 percent (321/335) compare to 96.6 percent (143/148) in the inadequacy specimen collection group. This result seemed to show similarity of NPV among both groups. Compared this finding to the work of Lee et al (Lee et al., 2009) from Korea, Chen et al (Chen et al., 2012) from China and Nessa et al (Nessa et al., 2013) from Bangladesh. Their NPV were 98.8 (478/484), 94.3 (700/742) and 79.3(46/58) percent, respectively. Our NPV did not differ from Lee's, Chen's and Nessa's work. The limited number of cases in this study was the explanation of this result. This investigation was conducted on limited hysterectomy specimens with negative Pap tests before operations. In case of abnormal Pap test, the patient was excluded from this study. The finding indicated that we should treat each future patient more carefully with the most mundane procedure as Pap smear.

In this investigation it was found that among 30 patients diagnosed with endometrial cancer, 10 of them had cervical involvement (33%). This was identified as stage 2 endometrial cancer. When the Pap smear results read negative they were provisional considered as stage 1. Cervical invasion from histopathology is needed to confirm stage 2 endometrial cancer. If these patients had known before the operation that they harbored stage 2 endometrium cancer from a better Pap smear result they would have two choices. The choices were either receiving simple hysterectomy (Rutledge type I) followed by radiology or receiving primary radical hysterectomy (Rutledge type III). If choice two was selected no radiation was required thus the survival rate of the patients greatly increased compared to simple hysterectomy (Friedlander et al., 2010). Another benefit of a better Pap smear result was the chance for thoroughly investigation before surgery for example magnetic resonance imaging (MRI) or computed tomography (CT) scan. This investigation may distinguish between stage 1 cervical cancer with endometrial involvement from stage 2 endometrial cancer.

Due to 33.3% of endometrial cancer in this study was identified to stage 2 post-operatively. These patients loss

opportunity to undergo radical hysterectomy (Rutledge type III) that gave the better survival rate. This finding suggested that in endometrial cancer cases, we need the higher sensitivity Pap smear than normal cases. LBC (physician or self-sampling) which had higher sensitivity than conventional Pap smear should be used as a tool for a better detection of cervical involvement (Nandini et al., 2012; Yoshida et al., 2013; Moosa et al., 2014).

In conclusion, this study, silent cervical pathology in normal preoperative Pap smear was 4 % and NPV at the percentage of 96. Inadequate Pap smear collection is still the major problem in this study. Reducing of inadequate Pap smear collection should reduce the false negative rate.

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